

**A COMPARATIVE STUDY OF THE DETERMINANTS OF BONE
STRENGTH AND THE PROPENSITY TO FALLS IN BLACK AND
WHITE SOUTH AFRICAN WOMEN**

MAGDA CONRADIE

Dissertation presented for the Degree of



Doctor of Medicine at Stellenbosch University

Promotor : Professor F. S. Hough

December 2008

DECLARATION

By submitting this dissertation electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the owner of the copyright thereof (unless to the extent explicitly otherwise stated) and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

Date: 19 December 2008

Dedicated to my family

- for their love, understanding and support.

SUMMARY

The comparative study presented in this dissertation specifically aimed to assess fracture risk in black (Xhosa) and white South African women by evaluating known determinants of bone strength as well as the propensity to falls. We thus compared the prevalence of clinical (historic) risk factors for osteoporosis, measured and compared vertebral and femoral bone mineral density (BMD) employing dual energy X-ray absorptiometry (DEXA), ultrasound variables using the Sahara sonometer, serum parathyroid hormone (PTH) and 25-OH Vitamin D, mineral homeostasis and modern biochemical markers of bone turnover, bone geometry and the propensity to falls. Finally, we determined the prevalence of vertebral fractures in these black and white South African females.

1. Significant ethnic differences were noted in the presence and frequency of historical clinical and lifestyle risk factors for osteoporosis. Blacks were heavier and shorter, they consumed less calcium, were more inactive, preferred depot-medroxyprogesterone acetate as contraceptive agent and were of higher parity. Whites smoked more, preferred oral oestrogen containing contraceptive tablets and were more likely to have a positive family history of osteoporosis. Hormone therapy was used almost exclusively by postmenopausal whites. Inter-ethnic differences in weight, physical activity and high parity was most marked in the older subjects.
2. We found that peak spinal BMD was lower, but peak femoral BMD similar or higher (depending on the specific proximal femoral site measured) in black South-African females compared with whites. The lower peak spinal BMD was mainly attributed to lower BMD's in the subgroup of black females with normal to low body weight, indicating that obesity either protected black females against a low spinal BMD or enhanced optimal attainment of bone mineral. An apparent slower rate of decline in both spinal- and femoral BMD with ageing was noted in the black females compared with whites in this cross-sectional study – an observation which will require confirmation in longitudinal, follow-up studies. This resulted in similar spinal BMD values in postmenopausal blacks and whites, but significantly higher femoral BMD measurements in blacks. The volumetric calculation of bone mineral apparent density (BMAD) at the lumbar spine and femoral neck yielded similar results to that of BMD. Spinal BMAD was similar in blacks and whites and femoral neck BMAD was consistently higher in all the menopausal subgroups studied. Weight significantly correlated with peak- and postmenopausal BMD at all sites in the black and white female cohorts. Greater and better maintained body weight may be partially responsible for slower

rates of bone loss observed in black postmenopausal females. Most of the observed ethnic difference in BMD was, in fact, explained by differences in body weight between the two cohorts and not by ethnicity per se.

3. A low body weight and advanced age was identified as by far the most informative individual clinical risk factors for osteopenia in our black and white females, whereas physical inactivity was also identified as an important individual risk factor in blacks only. Risk assessment tools, developed and validated in Asian and European populations, demonstrated poor sensitivity for identification of South African women at increased risk of osteopenia. The osteoporosis risk assessment instrument (ORAI) showed the best results, with sensitivities to identify osteopenic whites at most skeletal sites approaching 80% (78% - 81%). The risk assessment tool scores appear to be inappropriate for our larger sized study cohort, especially our black subjects, thus resulting in incorrect risk stratification and poor test sensitivity. General discriminant analysis identified certain risk factor subsets for combined prediction of osteopenia in blacks and whites. These risk factor subsets were more sensitive to identify osteopenia in blacks at all skeletal sites, compared with the risk assessment tools described in the literature.
4. Higher ultrasonographically measured broadband ultrasound attenuation (BUA) and speed of sound (SOS) values were documented in our elderly blacks compared with whites, even after correction for differences in DEXA determined BMD at the spine and proximal femoral sites. BUA and SOS showed no decline with ageing in blacks, in contrast to an apparent significant deterioration in both parameters in ageing whites. If these quantitative ultrasound (QUS) parameters do measure qualitative properties of bone in our black population, independent of BMD as has been suggested in previous work in Caucasian populations, the higher values documented in elderly blacks imply better preservation of bone quality in ageing blacks compared with whites. The correlation between QUS calcaneal BMD and DEXA measured BMD at the hip and spine was modest at best. QUS calcaneal BMD was therefore unable to predict DEXA measured BMD at clinically important fracture sites in our study population.
5. Bone turnover, as assessed biochemically, was similar in the total pre- and postmenopausal black and white cohorts, but bone turnover rates appeared to differ with ageing between the two racial groups. A lower bone turnover rate was noted in blacks at the time of the menopausal transition and is consistent with the finding of a lower percentage bone loss at femoral sites at this time in blacks compared with whites. Bone turnover only increased in *ageing* postmenopausal blacks, and this could

be ascribed, at least in part, to the observed negative calcium balance and the more pronounced secondary hyperparathyroidism noted in blacks. Deleterious effects of secondary hyperparathyroidism on bone mineral density at the proximal femoral sites were demonstrated in our postmenopausal blacks and contest the idea of an absolute skeletal resistance to the action of PTH in blacks. The increase in bone turnover and the presence of secondary hyperparathyroidism due to a negative calcium balance may thus potentially aggravate bone loss in ageing blacks, especially at proximal femoral sites.

6. Shorter, adult black women have a significantly shorter hip axis length (HAL) than whites. This geometric feature has been documented to protect against hip fracture. The approximately one standard deviation (SD) difference in HAL between our blacks and whites may therefore significantly contribute to the lower hip fracture rate previously reported in South African black females compared with whites. Average vertebral size was, however, smaller in black females and fail to explain the apparent lower vertebral fracture risk previously reported in this population. Racial differences in vertebral dimensions (height, width) and/or other qualitative bone properties as suggested by our QUS data may, however, account for different vertebral fracture rates in white and black women – that is, if such a difference in fact exists.
7. The number of women with a history of falls was similar in our black and white cohorts, and in both ethnic groups the risk of falling increased with age. There is a suggestion that the nature of falls in our black and white postmenopausal females may differ, but this will have to be confirmed in a larger study. Fallers in our postmenopausal study population were more likely to have osteoporosis than non-fallers. Postmenopausal blacks in our study demonstrated poorer outcomes regarding neuromuscular function, Vitamin D status and visual contrast testing and were shown to be more inactive with ageing compared with whites. An increased fall tendency amongst the black females could not however be documented in this small study. Quadriceps weakness and slower reaction time indicated an increased fall risk amongst whites, but were unable to distinguish black female fallers from non-fallers.
8. Vertebral fractures occurred in a similar percentage of postmenopausal blacks (11.5%) and whites (8.1%) in our study. Proximal femoral BMD best identified black and white vertebral fracture cases in this study. Quite a number of other risk factors i.e. physical inactivity, alcohol-intake, poorer physical performance test results and a longer HAL were more frequent in the white fracture cases and could therefore serve as markers of increased fracture risk, although not necessarily implicated in the pathophysiology of

OP or falls. However, in blacks, only femoral BMD served as risk factor. Similar risk factors for blacks and whites cannot therefore be assumed and is deserving of further study. White fracture cases did not fall more despite lower 25-OH-Vitamin D, poorer physical performance and lower activity levels than non-fracture cases. Calcaneal ultrasonography and biochemical parameters of bone turnover were similar in fracture and non-fracture cases in both ethnic groups. Our study data on vertebral fractures in this cohort of urbanized blacks thus cautions against the belief that blacks are not at risk of sustaining vertebral compression fractures and emphasize the need for further studies to better define fracture prevalence in the different ethnic populations of South Africa.

9. In our study, hormone therapy in postmenopausal white women improved bone strength parameters and reduced fall risk. In hormone treated whites compared with non-hormone users, a higher BMD at the spine and proximal femur as determined by DEXA were documented and all QUS measurements were also significantly higher. The biochemically determined bone turnover rate, as reflected by serum osteocalcin levels, was lower in hormone users. Fall frequency was lower in the older hormone treated women (≥ 60 yrs) and greater quadriceps strength and reduced lateral sway was noted. Only one patient amongst the hormone users (2%) had radiological evidence of vertebral fractures compared with four patients (6%) amongst the never-users. As hormone therapy was used almost exclusively by whites in this study population, the impact of hormone therapy on postmenopausal black study subjects could not be assessed.

.....

OPSOMMING

Die doel van die vergelykende studie vervat in hierdie verhandeling was om fraktuur-risiko in swart en wit Suid-Afrikaanse vroue te bepaal en te vergelyk via die evaluasie van bekende beensterkte parameters en beoordeling van hul neiging tot valle. Swart en blanke Suid-Afrikaanse vroue is derhalwe vergelyk ten opsigte van die prevalensie van bekende kliniese (historiese) risikofaktore vir osteoporose (OP), vertebrale en femorale beenmineraaldigtheid (BMD) gemeet met behulp van dubbel-energie-X-straal-absorptiometrie (DEXA), ultraklank parameters bepaal met die Sahara sonometer, biochemiese bepaling van serum paratiroidhormoon, 25-OD-Vitamien D, mineraal homeostase en moderne biochemiese merkers van beenomset sowel as been-geometrie en die valneiging. Die prevalensie van vertebrale frakture in hierdie twee etniese studiegroepe is ten laaste ook bepaal en vergelyk.

1. Betekenisvolle etniese verskille in die teenwoordigheid en frekwensie van historiese kliniese- en lewenstyl risikofaktore is genoteer. Swart vroue het 'n hoër liggaamsgewig en is korter, hul dietêre kalsium-inname is laer, hul is meer onaktief, verkies depot medroksiprogesteronasetaat as kontraseptiewe modaliteit en is van hoër pariteit. Wit vroue rook meer, verkies orale estrogeen-bevattende kontraseptiewe tablette en het 'n hoër voorkoms van familiële OP. Hormoonterapie is feitlik uitsluitlik in wit postmenopousale vroue gedokumenteer. Die etniese verskille in liggaamsgewig, fisiese aktiwiteitsvlakke en pariteit was mees uitgesproke in die ouer studiepasiënte.
2. Piek vertebrale BMD was laer, maar piek femorale BMD soortgelyk of hoër (afhangende van die spesifieke proksimale femorale area gemeet) in swart vergeleke met wit Suid-Afrikaanse vroue. Die laer piek vertebrale BMD in swart vrouens was hoofsaaklik toeskryfbaar aan die laer vertebrale beenmineraaldigtheid in die subgroep van swart premenopousale vroue met normale tot lae liggaamsgewig. Hierdie bevinding was aanduidend van óf 'n beskermende rol van obesiteit teen die ontwikkeling van 'n lae vertebrale BMD óf dat obesiteit die bereiking van optimale piek vertebrale BMD potensieër. 'n Oënskynlike stadiger afname in beide vertebrale- en femorale BMD met veroudering is verder gedokumenteer in swart vrouens vergeleke met wit vroue in hierdie deursnit studie – 'n observasie wat bevestiging benodig in longitudinale opvolgstudies. Hierdie stadiger afname in BMD word weerspieël in die bevinding van soortgelyke vertebrale BMD en betekenisvolle hoër femorale BMD in postmenopousale swart vroue vergeleke met wit vroue. Soortgelyke resultate word verkry wanneer die volumetries berekende vertebrale en femorale nek

beenmineraaldigtheid van die twee etniese groepe met mekaar vergelyk word. Vertebrale volumetries berekende beenmineraaldigtheid is soortgelyk in swart en wit vroue, maar die volumetries berekende beenmineraaldigtheid van die femorale nek konsekwent hoër in swartes in al die bestudeerde menopousale subgroepe. 'n Betekenisvolle korrelasie tussen gewig en piek- sowel as postmenopousale BMD van alle gemete skeletale areas was aantoonbaar in die swart- en wit studiegroepe. Die oënskynlik stadiger tempo van beenverlies in swart postmenopousale vroue mag deels toeskryfbaar wees aan hul hoër liggaamsgewig, asook die beter behoud van hul liggaamsgewig met veroudering. Verskille in beenmineraaldigthede tussen swartes en wit vroue in hierdie studie was inderwaarheid grotendeels verklaar deur verskille in liggaamsgewig en nie die gevolg van etnisiteit per se nie.

3. 'n Lae liggaamsgewig en gevorderde ouderdom is in hierdie studie geïdentifiseer as die belangrikste individuele kliniese risikofaktore vir osteopenie in ons swart en blanke vroue, terwyl fisiese onaktiwiteit ook as belangrike risikofaktor vir osteopenie in swartes alleen aangetoon is. Risiko-assesseringsinstrumente, ontwikkel en bevestig in Asiatiese en Europese populasies toon lae sensitiwiteit vir identifikasie van SA vroue met verhoogde risiko vir osteopenie. Die Osteoporose Risiko-Assesseringsinstrument (ORAI) vertoon die beste in ons studiepulasie, met 'n sensitiwiteit vir identifikasie van osteopeniese wit vroue in die omgewing van 80% (78-81%). Tellings gebruik in hierdie risiko-assesseringsinstrumente blyk meesal ontoepaslik te wees vir ons fisies groter studiepulasie, veral ons swart vroue, met gevolglike onakkurate risiko stratifikasie en swak toets sensitiwiteite. Risikofaktor kombinasies, geïdentifiseer by wyse van algemene diskriminant analise vir gekombineerde voorspelling van osteopenie, vertoon beter sensitiwiteite ten opsigte van die identifikasie van osteopenie vir alle skeletale areas in swartes vergeleke met die risiko-assesseringsinstrumente geëvalueer.
4. Hoër waardes van ultrasonografies gemete breëband ultraklank attenuasie (BUA) en spoed van klank (SOS) is gedokumenteer in ons ouer swart vroue vergeleke met wit vroue. Hierdie hoër waardes in swartes is bevestig selfs na korreksie vir etniese verskille in DEXA gemete vertebrale en femorale BMD. In kontras met 'n oënskynlik betekenisvolle verswakking van beide BUA en SOS parameters in wit vrouens met veroudering, is geen betekenisvolle afname in hierdie parameters in swartes gedokumenteer nie. Indien hierdie ultraklank parameters kwalitatiewe aspekte van been meet in ons swart populasie, onafhanklik van BMD, soos vantevore gesuggereer in Kaukasiërs, impliseer hierdie bevindings 'n beter behoud van beenkwaliteit in

verouderende swart vroue vergeleke met wit vroue. Die korrelasie tussen kwantitatiewe ultraklank gemete kalkaneale BMD en vertebrale sowel as femorale BMD soos gemeet met behulp van DEXA, was matig ten beste, en ultraklank gemete BMD dus by onvermoë om DEXA gemete BMD van die klinies relevante fraktuurareas te voorspel in ons studiepopulasie.

5. Biochemies bepaalde beenomset was soortgelyk in die totale pre- en postmenopousale swart en wit studiegroepe. Oënskynlike etniese verskille in die tempo van beenomset met veroudering is egter aangetoon. 'n Laer beenomset is genoteer in swart vroue ten tye van die menopousale oorgang en verenigbaar met die bevinding van 'n laer persentasie femorale beenverlies in swart vroue vergeleke met wit vroue. 'n Toename in beenomset is slegs aangetoon in swart, ouer postmenopousale vroue. Hierdie bevinding kan gedeeltelik verklaar word op grond van 'n meer negatiewe kalsium-balans en derhalwe meer uitgesproke sekondêre hiperparatireose in swartes vergeleke met wit vroue. Nadelige effekte van sekondêre hiperparatireose op proksimale femorale beenmineraaldigtheid is wel aangetoon in ons postmenopousale swart vroue en weerspreek die idêe van 'n absolute skeletale weerstandigheid teen paratiroïedhormoon in swartes. 'n Toename in beenomset, vanweë 'n onderliggende negatiewe kalsium-balans en sêkondere hiperparatireose, mag dus potensieël beenverliese, veral van die proksimale femorale areas, aksensueer in verouderende swartes.
6. Korter, volwasse Suid-Afrikaanse swart vroue het 'n betekenisvolle korter heup-axis-lengte (HAL) as wit vroue. Hierdie geometriese bevinding is vantevore in die literatuur gedokumenteer om beskerming te verleen teen die opdoen van heupfrakture. Die nagenoeg een standard deviasie verskil in HAL tussen swart en wit vroue mag derhalwe betekenisvol bydra tot die laer heupfraktuur-risiko soos voorheen gerapporteer in SA swart vroue vergeleke met wit vroue. Gemiddelde vertebrale grootte was egter kleiner in swart vroue en derhalwe by onvermoë om die skynbaar laer vertebrale fraktuur-risiko, vroeër gedokumenteer in SA swartes, te verklaar. Etniese verskille in werwelafmetings (hoogte, wydte) en/of kwalitatiewe beenaspekte soos gesuggereer deur ons ultraklank data, mag aanleiding gee tot verskille in vertebrale fraktuur-risiko en voorkoms in ons swart en wit vroue – indien sodanige verskille inderwaarheid bestaan.
7. Die aantal vroue met 'n positiewe geskiedenis van valle was soortgelyk in ons swart en wit studiegroepe en veroudering is aangetoon om valrisiko te verhoog in beide etniese groepe. Ons studiedata suggereer moontlike verskille in die aard van valle

tussen postmenopousale swart en wit vroue, maar hierdie observasie benodig bevestiging in 'n groter studie. Postmenopousale swart- en wit vroue met 'n positiewe valgeskiedenis was meer waarskynlik osteoporoties as dié sonder enige vooraf valle. Swakker neuromuskulêre funksie, 25-OD-Vitamien D status en visuele kontras toetsing is aangetoon in ons postmenopousale swart vroue vergeleke met wit vroue. Ouer swart vroue was addisioneel ook minder aktief as wit vroue. Ten spyte van hierdie bevindings is 'n verhoogde valneiging in swart vroue nie in ons studie aangetoon nie. Quadriceps swakheid en 'n stadiger reaksietyd was aanduidend van 'n verhoogde valrisiko in wit vroue, maar by onvermoë om te onderskei tussen swart vroue met 'n valgeskiedenis en dié daarsonder.

8. Vertebrale fraktuur voorkoms was soortgelyk in ons swart (11.5%) en wit (8.1%) studiepulasie. Proximale femoral beenmineraaldigtheid was die beste voorspeller van swart- en wit frakturegevalle in hierdie studie. 'n Hele aantal ander risikofaktore, te wete, fisiese onaktiwiteit, alkohol-inname, swakker uitkomst met fisiese toetsing en 'n langer heup-aksis lengte was meer algemeen in die wit frakturegevalle en kan dus beskou word as merkers van verhoogde fraktuur-risiko, alhoewel nie direk geïmpliseer in die patofisiologie van osteoporose of 'n valneiging nie. In teenstelling met hierdie observasie in wit vroue, is slegs laer femorale beenmineraaldigtheid as risikofaktor vir frakture in swart vroue geïdentifiseer. 'n Aanneme dat soortgelyke risikofaktore verantwoordelik is vir vertebrale frakture in swart- en wit vroue is dus foutief en behoort verder bestudeer te word. Ten spyte van laer 25-OH-Vitamien D, swakker uitkomst met fisiese toetsing, en laer fisiese aktiwiteitsvlakke kon 'n verhoogde valneiging nie in swart frakturegevalle aangetoon word nie. Kalkaneale ultrasonografie en biochemiese parameters van beenomset was soortgelyk in swart- en wit frakturegevalle. Vertebrale fraktuur data gedokumenteer in hierdie studie waarsku dus teen die veronderstelling dat swart vroue beskerm is, en derhalwe 'n lae risiko het vir die opdoen van vertebrale frakture, en beklemtoon die belang en nodigheid van verdere studies ten einde die huidige fraktuur prevalensie in die verskillende etniese groepe van SA beter te definieër.
9. Ons studie-data toon dat hormoon terapie in wit vroue beensterkte parameters betekenisvol verbeter en ook lei tot 'n verlaagde valrisiko. 'n Hoër vertebrale en femorale DEXA gemete BMD, asook betekenisvolle hoër ultraklank parameters is gedokumenteer in die hormoon behandelde wit vroue vergeleke met nie-gebruikers van hormoonterapie. Biochemiese evaluasie van beenomset, soos gereflekteer deur serum osteokalsien-vlakke, was laer in die hormoon-gebruikers. 'n Laer frekwensie

van valle, sowel as beter quadriceps spierkrag en 'n verminderde laterale bewegingsneiging is ook aangetoon in ouer hormoon-behandelde wit vroue (> 60jr). Radiologiese bewys van vertebrale frakture was slegs genoteer in een van die hormoon-behandelde wit vroue (2%) vergeleke met 4 gevalle (6%) onder die nie-hormoon gebruikers. Die skeletale impak van hormoonterapie op swart postmenopousale Suid-Afrikaanse vroue is onbekend en benodig verdere studie.

.....

Abbreviations

AA	African Americans
ALP	Alkaline Phosphatase
ANOVA	Analysis of Variance
BF	Breast Feeding
BMAD	Bone Mineral Apparent Density
BMC	Bone Mineral Content
BMD	Bone Mineral Density
BMI	Body Mass Index
BMP	Bone Morphogenic Protein
BUA	Broadband Ultrasound Attenuation
BW	Bone Width
Ca	Calcium
CaMOS	Canadian Multicenter Osteoporosis Study
CEE	Conjugated Equine Estrogen
CV	Coefficient of Variation
DEXA	Dual Energy X-ray Absorptiometry
DP	Depot-medroxyprogesterone
DPD	Deoxypyridinoline
EPIDOS	The Epidemiology of Osteoporosis Study
EPOS	European Osteoporosis Study
FBD	Femoral Bone Density
FN	Femoral Neck
FNAL	Femoral Neck Axis Length
FSH	Follicle Stimulating Hormone
F _N BMC	Femoral Neck Bone Mineral Content
F _N BMD	Femoral Neck Bone Mineral Density
F _N BMAD	Femoral Neck Bone Mineral Apparent Density

F _T BMC	Total Femoral Bone Mineral Content
F _T BMD	Total Femoral Bone Mineral Density
F _T BMAD	Total Femoral Bone Mineral Apparent Density
GFR	Glomerular Filtration Rate
HAL	Hip Axis Length
HPT	Hyperparathyroidism
HT	Hypertension
IGF-1	Insulin Growth Factor 1
IL-1	Interleukin-1
IRMA	Immunoradiometric
LH	Luteinizing hormone
M-CSF	Macrophage Colony Stimulating Factor
NHANES III	Third National Health and Nutrition Survey
NIH	National Institute of Health
NOF	National Osteoporosis Foundation
NOFSA	South African National Osteoporosis Foundation
OB	Osteoblast
OC	Osteocalcin
OCP	Oral Contraceptives
OP	Osteoporosis
OPG	Osteoprotegerin
ORAI	Osteoporosis Risk Assessment Instrument
OSIRIS	Osteoporosis Index of Risk
OST	Osteoporosis Self-assessment Tool
PEPI	Postmenopausal Estrogen/progestin Interventions
PBMD	Peak Bone Mineral Density
PPAR	Peroxisome Proliferator Activated Receptor
PTH	Parathyroid Hormone

QC	Quality Control
QUI	Quantitative ultrasound index
QUS	Quantitative ultrasound
RANK	Receptor Activator NF- κ B
RANK-L	Receptor Activator NF- κ B-ligand
RBD	Radial Bone Density
RFLP	Restriction Fragment Length Polymorphisms
RIA	Radio Immuno Assay
RSA	Republic of South Africa
SA	South Africa
SBD	Spinal Bone Density
SBMAD	Spinal Bone Mineral Apparent Density
SBMC	Spine Bone Mineral Content
SBMD	Spinal Bone Mineral Density
SD	Standard Deviation
SHBG	Sex Hormone Binding Globulin
SOF	Study of Osteoporotic Fractures
SOS	Speed of Sound
TNF	Tumour Necrosis Factor
TRP	Tubular Reabsorption of Phosphate
TSH	Thyroid Stimulating Hormone
U-DPD	Urinary Deoxypyridinoline
UK	United Kingdom
US	United States
VDR	Vitamin D Receptor
WHI	Women's Health Initiative
WHO	World Health Organization
YSM	Years Since Menopause

INDEX

Chapter 1	<i>Research Objectives.....</i>	3
Chapter 2	<i>Literature Review</i>	7
Chapter 3	<i>General Methodology</i>	52
Chapter 4	<i>Assessment of Clinical risk factors for Osteoporosis in Black and White South African females.....</i>	73
Chapter 5	<i>Bone Mineral Density in Black and White South African Females.....</i>	90
Chapter 6	<i>Which Clinical Risk Factors are able to Predict Low Bone Mass in Postmenopausal Black and White South African Females?.....</i>	135
Chapter 7	<i>Calcaneal Ultrasonography in Black and White South African Females.....</i>	149
Chapter 8	<i>Bone Turnover, Mineral Homeostasis and Calcitropic hormones in Black and White South African Females. ..</i>	168
Chapter 9	<i>Bone Geometry in Black and White South African Females.....</i>	190
Chapter 10	<i>Fall Risk in Black and White South African Females</i>	201
Chapter 11	<i>Vertebral Fracture Prevalence in Black and White South African Females.....</i>	218

<i>Chapter 12</i>	<i>The Impact of Hormone Therapy on Bone Mineral Density, Calcaneal Ultrasonography, Bone Turnover and Fall Risk in White Postmenopausal South African Females.....</i>	<i>231</i>
<i>Chapter 13</i>	<i>Final Conclusions and Reflective Summary.....</i>	<i>241</i>
<i>Addendums</i>	<i>.....</i>	<i>243</i>
<i>References</i>	<i>.....</i>	<i>254</i>
<i>Acknowledgements.....</i>		<i>287</i>

CHAPTER 1

RESEARCH OBJECTIVES

African-American females have a significantly lower fracture prevalence compared with white American females, which is readily explained by their higher bone mineral density (BMD) at all skeletal sites. The higher BMD is primarily the result of higher peak bone mass attainment, but a lower bone turnover and reduced early postmenopausal bone loss further enhance this difference by ensuring better preservation of the already higher peak bone mass in the African American.

South African blacks also have a very low hip fracture prevalence. In contrast to the American data, BMD is not consistently higher in Black versus white South African females. In the only recent study of adult female South Africans, employing sophisticated techniques to measure BMD¹, similar appendicular and lumbar bone densities were noted. Femoral bone density was, however, higher in both pre- and postmenopausal black females. These findings are in keeping with studies elsewhere on the African continent where bone mineral content (BMC) and bone mineral densities were noted to be similar or lower in Africans compared to white Europeans despite a paucity of fractures in the former. The rarity of fractures in these African communities, where BMC and BMD are low, challenges current concepts about the significance of bone mineral status as a primary determinant of fracture risk and imply the presence of other protective mechanisms that ensure skeletal integrity.

This comparative study in black and white South African women specifically aimed to assess fracture risk by evaluating known determinants of bone strength as well as the propensity to falls.

We specifically aimed to:

1. Compare the prevalence of *clinical (historic) risk factors*, previously shown to predispose local Caucasian women to osteoporosis.
2. Measure *vertebral and femoral BMD* (in pre- and postmenopausal women) employing DEXA, to confirm previous reports suggesting that lumbar BMD was similar in white and black South African women.
3. Compare *ultrasound variables* (SOS, BUA, stiffness index) in black and white women, and to correlate these variables with BMD measurements (employing DEXA) made in the same patient. It has been suggested that speed of sound (SOS) primarily reflects

bone mass and that broadband ultrasound attenuation (BUA) is a parameter of porosity and bone quality². While ultrasound seems to reflect many of the same influences as bone mass (e.g. age, menopause, exercise), it may also provide information about bone "quality" and could therefore complement BMD data.

4. Measure serum parathyroid hormone (PTH) and 25-OH Vitamin D, mineral homeostasis and modern biochemical markers of *bone turnover* (serum osteocalcin, urine deoxypyridinoline) to determine whether our black population's low fracture risk might be ascribed to a lower bone turnover and relative *skeletal resistance to PTH*. These biochemical parameters will also be correlated with BMD and ultrasound data in the same patient.
5. Compare *bone geometry* (e.g. hip axis length) in white and black women. A longer HAL has been reported in whites³⁻⁶.
6. The *propensity to falls* will be compared in black and white women, employing a standardized questionnaire and physical examination, as well as a number of validated tests to assess muscle strength, reaction time, body sway and visual contrast sensitivity.
7. Determine the *prevalence of vertebral fractures* in these black and white South African females.

.....

CHAPTER 2

LITERATURE REVIEW

A.	GENERAL OVERVIEW	7
1.	BACKGROUND	7
2.	THE WORLD-WIDE EPIDEMIOLOGY OF OSTEOPOROTIC FRACTURES.....	8
3.	PATHOGENESIS OF OSTEOPOROSIS AND FRACTURES.....	9
3.1.	BONE STRENGTH.....	9
3.1.1.	<i>Bone mineral density (BMD).....</i>	9
3.1.1.1.	<i>Pathogenesis of a low bone mass</i>	10
3.1.1.2.	<i>Cellular control of bone mass</i>	11
3.1.1.3.	<i>Genetic determinants of susceptibility to osteoporosis and fracture</i>	13
3.1.1.4.	<i>Clinical risk factors for low bone mineral density</i>	15
3.1.2.	<i>Cellular control of bone mass</i>	11
3.1.2.1.	<i>Bone quality and fracture risk</i>	13
3.1.2.2.	<i>Clinical risk factors for low bone mineral density</i>	15
3.1.3.	<i>Bone Quality.....</i>	22
3.2.	FALL RISK	28
B.	OSTEOPOROSIS IN AFRICAN-AMERICAN WOMEN	29
1.	BACKGROUND	29
2.	BONE STRENGTH	30
2.1.	Bone Mineral Density (BMD)	30
2.1.1.	<i>Methodological Considerations</i>	30
2.1.2.	<i>Peak bone mineral density (PBMD).....</i>	32
2.1.3.	<i>Age-related bone loss.....</i>	32
2.1.4.	<i>Clinical risk factors for low bone mineral density.....</i>	33
2.1.5.	<i>Clinical Significance of BMD measurements</i>	34

2.2.	Bone quality	34
2.2.1.	<i>Micro-architecture and bone size</i>	34
2.2.2.	<i>Bone Turnover and Calcium homeostasis</i>	35
2.2.3.	<i>Bone Geometry</i>	37
3.	FALL RISKS	37
4.	FRACTURE DATA	37
5.	CONCLUSION	39
C.	OSTEOPOROSIS ON THE AFRICAN CONTINENT	40
1.	BACKGROUND	40
2.	BONE STRENGTH	40
2.1.	Bone mineral density (BMD).....	40
2.1.1.	<i>South Africa</i>	40
2.1.2.	<i>Rest of Africa</i>	43
2.2.	Bone Quality	44
2.2.1.	<i>Micro-architecture</i>	44
2.2.2.	<i>Bone Turnover and Calcium homeostasis</i>	45
2.2.3.	<i>Bone Geometry</i>	46
3.	FALL RISKS	46
4.	FRACTURE DATA	47
5.	CONCLUSIONS	49

CHAPTER 2

LITERATURE REVIEW

A GENERAL OVERVIEW

1. BACKGROUND

Osteoporosis is a common, costly and serious systemic skeletal disorder and is expected to increase in significance with the growing elderly population. The condition affects both sexes and all races, albeit to different degrees. Osteoporosis predominantly affects postmenopausal Caucasian females. The disease is characterized by low bone mass and qualitative micro-architectural alterations of bone tissue leading to enhanced bone fragility and increased fracture risk. The most serious consequence of osteoporosis is hip fracture with significant morbidity (less than 50% able to function independently) and mortality ($\sim 20\%$ die within 1 year of the event)⁷⁻¹¹.

Osteoporosis is a silent disease until complicated by fracture. Clinical application of bone densitometry has made it possible to diagnose osteoporosis before the first fracture has occurred. Bone mineral density (BMD) is strongly correlated with bone strength in vitro and a good predictor of future fracture risk. Since the relationship between bone density and fracture risk is a continuous one, similar to that between blood pressure and stroke, the choice of a BMD-value to define osteoporosis is necessarily somewhat arbitrary.

In 1994, the World Health Organization (WHO) selected a BMD value of 2.5 standard deviations (SD) or more below the mean for normal young white women, or a T-score of ≤ -2.5 ¹², to define osteoporosis in the white post-menopausal female population. This cut-off value was based on epidemiologic fracture threshold data which captures most women at risk of osteoporotic fracture (hip, vertebrae, forearm, humerus and pelvis). The relationship between low BMD and fracture risk is, however, a gradient and not a threshold. Therefore this classification was extended to include a subset of patients with osteopenia (BMD more than 1 SD, but less than 2.5 SD below young normal mean) in whom the presence of additional risk factors other than BMD may lead to increased fracture risk¹³ (table 1).

Table 1: Definition of osteoporosis:

World Health Organization Classification of Osteoporosis	
Definition	Criteria
Normal	BMC or BMD value greater than 1 SD below the young normal mean
Low bone mass (osteopenia)	BMC or BMD 1–2.5 SD below the young normal mean
Osteoporosis	BMC or BMD more than 2.5 SD below the young normal mean
Established osteoporosis	Osteoporosis (above) with one or more fragility fractures

BMD = bone mineral density, BMC = bone mineral content, SD = standard deviation.

Adapted from World Health Organization Study Group, 1997¹³

2. THE WORLD-WIDE EPIDEMIOLOGY OF OSTEOPOROTIC FRACTURES

As the average age of the world's population increases, the incidence of osteoporosis and its economic burden on society will increase further. Worldwide, approximately one-third of women aged 60-70 years and two-thirds of women aged 80 and older have osteoporosis¹⁴. The percentage of patients with osteoporosis increases progressively with age – 13% of US women in their 50's, 27% in their 60's, 47% in their 70's and 67% in their 80's meet the diagnostic criteria for osteoporosis¹⁵.

Fragility fractures are projected to increase as well, because of larger numbers of persons at risk and age-specific increases in fracture incidence. The US surgeon general's report on bone health and osteoporosis noted that 1 in 2 individuals older than 50 years will be at risk of sustaining an osteoporotic fracture¹⁶. Estimates indicate that the number of osteoporotic hip fractures occurring in the world each year will rise from the estimated 1.66 million in 1990 to 6.26 million by the year 2050¹⁷, thereby implying an urgent need for preventative strategies.

The overall prevalence of osteoporotic fractures rises dramatically in menopausal women. Bone loss is more abrupt for the first decade after the onset of menopause, followed by more gradual loss thereafter¹⁸. The incidence of hip fractures increases exponentially with age, particularly after age 70, and is most commonly seen in white women¹⁹ in developed

countries (figure 1). In developing countries, the gender difference in hip fracture incidence is largely eliminated²⁰.

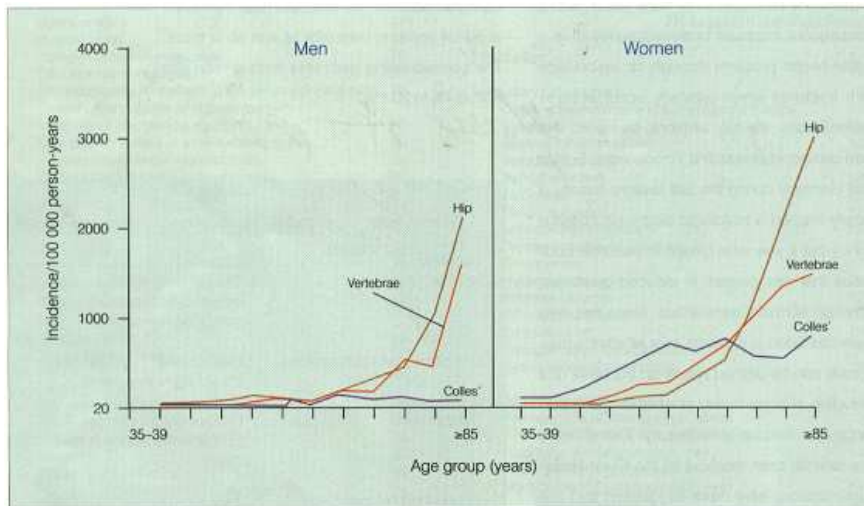


Figure 1: Age-specific incidence for hip, vertebral and distal forearm fractures in women. Adapted from Cooper et al, *J Bone Miner Res* 1992; 7: 221–227¹⁹

Hip fractures occur in about 32% of Caucasian women^{21,22}. A Caucasian women's risk of a hip fracture equals the combined risk of breast, uterine and ovarian cancer, and the risk of dying of hip fracture is equal to that of breast cancer²³.

3. PATHOGENESIS OF OSTEOPOROSIS AND FRACTURES

The two main etiopathogenetic factors involved in the development of skeletal fracture are decreased bone strength and increased risk of trauma and falls.

3.1. BONE STRENGTH

Osteoporosis is defined by the NIH as a systemic skeletal disorder characterized by compromised bone strength predisposing to an increased fracture risk²⁴. Bone strength is a function of BMD and bone quality.

3.1.1. Bone mineral density (BMD)

BMD is an excellent predictor of bone strength and fracture risk at all skeletal sites. Ex vivo studies performed on human material have indicated a good correlation between BMD and bone strength (femoral neck, $r=0.77, 0.84$; vertebrae, $r=0.66, 0.86$) as evaluated by mechanical tests of the femoral neck^{25,26} or uni-axial compression testing of the vertebrae²⁷⁻²⁹. These studies indicated that BMD predicts approximately 66-74% of the variation in bone strength. As BMD declines, fracture risk increases in a predictable manner.

A decrease of 1 SD in BMD results in a doubling of fracture risk, irrespective of fracture type and site of BMD measurement³⁰. In recent years, BMD testing has become more widely available and many countries have developed guidelines regarding testing. There is general agreement that a BMD measurement is indicated in individuals with clinical risk factor(s). The United States Preventative Services Task Force recommends that all women ≥ 65 years should be screened with DEXA irrespective of risk factors³¹. According to UK³² and SA³³ guidelines, routine BMD screening is, however, not deemed cost-effective and the prevention and treatment of osteoporosis are thought to be best managed using a case finding approach employing specific risk factors.

3.1.1.1. Pathogenesis of a low bone mass

Changes in bone mass are brought about by an imbalance between bone resorption and bone formation, processes that are normally tightly coupled. Once peak bone mass has been reached in the third decade of life, bone resorption generally outstrips bone formation, and there is loss of skeletal mass. There are thus two major pathogenetic reasons for low bone mass i.e. failure to achieve an optimal peak bone mass or increased bone loss after peak bone mass has been reached. Each can have genetic and environmental causes.

(i) Failure to achieve an optimal peak bone mass

Although peak bone mass is largely ($\pm 70\%$) genetically determined, it can be substantially affected by environmental factors such as poor nutrition, especially low calcium intake³⁴⁻³⁷ and little physical activity during skeletal growth³⁸⁻⁴⁰. Peak bone mass can also be affected by alterations in gonadal hormones from a variety of causes, including delayed onset of puberty^{41,42}, excessive exercise⁴³⁻⁴⁷, anorexia nervosa^{48,49} and hyperprolactinemia^{50,51}.

(ii) Increased Bone loss

(a) Increased bone resorption

Oestrogen-deficiency is a major factor contributing to increased bone resorption in women, especially after the menopause, and in ageing men as well^{52,53}. During the menopausal transition in women, which is associated with dramatic reductions in circulating oestrogen levels, there is an increase in the rate of bone remodelling and an imbalance between formation and resorption within each bone remodelling unit. This imbalance appears to be due to aggressive osteoclastic resorption, with an increase in resorption cavity depth and an inability of osteoblasts to keep pace. Calcium and vitamin D deficiency and reduced calcium absorption in older individuals, leading to parathyroid hormone excess, may contribute to bone loss⁵⁴.

(b) Inadequate bone formation

This may be due to complete loss of skeletal elements by excessive resorption, so that there is no template on which to form new bone, to age-related impairment of osteoblast function or to changes in local and systemic factors that regulate bone formation.

3.1.1.2. Cellular control of bone mass

(i) Regulation of bone resorption

Bone resorption is controlled by a complex interaction of cells of the osteoblastic and osteoclastic lineages. Osteoblasts appear to control the activity of osteoclasts and may be the primary regulators of both bone formation and resorption.

(a) Stimulation of osteoclastogenesis and bone resorption

Osteoclasts are recruited from hematopoietic precursors as a result of interaction with cells of the osteoblastic lineage⁵⁵. Osteoclast recruitment is effected by the expression of an osteoclast differentiation factor known as RANK-L (receptor activator of NF- κ B-ligand) by cells of the osteoblastic lineage. RANK-L binds to a receptor (RANK) located on the surface of osteoclast precursors to initiate osteoclastogenesis⁵⁶. Osteoblasts also produce macrophage colony stimulating factor (M-CSF) which enhances the replication of osteoclast precursors via its action on the c-fms receptor. Numerous other local factors also lead to expansion of the osteoclastic pool due to increased osteoclast formation and elongation of their life-span^{57,58}. These cytokines include TNF (tumour necrosis factor), prostaglandin E2, Interleukin (IL)-1 and IL-6 and are well recognized to stimulate bone resorption. Estrogen prevents bone loss by blocking the production of these pro-inflammatory cytokines. There is now substantial evidence supporting the hypothesis that a network of estrogen-regulated cytokines (especially TNF and IL-1) is responsible for the changes in bone turnover, increased bone resorption and the loss of bone induced by estrogen deficiency⁵⁹⁻⁶¹.

Systemic hormones known to control bone metabolism, most notably parathyroid hormone (PTH) and 1,25 dihydroxy-vitamin D, do not generally act directly on the osteoclast, but interact with receptors on the stromal/osteoblastic cells that support them and have been shown to enhance RANK-L expression^{62,63}. Recently Dempster et al demonstrated the presence of functional PTH-receptors on human osteoclasts suggesting that PTH may mediate bone resorption both indirectly (via OB) and directly (via OC)⁶⁴. Glucocorticoid exposure is known to stimulate osteoclastic bone resorption indirectly, by causing a negative calcium balance (impaired intestinal absorption, increased renal calcium wasting) and

secondary hyperparathyroidism. Chronic glucocorticoid exposure is, however, characterized by inhibition of osteoclastogenesis⁶⁵.

(b) Inhibition of osteoclastogenesis and bone resorption

Inhibitors of bone resorption can act through the osteoblastic and osteoclastic lineages. Osteoprotegerin, another osteoblast-derived cytokine and member of the TNF family, inhibits differentiation of osteoclasts by acting as a decoy receptor – it binds RANK-L and prevents its interaction with RANK⁵⁶.

It is well documented that oestrogen, the most important systemic inhibitor of bone resorption, reduces the number of osteoclasts in vivo, probably by suppressing osteoclast formation. Estrogen acts through altering cytokines such as IL-1, IL-6 or TNF- α as mentioned before, but there is also evidence for a direct action on osteoblasts to increase OPG production⁶⁶, and on osteoclasts to enhance osteoclast apoptosis⁶⁷. The other circulating inhibitor of bone resorption, calcitonin, acts largely by direct inhibition of osteoclasts, which express receptors for this hormone⁶⁸.

(ii) Regulation of bone formation

Inadequate bone formation may result from:

(a) Too little scaffold / template

Excessive bone resorption may lead to complete loss of skeletal elements, so that there is no template on which to form new bone.

(b) Senescent osteoblasts

Part of the pathogenesis of osteoporosis is the inability of bone formation to keep pace with the increase in age related bone resorption. Some osteoporotic patients, however, could primarily have low bone formation rates, which could result in bone loss.

(c) Local and systemic factors

IGF-1 has been proposed as a candidate in the pathogenesis of osteoporosis⁶⁹⁻⁷¹. Circulating IGF-1 decreases with age, and there is some clinical association between osteoporosis and low IGF-1 in serum. Insulin is also an important mitogen with decreased BMD documented in patients with absolute insulin deficiency (type 1 diabetes mellitus), and normal to high BMD noted in insulin resistance states with hyperinsulinism⁷².

Sex hormone deficiency may play a role in impaired bone formation. There is evidence that both oestrogen and testosterone can increase bone formation⁷³⁻⁷⁶, although they may

indirectly diminish the overall rate of bone formation secondary to their inhibitory effects on bone resorption. Glucocorticoids inhibit bone formation via its effect on osteoblast proliferation and osteoblast survival (increase osteoblast apoptosis and increase transdifferentiation of osteoblasts to fat cells). Both thyroid hormone, as well as intermittent low dose PTH increase osteoblast proliferation and may enhance bone formation. Leptin, an adipocyte derived hormone, has been recognized as a mediator of many biological processes and has also emerged as a potential regulator of bone metabolism⁷⁷⁻⁷⁹. Findings from in vitro studies have suggested that leptin enhances osteoblastic differentiation and inhibits osteoclastic generation via local mechanisms^{77,78}. Cross-sectional studies in humans have, however, yielded contradictory results, varying from no association between BMD and leptin⁸⁰ to a positive relationship that persisted⁸¹ or did not persist^{82,83} after adjustment for body mass index (BMI) or fat mass. Other studies found negative associations^{84,85}.

In 1965, Marshall Urist discovered that the extracellular matrix of bone contains a substance that has the capacity to induce new bone formation when implanted into extraskeletal sites⁸⁶. Over the past fifteen years, investigators elucidated the molecular genetics of bone morphogenetic protein (BMP) biology and identified fourteen individual human BMP's (BMP 2–15) possessing varying degrees of cartilage and or bone inductive activities^{87,88}. Clinical trials are currently conducted to evaluate the ability of certain BMP's to induce/ promote fracture healing and spinal fusion in view of their osteogenic properties.

(d) Transdifferentiation of osteoblasts

Impairment of bone formation during remodelling could occur, not only because of diminished cell function or a change in local regulators of osteoblasts, but also because the stromal cell population that normally gives rise to osteoblast precursors is diverted along another differentiation pathway i.e. is converted to adipocytes by activation of the PPAR- γ receptor⁸⁹.

3.1.1.3. Genetic determinants of susceptibility to osteoporosis and fracture

(i) Peak bone mineral density (PBMD)

Studies on the genetics of osteoporosis have focused mainly on the regulation of bone mineral density (BMD), a major determinant of osteoporotic fracture risk. The majority of studies have concentrated on peak bone mass in females and have shown remarkably consistent results. Evidence for a genetic contribution to PBMD regulation comes primarily

from twin studies. The heritability of BMD at the spine and hip has been estimated to lie between 70-85%, with values of 50-60% for wrist BMD⁹⁰⁻⁹³.

Genetic modelling has suggested that BMD is a polygenic trait and various candidate genes have been implicated in the regulation of BMD (table 2). These include polymorphisms in the genes that encode collagen, the estrogen receptor, TGF β , IL-6 and the Vitamin D receptor⁹⁴⁻¹⁰¹. The vitamin D receptor (VDR) alleles defined by BsmI, ApaI, TaqI and FokI restriction fragment length polymorphisms (RFLP) have been shown to be associated with variations in BMD in Australian¹⁰¹, black and white North American⁹⁹, Japanese⁹⁶, Mexican⁹⁷ and other premenopausal women.

The effect of the VDR genotype on BMD appears to be greatest, although not exclusively, in young adulthood, and declines in the elderly unless confounding factors (e.g. years since menopause, body mass etc.) are corrected⁹⁷. A meta-analysis in 1996 concluded that the VDR genotype was associated with modest effects on BMD, amounting for a difference of about 0.15-0.20 Z-score units between genotypes¹⁰². The authors of a recent prospective multicenter large-scale association study including 26 242 participants concluded that the BsmI, ApaI, TaqI and FokI VDR polymorphisms are not associated with BMD or with fractures, but the CdX2 polymorphism may be associated with risk for vertebral fractures¹⁰³. The genes encoding type 1 collagen (COLIA 1 and COLIA 2) are important candidates for the pathogenesis of osteoporosis. The COLIA1 Sp1 polymorphism is associated with reduced BMD and predispose to incident vertebral fractures independent of BMD¹⁰⁴. Significant ethnic differences have been reported in the population prevalence of COLIA 1 Sp1 alleles, it is common in Caucasian populations, but is rare in Africans and Asians¹⁰⁵. This polymorphism may be of value as a marker of osteoporotic fracture risk, because it predicts fractures that are independent of BMD and interacts with BMD to enhance fracture prediction^{104,106}.

Table 2: Candidate genes that have been studied in relation to bone mass.

Category	Candidate gene
Calcitropic hormones and receptors	VDR
	ER
	Aromatase
	PTH
	PTHR1
	Calcitonin receptor
	Glucocorticoid receptor
Cytokines, growth factors, and receptors	Calcium-sensing receptor
	TGF β -1
	IGF-1
	IL-6
	IL-1 β
	IL-1RA
	TNFR2
Bone matrix	BMP-4
	COL1A1
	Osteocalcin
	Collagenase
Miscellaneous	α HS2 glycoprotein
	ApoE
	MTHFR
	P57 Kip
	HLA
	PPAR γ
	Werner Helicase gene

PTHR1, PTH receptor type 1; IL-1RA, IL-1 receptor antagonist; TNFR2, TNF receptor type 2; BMP-4, bone morphogenic protein 4; MTHFR, methylene tetrahydrofolate reductase; HLA, human leukocyte antigen.

Adapted from Ralston SH et al. *J Clin Endocrin Metab* 2002; 87(6):2460-66¹⁰⁷

(ii) Bone loss

Longitudinal studies of axial bone loss in perimenopausal women have shown that most of the variance is unexplained by environmental variables¹⁰⁴. Although this suggests that genetic factors may also play a role in regulating bone loss, direct evidence in favour of this is conflicting^{90,108} and further work is required to determine whether genetic factors do contribute significantly to the regulation of bone loss.

(iii) Fracture risk independent of bone mineral density

In population based studies, a family history of hip fracture has been consistently shown to be a risk factor for fracture, *independent of BMD*¹⁰⁹. Twin and family studies have also shown that genetic factors play a role in the determination of bone turnover¹¹⁰, skeletal geometry^{93,111}, ultrasound properties of bone⁹³, body mass index¹¹², muscle strength¹¹³, age at menarche and age at menopause^{112,114}.

3.1.1.4. Clinical risk factors for low bone mineral density

An individual's peak bone mass attained and the subsequent bone loss that occurs with ageing determine his/her bone mineral density at any given time. A study on various sample populations' show that about 50-85% of the variance in peak bone mass is attributable to hereditary factors⁹⁰⁻⁹³. The remaining variance in peak bone mass is caused by

environmental factors. Age-related bone loss is largely a function of osteoblast incompetence and the menopause. Lifestyle factors, drugs and diseases may augment the physiological osteopenia of ageing.

(i) Clinical Risk factors

Many risk factors for bone loss have been identified and are summarized in table 3.

Table 3: SUMMARY: Clinical risk factors for bone loss

CLINICAL RISK FACTORS FOR BONE LOSS	
<p><i>NON-MODIFIABLE RISKS:</i></p> <ul style="list-style-type: none"> ● INCREASING AGE ● FAMILY HISTORY/GENETICS ● GENDER ● ETHNIC ORIGIN ● HEIGHT <p><i>MODIFIABLE RISKS:</i></p> <ul style="list-style-type: none"> ● PREVIOUS FRAGILITY FRACTURE ● LIFESTYLE: <ul style="list-style-type: none"> ○ Dietary ○ Smoking ○ Alcohol ○ Sedentary lifestyle ● ANTHROPOMETRY: <ul style="list-style-type: none"> ○ Body size: Fat /Lean mass ○ Excessive leanness ● GYNAECOLOGICAL VARIABLES <ul style="list-style-type: none"> ○ Oral contraceptive use ○ Parity ○ Breast feeding (BF) ○ Age of menarche ○ Menstrual cycle irregularities ○ Menopause ○ Years post menopause (YSSM) 	<p><i>IMPACT ON BONE STATUS</i></p> <p>The older, the more likely. Strongest known association with BMD and fracture</p> <p>Positive, especially maternal</p> <p>More in females. Hip fracture prevalence similar in men and women in developing countries</p> <p>More in Caucasians and Asians, also mixed race population in RSA</p> <p>Taller stature associated with higher BMD</p> <p>Markedly increased risk (3-5 fold) for subsequent fractures</p> <p>Low calcium intake, Vitamin D</p> <p>Excess caffeine and protein (may be calciuric), protein malnutrition – fragile bone</p> <p>Mediated via changes in endogenous estrogen metabolism.</p> <p>Positive association noted between moderate consumption and BMD in postmenopausal females, excessive intake (> 2U/day) has direct toxic effect and indirect adverse impact on bone health.</p> <p>Weight bearing has positive influence on skeleton, still subject of contention re bone loss in the postmenopausal years. Maintain muscle mass, reduce falls.</p> <p>Rate of bone loss related to both variables, dependent on age and menopausal status</p> <p>BMI < 19kg/m²</p> <p>May have positive or negative impact on BMD</p> <p>Conflicting data, effect of increasing parity may be positive, negative or absent</p> <p>Similar to parity, duration of BF may play role</p> <p>Younger age at menarche associated with higher BMD</p> <p>Oligomenorrhoea, amenorrhoea and lengthy cycles may have negative effects on BMD</p> <p>Oestrogen withdrawal following menopause associated with marked increase in bone loss</p> <p>BMD more dependent on YSSM than on the chronological age of the patient</p>

(ii) Clinical prediction of OP and fracture

Numerous epidemiological studies on the ability of clinical risk factors to predict the presence of osteopenia have found no consistent set of predictors for OP. In one of the most comprehensive investigations to date, the determinants of bone density were assessed cross-sectionally in the Study of Osteoporotic Fractures, a cohort of over 9500 elderly White and Asian women¹¹⁵ (table 4). Risk factors for reduced axial and appendicular (radial and femoral) bone density were analysed separately.

Table 4: Risk factors (-) and Protective factors (+) for axial and appendicular bone density among elderly white women

Variable	Lumbar spine	Femoral neck	Distal radius
Age		--	--
Weight	+++	+++	+++
Height	++	++	++
Fracture in mother	--	--	--
Age at menopause	+	+	++
Estrogen use	+++	+++	+++
Quadriiceps strength		++	
Grip Strength			+++
Thiazide use	+++	++	+++
Current smoker			--
# of alcoholic drinks in lifetime	+		
Dietary calcium intake		++	+
Lifetime caffeine intake			-
Recent or past physical activity	+	+	

The strength of correlations from multivariate analysis is indicated by the number of symbols. Three symbols indicate > 3% change in bone density per unit change in the variable; two symbols a 1-3% change and one symbol a change of < 1%. Adapted from: Orwoll ES, Bauer DC, Vogt TM, et al. *Ann Intern Med* 1996; 124: 187-96¹¹⁵

Greater height and weight, older age at menopause, greater physical activity, and use of alcoholic beverages, diuretic treatment, and current oestrogen replacement therapy were associated with higher *spinal BMD* (SBMD), whereas later age at menarche and a maternal history of fractures were associated with lower SBMD values¹¹⁵. Increasing age was positively associated with SBMD in these ladies; probable because of associated degenerative spinal changes and false high SBMD readings on DEXA. Age was a risk factor for both low radial and femoral neck BMD.

Later age at menopause, estrogen or thiazide use, and greater height, weight, muscle strength and dietary calcium intake were all positively associated with *distal radial BMD*, whereas age, cigarette smoking, caffeine intake and maternal history of fracture were all negatively associated¹¹⁶.

Femoral neck BMD was positively associated with most of the same protective factors, along with quadriceps strength and calcium intake. A maternal history of fracture and a personal history of previous wrist fracture correlated with low femoral neck BMD.

Despite the large number of potential risk factors assessed in the Study of Osteoporotic Fractures, however, models incorporating all of the independent predictors together explained only 20% to 34% of the variance in bone density at the different skeletal sites¹¹⁶. In a population based study of 1600 perimenopausal females by Kröger and colleagues, only 18.7–25.4% of the variance in BMD could be explained by current anthropometric and lifestyle factors¹¹⁷.

Broussard et al¹¹⁸ identified a set of modifiable risk factors from published population based studies in white women and men and then determined the ability of these risk factors to predict osteoporosis and low BMD in a multi-ethnic population. The most frequently recurring statistically significant risk factors in addition to age were low BMI, inadequate dietary calcium intake, current cigarette smoking and low levels of physical activity.

A single study by Blaauw et al in 1993¹¹⁹ identified a positive family history of OP, a fair complexion, lower body mass and height, no breastfeeding of babies, a history of smoking and fat distribution around the waist to be significant risk factors for OP in a subset of white South African females.

To our knowledge no studies evaluating clinical risk factors for osteoporosis has been done in other SA ethnic groups, and thus no data exist regarding the performance of risk assessment tools in these groups.

Numerous screening instruments based on clinical risk factors have also been developed to aid the assessment of osteoporotic risk in women¹²⁰⁻¹²⁶. These instruments facilitate identification of women most likely to have a low BMD, but cannot be used to diagnose osteoporosis and are not a substitute for BMD measurements¹²⁵ (table 5).

Table 5: Instruments for estimation of risk of osteoporosis

Instrument	Objective	Elements	Sensitivity (%)	Specificity (%)
<u>SCORE ≥6</u>	Identify women likely to have femoral neck T-score ≤ -2.0	Age, race, weight, history of fracture, history of oestrogen use, history of rheumatoid arthritis	89	50
<u>ORAI ≥9</u>	Identify women likely to have femoral neck or lumbar spine T-score ≤ -2.0	Age, weight, current oestrogen use	90	45
<u>SOF SURF >3</u>	Identify women likely to have total hip T-score ≤ -2.0	Age, weight, history of fracture, current smoking	Not reported	Not reported
<u>OST ≤ -1</u>	Identify Asian women likely to have femoral neck T-score ≤ -2.5	Age, weight	91	45

The threshold values for recommending BMD testing are shown next to the name of the instrument. The objective of the instrument is to identify four testing groups as specified, using risk factors as shown in elements column. The performance of each instrument is evaluated by sensitivity and specificity. Adapted from: Wehren LE, Siris ES *Journal of Internal Medicine* 2004; 256: 375-380¹²⁵

Age has the strongest known association with BMD and along with weight is included in all instruments. The prevalence of osteoporosis increases substantially with age, as reported in the Third National Health and Nutrition Survey (NHANES III)¹²⁷ and shown in figure 2. These two variables have also been noted in other studies to be the most informative predictors for low bone mineral density¹²⁶.

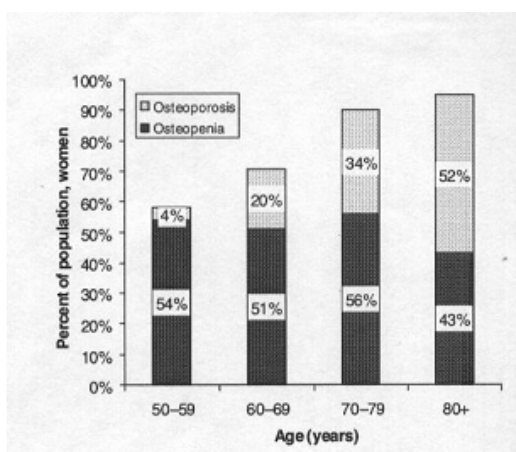


Figure 2: Prevalence of low bone mass (osteopenia, shown in dark bars) and osteoporosis (shown in grey bars) amongst women in the US by age group, based on BMD measurements at the femoral neck in NHANES III. Osteoporosis was defined as a T-score ≤ 2.5 and osteopenia as a T-score below -1.0 and above 2.5 in NHANES III. Adapted from Looker et al *J Bone Miner Res* 1995; 10: 96-802¹²⁷

A great deal of work remains to be done before patients at high risk of osteoporosis can be identified on the basis of clinical risk factors only. Until that time, clinical risk factors may help the physician to identify a subset of patients for densitometric evaluation.

(iii) Known causes of excessive bone loss – the so called secondary osteoporoses

Primary osteoporosis' is often used to describe the condition in postmenopausal women and older subjects in whom no specific pathogenetic mechanisms other than estrogen deficiency, calcium deficiency, and age can be identified. 'Secondary osteoporosis' is used when specific pathogenetic mechanisms, such as systemic diseases and drugs are present. Osteoporosis, similar to other chronic degenerative diseases, is however often a multifactorial disease. Clinical risk factors and secondary causes of excessive bone loss may thus both be present in the same individual and the clear distinction between primary and secondary disease is not always possible. It is also sometimes difficult to decide whether a specific factor i.e. excessive alcohol intake, is a risk factor or a secondary cause.

Regardless of the terminology employed, it is very important that the physician attending the patient with osteoporosis should be aware of all contributors to excessive bone loss, including conventional risk factors as well as possible underlying pathological processes. These factors should be actively sought, especially in low risk individuals presenting with excessive bone loss, i.e. males and the young^{128,129} (figure 3).

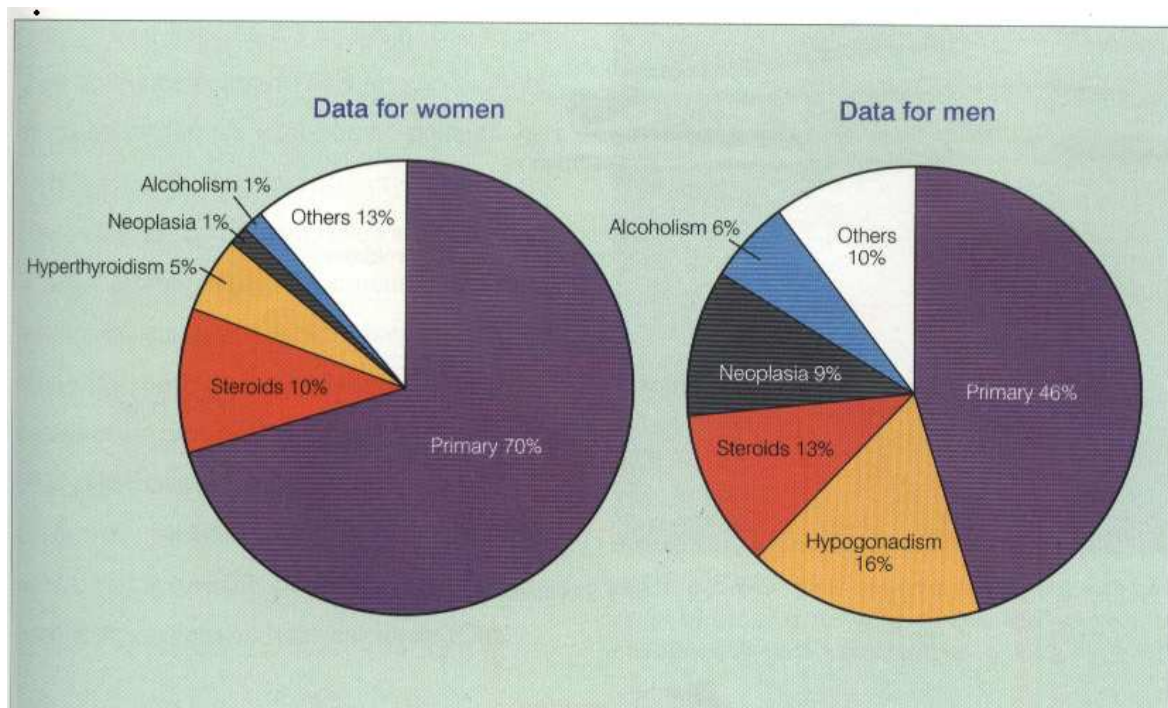


Figure 3: Prevalence of secondary osteoporosis in women and men with vertebral fractures Adapted from Caplan et al, *J R Soc Med* 1994; 87: 200-202 and Baillie SP et al, *Age Ageing* 1992; 21: 139-141^{128,129}

The most frequently encountered secondary causes of osteoporosis are systemic glucocorticoid therapy, hypogonadism, alcoholism, myeloma and skeletal metastases as tabulated in table 6.

Table 6: Causes of Secondary Osteoporosis

SECONDARY OSTEOPOROSIS
<i>ENDOCRINE</i>
Premature hypo-oestrogenemia
Hypercortisolism
Male hypogonadism
Hyperthyroidism
Type 1 Diabetes Mellitus
Hyperprolactinemia
<i>DRUGS and TOXINS</i>
Glucocorticoids
Chronic alcoholism
Anticonvulsants
Excessive thyroid hormone replacement
Heparin
Chemotherapy, Lithium, GnRH antagonists
<i>MALIGNANCY</i>
Multiple myeloma
Solid tumours
<i>GASTRO-INTESTINAL DISEASE</i>
Inflammatory bowel disease
Celiac disease
<i>COLLAGEN DISEASES</i>
Osteogenesis Imperfecta
Marfan's
Ehlers Danlos
Rheumatoid Arthritis
<i>OTHER</i>
Malnutrition / eating disorders (e.g. Anorexia Nervosa)
Transplantation
Organ failure (lung, liver, kidney)
Thalassaemia, Mastocytosis

3.1.2. Bone Quality

Bone strength is a function of both BMD and bone quality. Bone quality describes the set of characteristics that influence bone strength independent of BMD and include both structural and material properties. The structural properties of bone include its geometry (size and shape) and microarchitecture (trabecular architecture – orientation, thickness, spacing and

connectivity of the trabeculae and cortical architecture - thickness/porosity). The material properties of bone include its mineral and collagen composition as well as the number, size and localization of microdamage. The bone turnover rate is a function of the bone renewal process (modelling and remodelling) in which old or damaged bone is resorbed and new bone is created to replace it. An imbalance of bone turnover may significantly impact on all qualitative aspects of bone (figure 4).

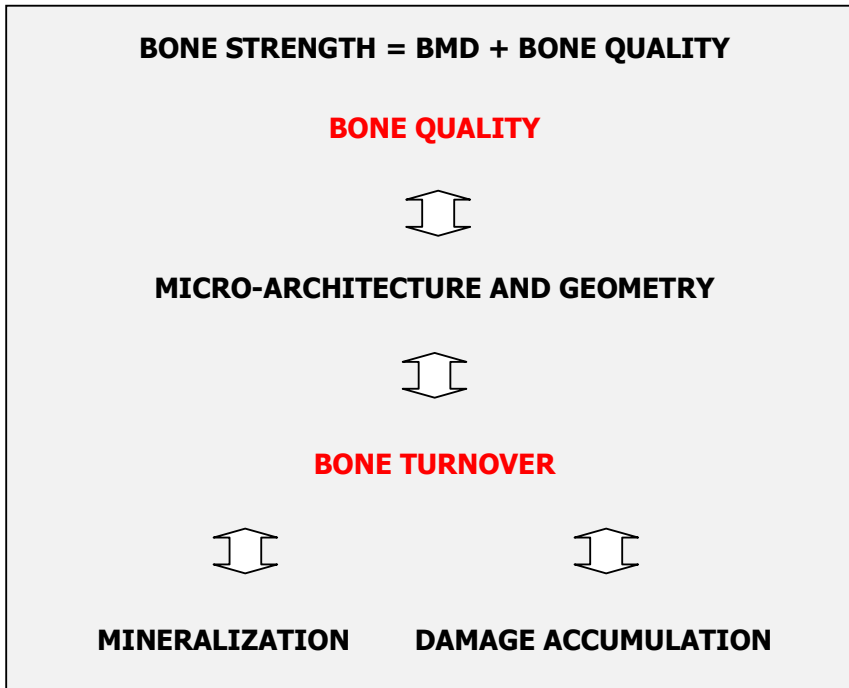


Figure 4: Factors that influence bone quality

3.1.2.1. Bone quality and fracture risk

At any given BMD, fracture risk may be modified by a set of BMD-independent determinants via their ability to impact on bone quality (table 7).

Table 7: BMD-independent determinants of bone strength

Determinants
Age
Genetics
Ethnicity
Bone Turnover status
Previous fragility fractures
Drugs and toxins (glucocorticoids, alcohol)

(i) Age

Fracture risk increases as a function of *age*¹³⁰ (figure 5). Numerous adverse qualitative changes affect bone with ageing. Trabecular micro-architecture suffers progressive disruption with age due to a decline in trabecular thickness, a reduction in trabecular number and an increase in trabecular separation due to plate perforation¹³¹. Perforation of horizontal trabeculae that occurs predominantly in postmenopausal females¹³² along with the other qualitative changes may lead to a loss of bone strength which is disproportionate to the decrease in bone mass.

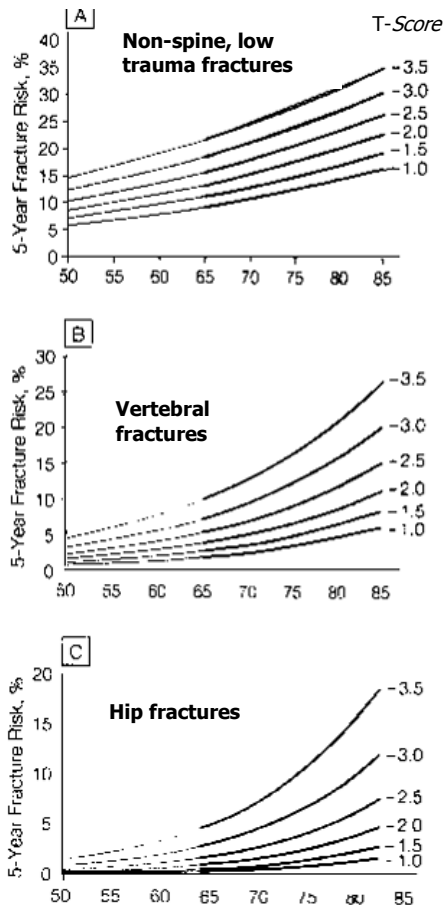


Figure 5: Baseline BMD and fracture risk. Adapted from Cummings SR et al, JAMA 2002;288:1889- 1897.³⁰

(ii) Genetics

Osteoporosis and fracture risk is partially genetically determined. Certain genetic variants have been described that influence fracture risk independent of BMD and include the COLIA1 Sp1 polymorphism and TT genotype and the VDR CC genotype, the Cdx2 polymorphism and others^{102-104,106}. A parental history of fracture (especially hip fracture) confers an increased risk of fracture that is independent of BMD^{133,134}. The mechanisms by which these genetic variants influence bone strength remain to be determined.

(iii) Ethnicity

Since a reduced absolute fracture risk at a given BMD has been documented in blacks^{135,136}, it implies that factors other than BMD affecting bone fragility may also differ amongst different ethnic/race groups. These factors may include differences in inherent skeletal structure¹³⁷, bone turnover rates¹³⁸⁻¹⁴² and calcium and mineral homeostasis¹³⁸⁻¹⁴⁷.

(iv) Bone Turnover

Bone turnover is achieved by the process of bone remodelling. Remodelling occurs in both cortical and trabecular bone. Under normal circumstances the temporal sequence is always that of resorption followed by formation with these processes tightly coupled and balanced to ensure that the amount of bone resorbed and formed within individual bone remodelling units are quantitatively similar. An imbalance of bone turnover may significantly impact on bone quality.

(a) High bone turnover

In a high turnover state:

- (i) if the rate of resorption outstrips that of formation, more bone is removed in each remodelling cycle than is replaced and thus may result in a nett loss of bone.
- (ii) irreversible micro-architectural changes^{148,149}, due to an increase in the number and depth of resorption cavities within the skeleton may occur. Increased resorption may lead to thinning and even perforation of trabeculae with permanent loss of trabecular connectivity, thereby markedly compromising skeletal integrity and strength. It is especially loss of trabecular horizontal links that occur, thereby reducing bone strength. Thinning and increased porosity of cortical bone are also potential consequences of a high turnover state rendering bone more susceptible to injury.
- (iii) reversible structural changes also occur. Resorption cavities result in stress risers (figure 6), areas in trabecular bone that are thinner and thus prone to mechanical failure when loaded¹⁵⁰.

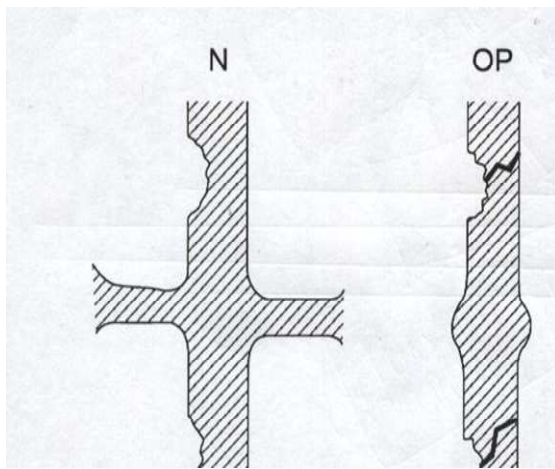


Figure 6: Diagrammatic representation of stress risers in trabecular bone. In osteoporotic bone in which horizontal trabeculae have been lost, (shown on the right side of the figure) stress is concentrated in the vicinity of resorption cavities, and fractures occur, as indicated by the heavy black lines. In normal bone on the left, in contrast, cross-bracing from the horizontal trabeculae stabilizes the vertical trabeculae despite the presence of resorption cavities. Adapted from Parfitt et al (1991)¹⁵⁰.

(iv) mineralization may be impaired. A greater degree of mineralization of trabecular bone leads to greater stiffness and compressive strength. Secondary mineralization in newly formed bone may take years to complete and in states of high turnover there is a disproportionate increase in poorly mineralized bone rendering bone weaker and softer.

(b) Severely Suppressed Bone Turnover

Chronic over suppression of bone turnover, as a consequence of long-term antiresorptive therapy, may potentially impair some of the biomechanical properties of bone²¹⁶⁻²¹⁹. Potent inhibition of bone formation may result in increased mineralization and accumulation of microdamage. Hypermineralization render bone more ‘brittle’ and may contribute to reduced fracture toughness. In experimental animals marked suppression of bone turnover by pharmacological doses of bisphosphonates resulted in microdamage accumulation with associated reduction in bone toughness (the ability to sustain deformation without breaking)^{151,152}. Histomorphometric analysis in nine patients, who sustained spontaneous non-spinal fractures on long-term bisphosphonate therapy, showed markedly suppressed bone formation. This excessive suppression of bone turnover may affect biomechanical competence of bone and potentially increase susceptibility to fracture^{153,154}. Recently bisphosphonate therapy has also been linked to painful refractory bone exposures in the jaws (osteonecrosis)¹⁵⁵.

(v) History of fragility fractures

When patients are matched for BMD, those who have already sustained a fracture are at higher risk of sustaining another fracture; and, the greater the number of prevalent fractures

the greater is that risk, implying that some skeletons are inherently more fragile than others. That is, they have poorer bone quality than others at any given BMD (table 8). In fact, the most important risk factor for fracture, independent of bone mineral density and age, is a previous fragility fracture¹⁵⁶⁻¹⁵⁸.

Table 8: Fracture risk and the presence of previous fragility fractures

Number of Prevalent Vertebral fractures	Incidence (%)	Odds Ratio
0	3.8	1.0
1	8.9	1.9
2	19.4	4.2
3-4	30.8	5.6
5+	54.2	16.4

Adapted from Nevitt MC, et al Bone 1999 25: 613-619¹⁵⁶

(vi) Drug trial data (anti-resorptive agents)

Anti-resorptive agents vary in their ability to increase BMD (1-8%), yet are quite similar (35-40%) in their ability to lower vertebral fracture risk. In other words, the reduction in fracture risk is not proportional to the change in BMD. This is once again indicative that factors other than absolute bone mass (e.g. reduction in trabecular plate perforation, improved bone mineralization in undermineralized bone) are modified by these agents and thus influence bone strength and future fracture risk¹⁵⁹ (figure 7).

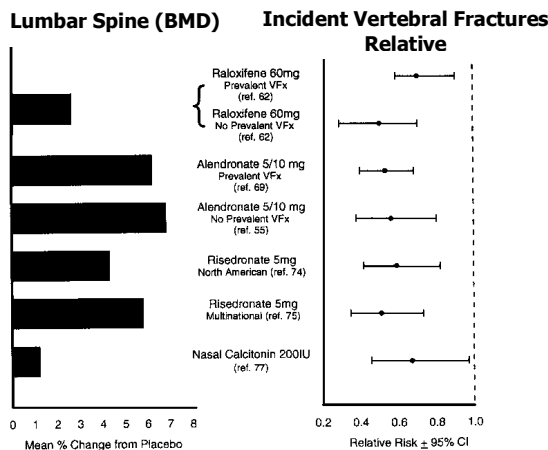


Figure 7: Change in BMD versus reduction in vertebral fracture risk. *Adapted from Marcus R et al Endocrin Rev 2002; 23: 16-37¹⁵⁹*

3.1.2.2. Bone geometry

Fracture risk can also be affected by the macro-architecture of bone. Differences in the width, length and angle of the femoral neck may affect hip fracture risk¹⁶⁰⁻¹⁶⁶, whereas differences in vertebral body size may influence vertebral fracture risk¹⁶⁷.

Numerous studies have shown a relationship between femur neck axis length or *hip axis length* (HAL) and risk of hip fracture, independent of bone mineral density status. Other geometric variables also noted to influence hip fracture risk include *femoral neck width* and the *femoral neck-shaft angle*. Studies have demonstrated that reduced thickness of the femoral neck, a wider intertrochanteric region and a longer hip axis length are predictive of hip fracture¹⁶⁰⁻¹⁶⁶. Analyses of results obtained in the study by Faulkner et al¹⁶⁶ showed a near doubling of the risk of hip fracture with every SD increase in hip axis length.

It has also been suggested that the *intertrochanteric-head centre distance*, a segment of the longer hip axis length, is an even better predictor of hip fracture risk than HAL per se¹⁶³. A larger femoral neck-shaft angle has also been implicated in hip fracture risk¹⁶¹. Identifying women at high risk of hip fracture is likely to be substantially enhanced by combining bone density with data on the structural geometry of the hip.

Vertebral bone size has been found to be reduced in women with spinal fractures¹⁶⁷. Smaller vertebral bone size was observed when patients with vertebral fracture were matched with controls with the same areal BMD.

3.2. FALL RISK

Bone density at the age of 75 is only about 4% lower than at the age of 65¹⁰⁹. The incidence of hip fracture, however, is about four times as great at 75 as at 65 years and 12 times as great at 85 years. This increase is not primarily due to further loss of bone, but rather to a large increase in the risk of falling at more advanced ages. The increased propensity to fall and loss of protective responses constitute further role players in the etiopathogenesis of osteoporotic fractures. Hip fractures occur almost exclusively after a fall, spontaneous hip fractures without prior falling is extremely rare. About 90% of hip fractures in elderly people result from a fall¹⁶⁸. A history of recent falls is a major contributing factor to the occurrence of symptomatic fractures in postmenopausal women, independent of and additive to the risk attributable to age and osteoporosis¹⁶⁸⁻¹⁷².

Epidemiological data have revealed that some 50% of osteoporotic patients have *muscle loss/weakness* ("sarcopenia"), 30% have *postural hypotension* and many have *poor visual acuity* or *problems with depth perception*, *cognitive dysfunction* or use *drugs* that may predispose to falls¹⁷³⁻¹⁷⁸. The skeletal protection provided by drugs such as estrogen, may be ascribed in part to their ability to improve reaction time which decreases the propensity of an individual to fall¹⁷⁶.

.....

B OSTEOPOROSIS IN AFRICAN-AMERICAN WOMEN

1. BACKGROUND

The prevalence of osteoporosis and minimal trauma fractures is thought to be substantially lower in people of African ancestry compared to Caucasians as shown by studies on the African Continent and in the United States of America.

Osteoporosis and its consequences, however, is a real risk for any ageing women with an exponential increase in fracture risk associated with advancing age. The increase in fracture risk is expected to be more pronounced in developing countries of Asia and Africa, with a high population growth rate, versus developed first world countries¹⁴. As the world population ages, a significant number of black females across the world is expected to be affected by this potentially debilitating disease. Moreover, the impact of hip fracture is particularly devastating in black women, because the mortality and disability after fracture are higher than amongst white women¹⁷⁹.

Specific diagnostic criteria for osteoporosis in premenopausal females, men and blacks have not been formally established as the WHO-criteria were originally designed specifically for evaluation of postmenopausal White females^{12,13}. The relationship between BMD and fracture risk is similar in women and men, even though gender differences in bone size and geometry cause men's bones to fracture at a higher mean areal BMD than that of women¹⁸⁰. The use of a young adult male mean reference to determine BMD T-scores produces estimates of osteoporosis occurrence that are more consistent with current fracture rates in men^{180,181}. Based on such data, an international consensus development panel recommended that T-scores in men be derived from a male normative data source¹⁸².

Older African-American women have higher mean BMD values compared with whites. The use of race/ethnic specific T-scores in African-Americans would thus yield a higher prevalence of osteoporosis in this ethnic group than that calculated when white reference data are used. A recommendation regarding the use of race/ethnic group-specific T-scores can, however, not be made due to a lack of fracture data from various race/ethnic groups. The use of white women as a reference for all persons in a multi-ethnic population may well not be appropriate, but until these ethnic specific reference ranges become available, current clinical recommendation is to diagnose osteoporosis among blacks and other ethnic groups at or below a T-score threshold of -2.5 using the uniform normative database for whites¹⁸³.

2. BONE STRENGTH

2.1. Bone Mineral Density (BMD)

Numerous studies have looked at BMD status in the African American population. Populations studied have included children, men and premenopausal, perimenopausal and postmenopausal females. Skeletal sites evaluated include the distal forearm, lumbar spine, proximal femur and the total body. Bone mineral density in these populations has also been assessed by various techniques, namely radiogrammetry, single photon absorptiometry, dual energy X-ray absorptiometry, quantitative computed tomography and ultrasonography.

Higher BMD values at all skeletal sites have been repeatedly and consistently documented in African Americans (AA) compared to whites^{135,138,139,143-145,184-199}. In the most recently published study, Finkelstein and co-workers¹⁹⁹ studied BMD in a large multi-ethnic population including amongst others African-American and Caucasian females. Consistently higher BMD-values were documented in the African-American compared to the Caucasian females.

2.1.1. Methodological Considerations

There is always concern, when comparing subjects from different ethnic and racial groups and thus potentially different body and bone size, that the observed difference in areal BMD is largely accounted for by these differences and thus more apparent than real. Assuming that bone mass acquisition increases in proportion to the skeletal bone volume, the traditional two-dimensional BMD measurement will tend to overestimate the BMD of taller/larger subjects while underestimating the BMD of shorter/smaller subjects (figure 8)²⁰⁰.

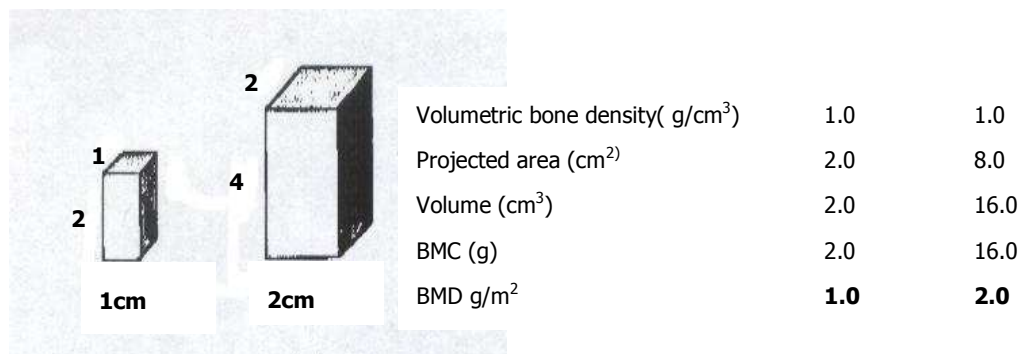


Figure 8: Effect of specimen size on commonly measured bone mineral parameters. Using projected densitometry techniques one identifies a region of interest, or projected area, which is equal to the area of the front face of the sample. The bone mineral content (BMC) is the total amount of bone mineral (g) in the sample. An areal density (g/m²), bone mineral density (BMD) is calculated as BMC/ over projected area. Both samples have identical volumetric densities; however, the BMD of the larger sample is twice that of the smaller sample. Adapted from Carter et al. *J Bone Miner Res.* 1992; 7 (2): 137-145²⁰⁰

In an attempt to minimize the effect of differences in bone size, BMD is often statistically adjusted for, using height and weight or body mass index. These indices are unfortunately poor surrogates for the actual size of the bone being measured. In view of abovementioned shortfalls, several investigators have suggested techniques to adjust bone mass measurements for volumetric differences in body size, and thus bone size. Carter et al²⁰⁰ and Katzman et al²⁰¹ recommend using a volumetric calculation of bone mineral density at the lumbar spine and femoral neck respectively. This volumetric assessment is referred to as bone mineral apparent density (BMAD) and is based on the assumption that the volume of bone can be calculated from the DEXA determined areal measurements.

BMAD	
Lumbar spine:	mean BMC / (mean area)^{3/2} (Carter²⁰⁰)
Femoral neck:	mean BMC / (area)² (Katzman²⁰¹)

Significant ethnic differences do, however, remain after adjustment for bone size (via correction for body size or via use of calculated volumetric assessments)^{135,138,143,185,187,191,193,195,198,199} in most studies comparing African-American and Caucasians, including the large study of Finkelstein et al (figure 9)¹⁹⁹.

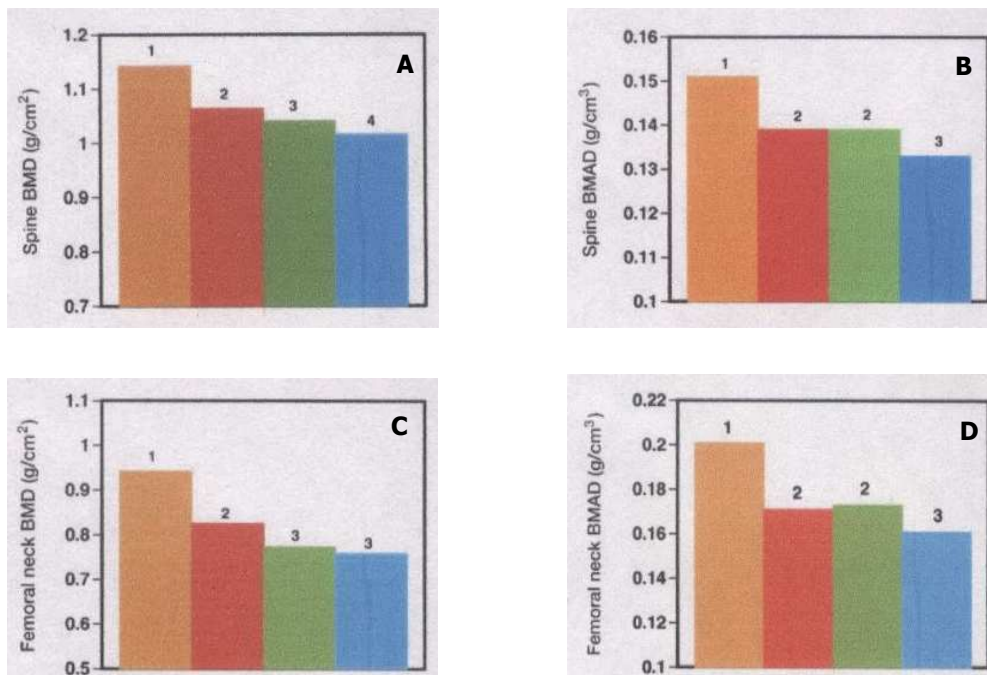


Figure 9: Lumbar spine BMD (A), lumbar spine BMAD (B), femoral neck BMD (C) and femoral neck BMAD (D) in the entire SWAN cohort. African-American women data illustrated by the brown bars and Caucasian data by the red bars. The green and blue bars represent data on Chinese and Japanese women respectively. Bars with different numbers are significantly different. BMD and BMAD values (A-D) for African-American women statistically significantly higher than Caucasian women (p<0.001). Adapted from Finkelstein et al. *J Clin Endocrinol Metab.* 2002; 87(7):3057-3067¹⁹⁹

2.1.2. Peak bone mineral density (PBMD)

Much of the difference in BMD between AA and whites arises during childhood and adolescence and the majority of studies indicate that the higher bone mass in AA women is due to the attainment of a greater peak bone mass by early adulthood^{185,186,190,191,193,196-199}. The magnitude of the increase in vertebral bone mineral density has been noted to be markedly higher in black versus white children in the later stages of puberty contributing to the finding of higher PBMD in blacks¹⁹⁰ (figure 10).

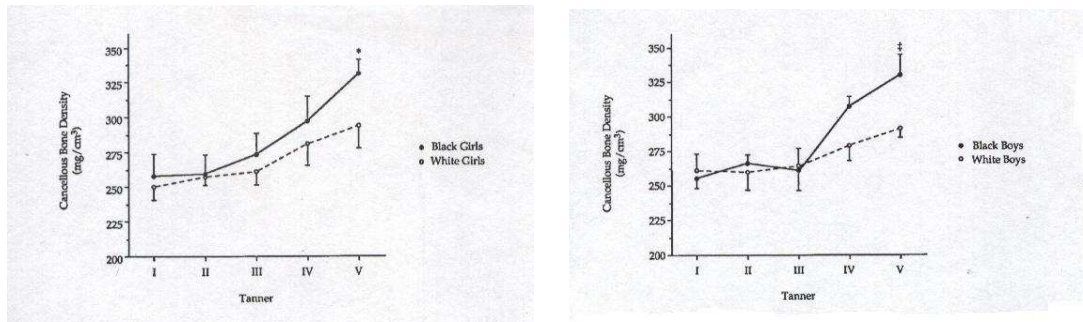


Figure 10: Vertebral cancellous bone density, black and white girls and boys at each stage of sexual development. Values are the mean \pm SE. *, $p = 0.05$; † $p = 0.007$. Adapted from Gilsanz et al, *NEJM* 1991; 325 (23): 1597-1600¹⁹⁰

2.1.3. Age-related bone loss

A slower rate of cortical and trabecular bone loss, especially in the early postmenopausal period, has been noted in blacks in some^{139,184,197}, but not all^{144,194,196} studies and may positively enhance the already present skeletal advantage in blacks (figure 11).

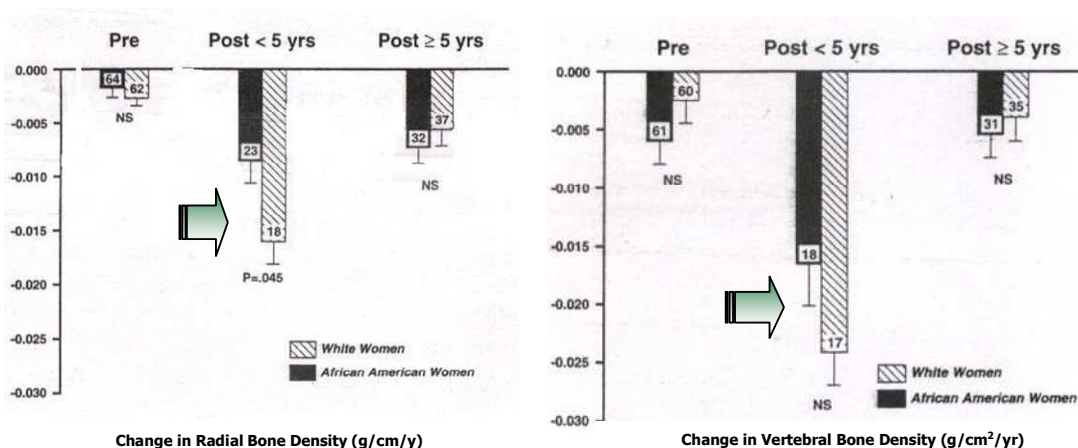


Figure 11: Comparison of the rates of radial and vertebral bone loss in pre- and postmenopausal women. The numbers within the bars represent the number of women within each group. African-Americans: pre-vs. early postmenopause, $p < 0.01$, pre- vs. late postmenopause, $p < 0.01$; early vs. late postmenopause, $p = NS$; whites pre- vs. early postmenopause, $p < 0.01$, pre- vs. late postmenopause, $p = 0.1$; early vs. late postmenopause, $p < 0.01$. Large green arrows indicate more pronounced bone loss in white women in early postmenopause. Adapted from Luckey et al; *JCEM* 1996; 81(8) 2948-2956¹⁸⁴

2.1.4. Clinical risk factors for low bone mineral density

Early detection of osteoporosis through BMD measurement is essential to decrease the morbidity and mortality of osteoporotic fractures. One of the major clinical challenges of fracture prevention is the identification of patients who qualify for a BMD measurement. Universal BMD testing (mass screening) has been recommended by the American NOF for Caucasian women aged 65 years and older³¹. Mass screening of younger postmenopausal women is not recommended because there are few studies that address screening cost-effectiveness or long-term benefits of drug treatment in this group. The IOF³² and NOFSA³³ guidelines recommend a case finding approach based on clinical risk factors. There is also at present no data as to what BMD levels should be considered thresholds for future fractures in black women.

Most clinical/historic risk assessment tools are based on data obtained in white postmenopausal women. It is not known how well these tools would perform in a multi-ethnic population of women. Broussard and colleagues therefore specifically looked at potential modifiable clinical risk factors in a multi-ethnic population utilizing the study population of the third National Health and Nutrition Examination Survey (NHANES III)¹¹⁸. Modifiable risk factors assessed included a low body mass index (BMI), low calcium intake, current cigarette smoking and physical inactivity. Age, a low BMI, current cigarette smoking and physical inactivity, which predicted low BMD and bone loss in longitudinal and cross-sectional population-based studies of Whites, also identify African-Americans and Mexican-Americans with low BMD and osteoporosis. A *low body mass index (BMI)* was shown to be the *strongest modifiable determinant of low BMD* in all groups studied. The risk estimates for osteoporosis strengthened in the presence of more than one risk factor in a given individual (table 9).

Table 9: Age-adjusted estimates of risk or osteoporosis and osteopenia given the presence of one or more (1+) and two or more (2+) risk factors (low BMI, current cigarette smoking and physical inactivity) for AA, MA and white women (n = 2590).

Race/ethnicity	No. of risk factors	n	Osteoporosis OR (95% CI)	Osteopenia OR (95% CI)	Low BMD OR (95% CI)
Women					
AA	1+	625	1.8 (0.9, 3.3)	1.3 (0.9, 1.9)	1.6 (1.1, 2.3)
MA	1+	540	2.0 (1.2, 3.5)	1.4 (1.0, 2.0)	2.0 (1.4, 2.9)
White	1+	1,425	3.1 (2.2, 4.3)	1.3 (1.0, 1.6)	2.3 (1.8, 2.9)
AA	2+		6.1 (3.3, 11.3)	1.4 (0.9, 2.1)	3.4 (2.1, 5.4)
MA	2+		2.8 (1.5, 5.4)	1.5 (0.9, 2.5)	3.4 (1.8, 6.4)
White	2+		5.0 (3.4, 7.5)	1.2 (0.9, 1.7)	4.1 (2.7, 6.2)

Adapted from: Broussard et al. *Osteopor Int* 2004; 15:349-360¹¹⁸

A low BMI and a sedentary lifestyle were also identified in a study by Woodson et al²⁰² as modifiable risk factors for osteoporosis in postmenopausal African-American females. A

positive family history and a bilateral oophorectomy also contributed to the risk of osteoporosis in the black women.

2.1.5. Clinical Significance of BMD measurements

Despite consistently higher mean BMD values documented in African-American female cohorts compared to Caucasian female cohorts, there is considerable overlap in BMD values amongst individuals within these ethnic groups and a substantial number of elderly blacks has reduced bone mass. This implies that a significant percentage of black patients may still be at risk to develop osteoporosis and its consequences especially as the world population is expected to age (table 10)¹⁹².

Table 10: Occurrence of osteoporosis, osteopenia and low BMD among African American, Mexican-American and white women aged 50-64 and 65-79 years from NHANES III.

Age group (years)	AA		MA		White	
	50-64	65-79	50-64	65-79	50-64	65-79
Women						
Sample size	n = 373	n = 252	n = 308	n = 232	n = 680	n = 745
By use of race/ethnic specific T scores						
Osteoporosis (%)	4.3	17.9	10.4	20.7	5.9	20.9
Osteopenia (%)	35.4	48.4	35.1	50.4	37.7	49.3
Low BMD (%)	39.7	66.3	45.5	71.1	43.5	70.2
By use of white female T score						
Osteoporosis (%)	3.0	7.5	7.5	14.2	-	-
Osteopenia (%)	19.8	41.3	34.4	55.2	-	-
Low BMD (%)	22.8	48.8	41.9	69.4	-	-

*Race/ethnic and white T-score were used. Adapted from Looker et al. *Osteoporos Int* 1998;8: 468-489¹⁹²

2.2. Bone quality

A lower bone turnover and alterations of the Vitamin D-Endocrine system in blacks with better renal calcium conservation and decreased sensitivity to parathyroid hormone (PTH) have been proposed as explanations for their higher PBMD and the slower rate of postmenopausal bone loss. To what extent these differences in hormones and biochemical markers contribute to and influence bone quality is uncertain. Since a reduced absolute fracture risk at a given BMD has been documented in blacks^{135,136}, it implies that factors other than BMD affecting bone fragility may also differ amongst different ethnic/race groups. These factors may include bone architecture, turnover rates and differences in calcium homeostasis.

2.2.1. Micro-architecture and bone size

Racial differences in trabecular architecture have been described. African-Americans have thicker trabeculae than whites at the spine and iliac crest^{141,142,191}. A greater cross-sectional area of the long bones in the appendicular skeleton of black versus white children was documented by Gilsanz and colleagues¹⁹¹. The placement of cortical bone further from the

central shaft axis in blacks than whites may confer greater resistance to bending irrespective of BMD²⁰³.

2.2.2. Bone Turnover and Calcium homeostasis

Few studies have compared bone turnover between people of different ethnic groups (most comparisons are between Caucasians and African-Americans).

Biochemical assessment of bone formation markers (osteocalcin and bone specific alkaline phosphatase in serum) and bone resorption markers (urinary deoxypyridinoline, cross linked N-telopeptides of Type I collagen and hydroxyproline) suggest that bone turnover is either lower^{138,142,147,196} or similar^{142,144,145} in American blacks compared with whites. The reasons for these somewhat discrepant results are not apparent. Ethnic differences in skeletal size may influence these measurements and should be corrected for.

A lower bone turnover in blacks, as shown in most of the studies, may be responsible for the slower postmenopausal decline in trabecular and cortical bone observed in this ethnic group. In addition to the protective effects of a higher peak bone mass, a lower turnover could contribute significantly to the lower risk of fractures in African-American women.

Whilst numerous non-invasive studies of bone turnover in American blacks and whites have been reported, only a few histological studies have been performed^{140,141,204}. Weinstein and Bell¹⁴⁰ reported on bone histomorphometry in free living American subjects pre-labelled with tetracycline. The rates of mineral apposition and bone formation were significantly lower in the black than in the white men and women based on dynamic indices of bone remodelling. On the assumption that coupling between resorption and formation is maintained, the authors suggested that the expected lower rate of bone resorption would help maintain bone mass and explain the higher peak bone mass observed in blacks compared with whites. The number of subjects in each group was, however, small and data in men and women were combined. Parfitt et al¹⁴¹ studied a group of 142 healthy black and white women and also noted a lower bone formation rate in blacks compared to whites. Looking at healthy premenopausal women, Parisien and co-workers²⁰⁴ could not document any significant difference in bone turnover between blacks and whites. Significant differences in the mechanism of bone formation were, however, noted with a lower rate of mineralized matrix apposition within each remodelling unit and a longer total formation period in the black subjects. These differences might potentially enhance bone mineral deposition and help explain the higher bone mass and better bone quality in black than white women.

Compared with whites, studies have reported lower 25-OH Vitamin D, higher 1,25 OH-Vitamin D, higher PTH levels and lower urinary calcium excretion rates in blacks^{138,143-147,196}. The lower levels of 25-OH Vitamin D observed in blacks are largely the result of reduced skin synthesis of Vitamin D precursors due to increased skin pigment, and lead to mild secondary hyperparathyroidism. The resultant higher PTH-levels are expected to increase osteoclastic activity and bone turnover in blacks. Findings of similar or lower bone turnover rates in African-Americans compared with whites, along with consistently higher BMD values, have thus prompted the theory of a relative skeletal resistance to the action of PTH in African-Americans^{138,144,146,196}.

Studies in low income, elderly black and white individuals with secondary hyperparathyroidism (HPT) caution against the belief that this is a benign condition with no deleterious skeletal effects¹⁴⁵. The prevalence of secondary HPT is higher in African-Americans compared with Caucasian adults. Although bone turnover has repeatedly been shown to be lower in black versus white groups, bone turnover is higher and BMD lower in the subgroups of patients with secondary HPT in both black and white ethnic groups¹⁴⁵ (figure 12).

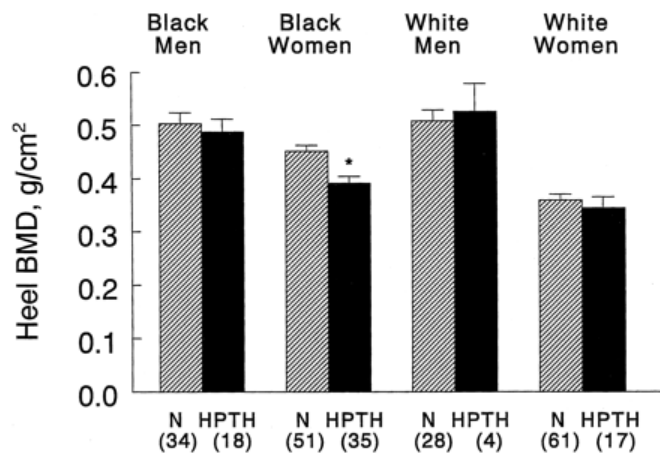


Figure 12: Mean heel BMD adjusted for age, sex, weight, and use of a walking aid in black and white adults by normal (N: bars with diagonal lines) and hyperparathyroid (HPTH: solid bars) status. Error bars, SEM; asterisks, differences by PTH status within race/sex groups ($p < 0.05$); parentheses, sample sizes. Adapted from Harris et al. *JCEM*(2001); 86(8): 3801-3804¹⁴⁵

Combining the histological and biochemical data, we can conclude that bone turnover is similar or lower in African-Americans compared with Caucasian adults despite a higher prevalence of secondary HPT. This supports the theory of skeletal resistance to the actions of PTH in blacks. The resistance is, however, relative and secondary hyperparathyroidism is known to exert deleterious skeletal effects in all ethnic groups.

2.2.3. Bone Geometry

Worldwide data suggest that a longer hip axis length (HAL) or femur neck axis length (FNAL) is an independent risk factor for hip fracture in Caucasian females¹⁶⁰⁻¹⁶⁶. A study by Faulkner et al showed a near doubling of the risk of hip fracture with every SD increase in hip axis length¹⁶⁶. A larger femoral neck-shaft angle has also been implicated in hip fracture risk¹⁶¹. Most studies looking at hip geometry have documented a shorter HAL in Blacks versus Caucasians^{3,4}. This finding may enhance the protective effects of a higher BMD in blacks with regard to fracture risk. The femoral-shaft angle was not found to be statistically significantly different in blacks compared with, whites³.

Vertebral bone size has been found to be reduced in women with spinal fractures¹⁶⁷. Smaller bone size was also observed when patients with vertebral fracture were matched with controls with the same areal BMD. Although African-American women are heavier than Caucasian women, their lumbar spine and femoral neck bone areas are actually smaller¹⁹⁹. It has been noted that there are racial differences in upper and lower body segments. Although matched for height, American blacks have longer legs and shorter trunks than whites. This has been hypothesized as indicative of reduced skeletal sensitivity to estrogens in blacks as trunk growth is estrogen dependent whereas lower limb growth is primarily growth hormone dependent²⁰³. A shorter trunk implies reduced vertebral size and may potentially compromise vertebral strength and enhance vertebral fracture risk in blacks.

3. FALL RISKS

Falls are a major contributing factor to the occurrence of symptomatic fracture in postmenopausal women. Some studies^{205,206}, but not all^{207,208}, suggest that Caucasians may fall as much as 50-60% more often than African Americans or other ethnic groups. In a study by Faulkner and co-workers²⁰⁹ the frequencies of falling between older Caucasian and African-Americans were similar, but the circumstances of falling differed. Ethnic differences in the fall location and surface, fall direction, and likelihood of falling on the hand/wrist were identified. These disparities in fall mechanisms may have an important role in serious fall-related injuries and might partially explain ethnic differences in fracture risk.

4. FRACTURE DATA

Black women fracture less than their white counterparts^{135,136,243}. Using data from women \geq 65 years of age enrolled in the US Medicare program from 1986 to 1990, Barrett et al found that the overall incidence of fractures attributed to osteoporosis was 3.1% in African-American and 8% in white women²³⁷. Thus, osteoporotic fractures are 2.6 times more

common in older white women. The lower fracture risk in American blacks has been readily attributed to their higher bone mineral density as has been documented in numerous studies^{135,138,143-145,184-199}.

Bone mineral density has been shown to be an important predictor of fracture risk based primarily on studies of North American and European white women. Less is known about the association of BMD with fracture risk in other ethnic populations. In a recent study by Barrett-Conner et al low heel, forearm or finger BMD was associated with an increased one-year risk of non-spinal fracture in black women. All the women studied showed a similar pattern of increasing fracture risk with decreasing BMD levels, regardless of race or ethnicity. Women with osteopenia or osteoporosis had an increased risk of fracture in every ethnic group, but the absolute risk of fracture at any given BMD does differ among ethnic groups¹³⁶(table 11).

Table 11: Risk of fracture by ethnicity

	<i>Osteoporotic fractures</i> <i>(relative risk 95%CI)</i>	<i>Non-wrist fractures</i> <i>(relative risk 95%CI)</i>
Ethnicity		
White	1.00	1.00
Black	0.52 (0.38, 0.70)	0.45 (0.30, 0.66)
Asian	0.32 (0.15, 0.66)	0.42 (0.19, 0.94)
Hispanic	0.95 (0.76,1.20)	1.01 (0.77, 1.33)
BMD		
(per 1SD decrease in T-score)	1.54 (1.48, 1.61)	1.41 (1.34, 1.49)

Risk of fracture by ethnicity, adjusted for covariates including BMD T score. Relative risk and CI based on Cox proportional hazard model adjusted for age, education, current health status, years since menopause, weight, estrogen use, cortisone use and BMD site/device. White is referent population (RR 1.00) *Adapted from Barrett-Connor et al. J Bone Miner Res 2005; 20(2): 185-194*¹³⁶

These findings were confirmed in a prospective study by Cauley et al¹³⁵ who showed that reduced BMD of the total hip and femoral neck is associated with an increased risk of all non-spinal fractures in older black women, but that the absolute fracture incidence was 30 – 40% lower among black women compared to whites. The lower fracture rate in black compared with white women was *independent of BMD and other clinical risk factors*. (table 12).

Table 12: Relative Risk of Fracture in Black Compared with White Women

Adjustment	RR (95% CI)
Age alone	0.36 (0.28-0.47)
Femoral neck BMD plus	
Age	0.49 (0.38-0.64)
Age and multivariable model†	0.48 (0.36-0.64)
Femoral neck BMAD plus	
Age	0.40 (0.30-0.52)
Age and multivariable model†	0.43 (0.32-0.57)

* The referent group is white women.

† Multi-variable-adjusted model includes age, body weight, height, fracture since age 50 yrs, walking as form of exercise, current calcium supplement use, current hormone therapy use, alcohol consumption in the last 30 days, diagnosis of osteoarthritis, diagnosis of chronic obstructive airway disease, fallen 2 or more times in the past year, use arms to stand up from chair, and current smoking. *Adapted from Cauley et al; JAMA 2005; 293(17): 2102-2108*³⁵

Data pertaining to vertebral fracture prevalence in multi-ethnic populations are scanty and old. A population based study by Cooper et al suggested a lower incidence of vertebral fractures amongst black postmenopausal females based on hospital discharge records²⁴⁹. Minimal published data is available regarding differences in the risk of spinal fractures between black and white females. Racial differences in the prevalence of vertebral fractures in older black and white men was recently documented in the Baltimore Men's Osteoporosis Study with a higher prevalence documented in older white men (7.3% whites versus 0.9% blacks)²¹⁰. It is unknown whether this racial difference also holds true for females.

5. CONCLUSION

It therefore appears as if African American females fracture less than their white counterparts. They fracture less because their BMD's are higher. Black Americans also fracture less than whites even when BMD has been corrected for and this might be ascribed to differences in bone quality, bone geometry and fall risk. African American women do, however, also fracture and should be considered for BMD testing if clinical risk factors for excessive bone loss are found to be present.

.....

C OSTEOPOROSIS ON THE AFRICAN CONTINENT

1. BACKGROUND

In the United States, the higher prevalence of osteoporosis and fractures in whites compared with blacks may be readily attributed to the higher bone density in both black children and adults. Both a higher peak bone mineral density and a slower rate of early postmenopausal bone loss have been documented in African Americans.

In South Africa, osteoporosis related fractures also occur more frequently in whites. The only documented fracture data in South Africa, however, dates back to the 1970's. Solomon et al²⁰ noted that the urban Black population of the Johannesburg Metropolitan Area had a more than ten fold lower hip fracture rate compared to that seen in Western European populations and that black males and females are affected equally. In 1968 Dent and co-workers²¹¹ published their data regarding spinal osteoporosis in 3 subgroups i.e. rural and urban black females and white females residing in the Durban area. They noted severe osteoporosis of the spine (as defined by structural abnormalities of the vertebrae) in 14% of Whites compared to a 3% and 2% prevalence in the rural and urban blacks respectively. In West Africa, a very low incidence of minimal trauma fractures of the hip and wrist has also been observed²¹². This clinical impression is supported by the experience of the UK Medical Research Council (MRC) field station in Keneba, The Gambia, where there have been no reported cases of osteoporosis-related fractures during the past 40 years.

2. BONE STRENGTH

Both the quantity and the quality of bone determine skeletal strength.

2.1. Bone mineral density (BMD)

Higher BMD at all skeletal sites have been repeatedly and consistently documented in Americans of African descent compared with whites^{135,138,143-145,184-199}. By contrast, African studies have not nearly been as unanimous on greater bone density in blacks.

2.1.1. South Africa

Appendicular bone mass appears to be similar or lower in black versus white South Africans. Earlier studies employing metacarpal radiogrammetry revealed similar or higher values in white compared with black South African adults²¹³. A study of SA schoolchildren using single photon absorptiometry, did not find any significant difference in appendicular bone mass between the black and white groups²¹⁴.

Despite markedly lower fracture rates noted in the urbanized black population of the Johannesburg Metropolitan Area compared to Caucasians, Solomon made the interesting observation that absolute values for skeletal mass and bone density were in fact greater in the Caucasians compared to the African blacks through most of the age range from 5 – 75 years²¹³.

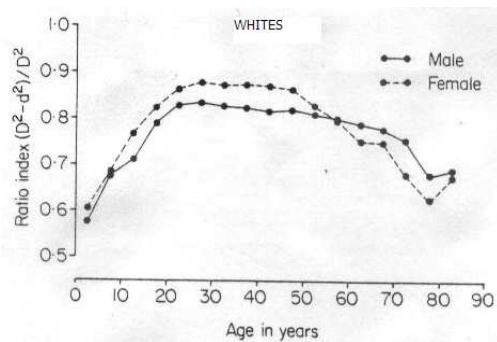


Figure 13: Mean values for bone density ($D_2 - d_2$)/ D_2 , in Caucasian males and females Adapted from Solomon et al 1979, *The Lancet*: 1326-1330²¹³

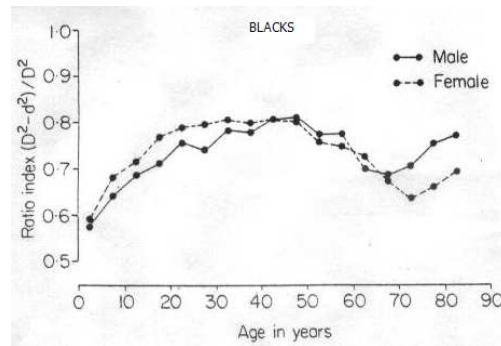


Figure 14: Mean values for bone density ($D_2 - d_2$)/ D_2 , in Black males and females. Adapted from Solomon et al 1979, *The Lancet*: 1326-1330²¹³

Based on metacarpal radiogrammetry, three distinct phases of change in bone mass was noted in the Caucasian population he studied i.e. an early phase of rapid increase in bone density during skeletal growth and maturation, a middle phase between the ages of 30–50 years during which bone density falls slightly, especially in women, followed by a late phase characterized by a rapid decline in bone mass from 50 years onwards²¹³ (figure 13). In Blacks, this middle phase is absent, implying that bone mass is either sustained at higher levels between the ages of 30–50 years or actually continues to rise (figure 14).

It seemed unlikely that these small differences in bone mass and patterns of bone loss could account for the marked difference in fracture risk and the possibility of qualitative differences in bone between Blacks and Whites was already proposed by Solomon in the late 70's²¹³.

In the only study to date employing more sophisticated techniques to assess BMD in South African adults, a selected group of Black and White South African nurses was studied by Daniels et al¹. Employing dual energy X-ray absorptiometry (DEXA), similar appendicular and areal lumbar bone mineral density values were documented in the black and white nurses, 20–64 years of age. Areal femoral bone density (FBD) was, however, higher in both pre- and postmenopausal black females.

After correction for weight and height, the black females had 7% higher FBD than whites in the premenopausal group and 13% higher FBD in the postmenopausal group. Bone density

was higher in blacks than in whites in all the anatomically different parts of the proximal femur, namely, the femoral neck, the trochanteric and intertrochanteric areas, and Ward's triangle. To further eliminate the possible confounding influence of ethnic differences in bone size on areal BMD measurements, volumetric bone mineral apparent density (BMAD) values were also calculated⁵. These BMAD findings suggest that pre- and postmenopausal white females have marginally lower bone mass at the lumbar spine and significantly lower bone mass at the femoral neck compared to black females.

The difference in femoral bone density between the black and white nurses was noted to be more pronounced in the postmenopausal versus the premenopausal females, suggestive of slower postmenopausal bone loss in the black subjects. The pattern of bone loss, although not always statistically significantly different between the two ethnic groups, is remarkably similar to that observed by Solomon more than 30 years earlier. The black females appeared to reach peak bone mass at a later stage and showed very limited loss in the middle phase (late pre-menopausal and perimenopausal periods). In addition, a slower rate of postmenopausal decline in spinal bone density (SBD), femoral bone density (FBD) and radial bone density (RBD) was noted in black versus white female nurses in this study.

Pettifor and colleagues recently studied a group of 9-year-old black and white South African children to determine the association between physical activity and bone mass²¹⁵. Although a lower level of physical activity and lower calcium intake was documented in the black kids, significantly greater bone mineral density at the hip and spine employing DEXA was noted in black children, even after adjustment for body size.

In a follow-up evaluation of a very similar cohort at age 10 years, Pettifor and colleagues once again documented significantly greater bone mass (BMC) at the proximal femur (femoral neck and total hip), whereas BMC of the lumbar spine was now noted to be similar in black and white children. These values were all corrected for gender, weight, height and puberty²¹⁶.

These findings suggest that the femoral neck and total hip bone mass patterns in our black children are likely to be under similar genetic influences to those of African-American children and that genetics are likely to significantly contribute to the finding of higher hip BMD in South African blacks compared with whites. This hypothesis is supported by studies that suggest that the South African black population and the African-American population share a common genetic pool as both originated and migrated from West-Africa²¹⁷. The finding of similar vertebral bone mass (BMC) in black and white South-African children is in

keeping with findings in adult black females from South Africa¹ and elsewhere on the African continent^{6,2,218-220}. The reason(s) for this site-specific difference is unclear.

Preferential increase in hip BMD in *exercising* (weight-bearing) school children have been described²²¹, but physical activity scores were lower in urbanized South African black children compared with whites in the study by McVeigh²¹⁵. *Greater mechanical loading due to higher body weight* in adult black versus white populations may potentially further enhance genetically determined femoral bone density more so than other “less weight-bearing” skeletal sites.

Development of the axial skeleton is known to be predominantly oestrogen dependent. It has been noted that there are racial differences in upper and lower body segments. The genetically determined shorter trunk length observed in American blacks may also be true for the South African blacks. This has been hypothesized as indicative of *reduced skeletal sensitivity to oestrogen* in blacks as trunk growth is oestrogen dependent whereas lower limb growth is primarily growth hormone dependent²⁰³. A shorter trunk implies *reduced vertebral size* and may potentially compromise vertebral strength and enhance vertebral fracture risk in blacks. *Delayed menarche* in South African blacks²¹⁴ may potentially further compromise optimal development of vertebral size and accumulation of bone mineral content. The femoral neck of the hip consists of 25% trabecular bone, whereas in a vertebral body the percentage ranges from 66% to 90%²²¹. Reduced calcium nutrition in blacks²¹⁴ may stimulate bone turnover and have a more marked impact on metabolically active trabecular bone versus cortical bone. Because the amount of trabecular bone in the vertebrae is so high, the impact of poor calcium nutrition may be particularly apparent in the spine.

2.1.2. Rest of Africa

Prentice et al compared the bone mineral content (BMC) of the midshaft radius, determined by single photon absorptiometry, between a group of rural Gambian and British women across a wide age-range of 18–80yrs²²². Gambian women had significantly lower forearm BMC than British women of the same age, but after adjusting for weight, height and bone width, the forearm BMC of Gambian women was shown to be slightly higher than that of British women (+2.1%, $p < 0.05$). When analysis was confined to subjects older than 45 years, there was no difference between the two studied groups (1%, $p = 0.6$).

In a more recent study in Gambia²¹², bone mineral content and bone mineral density were compared between rural Gambian women and white British females. The Gambian women had significantly lower BMC and BMD values at the lumbar spine and at the midshaft of the

radius. Comparative femoral BMD data was not obtained in this study. These findings were surprising given the apparent very low fragility fracture rate in Gambia.

In an attempt to explain the observed protection against fractures in Gambians compared with British whites despite very similar BMD-values, a detailed study comparing young Gambian men and women with British adults was conducted by Dibba, Prentice and co-workers⁶. In the female subgroup, BMD of the hip, spine and radius were similar in the Gambian and the British subjects.

In a study by Riggs et al²¹⁸ bone density was compared among persons of African Heritage and included African Americans and recent immigrants from Somalia. Compared to a group of white subjects, the Somali females had a lower lumbar spine BMD (4%), but a higher femoral neck BMD (11%). Similar lumbar spine BMD data was documented in women from Oman (a country close to Somalia), who were also found to have lower values than healthy European women²¹⁹. Spinal BMD Z-scores was significantly lower in recent sub-Saharan Sudanese immigrants than in African Americans or Caucasians in a study conducted in the United States²²⁰.

Collectively these studies suggest that appendicular and spinal bone mass in black populations from the African continent are similar or lower than that observed in white individuals. Proximal femur BMD measurements, on the other hand, are higher in Africans compared to whites in most, but not all studies.

2.2. Bone Quality

The low fragility fracture rate in African Americans is sufficiently explained by greater bone mass, but the same explanation cannot be advanced for blacks from the African continent. Bone quantity is not uniformly higher in African blacks compared with whites, therefore the possibility of a qualitative advantage must be considered.

2.2.1. Micro-architecture

A histomorphometric analysis carried out on iliac crest bone from 171 South African black and 175 white men and women revealed significant racial differences in trabecular bone architecture¹³¹. Trabecular thickness was greater in blacks than in whites ($p < 0.01$). Age related microstructural changes also differed between the races. Black females showed no decline in trabecular number and no increase in trabecular separation, whereas whites suffered deterioration of trabecular architecture with regard to trabecular thickness, number and connectivity. The trabecular bone of South African blacks therefore appears to have a

sturdier microstructure, and undergoes a less destructive ageing process than that of South African whites.

2.2.2. Bone Turnover and Calcium homeostasis

An imbalance in bone turnover may significantly impact on all aspects of bone quality. Some^{138,140-142,146,196} but not all studies^{142,144,145} employing either histomorphometry or biochemical bone turnover markers have documented a lower bone turnover status in African-Americans compared with whites. Lower 25-hydroxy-vitamin D and lower biochemical parameters of bone turnover despite higher plasma parathyroid hormone (PTH) levels in black women, suggest that American blacks have a decreased skeletal sensitivity to PTH. This concept is supported by the finding of higher BMD in blacks. American black women appear to conserve calcium more efficiently compared to whites with significantly lower urinary calcium excretion rates^{143,146}.

In contrast to the American data, a single histomorphometric study by Schnitzler et al suggested that black South African adults may have a higher bone turnover than whites¹³¹. Although generally accepted to render bone more susceptible to fracture, these authors suggested that the relatively higher bone turnover rates in black South Africans may contribute to better bone quality by minimizing the volume of bone damaged by fatigue and stress fractures, and hence, result in lower fracture rates in blacks compared to whites.

Biochemical markers of bone turnover was, however, found to be comparable in black and white South African nurses in a more recent study and were unable to confirm the histological finding of a higher bone turnover rate in South African blacks⁵. The postmenopausal blacks in the nurses' study also had lower 25-OH Vitamin D, higher PTH and lower urinary calcium excretion rates than whites, data similar to that seen in African-Americans. Conversely, no differences in biochemical markers of bone turnover or calciotropic hormone concentrations were noted between British and Gambian subjects studied by Dibba et al⁶. Study numbers were, however, very small and may account for the lack of significant differences between groups (table 13).

Table 13: Markers of calcium metabolism and bone turnover in plasma obtained from fasting blood.

	Men				Women			
	Gambian		British		Gambian		British	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Calcium (mmol/L) ^a	2.30	0.07	2.31	0.12	2.23	0.21	2.23	0.15
Phosphate (mmol/L)	1.15	0.11	1.10	0.20	1.18	0.16	1.02	0.14
Osteocalcin (ng/ml)	3.75	1.67	3.48	1.23	1.57	1.01	2.69	0.71
Bone alkaline phosphatase (U/L)	63	25	60	23	45	7	39	13
Non-bone alkaline phosphatase (U/L)	70	28	67	20	57	18	65	34
Parathyroid hormone (pg/ml)	29.5	18.4	23.9	7.2	27.4	11.5	34.3	21.5
Calcitonin (pg/ml)	38.8	13.1	34.1	13.5	24.0	10.3	33.6	23.3
1,25-dihydroxyvitamin D pmol/L ^b	119	44	131	34	157	46	122	24
25-hydroxyvitamin D nmol/L	26.3*	12.0	55.5	13.9	46.9	22.8	48.5	26.3
Creatinine μ mol/L	102.9	11.6	92.9	14.1	72.5	8.2	79.0	8.8
Number	12		10		5		10	

^a Normalized to a plasma albumin concentration of 36 g/L by adding or subtracting 0.1 mmol/L Ca for every 4 g/L that the albumin concentration was above or below 36 g/L. ^b Five subjects per group.

* Significant difference between Gambian and British subjects of the same sex $p < 0.0001$. There were no significant differences in any other variable between the Gambian and British groups.

Adapted from Dibba et al. *Annals of human biology*. 1999; 26(3):229-24⁶

2.2.3. Bone Geometry

A longer hip axis length (HAL) or femur neck axis length (FNAL) is an independent risk factor for hip fracture¹⁶⁰⁻¹⁶⁶. In America, most studies have documented a shorter FNAL in Blacks versus Caucasians^{3,4}. A shorter FNAL was also noted in black versus white South African females⁵ and in Gambians compared with British subjects⁶.

Lumbar vertebral heights, before and after correction for anthropometric differences were less in black boys and girls ($p < 0.01$) in a study by Pettifor and colleagues²¹⁶. The vertebral bone area in these children was similar in black and white children and these findings suggested that the vertebrae of black children are shorter, but wider. Geometrically, wider bones are stronger bones and may, independently of BMD provide protection against fragility fractures. Smaller vertebral bone area, on the other hand, has been associated with increased risk of vertebral fractures.

3. FALL RISKS

No data regarding possible differences in the propensity to fall between black and white South Africans exist.

4. FRACTURE DATA

Higher femoral bone mineral density might partially explain the lower hip fracture prevalence in people of African ancestry compared to Caucasians. The rarity of other fragility fractures in African populations, however, cannot be explained on the basis of significantly higher BMD and challenges current ideas about the significance of bone mineral status as a the principal determinant of fracture risk, especially in these populations.

Solomon et al²⁰ performed the last epidemiological studies on the incidence of hip fractures in South Africa more than 30 years ago. He showed that hip fracture rates in South African Blacks are more than ten-fold lower than those observed in Caucasians, both locally and in Western European populations (Figures 15 and 16).

More severe degrees of vertebral deformities in White vs. both rural and urban Black South Africans were also noted in a study conducted by Dent and co-workers in 1968²¹¹. In-patients and subjects in old age homes were recruited and a total of 100 cases were included in the three respective groups. (white, rural black and urban black). Structural vertebral abnormalities in keeping with severe osteoporosis was documented in 14 whites (14%) and 5 blacks (2 urbanized and 3 rural blacks; 2.5% of blacks)[table 14].

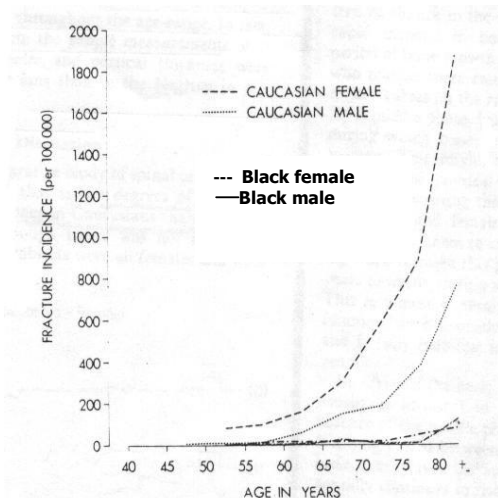


Figure 15: Annual incidence of femoral-neck fractures in the Johannesburg population over 40 years. Adapted from Solomon et al; *J Bone and Joint Surgery* 1968, 50(B): 2-11²¹¹

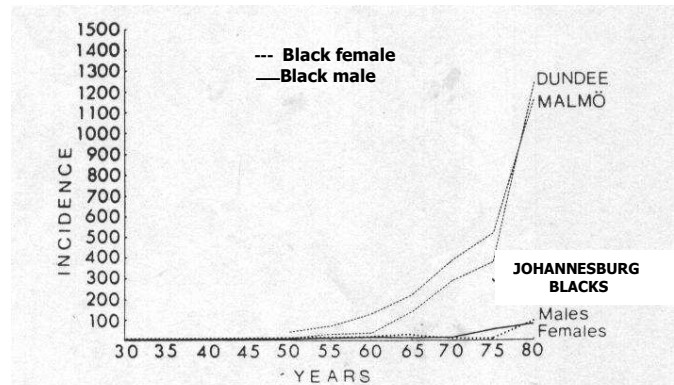


Figure 16: Age specific incidence of fractures of the femoral neck in Western European populations (Dundee and Malmö) and in the Johannesburg Blacks Adapted from Solomon et al; *J Bone and Joint Surgery* 1968, 50(B): 2-11²¹¹

Table 14: Number of patients with pathological changes seen on lateral x-ray

<i>X-ray Signs of</i>	Group A Rural blacks	Group B Urban Blacks	Group C Whites
Definite osteoporosis	3	2	14
Osteomalacia	10	5	1
Flattening of 5th lumbar vertebra	28	16	0
Degenerative changes (mild) ..	31	31	27
Degenerative changes (severe)	26	38	31
Spondylolisthesis L5-S1 or L4-5	8	8	4
Aortic calcification (mild) ..	1	6	35
Aortic calcification (severe) ..	0	0	24

Adapted from Dent et al. British Medical Journal. 1968; 4:76-79

This study has limitations. The majority of patients included in the study by Dent et al was hospitalized in-patients and very little is known regarding the reasons for admission, especially in the white cohort. The study population may thus not be truly representative of the population at large. The mean age of the urbanized black cohort was lower than that of the white cohort and may influence the prevalence of fracture irrespective of race in the different studied groups. More white patients above the age of 75 years were also included in this study compared with both black cohorts (figure 17).

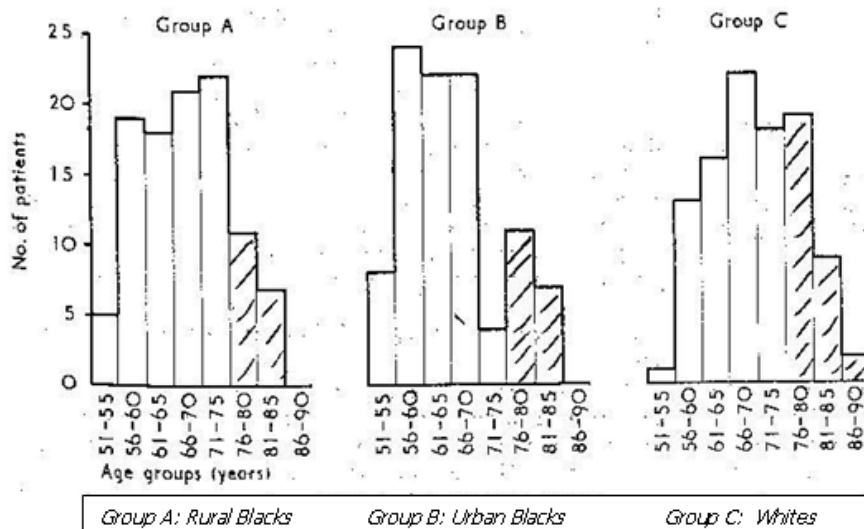


Figure 17: Age distribution of the three groups. *Adapted from Dent et al. British Medical Journal 1968; 4:76-79²¹¹*

The prevalence of vertebral fractures in other countries on the African continent is unknown. Data on the prevalence of osteoporosis related fractures in Africans are thus limited and nearly entirely based on old studies. Further research is clearly needed to define the current prevalence of spinal and non-spinal fractures in the different ethnic populations of Africa.

5. CONCLUSIONS

Studies suggest that South African black females, similar to their American counterparts, have a genetic tendency to greater proximal femur BMD than white females²¹⁵. In adulthood, SA black females, realize this potential and femoral BMD appears to be significantly higher in blacks compared with whites¹. Vertebral BMD, on the other hand, appears to be similar in blacks and whites, both in childhood²¹⁶ and in adult life¹.

Osteoporosis related hip fractures occur less in black compared to white South African females²⁰. This can be readily attributed to significantly higher femoral BMD¹, potentially better preservation of bone micro-architecture¹³¹ and a shorter FNAL⁵.

It is uncertain whether, and if so, why SA black women have a lower vertebral fracture prevalence compared with white women²¹¹. The lower fracture rate cannot be ascribed to marked differences in spinal BMD since similar values were documented in adult black and white females¹. Blacks do, however, appear to preserve bone quality better than whites with ageing¹³¹. Sturdier and better connected trabeculae may indeed enhance bone strength and provide better protection against fracture. Geometric differences with wider vertebrae may also potentially enhance resistance against vertebral injury²¹⁶.

No work has been done to assess fall risk, as a known significant contributor to fracture risk, in South Africans.

.....

CHAPTER 3

GENERAL METHODOLOGY

1.	SUBJECTS.....	52
1.1.	Recruitment and patient selection.....	52
1.2.	Exclusion criteria.....	52
1.2.1.	<i>Exclusions</i>	53
1.3.	Classification and patient subgroups	53
2.	METHODS.....	55
2.1.	Clinical assessment	55
2.1.1.	<i>Risk factor analysis.....</i>	55
2.1.1.1.	<i>Standardization of risk categories</i>	57
2.1.1.2.	<i>Individual Risk Factors</i>	57
2.1.1.3.	<i>General discriminant analysis</i>	58
2.1.1.4.	<i>Risk Assessment Tools</i>	58
2.1.2.	<i>Diet history.....</i>	59
2.1.3.	<i>Physical evaluation.....</i>	59
2.1.4.	<i>Anthropometric assessment</i>	59
2.2.	Bone Mineral Density determinations	61
2.2.1.	<i>Dual Energy X-ray Absorptiometry (DEXA)</i>	61
2.2.2.	<i>Computation of bone mineral apparent density (BMAD).....</i>	63
2.3.	Ultrasonography	63
2.4.	Femoral Geometry	65
2.5.	Conventional Radiology	66
2.6.	Biochemical assessment	66
2.6.1.	<i>Serum minerals, creatinine and alkaline phosphatase levels and urine minerals ..</i>	67
2.6.2.	<i>Bone Turnover.....</i>	68
2.6.3.	<i>Vitamin D-PTH Endocrine system.....</i>	69
2.6.4.	<i>Hormonal studies.....</i>	69

2.7.	Assessment of propensity to falls.....	69
3.	Statistical analysis	71

CHAPTER 3

GENERAL METHODOLOGY

This is a descriptive and cross-sectional study which compares fracture risk of White and Xhosa females by evaluating known determinants of bone strength as well as the propensity to falls. Informed consent was obtained from each subject, and the study was approved by the Ethical Review Board of the Faculty of Medicine, University of Stellenbosch.

1. SUBJECTS

1.1. Recruitment and patient selection

The study population consisted of community-dwelling healthy Caucasian and Xhosa women residing in the Western Cape, South Africa. Volunteer subjects were recruited by word of mouth and through local church and community centers from the geographical area normally supplied of medical care by the Tygerberg Hospital. Due to known socio-economic differences between the two ethnic groups, recruitment aimed to include a representative sample of White and Xhosa females and did not specifically stratify patients based on socio-economic status.

Recruitment took place between May 1999 and November 2004 and all subjects were evaluated once by a single observer (Magda Conradie).

Black and White race was determined by self-declaration and all women were resident in the Western Cape for the majority of their adult life.

1.2. Exclusion criteria

A telephonic questionnaire was used to screen volunteers prior to study entry (Addendum I). Any individual with a known metabolic bone disease (osteoporosis, osteomalacia, hyperparathyroidism, renal bone disease or Paget's), those who suffered from diseases (e.g. endocrinopathies, malabsorption syndromes, malignancies, chronic alcoholism, renal or hepatic dysfunction) or used drugs (e.g. glucocorticoids, anticonvulsants, antacids, fluoride, bisphosphonates, pharmacological doses of Vitamin D) known to affect bone or mineral metabolism, were excluded from study entry.

Only premenopausal subjects with a regular menstrual cycle were eligible for study entry. Postmenopausal subjects on hormone therapy were not excluded from this study, but bone mineral density employing DEXA, ultrasonography, biochemistry (including biochemical

assessment of bone turnover) and fall risk were analyzed separately. Only three of the postmenopausal black women entered into this study used hormone therapy compared with 44 whites.

1.2.1. Exclusions

A total of 411 patients were evaluated, including 198 Caucasian females and 213 Xhosa females.

Thirty eight volunteers (12 Caucasian females, 26 Xhosa females) who were included following the telephonic contact were subsequently excluded in view of the following (information not volunteered and/or unknown to patient at time of telephonic contact):

- ⊗ *Active use of Depo Provera contraception with amenorrhea (19 patients, 17 blacks, 2 whites)*
- ⊗ *Irregular menstrual cycles with oligo-/ amenorrhea, suspected perimenopausal state (7 patients)*
- ⊗ *Amiodarone induced hyperthyroidism (1 patient)*
- ⊗ *Heart failure, cause unknown (1 patient)*
- ⊗ *Primary ovarian failure (1 patient)*
- ⊗ *Eating disorder with hypogonadism (1 patient)*
- ⊗ *Diabetic nephropathy with renal failure (1 patient)*
- ⊗ *Positive HIV status (2 patients)*
- ⊗ *Immobility due to motor deficit L. arm and leg, associated R. optic atrophy (1 patient)*
- ⊗ *Suspected alcohol abuse (4 patients)*

1.3. Classification and patient subgroups

Subjects 20 – 82 years of age were recruited and stratified into premenopausal and postmenopausal groups. Women were classified as premenopausal if they reported monthly menstrual bleeding during each of the three months preceding study entry. The postmenopausal state was verified by a serum FSH-level > 40mIU/ml in all subjects.

Postmenopausal women were sub-classified based on age into an early postmenopausal group (age less than 60 years) and a late postmenopausal group (age equal or older than

60 years). White postmenopausal females were further subdivided based on whether they were currently using hormone therapy (HT+) or not (HT-).

To control for adiposity, BMD data were also analysed by dividing premenopausal and postmenopausal patients into weight subgroups i.e. those with normal to low body mass index (BMI <25kg/m²) and those defined as overweight based on BMI (BMI ≥ 25 kg/m²)²²³. To ensure sufficient numbers within each weight subgroup, the postmenopausal women were evaluated in total. As weight groups were compared primarily with regard to densitometric data, only postmenopausal women not on hormone therapy were included in these weight subgroups.

FINAL COHORT = 373
√ BLACKS = 187
√ WHITES = 186

PREMENOPAUSAL SUBJECTS			
<i>Blacks (B)</i> n = 87		<i>Whites (W)</i> n = 76	
<i>Normal to low</i> n = 23	<i>Overweight</i> n = 64	<i>Normal to low</i> n = 47	<i>Overweight</i> n = 29
POSTMENOPAUSAL SUBJECTS (total)			
< 60 years		≥ 60 years	
<i>Blacks</i> n = 52	<i>Whites</i> n = 63	<i>Blacks</i> n = 48	<i>Whites</i> n = 47

<i>POSTMENOPAUSAL SUBJECTS (weight groups)</i>			
<i>Blacks (B)</i> <i>n = 97</i>		<i>Whites (W)</i> <i>n = 66</i>	
<i>Normal to low</i> <i>n = 22</i>	<i>Overweight</i> <i>n = 75</i>	<i>Normal to low</i> <i>n = 27</i>	<i>Overweight</i> <i>n = 39</i>

2. METHODS

An extensive clinical, biochemical, radiological and densitometric evaluation was performed on each subject during a single visit to the Department of Endocrinology and Metabolism, at Tygerberg Hospital. This evaluation included the following:

- ⊗ *Standardized interviewer administered questionnaires were used to assess conventional osteoporosis risk factors (Addendum II)*
- ⊗ *A detailed dietary history (Addendum III)*
- ⊗ *Anthropometric evaluation*
- ⊗ *Full physical evaluation*
- ⊗ *Assessment of fall risk*
- ⊗ *Evaluation of Bone mineral density (BMD) employing Dual energy X-ray absorptiometry (DEXA)*
- ⊗ *Qualitative Bone Ultrasonography employing a Sahara clinical bone sonometer*
- ⊗ *Assessment of Vertebral structure via Conventional Radiology*
- ⊗ *Venesection and urine collection for biochemical evaluation*

2.1. Clinical assessment

2.1.1. Risk factor analysis

A standardized interviewer administered questionnaire (Addendum II) was used to assess the following parameters with a potential impact on BMD: age (years), ethnic group (Xhosa or White), history of previous fragility fractures, family history of osteoporosis, other medication, physical activity, alcohol intake, cigarette smoking, calcium intake (see dietary analysis- section 2.1.2), known ailments, gynecological history and a history of recent falls (see propensity to falls – section 2.7).

PREVIOUS FRACTURES were defined by position, number, date of occurrence and associated trauma.

PHYSICAL ACTIVITY was scored by the following criteria and expressed numerically as follows:

- 0: nil physical activity
- 1: light office work
- 2: active in-house (own housework)
- 3: active in-house and outdoors (regular walking, gardening)
- 4: partaking in competitive sporting activities, walking daily for 1/2hour or more
- 5: extreme sporting activities i.e. marathons...

ALCOHOL INTAKE was expressed in units per week, a unit being equivalent to 28g alcohol i.e. one bottle of beer, one glass of wine or one drink of spirits.

CIGARETTE SMOKING STATUS was expressed as ever, current, never and number of pack-years.

The GYNAECOLOGICAL HISTORY included the following:

- ⊗ *Age at menarche*
- ⊗ *Menstrual cycle i.e. regularity and cycle length*
- ⊗ *Use of hormonal contraceptives (Yes/No)*
 - *Type*
 - *Current or past use*
 - *Duration of usage*
- ⊗ *Menopause*
 - *Age at onset*
 - *Spontaneous or surgical*
 - *Years since the start of menopause (YSM)*
 - *Hormone therapy (Yes/ No)*
 - *Date commenced*
 - *Menopausal years without hormone therapy*

- *Duration and type of hormone therapy*
- ⊗ *Number of pregnancies*
- ⊗ *Breastfeeding (Yes/No)*
 - *Duration of lactation*

2.1.1.1. Standardization of risk categories

The average of the lowest quartile of weight, height and BMI for each of the two ethnic groups was calculated within the pre- and postmenopausal cohorts and rounded up to low cut-off values for the pre- and postmenopausal cohorts as follows: weight: 55kg and 60kg; height: 155cm and 156cm; and BMI: 21kg/m² and 23kg/m² respectively. Mean calcium intake for black and white women in this study cohort was 613.2 and 864.8 mg respectively. A low dietary intake threshold of 500mg/day was used in the present study. Current cigarette smoking was categorized as either “yes” or “no” and low physical activity was classified as no outdoor activity, i.e. a score of 2 or less (see section 2.1.1). Alcohol intake was regarded as excessive if intake exceeded 1U/day, every day or 10U/week. Due to a very small percentage of both black and white females who met the criteria for excess alcohol, alcohol intake was in fact categorized as “yes” or “no” and compared. A maternal history of osteoporosis, prior or current use of contraception (either depo provera or oral preparations) and breastfeeding were categorized as either “yes” or “no”. High parity was classified as 3 or more prior pregnancies. Past or current use of hormone therapy was noted for the two postmenopausal cohorts.

2.1.1.2. Individual Risk Factors

One way analysis of variance was used to determine differences between the various ethnic subgroups in terms of anthropometric, menstrual and lifestyle risk factors. The prevalence of clinical risk factors were also reported on in premenopausal and postmenopausal cohorts and compared between the two ethnic groups.

The frequency for each risk factor, as outlined in section 2.1.1.1, in patients with normal bone mass (BMD T-score >-1) and in those with osteopenia (BMD T-score ≤-1SD) was determined for spinal and femoral sites. Cross tabulation and the Chi-square test was used to determine univariate relationships between risk factors and low bone mass.

2.1.1.3. General discriminant analysis

General discriminant analysis was used to identify variables able to predict osteopenia in post-menopausal black and white females. Associations were determined between clinical risk factors, as outlined in section 2.1.1.1, and low BMD (T-score \leq -1SD as assessed against a uniform white reference population) at the lumbar spine and at the proximal femur (total BMD and femoral neck BMD). Linear discriminant analysis was used to pick out the best combinations of predictor variables.

2.1.1.4. Risk Assessment Tools

Numerous simple risk assessment instruments have also been constructed to identify patients who are most likely to have a low BMD warranting a bone density test¹²⁰⁻¹²⁵. These risk instruments have been developed based on data obtained via epidemiological risk factor identification in Asian countries, the US and Europe. The purpose of these risk assessment tools is not to diagnose osteoporosis or low BMD, but to identify women who are more likely to have low BMD and who can then be selectively referred for BMD measurements. The performance of these risk assessment tools in multi-ethnic populations has never been published.

We calculated risk assessment scores based on the OST, OSIRIS and ORAI tools, and evaluated the performance of these tools in identifying non-hormone treated postmenopausal black and white women at risk of osteopenia i.e. a T-score \leq -1 at various BMD measurement sites (table 1). We also determined the sensitivity, specificity, positive predictive value and negative predictive value for each of the risk assessment instruments in black and white postmenopausal females respectively.

The Osteoporosis Self-assessment Tool (OST) is based simply on age and weight^{123,124}. The score is calculated by subtracting age from weight and then multiplying by 0.2¹²³. Other risk tools are also based on age and weight, in combination with up to four additional risk factors. These include, amongst others, the Osteoporosis Risk Assessment Instrument (ORAI) and the Osteoporosis Index of Risk (OSIRIS). ORAI differentially score weight and age within certain cut-off ranges and include hormone therapy as a risk index to identify women likely to have either femoral neck or lumbar spine T-scores \leq -2.0¹²¹. The Osteoporosis Index of Risk (OSIRIS) is based on four variables: age, body weight, current hormone therapy and a history of previous low impact fractures²²⁴. Any patient with a OST score of less than 2, an ORAI score of 9 or more and a OSIRIS score of 1 or less would be advised to have BMD testing.

Table 1: Clinical Risk Assessment Instruments – Calculation of the evaluated indices

Factor	Score
ORAI	
Age > 75 years	+ 15
Age 65–74 years	+ 9
Age 55–64 years	+ 5
Body weight < 60 kg	+ 9
Body weight 60–70 kg	+ 3
Oestrogen therapy	+ 2 if not currently using oestrogen
OSIRIS	
Body weight (kg)	+ 0.2 x body weight
Age (years)	- 0.2 x age
History of low impact fracture(s)	- 2
Oestrogen therapy	+ 2
OST	
Body weight (kg)	
Age (years)	0.2 x (body weight-age)

2.1.2. Diet history

The diet history of all study subjects was obtained by a single qualified dietician (Madele du Plessis). The method used was dietary recall (usual intake during two normal week days and one weekend day at time of evaluation) obtained during a personal interview (Addendum III). The Foodfinder program (Dietary Analysis Software – Medical Technology, South African Medical Research Council) was used to analyze the dietary histories. This enabled us to obtain estimates of intake for individual nutrients, including calcium, protein, phosphate, sodium and Vitamin D.

2.1.3. Physical evaluation

A thorough physical examination was performed by a single physician (Magda Conradie) on every study subject to ascertain the presence of unsuspected systemic disease (Addendum II).

2.1.4. Anthropometric assessment

Anthropometric data were obtained from every subject and included weight, height, skin-fold measurements, waist and hip circumferences and elbow breadth determination.

The following methods were employed:

- ⊗ *subjects were weighed on a balanced beam scale wearing the minimum of clothes to the nearest kilogram*
- ⊗ *height was measured with a sliding headpiece to increase the accuracy of the reading, which was taken to the nearest centimeter (cm); the lower segment was determined as the distance from the pubic symphysis to the floor and the upper segment calculated as total height minus lower segment*
- ⊗ *skinfolts were measured using a Harpenden caliper; all measurements were taken on the right side of the body to the nearest millimeter (mm), as follows:*
 - *biceps – at the midpoint of the biceps muscle*
 - *triceps – over the triceps muscle,*
 - *subscapular – just below the tip of the scapula, at 45° to the vertical*
 - *supra-iliac – just above the iliac crest in the mid-axillary line*
- ⊗ *waist circumference was determined in the erect position through a point one third of the distance between the xiphoid process and the umbilicus*
- ⊗ *hip circumference was assessed in the erect position, through a point 4 cm below the superior anterior iliac spine*
- ⊗ *elbow breadth was measured with a sliding caliper to the nearest 0.1cm, at the point of greatest breadth across the joint.*

All the measurements were done by the same researcher (Madele du Plessis) in triplicate, and the results averaged. Weight and height measurements were used to calculate body mass index (BMI)* and the patients were classified, based on BMI values, as follows:

$$*BMI (kg/m^2) = \text{Weight (kg)} / \text{Height (m}^2)$$

Normal reference values for all adult ages²²⁵

Normal to low body weight < 25

Overweight to obese ≥ 25

2.2. Bone Mineral Density determinations

2.2.1. Dual Energy X-ray Absorptiometry (DEXA)

Bone mineral content and bone mineral density of the lumbar spine and proximal femur were quantitated employing dual-energy X-ray absorptiometry (DEXA) by using a Hologic QDR 1000 according to standard procedures in a study cohort who included 187 black women and 186 white women. The BMD of L1-4 was measured in the antero-posterior position and the mean BMD of these four vertebrae was calculated and used. BMD of various proximal femur sites were measured (femoral neck, trochanter, intertrochanteric, total hip and Ward's triangle). A spine phantom was scanned weekly to determine the intrinsic coefficient of variation of the machine. During the course of the study, coefficients of variation for BMD were < 1.5%. A single trained DEXA technician (Riana Eager) performed scans on all study subjects and the intra-operative variation was found to be below 1% for all skeletal sites.

Bone mineral content (BMC) and bone mineral density (BMD) are common expressions of bone mineral status. BMC (g) represents the amount of mineral in a section of bone 1 cm in length. BMD (g/cm^2) is derived, at the radius and hip, from BMC divided by bone width (BW) and at the lumbar spine by scan area. It represents a partial correction of bone mineral status for bone and body size, but is not a true measurement of density, since no information is available about bone volume from a two-dimensional scan. Areal BMD is, however, strongly correlated with bone strength in vitro and a good predictor of future fracture risk²⁵⁻³⁰.

Bone mineral density is conventionally expressed as either an absolute value (g/cm^2) or a deviation from the norm defined as a T-score or Z-score. A T-score refers to the BMD of a subject compared to the mean BMD of the young adult reference mean. The Z-score compares the BMD of the individual with that of age and gender matched controls within a specific ethnic group. As alluded to before, the WHO's classification^{12,13} of osteopenia/osteoporosis was designed to provide a practical basis for the identification of specifically postmenopausal Caucasian women at risk to sustain fragility fractures (please refer to chapter 2, pages 3-4).

No normative data for black South African women exist. In this study we therefore used a white female reference population to calculate T- and Z-scores for both ethnic groups. The use of white women as a reference for all persons in a multi-ethnic study may well not be appropriate, but until these ethnic specific reference ranges become available, it is currently

recommended to diagnose osteoporosis among non-Caucasians by using the uniform normative database for Whites, as alluded to before¹⁸³.

In premenopausal subjects Z-scores were used to define BMD status. A Z-score ≤ -1 indicated osteopenia, whereas a Z-score ≤ -2 was regarded as diagnostic for osteoporosis. In postmenopausal subjects, osteopenia and osteoporosis were defined based on WHO criteria and as measured against a uniform white reference population. In 1994, the World Health Organization (WHO) selected a BMD value of 2.5 standard deviations (SD) or more below the mean for normal young white women, or a T-score of ≤ -2.5 ¹², to define osteoporosis in the white postmenopausal female population. This cut-off value was based on epidemiologic fracture threshold data which captures most women at risk of osteoporotic fracture (hip, vertebrae, forearm, humerus and pelvis). The relationship between low BMD and fracture risk is, however, a gradient and not a threshold. Therefore this classification was extended to include a subset of patients with osteopenia (BMD more than 1 SD, but less than 2.5 SD below young normal mean) in whom the presence of additional risk factors other than BMD may lead to increased fracture risk¹³.

Ethnic differences in bone mineral data were analyzed and reported on in the following patient subgroups:

- Premenopausal black and white subgroups
- Early and late postmenopausal black and white groups as outlined in section 1.3.
- Pre-and postmenopausal black and white weight subgroups as outlined in section 1.3 in order to control for adiposity.

For all skeletal sites, BMD's were first compared between the ethnic subgroups by ANOVA before adjustment for covariates. To determine whether observed ethnic differences in bone mineral status were due to ethnic factors that affect these measurements, the differences were then recompared after adjustment for certain covariates. Analysis of co-variance was performed to identify covariates with significant univariate association with lumbar and femoral BMD. For the premenopausal subjects, covariates included ethnicity, age, weight, height, daily calcium intake, pack years of smoking, alcohol intake, physical activity, age at menarche, hormonal contraception and number of prior pregnancies. For the postmenopausal subjects, covariates included years since menopause in addition to the abovementioned. For post hoc testing, the Bonferonni test was used.

The correlation between BMD at all skeletal sites and anthropometric variables as well as between BMD's and age and years since menopause (where applicable) were determined in

blacks and whites in the different patient subgroups as noted above. The distribution of BMD's at all skeletal sites, expressed as either T-or Z-scores, were also compared between the two ethnic groups within the menopausal subgroups as described in section 1.3

2.2.2. Computation of bone mineral apparent density (BMAD)

Conventional BMD measurements by DEXA are expressed in g/cm^2 and are more properly referred to as areal BMD than true volumetric BMD expressed in g/cm^3 . Areal BMD, as alluded to before, introduces a scale artifact that causes small bones to have lower areal BMD than larger bones. When comparing people from different ethnic groups with potential differences in bone size, BMD differences may thus be more apparent than real. This scale artifact is reduced by expressing BMD as BMAD, a calculated three-dimensional variable that helps account for differences in bone size. For the lumbar spine, BMAD was computed as the $\text{BMC}/(\text{area})^{3/2}$ using the method of Carter et al²⁰⁰. For the femoral neck, BMAD was computed as the $\text{BMC}/(\text{area})^2$ using the method of Katzman et al²⁰¹.

The calculated volumetric BMAD of the lumbar spine and femoral neck, similar to BMD, were first compared between the ethnic groups by ANOVA before adjustment for covariates. BMAD data were then compared after adjustment for covariates with significant univariate association with BMAD as determined by analysis of co-variance (see section 2.2.1, covariates as for BMD).

2.3. Ultrasonography

Quantitative ultrasound *may* be a useful measure of both the quality and quantity of bone. The technology has evolved from the observation that sound waves through porous materials like bone are absorbed, scattered and travel in a manner that reflects the elasticity, stiffness and to a lesser degree the density of the material^{226,227}. Indirect and in-vitro experience has suggested that ultrasonography may give information not only about the bone density, but also about the bone structure, trabecular orientation and micro-architecture²²⁸⁻²³¹. The speed with which sound travels through bone (SOS) has been shown to be a function of both the elasticity of the bone as well as its density²²⁹. Broadband ultrasound attenuation (BUA) has been found to be related, not only to BMD, but also to architectural characteristics such as trabecular density, spacing and orientation²²⁸⁻²³¹.

We measured calcaneal ultrasonography by using the Sahara Clinical Bone Sonometer (Hologic).

The non-dominant heel was scanned using the scanning protocol provided by the manufacturer. A single trained technician (Riana Eagar) performed the calcaneal ultrasonography on all study subjects. A quality control phantom (QC) was scanned weekly over the time period of the study to monitor system performance prior to using the system to measure patients. The QC was passed prior to using the system to measure patients. A passed QC result indicated that the system was functioning properly and that QC results were within the acceptable range. Calcaneal QUS was performed on 230 pre-and postmenopausal black and white subjects, 97 blacks and 133 whites. This sub-cohort was randomly selected based on test availability.

QUS calcaneal broadband ultrasound attenuation (BUA) and speed of sound (SOS) were measured and the quantitative ultrasound index calculated ($QUI = 0.41 \times SOS + 0.41 \times BUA - 571$). A 'predicted' calcaneal ultrasound BMD value was obtained by a simple re-scaling of the QUI value and is reported as the 'estimated' heel BMD in g/cm^2 . No sonographic normative BMD ranges are available in South Africa. Using the manufacturer's (Sahara) normative range for Caucasian females, a BMD T-score was also calculated in the black and white postmenopausal subjects.

Ethnic differences in QUS measurements were analyzed and are reported on in the following patient subgroups:

- Premenopausal black and white subgroups
- Early and late postmenopausal black and white groups as outlined in section 1.3.

Parameters directly measured by the Sahara Clinical Bone Sonometer i.e. BUA and SOS were first compared between the two ethnic groups by ANOVA before adjustment for covariates in the different patient subgroups. To determine whether observed ethnic differences in bone mineral status were due to ethnic factors that affect these measurements, the differences were then re-compared after adjustment for certain covariates. Analysis of co-variance was performed to identify covariates with significant univariate association with BUA and SOS. For the pre- and postmenopausal subjects, covariates evaluated, included ethnicity, age, weight, height, daily calcium intake, physical activity, pack years of smoking, alcohol usage, age at menarche, hormonal contraceptive use and number of prior pregnancies. In the postmenopausal cohorts years after menopause was also included as covariate. BUA and SOS were also compared between blacks and whites after adjustment for differences in DEXA measured BMD of the spine and proximal femur in both pre-and postmenopausal cohorts.

2.4. Femoral Geometry

DEXA scan printouts were used to measure hip axis length (HAL) and femur neck width as described by Faulkner et al (figure 1)¹⁶⁶. The femoral DEXA measurements were all performed using a Hologic QDR-1000 scan and all geometric measurements were conducted by one investigator. Employing standard DEXA software, HAL was defined as the length along the femoral neck axis, from below the lateral aspect of the greater trochanter, through the femoral neck, to the inner pelvic brim. Femoral neck width was defined as the shortest distance within the femoral neck region of interest (as defined by the DEXA analysis software) perpendicular to the femoral neck axis.

Vertebral size was also determined directly from the DEXA-scan printouts and expressed as the total vertebral cross-sectional area and the mean area of vertebrae L1-L4.

Geometric assessments were performed on the total study cohort and ethnic differences were determined and are reported on in the following patient subgroups:

- Premenopausal black and white subgroups
- Early and late postmenopausal black and white groups as outlined in section 1.3.

ANOVA was used to determine significant ethnic differences in geometry between the various patient subgroups. Spearman correlations were used to determine relationships between geometric measurements and anthropometry (i.e. weight and height) as well as between certain femoral geometric measurements (HAL and femoral neck width) and between certain anthropometric measurements (weight and height).

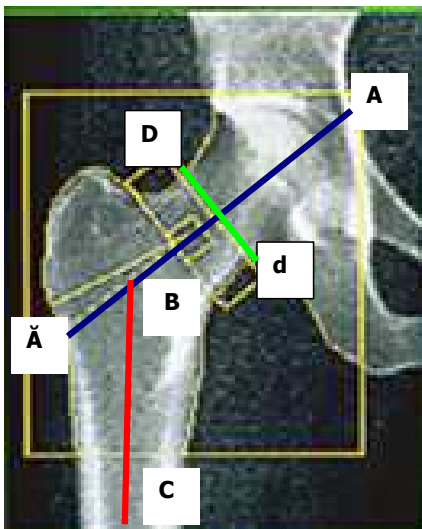


Figure 1: Definition of geometric measurements from femoral DEXA scan printout.

AA: hip axis length, defined as the length along the femoral neck axis as determined by the DEXA analysis software, from below the lateral aspect of the greater trochanter, through the femoral neck, to the inner pelvic brim

Dd: neck width, defined as the shortest distance within the femoral neck region of interest, as defined by the DEXA analysis software, perpendicular to the femoral neck axis

Adapted from Faulkner et al. 1993, J Bone Miner Res; 8(10): 1211-1217¹⁶⁶

2.5. Conventional Radiology

Conventional radiology of the thoraco-lumbar vertebrae was obtained randomly in as many of the study subjects as possible. Patients were referred for radiological evaluation whenever possible, but due to financial constraints and logistical difficulties the total cohort was not examined. Two hundred and eighty nine of the subjects underwent conventional radiology and included 116 blacks (55 premenopausal and 61 postmenopausal subjects) and 173 whites (69 premenopausal and 104 postmenopausal subjects of whom 42 were on hormone therapy). The evaluation was thus performed in 77% of the total study cohort. We used a fixed percentage reduction in vertebral height to define incident vertebral deformities. A prevalent morphometric vertebral fracture was defined as vertebral height loss of 20% or more^{158,232} when compared with the vertebrae directly above or below the specific vertebra in question or a difference in height of 20% or more amongst anterior, middle and posterior vertebral diameters. Vertebrae T4 – L5 were assessed and all radiographs were evaluated and interpreted by a single specialist radiologist (Professor Alan Sher).

Females with prevalent vertebral fractures, i.e. vertebral height loss of 20% or more, and those with normal vertebral morphometry were compared with regard to clinical characteristics, densitometry, ultrasonography, geometry and biochemically determined bone turnover and fall tendency within their specific ethnic group.

2.6. Biochemical assessment

A fasting overnight blood sample was drawn between 09h00 – 11h00 in all subjects. Fifty milliliters were used for immediate analysis. A second-voided, spot morning urine sample was obtained in all study subjects. A 5ml aliquot of urine was immediately protected from light (by wrapping the collection tube in foil) for measurement of urinary free deoxypyridinoline and creatinine. Subjects then drank 200ml distilled water, following which a 2 hour timed urine specimen was collected. The urine was collected in containers specially prepared for analysis of a 2 hour hydrated urine specimen for measurement of renal calcium, phosphate and sodium handling.

ANOVA was used to determine significant ethnic differences in biochemical measurements between the various patient subgroups. Spearman correlations were used to determine relationships between certain biochemical measurements (serum osteocalcin, urinary free DPD, serum PTH and serum 25-OH-Vitamin D), as well as between these biochemical measurements and DEXA determined BMD at the spine and proximal femoral sites.

2.6.1. Serum minerals, creatinine and alkaline phosphatase levels and urine minerals

The following serum mineral and biochemical parameters were analysed using a multi-channel analyzer (Technicon DAX 48): serum total calcium, magnesium, phosphate, creatinine and total alkaline phosphatase (ALP). Enzymatic, timed end-point calorimetric methods were used for quantitation of calcium (reaction with o-cresolphthalein), magnesium (xilidyl blue methods) and phosphate (reduction with ammonium molybdate). The serum calcium was corrected for albumin employing the following formula: corrected calcium = serum calcium + [(40-albumin) x 0.025].

The two hour hydrated urine specimen was analysed spectrophotometrically by the ADVAI® 1650 system and the following parameters measured: calcium, sodium and creatinine. Urinary calcium (Ca) and sodium (Na) were expressed as a function of creatinine and documented as U-Ca/U-Creat, U-Ca/100ml GFR and U-Na/U-Creat.

U- Ca/100ml GFR was calculated using the formula:

$$\frac{\text{urine calcium (mmol/l)}}{\text{urine creatinine (mmol/l)}} \times \text{serum creatinine (mmol/l)}$$

The fractional tubular reabsorption of phosphate (TRP) was calculated using the formula:

$$1 - \left\{ \frac{\text{serum creatinine (mmol/l)} \times \text{urine phosphate (mmol/l)}}{\text{serum phosphate (mmol/l)} \times \text{urine creatinine (mmol/l)}} \right\}$$

The ratio of the renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate (TmP/GFR) was calculated using the nomograms of Walton and Bijvoet based on the TRP and the serum phosphate concentration.

Normal reference values for our laboratory:

S-Calcium (albumin corrected)	2.10 – 2.60 mmol/l
S-Magnesium	0.75 – 1.00 mmol/l
S-Phosphate	0.8 – 1.40 mmol/l
S-Creatinine	80 – 120 µmol/l
S-Alkaline Phosphatase (ALP)	30 – 85 IU/l

Urine

TRP %	85 – 95%
TmP/GFR	1.00 – 1.68

2.6.2. Bone Turnover

Bone turnover was assessed by measuring osteocalcin in serum and deoxypyridinoline in urine. Serum osteocalcin was measured using an immunoradiometric assay (RIA kits, CIS Bio International, France manufactured by Nicholls). Urinary deoxypyridinoline was measured using a chemiluminescence system (Bayer Automated Chemiluminescence System; ACS:180[®]). Results obtained using the Bayer ACS:180[®] system are expressed as a ratio of deoxypyridinoline to creatinine (nanomoles of bone collagen equivalents per liter per millimole creatinine per liter, Nm DPD/mM Creatinine). The minimum detectable concentration for this system is 5.0nM. Typical recoveries are in the region of 90-95% with CV's for running controls of approximately 8%.

We attempted to minimize pre-analytical variability of these biochemical bone turnover markers by limiting the factors known to contribute²³³. Serum osteocalcin and urinary free DPD was collected in the fasting state and at a specific time of day i.e. in the morning between 09h00 and 11h00 to avoid diurnal variability. We used a second voided spot urine sample for collection of urinary DPD as it is the most practical urine type and protected urine specimens from UV-light immediately after collection. As serum osteocalcin is rapidly degraded in serum in vitro, we collected these specimens on ice and the serum was promptly separated and frozen.

We furthermore analyzed serum osteocalcin and U-DPD in the postmenopausal cohorts separately for the early and late postmenopausal groups as age is an important variable to control for. All subjects in our study resided in the Western Cape thus eliminating the potential impact of geographical differences.

Normal reference values for our laboratory:

Osteocalcin	2.4 – 10.0	ng/ml
Urinary free DPD/Cr ratio	3.0 – 7.4	nM DPD/mM Creatinine

2.6.3. Vitamin D-PTH Endocrine system

Serum albumin was measured with a multi-channel analyser (Technicon DAX 48). 25-OH-Vitamin D determination, described by Shephard et al²³⁴, involves a competitive protein-binding technique, utilizing titrated 25-OH-cholecalciferol as radio-labelled ligand, unlabelled 25-OH cholecalciferol as standard, Vitamin D deficient rat serum as binding protein and dextran-coated charcoal for phase separation. Typical recoveries are in the region of 90% (CV<5%) with CV's for running controls of approximately 6%. Serum intact PTH was measured using a chemiluminometric system (ADVIA Centaur® system). The ADVIA Centaur intact PTH assay measures intact PTH concentrations up to 201pmol/L with a minimum detectable concentration (analytical sensitivity) of 0.265pmol/L.

Normal reference values for our laboratory:

S-Albumin	35 – 50 g/L
25 (OH) Vitamin D	> 18 ng/L
PTH	1.3 – 7.6 pmol/L

2.6.4. Hormonal studies

Luteinizing hormone (LH), follicle stimulating hormone (FSH) and prolactin were quantified by a manual method using the IRMA (immunoradiometric assay) principle with magnetic separation (Sereno diagnostics, Switzerland). Biochemical evaluation of estradiol was quantitated by RIA kits (in house) and sex hormone binding globulin (SHBG) by an in-house radiometric method. The quantitation of serum total cortisol was performed using a coated tube RIA method (Incstar Corporation, Stillwater, USA). Thyroid stimulating hormone (TSH) was quantitated by manual methods using the IRMA principle with magnetic separation (Sereno Diagnostics, Switzerland). The determination of serum free thyroxin (T4) was carried out using the Amerelex-MAB kit (Kodak Clinical Diagnostics).

2.7. Assessment of propensity to falls

This assessment was carried out by a single observer (Magda Conradie) throughout the study period and included the following:

QUESTIONNAIRE

Questions regarding fall tendency were included in the standardized interviewer administered questionnaire (Addendum II) and addressed the following:

- ⊗ Recent fall(s) – within the last 12 months (yes/no)
 - Number of falls
 - Where the fall(s) occurred
 - Direction of fall(s) i.e. forward, backwards or sideways
 - Known injuries sustained

STANDARDIZED TESTS TO ASSESS SENSORY AND NEUROMUSCULAR FUNCTION

Permission was obtained from Eli-Lilly Pharmaceuticals U.S.A. (Drs Mike Draper, Olaf Johnell) to utilize a battery of validated tests²³⁵, well established in our Department, as part of a previously conducted Raloxifene study (Protocol H3S-MC-GGHV(b) to assess these functions (Addendum IV). These tests included:

- ⊗ Body sway: Body sway was measured using a sway meter - a specialized rod is attached to the individual's waist, and anterior-posterior and lateral sway is recorded on graph paper (positioned behind the subject) while she stands on a firm surface and on a 15cm thick piece of foam rubber (reduces proprioceptive inputs so that the individual is dependent on visual and vestibular cues to maintain a steady stance)²³⁵.
- ⊗ Reaction time: Reaction time, recorded in milliseconds, is measured using a simple reaction time task which employs a light as the stimulus and depression of a switch by the hand as the response²³⁵.
- ⊗ Visual contrast sensitivity: Contrast sensitivity was assessed by the Melbourne Edge Test²³⁵
- ⊗ Muscle strength: Quadriceps strength was assessed using a strain gauge system attached to a specially constructed chair on which the patients were seated with their hips and knees flexed to approximately 90°. In this position, the presence and degree of quadriceps activation was measured. Three maximal voluntary contractions were recorded and analyzed offline. The strongest maximal voluntary contraction of the dominant leg was noted in data analysis²³⁵.

One way analysis of variance was used to determine ethnic differences in the various patient subgroups for fall data and sensory and neuromuscular function tests. Analysis of covariance was performed to assess the association between serum 25-OH Vitamin D status and fall risk in postmenopausal females.

3. Statistical analysis

All analyses were conducted using Statistica 7.1 software. Cross tabulation and the Chi-square test was used to compare categorical variables. Spearman correlation was used for comparing continuous variables. One way analysis of variance and analysis of co-variance was used for comparing measurements between groups. A p-value <0.05 was used as guideline for determining statistical significance.

.....

CHAPTER 4

ASSESSMENT OF CLINICAL RISK FACTORS FOR OSTEOPOROSIS IN BLACK AND WHITE SOUTH AFRICAN FEMALES

1.	INTRODUCTION.....	73
2.	PATIENTS AND METHODS	73
3.	RESULTS.....	74
3.1.	Clinical characteristics of the study population	74
3.1.1.	<i>Anthropometric and menstrual data.....</i>	<i>74</i>
3.1.2.	<i>Weight distribution amongst study subjects.....</i>	<i>76</i>
3.1.3.	<i>Lifestyle</i>	<i>76</i>
3.2.	Prevalence of clinical risk factors	78
3.2.1.	<i>Literature-based risk factors for white women</i>	<i>78</i>
3.2.2.	<i>Prevalence of clinical risk factors by ethnicity and menopausal status</i>	<i>79</i>
4.	DISCUSSION.....	81

CHAPTER 4

ASSESSMENT OF CLINICAL RISK FACTORS FOR OSTEOPOROSIS IN BLACK AND WHITE SOUTH AFRICAN FEMALES

1. INTRODUCTION

Age, a positive family history, low weight and BMI, inadequate dietary calcium intake, current cigarette smoking, physical inactivity and a history of previous fragility fractures have all been shown to be independent risk factors for osteoporosis in population based studies of postmenopausal white women^{115,116,126,236}. Age and weight have been shown to be the most informative predictors for low bone mineral density¹²⁶. Studies evaluating clinical risk factors for osteoporosis in multi-ethnic groups are limited^{118,202}, but do suggest that risk factors similar to those identified in white populations also impact on bone health in other ethnic groups. A single study by Blaauw et al in 1993¹¹⁹ identified a positive family history of osteoporosis, a fair complexion, lower body mass and height, no breastfeeding of babies, a history of smoking, alcohol consumption and fat distribution around the waist to be significant risk factors for osteoporosis in white South African females residing in the Western Cape. To our knowledge no studies evaluating clinical risk factors for osteoporosis have been done in other ethnic groups in South Africa.

This chapter is a brief overview of the clinical and lifestyle characteristics of our study population and an assessment of clinical risk factors regarded to predispose to the development of osteoporosis.

2. PATIENTS AND METHODS

Our study population consisted of community-dwelling healthy White and Xhosa women residing in the Western Cape, South Africa and included 187 blacks and 186 whites. Due to known socio-economic and anthropometric differences between the two ethnic groups, recruitment aimed to include a representative sample of white and black females and did not specifically stratify patients based on socio-economic status or phenotype.

We analyzed and report results of these 373 subjects in the following patient subgroups:

- Premenopausal black and white groups
- Early and late postmenopausal black and white groups:
As alluded to in chapter 3, postmenopausal subjects were classified based on age and

subdivided into early and late postmenopausal groups, i.e. postmenopausal females less than 60 yrs of age were included in the early postmenopausal groups whereas postmenopausal women 60 yrs and older represented the late postmenopausal groups.

The clinical characteristics of black and white patient subgroups were compared. One way analysis of variance was used to determine differences between the various ethnic subgroups in terms of anthropometric, menstrual and lifestyle risk factors. The prevalence of clinical risk factors were also reported on in premenopausal and postmenopausal cohorts and compared between the two ethnic groups. The standardization of risk categories are described in detail in chapter 3 (refer to section 2.1.1.1).

3. RESULTS

3.1. Clinical characteristics of the study population

3.1.1. Anthropometric and menstrual data

The anthropometric and menstrual data are summarized in table 1. Blacks and whites had similar mean ages in all the comparable groups studied. In the total study population, blacks were on average 4 cm shorter and 11 kg heavier than whites. Blacks were significantly shorter in the premenopausal (± 7 cm) and early postmenopausal groups (± 5 cm). Of interest was the finding of similar heights in the late postmenopausal black and white females. The mean height measured in these subjects was near identical to that of the younger black females. Premenopausal and postmenopausal blacks were significantly heavier with greater BMI's than whites, but elbow width, an index of skeletal frame size, was similar in all studied groups. The waist-hip ratio was also higher in black subjects. Age at menarche was statistically significantly older in blacks. In the postmenopausal women younger than 60 years of age, white females were older at menopause and the number of years since menopause was less compared with the black females. These parameters were similar in the older black and white postmenopausal females.

Table 1: Summary of Anthropometric and Menstrual data

Anthropometric and Menstrual data	Premenopausal			Postmenopausal					
				<60 years			≥ 60 years		
	Blacks n=87	Whites n=76	<i>p-value</i>	Blacks n=52	Whites n=63	<i>p-value</i>	Blacks n=48	Whites n=47	<i>p-value</i>
Age (yr)	37 ± 8	39 ± .7	0.1	52 ± 6	52 ± 5	0.43	68 ± 6	68 ± 6	0.49
Height (cm)	160 ± 6	167 ± 6	<0.01	160 ± 7	165 ± 6	<0.01	159 ± 6	160 ± 7	0.16
Weight (kg)	79 ± 21	69 ± 15	<0.01	80 ± 19	71 ± 15	<0.01	86 ± 19	71 ± 14	<0.01
BMI (kg/cm ²)	31 ± 8	25 ± 5	<0.01	32 ± 8	26 ± 5	<0.01	34 ± 8	28 ± 5	<0.01
W/H ratio	0.85 ± 0.1	0.78 ± 0.8	<0.01	0.87 ± 0.1	0.8 ± 0.1	<0.01	0.9 ± 0.1	0.85 ± 0.1	0.03
Elbow width (mm)	65 ± 5	66 ± 3	0.78	67 ± 4	66 ± 4	0.15	68 ± 6	67 ± 4	0.23
Age menarche(yrs)	15 ± 3	13 ± 2	<0.01	14 ± 2	13 ± 2	<0.01	14 ± 2	13 ± 2	<0.01
Age menopause (yrs)				46 ± 5	48 ± 5	0.02	49 ± 5	48 ± 5	0.20
YSM (yrs)				7 ± 5	5 ± 5	0.04	19 ± 8	19 ± 7	0.37

Values reported are the mean ±SD. Abbreviations: W/H: waist-hip; YSM: years since menopause

3.1.2. Weight distribution amongst study subjects

The weight distribution between the black and white female cohorts differed greatly (Table 2). In the premenopausal cohort, a weight above 90 kg was noted in 27% of blacks, whereas only 8% of premenopausal whites weighed more than 90 kg. In the postmenopausal subjects a similar trend was noted i.e. 41% of blacks and 12% of whites had a weight above 90 kg respectively. It was especially in the older postmenopausal females where blacks predominated in the upper portion of the weight range (48% blacks vs. 11% whites).

Table 2: Distribution of study subjects by ethnicity and weight

Weight (kg)	Premenopausal		Postmenopausal			
			<60 years		≥ 60 years	
	Blacks n=87	Whites n=76	Blacks n=52	Whites n=63	Blacks n=48	Whites n=47
<50	5 (6)	1 (1)	0	1 (2)	1 (2)	2 (4)
50 – 59	13 (15)	18 (24)	4 (8)	13 (21)	5 (10)	6 (13)
60 – 69	13 (15)	30 (40)	16 (31)	21 (34)	3 (6)	15 (32)
70 – 79	11 (13)	11 (14)	11 (21)	14 (23)	8 (17)	16 (34)
80 – 89	21 (24)	10 (13)	3 (6)	5 (8)	8 (17)	3 (6)
90 – 100	9 (10)	3 (4)	8 (15)	5 (8)	13 (27)	4 (9)
> 100	15 (17)	3 (4)	9 (17)	3 (5)	10 (21)	1 (2)

Distribution expressed as total number of subjects within the different ethnic cohorts (percentage in brackets)

3.1.3. Lifestyle

Table 3 shows the lifestyle characteristics of black and white subjects. Mean calcium intake was lower in the black patients compared with white patients in the total study population and in all comparable groups studied. Postmenopausal black subjects smoked significantly less compared with whites. Mean alcohol intake was well within accepted limits in all the black and white studied groups. Intake was comparable amongst the postmenopausal subgroups, but premenopausal blacks consumed significantly less alcohol than whites. This statistical difference is, however, unlikely to be of any clinical relevance. Postmenopausal white females maintained a higher level of physical activity compared with their black counterparts especially into old age.

A positive family history of osteoporosis was present in 49 patients of whom 96% were white (47/49 subjects).

Table 3: Summary of lifestyle characteristics of the study subjects

Lifestyle factor	Premenopausal			Postmenopausal					
	Blacks n=87	Whites n=76	p-value	<60 years			≥ 60 years		
				Blacks n=52	Whites n=63	p-value	Blacks n=48	Whites n=47	p-value
Ca-intake mg/d	594 ± 298	876 ± 270	<0.01	597 ± 237	891 ± 231	<0.01	667 ± 304	821 ± 272	<0.01
Smoking (pack yrs)	0.6 ± 1.8	3.8 ± 18	0.24	1.6 ± 4.7	7.2 ± 14	<0.01	0.17 ± 1	8.9 ± 4.1	<0.01
Alcohol (U/week)	3.8 ± 8.8	4.2 ± 5.3	0.04	3.7 ± 11	2.3 ± 3.7	0.17	1.4 ± 4.2	1.8 ± 3.8	0.3
PA score (0-4)	2.7 ± 0.9	2.8 ± 1	0.73	2.4 ± 1	2.8 ± 0.9	0.04	1.9 ± 0.9	2.7 ± 0.8	<0.01
Positive FH (%)	1	28		2	31		0	13	
OC usage (%)	17	72		16	57		29	30	
DP usage (%)	45	3		33	3		6	2	
Pregnancies (n)	3 ± 2	2 ± 1	0.03	3 ± 2	2 ± 1	<0.01	6 ± 3	3 ± 2	<0.01
B-feeding+ (%)	70	58		78	62		88	68	
HT—current n(%)				3 (6)	30 (46)		0 (0)	18 (38)	

Values reported are the mean ± SD. Abbreviations: Ca-intake: calcium intake; PA: physical activity; FH: family history; OC: oral contraceptive;

Black females had more pregnancies than whites in all the studied groups. The oldest cohort had the highest pregnancy rate for both ethnic groups. A high percentage of both black and white females breastfed their babies, with consistently higher percentages documented in blacks.

Pharmacological contraception was used by a significant percentage of the study cohort at some time in their lifespan. It appears as if the use of contraception has gained popularity with time since the percentage users amongst both black and white females were highest in the younger age groups (62 & 75% respectively). An important observation is the increase in popularity of depot-medroxyprogesterone acetate (DP) vs. oral estrogen containing contraception amongst the younger black females. Only 6% of the black subjects over the age of 59 years made prior use of DP compared to 45% of young premenopausal blacks. Amongst the premenopausal ever-users of contraception 4 blacks were currently on oral contraceptives and 14 (16%) on DP. As only premenopausal subjects with a regular menstrual cycle were eligible for study entry, we excluded 17 black current users of DP at the start of the study due to DP induced amenorrhea. The percentage current users of DP are thus most likely significantly higher in young South African blacks than that noted in our study group. In whites, 12 (16%) were currently on oral contraception and 1 patient used depot-medroxyprogesterone acetate at the time of the study. Only premenopausal women with a regular menstrual cycle were eligible for inclusion into this study, and thus 19 patients with oligo-amenorrhea on depo provera (2 white, 17 black) were excluded from study entry (chapter 3, section 1.2).

Past and current use of hormone therapy amongst postmenopausal females was, with the exception of 3 blacks, confined to the white cohort.

3.2. Prevalence of clinical risk factors

3.2.1. Literature-based risk factors for white women

In addition to the most significant clinical risk factors for osteoporosis in population based studies of white postmenopausal women^{115,116,126,236} (age, a positive family history, low BMI, inadequate dietary calcium intake, current cigarette smoking and physical inactivity), we included weight and height (additional anthropometric variables), alcohol intake, the use of contraceptives (oral estrogen containing tablets and depo provera), hormone therapy, parity (number of prior pregnancies) and absence of breastfeeding in our analysis as there were significant differences in these parameters between the two ethnic groups and because they have been found to be significant risk factors for osteoporosis in white females, both

locally¹¹⁹ and abroad^{115,116,236}. As mentioned earlier, the standardization of risk categories are described in detail in chapter 3 (please refer to section 2.1.1.1).

3.2.2. Prevalence of clinical risk factors by ethnicity and menopausal status

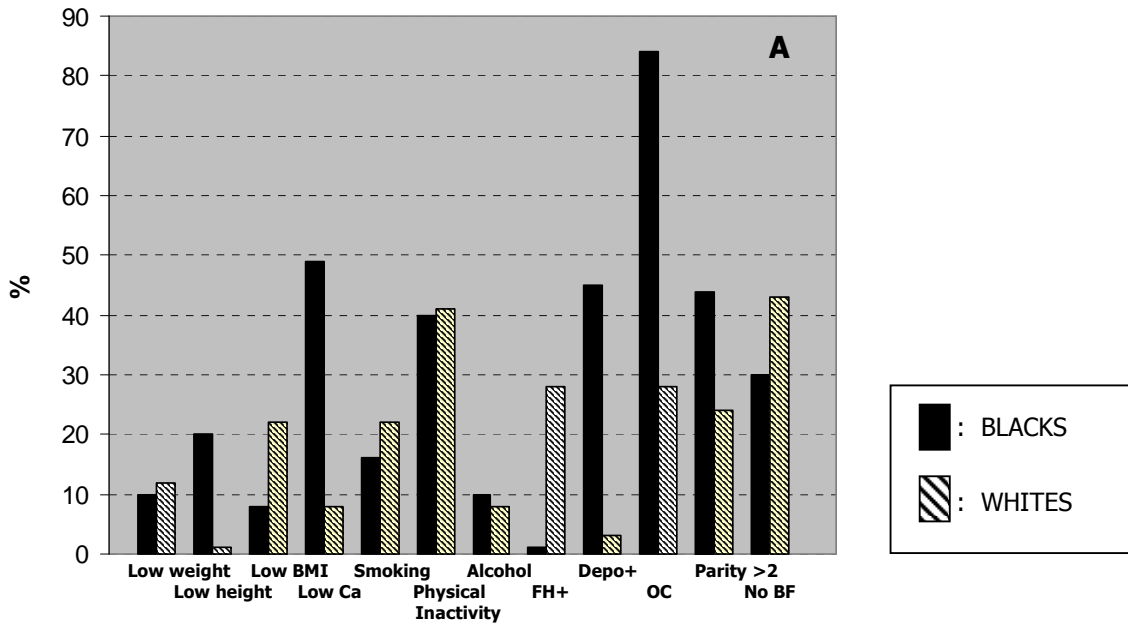
PREMENOPAUSAL COHORT

The frequency of each risk factor in premenopausal blacks and whites is presented in figure 1A. Marked differences in the frequency of many clinical risk factors for osteoporosis were observed between these two racial groups. Blacks were more likely to be short, have a low calcium-intake, be an ever-user of DP and be of high parity. A positive family history of OP and ever-use of oral contraceptives dominated in whites. Although mean body weight was significantly higher in premenopausal blacks (see table 2), the subset of premenopausal females presenting with a low body weight was similar in the two ethnic groups (10% blacks, 12% whites). The lower percentage of premenopausal blacks with a low BMI is due to their significantly lower heights.

POSTMENOPAUSAL COHORT

The frequency of each risk factor in postmenopausal blacks and whites is presented in figure 1B. Inter-ethnic comparison of risk factors differed between pre- and postmenopausal women. A higher percentage of postmenopausal blacks had low height, low calcium intake, physical inactivity and high parity. Whites were more likely to be of low body weight and BMI and a positive family history and hormone use were almost confined to this ethnic group. Black females appear to increase their body weight with ageing (table 1), and it is therefore not surprising to find a more pronounced ethnic difference in the percentage of females with low body weight and BMI in the postmenopausal cohorts (blacks vs. whites; 10 vs. 20% for low weight; 6 vs. 27% for low BMI). A low BMI was only present in a small minority of black females (6%).

Prevalence of clinical risk factors in premenopausal cohorts



Prevalence of clinical risk factors in postmenopausal cohorts

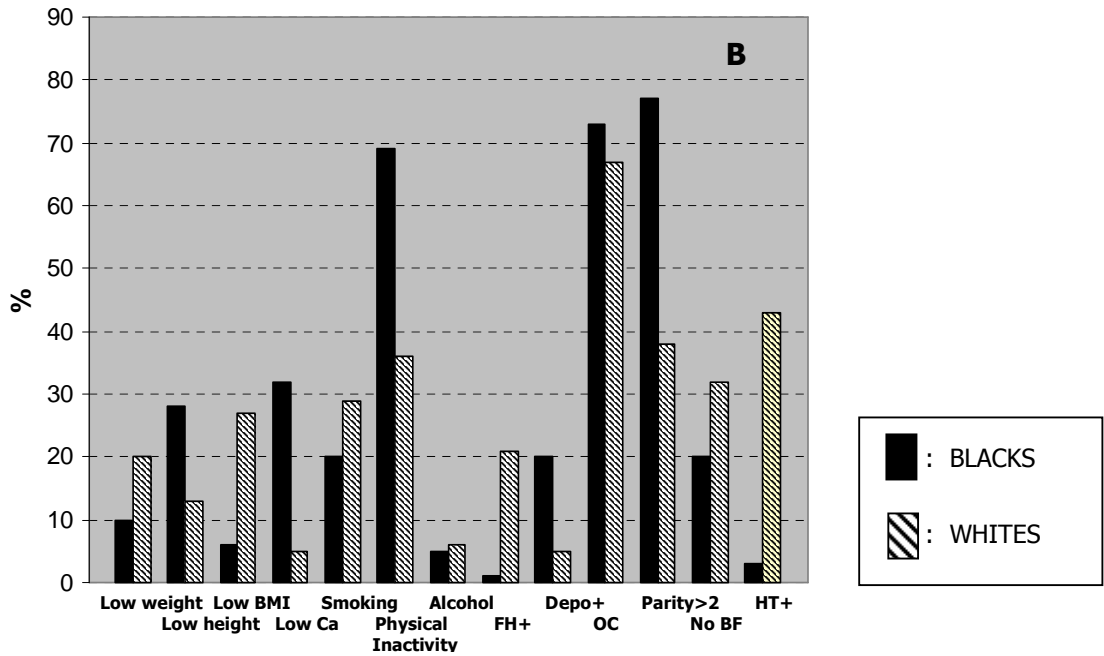


Figure 1 A & B: Frequency of low weight, height, BMI, low calcium intake, current smoking, physical inactivity, high alcohol intake, positive maternal history of OP, prior or current use of depo provera, no prior or current use of oral contraceptives, parity and no breastfeeding in premenopausal (fig. 1A) and postmenopausal (fig. 1B) black and white females. Current use of hormone therapy was evaluated in the postmenopausal cohorts only

4. DISCUSSION

We studied black and white females aged 20-82 years with regard to clinical characteristics and lifestyle factors known to affect bone health. Significant ethnic differences were noted in the presence and frequency of historical clinical and lifestyle risk factors for osteoporosis, especially pertaining to body size, mode of contraception, calcium-intake and physical activity.

ANTHROPOMETRY

Weight

Blacks were heavier than whites in all the subgroups studied. The percentage of premenopausal blacks and whites with low body weight were, however similar, whereas more older whites were noted to have a low body weight. The higher mean body weight in the black females was accentuated with ageing due to an apparent increase in mean body weight in the black females only. Previous research consistently documented higher body weight in the black populations of America^{144,184,186,193,199} and South Africa¹ compared with whites. Mean total body weight in our study population was markedly higher in blacks compared with whites, especially in the postmenopausal subjects.

Body weight has been identified as one of the most important determinants of BMD at most skeletal sites in postmenopausal black and white women^{126,184,193,195,199,238,239}. Obesity is associated with increased peak bone mineral density^{193,199}, with higher bone mineral density in postmenopausal women^{195,238,239} and with slower rates of vertebral and femoral bone loss^{239,240}. A low body weight, on the other hand, has been identified in numerous studies, some performed in multi-ethnic populations, as an important risk factor for low bone density and fracture^{118,136,202,241-245}.

Different mechanisms whereby obesity exerts its skeletal protection have been proposed and include both mechanical and hormonal effects²³⁹. The mechanical loading of body weight per se results in stress on the skeleton and preferentially enhances the bone mass of weight-bearing sites^{193,239}. Skeletal loading has the greatest impact on bone mass at those sites that directly bear the greatest gravitational force such as the proximal femur²³⁹. Excess adipose tissue is also positively associated with circulating levels of leptin^{81,83,85}, insulin⁷², adiponectin²⁴⁶, androgens and oestrogens^{247,248}, hormones known to either enhance bone formation and/or reduce bone resorption. After menopause, body fat becomes the main determinant of endogenous estrogen activity. The production of androgens is higher in obese than in normal weight women, and the excess body fat will increase adipocyte conversion of androgens to estrogens.

These metabolic effects may be more important than the direct mechanical impact of obesity at the non-weight-bearing sites of the skeleton, especially in postmenopausal females. The relationship between body mass and bone loss is thus influenced by the different mechanisms whereby obesity exerts its skeletal protection, as mentioned earlier. One can therefore hypothesize that obesity, due to its oestrogenic effects, will preferentially protect against rapid trabecular bone loss from the spine in the early postmenopausal period. The mechanical loading of obesity, on the other hand, will be expected to exert its dominant protective effect on the femoral region and this may be more important in the later postmenopausal period when hip fracture risk is highest.

The effects of weight on BMD are also known to be mediated via both fat and lean body mass²³⁹. Total body fat mass is a major determinant of BMD in Caucasians and African-Americans²⁵⁰, but there is also evidence that fat-free (lean) body mass plays an important role in determining BMD in both ethnic groups²⁴². The relative contribution of lean versus fat mass remains controversial and depends in part on the age of the population studied. Reid et al²⁵⁰ have documented that total body fat is the most significant predictor of BMD throughout the skeleton in normal postmenopausal females. Zhao et al²⁵¹ studied Caucasian females aged 62 ± 11 yrs and reported that fat mass is inversely correlated with bone mass when the mechanical loading effects of body weight on bone mass are controlled for, and a recent study by Gilsanz and co-workers documented no beneficial effect of fat mass to bone mass in white adolescents and young adults²⁵².

Although it appeared as if body weight was maintained with ageing in both our ethnic groups, a low body weight was present in a higher percentage of older white females, which may potentially contribute to femoral bone loss. In elderly women, a low body mass or weight loss irrespective of current weight, have been identified as risk factors for increased femoral bone loss^{244,253}. A low body weight and weight loss are also risk factors for hip fracture in older women, partially because of its association with a lower BMD, but also increases hip fracture risk independently of BMD due to an increased propensity to fall or the absence of a cushioning effect upon falling^{253,254}.

Height

In our study, premenopausal and younger postmenopausal blacks were shorter than whites. Heights in the late postmenopausal blacks and whites were similar and similar to heights recorded in younger blacks, thus suggestive of an apparent height loss with ageing in whites only. Height may impact on bone strength via its influence on BMD and skeletal macro-geometry. Tallness, in youth, has been associated with higher spinal and femoral BMD^{115,119} and as such would protect against fragility fractures. Despite this association, tallness has

been implicated as a risk factor for hip fracture. Taller women have a longer hip-axis length which has been associated with a greater risk for hip fracture¹⁶⁰⁻¹⁶⁶, and they fall from a greater height.

A lower vertebral bone size has been found in women predisposed to spinal fractures¹⁶⁷. The shorter height in blacks may imply a shorter trunk length and smaller vertebral height and bone size²⁰³ and may as such potentially compromise vertebral strength and enhance vertebral fracture risk in blacks.

Height may thus have differing effects on fracture risk at different skeletal sites via its effects on bone mineral density and on skeletal geometry. Shortness in our black population may be associated with a lower BMD and thus increase fragility fracture risk. The expected shorter hip-axis lengths in blacks may, however, protect against hip fracture, whereas smaller vertebral size may potentially increase vertebral fracture risk.

REPRODUCTIVE SYSTEM

In our study, the mode of contraception and the frequency of hormonal therapy differed markedly between blacks and whites.

Mode of contraception

Oral contraceptives (OCP) were the preferred mode of contraception in white females, whereas, depot-medroxyprogesterone acetate (DP) was used most often, and almost exclusively, by the younger black females. Use of pharmacological contraception was notably low in the older postmenopausal cohorts, and the highest percentage ever users were amongst the premenopausal subjects. The impact of hormonal contraceptives on bone mineral density has produced conflicting results. OCP are mostly regarded as bone-sparing or without BMD effects^{255,256}, whereas DP unequivocally decrease bone mass^{255,257-262}.

Oral contraceptive use

Conceptually, the oestrogen content of the oral contraceptive pills should have a beneficial effect on the skeleton irrespective of age, but the evidence for this is by no means unequivocal. Although it is still generally believed that OCP has no untoward or even a beneficial effect^{255,256} on bone mass in premenopausal women, there has been accumulating evidence of late raising the concern that OCP use may interfere with normal acquisition of peak bone mass in young women, especially if started at a very young age. Prospective studies in young 19 – 22 year old Italian²⁶³ and Swedish women²⁶⁴ reported negative influences of OCP use on the normal age-related increase in bone mass. In addition, a cross-sectional study in 524 Canadian women²⁶⁵ documented that OCP use was associated with

lower spinal and femoral BMD relative to control subjects. Detrimental effects on peak spinal and femoral bone mass have also been documented in a group of healthy 18-24 year old German women²⁶⁶; the age of initiating OCP was a major determinant of bone loss. A 10% lowering of femoral neck BMD was observed in girls with OCP use of more than 2 years and initiation of therapy within 3 years of menarche in the study by Hartard et al²⁶⁶. Last mentioned author hypothesized that potential suppression of periosteal bone apposition by estrogen²⁶⁷⁻²⁶⁹ and profound lowering of androgen levels due to feedback inhibition of the hypothalamus-pituitary axis²⁷⁰ may be responsible for the detrimental effects of OCP use in young women. It is unclear at present whether the observed negative effect of OCP use on bone mass in young women is reversible after discontinuation of OCP's or whether it poses a significant long-term risk for osteoporosis later in life. Most studies suggest a limited impact of past use of OCP on BMD in older peri- and postmenopausal women²⁷¹⁻²⁷⁴ and no protective effect of past OCP use on fracture risk could be demonstrated in two large epidemiological studies in Great Britain^{275,276}.

The influence of OCP use on BMD has mostly been studied in Caucasian populations and little is known regarding the impact of OCP on BMD in blacks. OCP use was unrelated to BMD in African-American women in a study by Cobb et al²⁷⁷. It has been hypothesized that oestrogen protects against PTH-mediated bone loss. Most previous studies have noted lower bone turnover rates in black compared with white women^{138,140-142,146,196} despite higher endogenous PTH-levels. This is ascribed to a relative skeletal resistance to the action of PTH^{138,144,146,196} in blacks, which may explain their relative insensitivity to the oestrogenic actions of OCP's. Due to their higher body weight, black women may also have a higher steady state oestrogen production and this might also explain the lack of association between OCP's and BMD in black women.

Depot-medroxyprogesterone acetate

In our study depot-medroxyprogesterone acetate (DP) was the preferred hormonal method of contraception amongst blacks with the highest percentage ever-users amongst our younger black females (40%). In South Africa, hormonal injectable contraceptive use is high, with about 60% of black African women practicing contraception either using DP or norethisterone enanthate²⁷⁸.

The main contraceptive action of DP is the suppression of ovulation. Hypo-oestrogenemia, as is the case in DP users, may adversely affect bone mass and increase the likelihood of osteoporosis. Most^{255,257-262} studies show that depot-medroxyprogesterone acetate has a negative effect on bone mass. These detrimental effects are particularly apparent when DP is used in adolescents who have not yet achieved peak bone mass. In cross-sectional

studies^{258,260,261}, the mean BMD of Depo Provera users were below that of non-users, with some of the studies suggestive of a preferential impact on lumbar spine BMD²⁶¹. In longitudinal studies, BMD generally decreased more over time in users of DP than among nonusers^{259,262}. It has also been noted that associated low BMI enhanced the negative impact of DP at the spinal and femoral sites²⁶¹. The negative effect of DP on BMD was, however, noted to be reversible upon discontinuation in longitudinal studies^{259,262} and the impact of past use of Depo Provera on BMD small in postmenopausal women^{271,279}.

Hormonal contraception, whether in the form of OCP or injectable depot-medroxyprogesterone acetate, may thus be deleterious to bone health, especially if commenced at an early age, used for a prolonged period of time and currently in use. Negative effects on bone mass, as a result of hormonal contraception, appears to be temporary with significant bone gain observed upon discontinuation of especially DP^{259,262}. Whether either mode of contraception has any significant impact on bone mineral density in later life, when fracture risk is highest, remains uncertain.

Menarche, parity and hormone therapy

Menarche was reached at a statistically significantly later age in blacks ($p < 0.01$) compared with whites. The clinical significance of a one year difference in menarchial onset is, however, uncertain.

High parity i.e. 3 pregnancies or more was noted in the majority of postmenopausal black females (78%) with the highest pregnancy rate noted amongst the older subjects. In whites the number of pregnancies was lower in all the subgroups evaluated. Over a lifetime, increasing parity might be expected to protect against bone loss because of pregnancy related increases in body weight, intestinal calcium absorption, cumulative estrogen exposure and a later age at menopause. Several reports have confirmed this positive correlation between parity and BMD^{280,281}, although other studies have reported no correlation between parity and BMD²⁸²⁻²⁸⁴ or a negative correlation²⁸⁵. Many of these studies have been performed in premenopausal women or in women younger than the age typically seen for osteoporotic fracture. In addition, many studies have been conducted in women with low (e.g. 1-3) parity^{280,282}. The few studies^{281,284,285} conducted in very high parity (more than or equal to five live births) postmenopausal women have provided conflicting results and data suggests that the skeletal benefit of high parity is modest and are overshadowed by the BMD changes that occur during the menopausal transition. To what extent differences in parity affects bone mineral density in later life remains uncertain.

Hormone therapy was used almost exclusively by whites in this study. The mean duration of therapy in current hormone users in our white postmenopausal women was 8 years (range 1–18 years). Current hormone therapy (estrogen ± progestin) protects against postmenopausal bone loss, results in significant “bone gain” over time and reduces subsequent fractures as shown by numerous previous epidemiological studies²⁸⁵⁻²⁸⁷, and meta-analyses²⁸⁸⁻²⁹⁰ in healthy postmenopausal subjects and also recently confirmed in the Women’s Health Initiative randomized trial²⁹¹⁻²⁹³.

LIFESTYLE FACTORS

In our study, the mean calcium-intake of pre- and postmenopausal blacks was significantly lower than whites and a low calcium intake (defined as a daily intake of less than 500mg daily) was present in a high percentage of pre- and postmenopausal blacks (48% and 32% respectively).

Calcium-intake

Calcium nutrition is commonly considered to be important for the attainment of peak bone mass and for optimal maintenance of skeletal mass³⁴⁻³⁷. However, calcium is also recognized as a threshold nutrient, i.e., the effect of variations in intake are evident only up to some threshold intake level, above which further increases in intake produce no further change in skeletal mass.

Precisely what those threshold values may be at various life-stages remain uncertain. A recent meta-analysis of randomized controlled trials by Winzenberg et al²⁹⁴ concluded that calcium supplementation in healthy, mostly white children, had no effect on bone mineral density at the hip and spine and only a small effect on the upper limb. These changes were regarded as insufficient to reduce the risk of fracture, either in childhood or later life. The meta-analysis only included a few studies in children with low baseline calcium intakes and more such studies are needed to assess potential benefit of calcium supplementation under such circumstances.

In postmenopausal women, there is now clinical trial evidence²⁹⁵⁻³⁰⁰ that calcium has a positive effect on bone mineral density at the hip and spine. Some studies have shown that the skeletal benefit of calcium is most evident in the first year of treatment^{299,300}. A sustained reduction in bone loss and turnover with long-term calcium supplementation was, however, confirmed in a recent large randomized controlled study in healthy older women²⁹⁵. These beneficial effects were present throughout the skeleton (lumbar spine, total hip and total body), were independent of age and were present in individuals with both high and low dietary calcium intakes. Recently published large studies on calcium supplementation^{295,301,302}

were, however, unable to confirm the anti-fracture efficacy of calcium supplementation. A Cochrane review³⁰³ in postmenopausal women concluded that calcium supplementation alone has a small positive effect on bone density. A trend toward reduction in vertebral fractures was shown, but it remained unclear if calcium reduces the risk of non-vertebral fractures.

Most studies assessing the skeletal effects of calcium, both in childhood and in later life, were conducted in white populations and less is known about the impact of calcium nutrition on skeletal health in black populations. Inadequate intake of calcium leads to reduced calcium absorption, increased serum parathyroid hormone concentrations, and bone loss⁵⁴. Skeletal resistance to the actions of PTH in blacks may potentially protect them against the effects of a low calcium intake. The resistance is, however, relative and secondary hyperparathyroidism is known to exert deleterious skeletal effects in all ethnic groups¹⁴⁵.

Smoking and alcohol-intake

White postmenopausal women smoked more (expressed as total pack years) and were more likely to be current smokers than blacks in this study. Alcohol intake was low and comparable between blacks and whites. Smoking^{115,118,119,241,247,304} and excessive alcohol-intake^{115,119,244,305} are known risk factors for bone loss, osteopenia and subsequent increased fracture risk. Women who smoke have lower serum estrogen levels, a lower body mass and undergo menopause at an earlier age.

Physical activity

In our study, physical activity levels were similar in the younger blacks and whites, but significantly less well maintained amongst blacks, with an impressive 69% of postmenopausal blacks not partaking in any form of out-door activity. Exercise has its greatest effect on the skeleton during growth and development^{1,39,40,306-308}, and in the weight-bearing regions of the skeleton, with the hip region being most receptive to differing levels of physical activity³⁰⁹. It is unclear at present whether the effect of exercise is maintained once it is stopped and whether prepubertal exercise has any impact on bone mass in later life. Life-long exercise may reduce fracture risk by limiting age related bone loss³¹⁰ and by improving muscle strength³¹¹ (thereby reducing the frequency and severity of falls). In a study on the association between physical activity and bone mass in black and white South African schoolchildren, physical activity levels were noted to be lower in blacks²¹⁵. A significant association between hip and spine BMC and BMD and increased levels of physical activity was found in white children whereas a significant positive correlation were found only between physical activity and whole body BMD in black children. This may imply that these black children just did not reach the "threshold" physical activity necessary to induce an osteogenic effect, but it remains unclear whether higher activity levels will

induce the same benefits in black children as seen in whites. Studies conducted in developed countries have shown that inactivity and activity patterns differ by ethnicity²⁰⁸, with black groups engaged in less physical activity as seen in our study subjects. Inactivity in our older blacks may potentially compromise bone strength and increase fall and fracture risk.

Family history of OP

A maternal family history of OP was almost exclusively reported by the white females. A maternal history of osteoporosis is associated with lower lumbar and femoral BMD among daughters^{115,116,133,134,312}.

To conclude, in our study population significant ethnic differences were noted in the presence and frequency of historical clinical and lifestyle risk factors for osteoporosis. These risk factors exert unique effects on skeletal health, varying in terms of magnitude of impact on bone mineral density, skeletal site affected, and influence on peak bone mineral density and/or on rate of bone loss. Blacks were heavier and shorter; they consumed less calcium, were more inactive, preferred depot-medroxyprogesterone acetate as contraceptive agent and were of higher parity. Whites smoked more, preferred oral contraceptive tablets and were more likely to have a positive family history of osteoporosis. Hormone therapy was used almost exclusively by postmenopausal whites. Inter-ethnic differences in weight, physical activity and high parity was most marked in the older subjects. The impact of these clinical risk profiles on bone strength parameters in blacks and whites may differ significantly and must be considered when these parameters are compared.

.....

CHAPTER 5

BONE MINERAL DENSITY IN BLACK AND WHITE SOUTH AFRICAN FEMALES

1.	INTRODUCTION.....	90
2.	PATIENTS AND METHODS	90
3.	RESULTS	95
3.1.	LUMBAR SPINE BONE MINERAL DENSITY	95
3.1.1.	<i>Premenopausal subjects</i>	95
3.1.1.1.	<i>Spinal bone mineral density</i>	95
3.1.1.2.	<i>Spinal bone mineral apparent density (SBMAD)</i>	101
3.1.2.	<i>Postmenopausal subjects.....</i>	102
3.1.2.1.	<i>Spinal bone mineral density</i>	102
3.1.2.2.	<i>Spinal bone mineral apparent density (SBMAD)</i>	105
3.2.	FEMORAL BONE MINERAL DENSITY	106
3.2.1.	<i>Premenopausal subjects</i>	106
3.2.1.1.	<i>Proximal femoral bone mineral status</i>	106
3.2.1.2.	<i>Femoral neck bone mineral apparent density (F_NBMAD)</i>	112
3.2.2.	<i>Postmenopausal females</i>	113
3.2.2.1.	<i>Proximal femoral bone mineral status</i>	113
3.2.2.2.	<i>Femoral neck bone mineral apparent density (F_NBMAD)</i>	119
3.3.	CORRELATION OF AREAL BMD WITH AGE AND PATTERNS OF BONE LOSS IN THE TOTAL STUDY COHORT.....	120
4.	DISCUSSION.....	123

CHAPTER 5

BONE MINERAL DENSITY IN BLACK AND WHITE SOUTH AFRICAN FEMALES

1. INTRODUCTION

Bone mineral density (BMD) is an excellent predictor of bone strength and fracture risk at all skeletal sites²⁵⁻³⁰. BMD and fracture rates vary among women of differing ethnicities. African-Americans have higher bone mineral density in the axial and appendicular skeleton compared with their white counterparts^{135,138,143-145,184-199}, and these differences may account for their lower incidence of osteoporotic fractures^{135,136,237,243}. On the African continent, including South Africa, studies are limited but not nearly as unanimous on greater bone density in blacks, yet they do have markedly lower fracture rates compared with whites^{20,211,212}. Limited studies have reported that South African blacks have similar appendicular and lumbar spine bone mineral density (BMD), but higher femoral BMD compared with whites^{1,213}. In the 70's, Solomon reported a ten-fold lower hip fracture rate in urbanized SA blacks compared with whites despite very similar bone mass values²⁰.

This chapter reports on bone mineral density results obtained via dual energy X-ray absorptiometry in blacks and whites.

2. PATIENTS AND METHODS

We assessed bone mineral density of the lumbar spine and the proximal femur employing dual energy X-ray absorptiometry in a study cohort which included 187 black women and 186 white women. Bone mineral density data pertaining to the group of postmenopausal subjects currently on hormone therapy, 44 white females and 3 black females, are not reported in this chapter. Due to the well documented skeletal protection offered by hormone therapy, data on these subjects were analyzed separately and reported on in Chapter 12.

We analyzed and report areal bone mineral density (BMD) and 'volumetric' bone mineral apparent density (BMAD) results in the following subgroups:

- Premenopausal black and white groups
- Early and late postmenopausal black and white groups i.e. as outlined in chapter 3 (section 1.4) postmenopausal females less than 60 yrs of age were included in the early postmenopausal groups whereas postmenopausal women 60 yrs and older represented the late postmenopausal groups.

- To control for adiposity, data were also analyzed by dividing pre- and postmenopausal subjects into weight subgroups i.e. a subgroup with normal to low body mass index (BMI <25kg/m²) and a subgroup defined as overweight (BMI ≥ 25 kg/m²)²²³. To ensure sufficient numbers within the different weight subgroups to allow analysis of BMD data, the total postmenopausal group were not subdivided based on age, but assessed in total.

The baseline clinical characteristics (table 1) of this DEXA cohort (n=326) were identical to the total study cohort (refer to chapter 4, tables 1 & 3). Blacks and whites had similar mean ages in all the comparable groups studied. In general, blacks were shorter and heavier than whites, reached menarche at a later age, preferred injectable hormone contraception, had a larger number of pregnancies and consumed less calcium daily. The white women smoked more, but maintained a higher level of physical activity post menopause. Mean alcohol consumption was low and comparable between the two groups.

The baseline clinical characteristics of the premenopausal weight groups are shown in table 2. The black females in the normal to low BMI subgroup were significantly smaller with lower mean weight and height compared with the white females. The mean BMI was, however, identical in the two ethnic groups. In the overweight subgroup, blacks were significantly heavier with greater BMI's than whites. The number of blacks classified as normal to low BMI was about half that of whites and the converse was true for the overweight subgroup i.e. the number of overweight blacks was about twice that of the whites. The waist-hip ratio was similar in the two ethnic groups in both the normal to low BMI and overweight subgroups. Elbow width was lower in the black females compared with whites in the normal to low BMI group, but similar in the overweight groups.

The baseline clinical characteristics of the postmenopausal weight groups are shown in table 3. The majority of postmenopausal blacks (77%) and whites (59%) were categorized as overweight based on BMI values. In the normal to low BMI group, only BMI and waist-hip ratio were noted to be higher in blacks, whereas all the anthropometric variables were significantly higher in the overweight blacks compared with whites. Elbow width as an index of skeletal frame size was similar between blacks and whites in both weight subgroups.

Methodological principles with regard to DEXA BMD and BMAD measurements are detailed in Chapter 3 (please refer to section 2.2). For all skeletal sites, BMD's were first compared, using ANOVA, between ethnic subgroups before adjustment for covariates. Thereafter, BMD's were also expressed as adjusted values based on findings of analysis of covariance. For the premenopausal subjects, covariates included ethnicity, age, weight, height, daily

calcium intake, pack years of smoking, alcohol intake, physical activity, age at menarche, hormonal contraception and number of prior pregnancies. For the postmenopausal subjects, covariates included years since menopause in addition to the abovementioned. Bonferonni testing were used for post hoc comparison.

Table 1: Summary of anthropometric, lifestyle and menstrual data of the DEXA cohort

Clinical characteristics	Premenopausal			Postmenopausal					
				< 60 years			≥ 60 years		
	Blacks n=87	Whites n=76	<i>p-value</i>	Blacks n=49	Whites n=35	<i>p-value</i>	Blacks n=48	Whites n=31	<i>p-value</i>
Age (yr)	37 ± 8	39 ± 7	0.1	52 ± 6	52 ± 5	0.43	68 ± 6	70 ± 5	0.49
Height (cm)	160 ± 6	167 ± 6	<0.01	160 ± 7	166 ± 7	<0.01	159 ± 6	160 ± 7	0.16
Weight (kg)	79 ± 21	69 ± 15	<0.01	80 ± 19	71 ± 17	<0.01	86 ± 19	72 ± 15	<0.01
BMI (kg/cm ²)	31 ± 8	25 ± 5	<0.01	32 ± 8	26 ± 6	<0.01	34 ± 8	28 ± 5	<0.01
Waist/Hip ratio (cm)	0.84 ± 0.1	0.78 ± 0.1	<0.01	0.87 ± 0.1	0.79 ± 0.1	<0.01	0.90 ± 0.1	0.88 ± 0.1	0.03
Elbow width (mm)	65 ± 5	66 ± 3	0.78	67 ± 4	66 ± 4	0.15	68 ± 6	68 ± 5	0.23
Age at menarche(yrs)	15 ± 3	13 ± 2	<0.01	14 ± 2	13 ± 2	<0.01	14 ± 2	13 ± 1	<0.01
Menopause age (yrs)				46 ± 5	49 ± 4	0.02	49 ± 5	49 ± 5	0.20
YSM (yrs)				7 ± 5	4 ± 4	0.04	19 ± 8	21 ± 7	0.37
Calcium intake (mg/d)	594 ± 298	876 ± 270	<0.01	597 ± 237	879 ± 230	<0.01	667 ± 304	821 ± 272	<0.01
Smoking (pack yrs)	0.6 ± 1.8	3.8 ± 18	0.24	1.6 ± 4.7	5 ± 11	<0.01	0.17 ± 1	8.9 ± 14.1	<0.01
Alcohol (U/week)	3.8 ± 8.8	4.2 ± 5.3	0.04	3.7 ± 11	2.9 ± 5.1	0.17	1.4 ± 4.2	1.8 ± 3.8	0.3
PA score (0-4)	2.7 ± 0.9	2.8 ± 1		2.4 ± 1	3.1 ± 0.9	0.04	1.9 ± 0.9	2.7 ± 0.8	<0.01
Family history (%)	1	28		2	29		0	13	
OCP use (%)	17	72		16	54		29	30	
DP use (%)	45	3		33	6		6	2	
Nr of pregnancies (n)	3 ± 2	2 ± 1	0.03	3 ± 2	2 ± 1	<0.01	6 ± 3	4 ± 2	<0.01
Breastfeeding+ (%)	70	58		78	62		88	68	

Values expressed as mean ± SD except where otherwise stated

Table 2: Comparison of anthropometric data in premenopausal blacks and white in normal to low BMI and overweight subgroups.

Clinical characteristics	Premenopausal groups			
	Normal to low BMI subgroup (BMI < 25kg/m ²)		Overweight subgroup (BMI ≥ 25kg/m ²)	
	Blacks (n=23)	Whites (n = 47)	Blacks (n= 64)	Whites (n= 29)
Age (yr)	35* ± 9	39 ± 6	37 ± 8	37 ± 7
Height (cm)	157* ± 5	167 ± 6	161* ± 6	167 ± 7
Weight (kg)	55* ± 7	61 ± 6	87* ± 7	83 ± 14
BMI (kg/cm ²)	22 ± 2	22 ± 2	34* ± 6	30 ± 4
Waist/Hip ratio (cm)	0.78 ± 0.06	0.77 ± 0.05	0.85 ± 0.09	0.81 ± 0.08
Elbow width (mm)	61* ± 3	64 ± 3	67 ± 5	68 ± 3

Values reported are the mean ± SD; *p < 0.01 premenopausal blacks vs. premenopausal whites within specific subgroup

Table 3: Comparison of anthropometric data in postmenopausal blacks and whites in normal to low BMI and overweight subgroups.

Clinical characteristics	Postmenopausal groups			
	Normal to low BMI subgroup (BMI < 25kg/m ²)		Overweight subgroup (BMI ≥ 25kg/m ²)	
	Blacks (n=22)	Whites (n = 27)	Blacks (n= 75)	Whites (n=39)
Age (yr)	60 ± 10	58 ± 11	60 ± 9	61 ± 10
Height (cm)	162 ± 6	164 ± 8	159* ± 7	162 ± 7
Weight (kg)	61 ± 6	59 ± 8	90* ± 17	80 ± 15
BMI (kg/cm ²)	23* ± 2	22 ± 2	36* ± 7	31 ± 4
Waist/Hip ratio (cm)	0.83* ± 0.1	0.77 ± 0.1	0.90* ± 0.1	0.86 ± 0.1
Elbow width (mm)	65 ± 4	65 ± 3	69 ± 5	68 ± 4

Values reported are the mean ± SD; *p < 0.01 postmenopausal blacks vs. postmenopausal whites within specific weight subgroup

3. RESULTS

3.1. LUMBAR SPINE BONE MINERAL DENSITY

3.1.1. Premenopausal subjects

The premenopausal cohort consisted of 87 black females and 76 white females.

3.1.1.1. Spinal bone mineral density

Mean lumbar spine bone mineral content (SBMC), bone area and unadjusted spinal bone mineral density (SBMD) were significantly lower in the black premenopausal females compared with the white subjects. Univariate tests of significance identified ethnicity, body weight ($p < 0.01$) and height ($p < 0.01$) to be significantly associated with SBMD (figure 1 and table 4). After adjustment for weight as a covariate, mean SBMD remained significantly lower in the black cohort, whereas the difference in SBMD between the two cohorts was non-significant after adjustment for height.

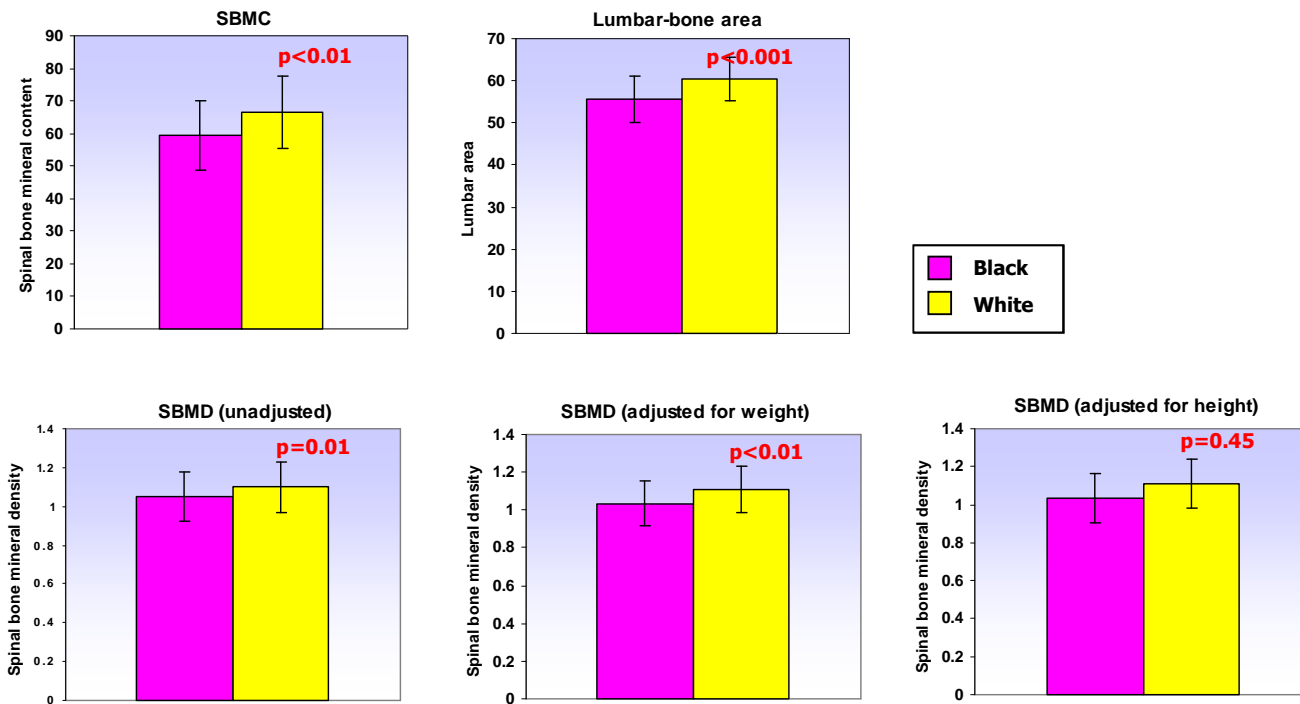


Figure 1: Mean lumbar spine bone mineral content (SBMC), mean lumbar bone area and unadjusted and adjusted mean SBMD.

Table 4: Comparison of mean SBMC, lumbar bone area and SBMD in premenopausal black and white females

Bone mineral data	Premenopausal subjects		
	Blacks (n=87)	Whites (n=76)	p-value
SBMC (grams)	59.57 ± 10.7	66.57 ± 11.2	<0.01
S-Bone area (cm ²)	56.23 ± 5.55	60.38 ± 5.23	<0.01
SBMD (g/cm ²)			
Unadjusted	1.047 ± 0.12	1.099 ± 0.13	0.01
Adjusted for weight	1.036 ± 0.12	1.110 ± 0.12	<0.01
Adjusted for height	1.064 ± 0.13	1.081 ± 0.13	0.45

Values reported are the mean ± SD

3.1.1.1.1. Correlation of SBMD with Anthropometric variables

Except for BMI in the white females, weight, height and BMI correlated significantly with SBMD. The association between weight and BMI, and SBMD, is markedly stronger in the black cohort (figure 2). This may be partially explained by the much wider weight and BMI distribution in the blacks. Elbow width as an index of skeletal frame size, was similar in the two premenopausal cohorts and correlated significantly with SBMD in the black group only.

3.1.1.1.2. SBMD in normal to low weight and overweight subgroups

As alluded to before, in view of differences in body size between the premenopausal black and white females that may partially explain observed ethnic differences in SBMD, BMD was reanalyzed in subsets of normal to low BMI and overweight premenopausal women (table 5).

SBMD was statistically significantly lower in the black females compared with the white females in the normal to low BMI group ($p < 0.01$), but similar between the black and the white subjects in the overweight group. The mean SBMD of normal to low BMI black patients was significantly lower compared with their overweight counterparts, but the mean SBMD of white subjects in the two subgroups was similar. Due to the fact that there was a slight, but statistically significant difference in age between the black (35 ± 9 yrs) and white (39 ± 6 yrs) females in the normal to low weight subgroup, BMD was also compared as Z-scores. Results were similar to that documented for the absolute BMD values i.e. these blacks had significantly lower Z-scores compared with their white counterparts and also significantly lower Z-scores compared to their overweight counterparts. *The difference in SBMD between the total black and white premenopausal cohorts can thus be mainly attributed to the difference in SBMD in the subjects with a BMI < 25kg/m².*

Body size in this subgroup of normal to low BMI premenopausal females was, however, significantly smaller in blacks than whites when based on weight and height per se and

might, in part, explain why there was a more marked negative impact on BMD in the black females compared with whites in this subgroup.

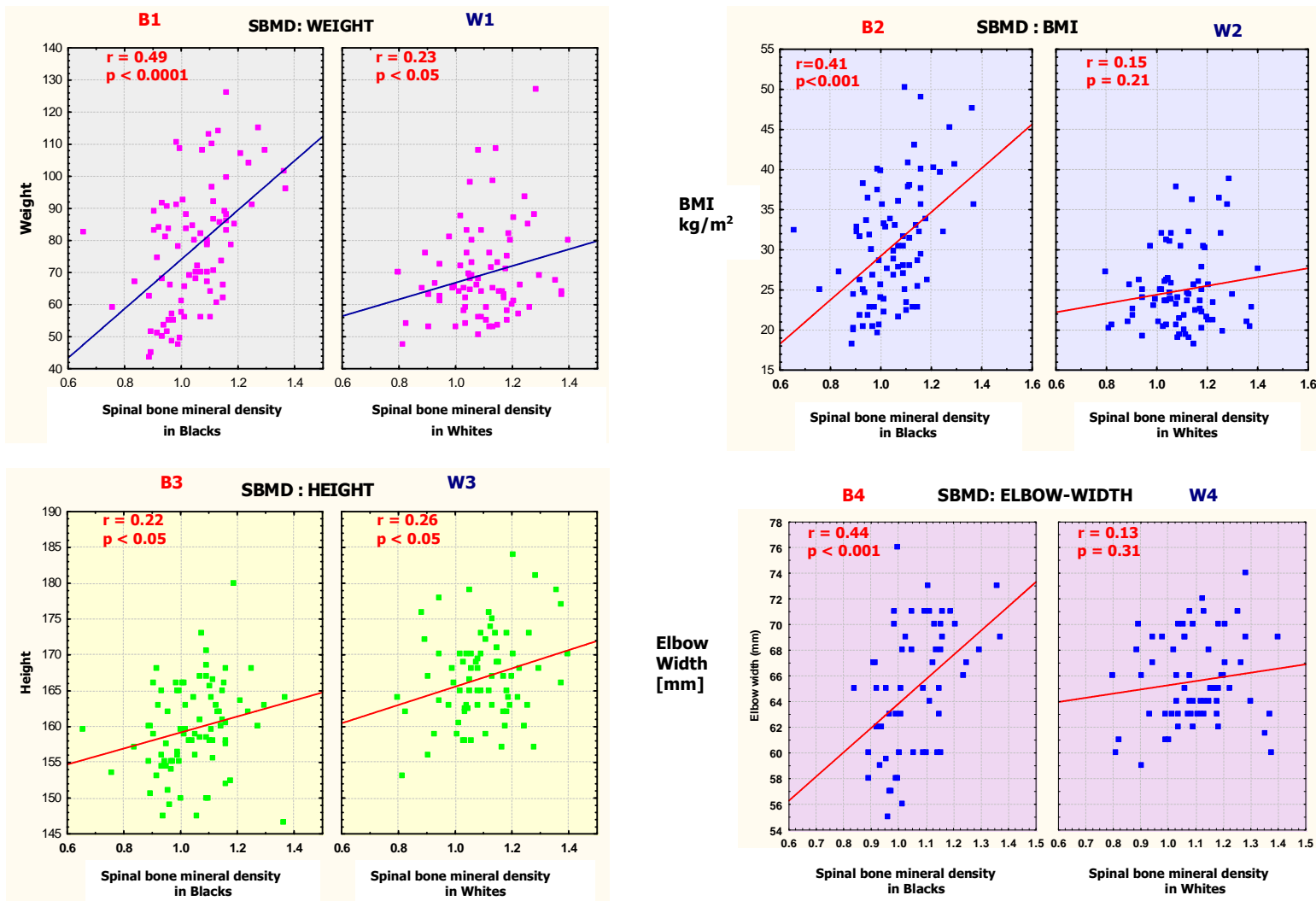


Figure 2: Correlation of SBMD with weight, BMI, height and elbow-width in premenopausal black (panels B1-B4) and white (panels W1-W4) groups.

Table 5: Spinal bone mineral density data in premenopausal subgroups based on BMI

BMD (g/cm²)	Premenopausal females					
	Normal to low BMI subgroup (BMI < 25kg/m²)			Overweight subgroup (BMI ≥ 25kg/m²)		
	Blacks (n = 23)	Whites (n = 47)	p-value	Blacks (n = 64)	Whites (n = 29)	p-value
SBMD	0.977 ± 0.09*	1.095 ± 0.13	<0.01	1.074 ± 0.13	1.106 ± 0.13	0.11
SBMD (Z-score)	-0.385 ± 0.86*	0.714 ± 1.17	<0.01	0.535 ± 1.18	0.719 ± 1.22	0.19

Values reported are the mean ± SD; p-values tabulated refers to comparison between blacks and whites within specific weight group * p-value < 0.01 compared to overweight subjects within the same ethnic group

3.1.1.1.3. Distribution of SBMD in premenopausal cohort

As previously outlined in chapter 3 (please refer to section 2.2.1) no normative data for black South African women exist. In this study we therefore used a white female reference population to calculate T- and Z-scores for both ethnic groups and also used the DEXA manufacturer's reference value for North-American blacks to calculate additional T- and Z-scores in blacks. A Z-score less than -1 indicated osteopenia, whereas a Z-score less than -2 met the diagnostic criterion for osteoporosis in these premenopausal subjects.

SBMD Z-scores were normal in the majority of premenopausal females in this study. Measured against a white reference population, 91% of black females had a normal SBMD, 9% were osteopenic and 2% (2 subjects) met the diagnostic criteria used to define osteoporosis in premenopausal subjects in this study cohort. Measured against the DEXA manufacturer's reference value for North-American blacks, 62% of black females had a normal SBMD, 38% were osteopenic and 6% (5 subjects) met the diagnostic criteria for osteoporosis. In the white cohort, 93% had a normal SBMD, 7% had osteopenia and 2% (3 subjects) met the diagnostic criteria for osteoporosis. A spinal bone mineral density of two standard deviations above an age matched white reference population was present in 7% and 13% of the black and white groups respectively (figure 3).

Distribution of SBMD in premenopausal cohorts

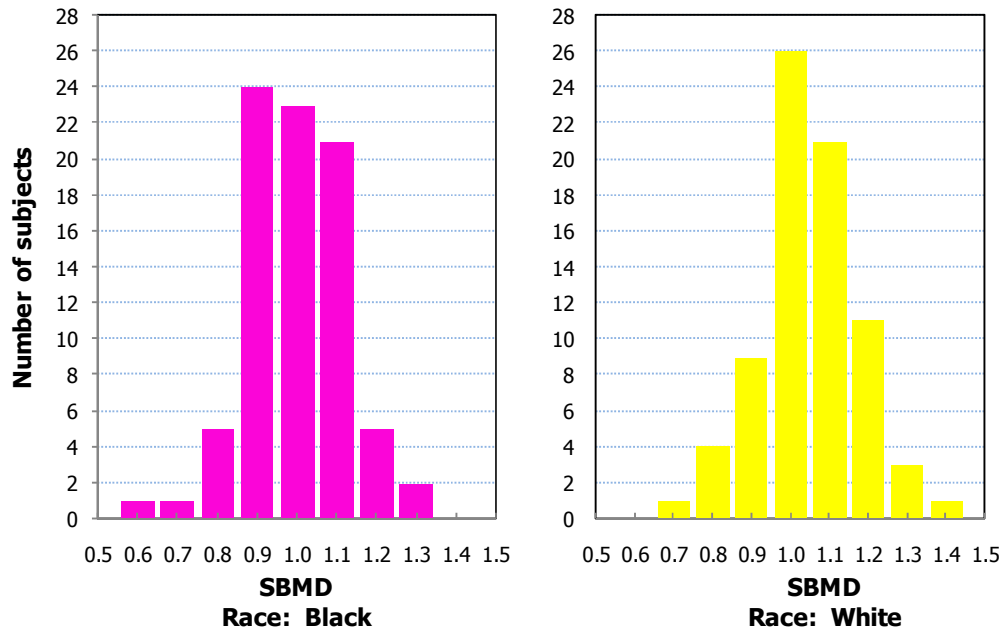


Figure 3: Distribution of absolute SBMD within the total black and white premenopausal

3.1.1.1.4. Correlation of SBMD with age

SBMD did not correlate with age in either of the two premenopausal ethnic groups (blacks: $r=0.13$, $p=0.23$; whites: $r=-0.04$, $p=0.74$).

3.1.1.2. Spinal bone mineral apparent density (SBMAD)

Unadjusted SBMAD was similar in the premenopausal black and white subjects ($p=0.50$). Only weight was positively associated with SBMAD ($p<0.01$). After adjustment for weight as a covariate, SBMAD remained similar in the two ethnic cohorts.

3.1.1.2.1. SBMAD in normal to low weight and overweight premenopausal subgroups

Comparison of SBMAD values in the premenopausal normal weight and overweight subgroups revealed results identical to that of the SBMD data (section 3.1.1.1.2). Significant differences were noted between the premenopausal black and white females of normal to low weight, as well as between normal to low weight and overweight black females (table 6).

Table 6: SBMAD in premenopausal subgroups based on BMI

BMAD (g/cm ³)	Premenopausal females					
	Normal to low BMI subgroup (BMI < 25kg/m ²)			Overweight subgroup (BMI ≥ 25kg/m ²)		
	Blacks (n = 23)	Whites (n = 47)	p-value	Blacks (n = 64)	Whites (n = 29)	p-value
SBMAD	0.133 ± 0.01*	0.141 ± 0.02	0.02	0.142 ± 0.02	0.142 ± 0.02	0.43

p-values tabulated refers to comparison between blacks and whites within specific weight group.

† Significantly lower compared with overweight black subjects (p = 0.02)

3.1.2. Postmenopausal subjects

The postmenopausal black and white females were divided into early (<60yrs) and late (≥60 yrs) postmenopausal groups based on age, and included 97 black subjects and 66 white females.

3.1.2.1. Spinal bone mineral density

Mean SBMC was similar in the blacks and whites, whereas mean spinal bone area was significantly lower in the black females. Unadjusted mean SBMD was similar amongst black and white females in both the early and late postmenopausal groups (table 7).

In the early postmenopausal group, in addition to ethnicity, body weight (p<0.01) was positively associated and alcohol intake showed a tendency towards a negative association (p=0.09) with SBMD. In the late postmenopausal group, body weight (p<0.01) was positively associated with SBMD, whereas a tendency towards an association was also noted for the number of pregnancies (p=0.07). After adjustment for weight as a covariate, SBMD was significantly lower in the black females compared with whites in the early postmenopausal group (p=0.01), whereas SBMD remained similar in the late postmenopausal cohorts (p=0.18). Mean SBMD in the early and late postmenopausal black groups were near identical, but tended to be lower in the late postmenopausal white female group compared with the early postmenopausal white group (p=0.07). This suggests that, compared with blacks, more pronounced postmenopausal spinal bone loss occurs in white females with ageing (table 7).

Table 7: Comparison of SBMC, lumbar bone area and SBMD in postmenopausal black and white females

	Postmenopausal females					
	< 60 years (Early)			≥ 60 years (Late)		
	Blacks (n= 49)	Whites (n=35)	<i>p-value</i>	Blacks (n=48)	Whites (n=31)	<i>p-value</i>
SBMC (grams)	52.79 ± 13.6	58.5 ± 13.6	0.22	53.39 ± 13.4	57.06 ± 14.8	0.81
S -Bone area (cm²)	55.72 ± 5.18	59.34 ± 5.18	0.01	56.70 ± 5.16	60.73 ± 7.20	<0.01
SBMD (g/cm²)						
Unadjusted	0.940 ± 0.18	0.988* ± 0.17	0.61	0.939 ± 0.21	0.925 ± 0.16	1.00
Adjusted for weight	0.921 ± 0.16	1.015 ± 0.16	0.01	0.911 ± 0.18	0.968 ± 0.18	0.18

Values reported are the mean ± SD; *p-values tabulated* refers to the comparison between blacks and whites within each age-group. **p* =0.07 compared with late postmenopausal white cohort

3.1.2.1.1. Correlation of SBMD with Anthropometric variables

Except for BMI in the late postmenopausal white group, weight and BMI correlated significantly with SBMD (figure 4). Height only correlated with SBMD in the late postmenopausal white group ($r=0.46$, $p=0.01$) and elbow width correlated with SBMD in the late postmenopausal blacks and whites.

3.1.2.1.2. SBMD in normal to low weight and overweight subgroups

SBMD was lower in the black females compared with the white females in the normal to low BMI group and neared statistical significance ($p=0.05$), but similar between the black and the white subjects in the overweight group. The mean SBMD of normal to low BMI black patients was significantly lower compared with their overweight counterparts ($p=0.01$). The mean SBMD of white subjects was lower in the normal to low weight group, but the difference did not reach statistical significance ($p=0.1$). The difference in SBMD between the total black and white postmenopausal cohorts can thus be mainly attributed to the difference in SBMD in the subjects with a BMI < 25kg/m², a finding similar to that observed in the premenopausal cohort (table 8).

Table 8: Spinal bone mineral density data in postmenopausal subgroups based on BMI

BMD (g/cm ²)	Postmenopausal females					
	Normal to low BMI subgroup (BMI<25kg/m ²)			Overweight subgroup (BMI ≥ 25kg/m ²)		
	Blacks (n = 23)	Whites (n = 47)	<i>p-value</i>	Blacks (n = 64)	Whites(n = 29)	<i>p-value</i>
SBMD	0.854* ± 0.12	0.926 ± 0.15	0.05	0.963 ± 0.21	0.981 ± 0.18	0.32

Values reported are the mean ± SD; *p-values tabulated* refers to comparison between blacks and whites within specific weight group. * Significantly lower compared with overweight black subjects ($p= 0.01$)

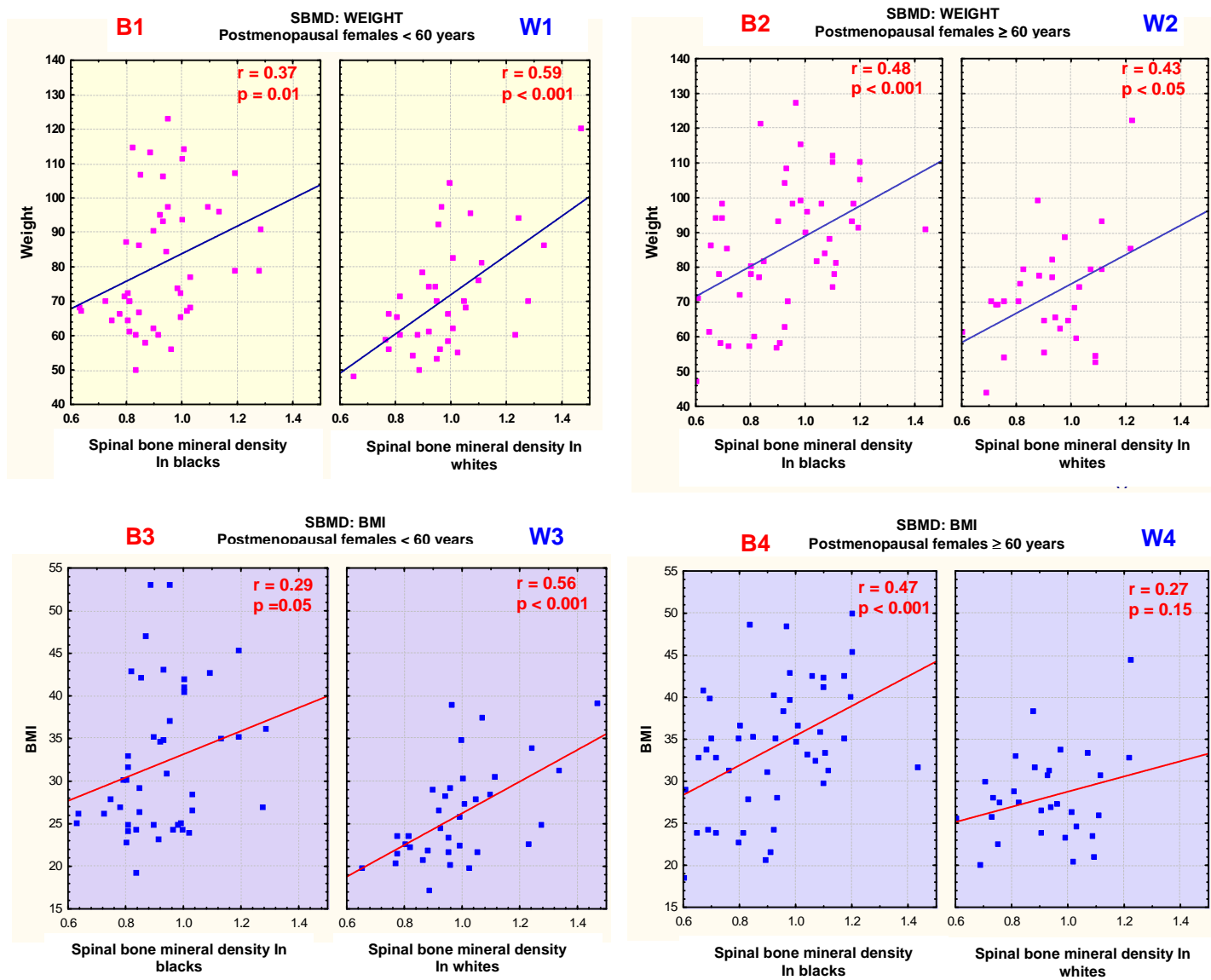


Figure 4: Correlation of SBMD with weight and BMI in postmenopausal black (panel B1-B4) and white (panel W1-W4) females. Significant correlations noted except for SBMD and BMI in the late postmenopausal white group (panel B4)

3.1.2.1.3. Distribution of SBMD in postmenopausal cohorts

Measured against a white reference population, 53% of the postmenopausal black subjects had spinal osteopenia (51 subjects) and 14% (14 subjects) met the diagnostic criteria of the WHO for spinal osteoporosis. Measured against the DEXA manufacturer's reference value for North American blacks 70% (68 subjects) had BMD measurements consistent with spinal osteopenia and 37% (36 subjects) had spinal osteoporosis. In the white postmenopausal cohort, 44% of females were osteopenic (29 subjects) and 14% (9 subjects) had spinal osteoporosis. A bone mineral density of 2SD above the normal reference population was present in less than 1% (6 black patients and 3 white patients) of both postmenopausal cohorts (table 9).

Table 9: Distribution of SBMD in the total postmenopausal black and white cohorts

SBMD status *	Blacks (n=97)	Whites (n=66)
Osteopenia n(%)		
White reference population	51 (53%)	29 (44%)
Black** reference population	68 (70%)	
Osteoporosis n(%)		
White reference population	14 (14%)	9 (14%)
Black** reference population	36 (37%)	
SBMD 2SD above normal n(%)	6 (<1%)	3 (<1%)

* Classification based on WHO criteria^{1,2}; ** DEXA manufacturer's reference for North-American blacks

3.1.2.1.4. Correlation of SBMD with age and years since menopause (YSM)

SBMD did not correlate significantly with age or the years since menopause in the black or the white postmenopausal cohorts [early and late postmenopausal groups combined] (table 10).

Table 10: Correlation of SBMD with age and years since menopause

	Blacks		Whites	
	r-value	p-value	r-value	p-value
SBMD and age	-0.04	0.74	-0.23	0.06
SBMD and YSM	-0.14	0.38	0.163	0.39

3.1.2.2. Spinal bone mineral apparent density (SBMAD)

SBMAD was similar in the black and white subjects in both the early and the late postmenopausal groups before and after adjustment for covariates, although there was a tendency towards higher SBMAD values in the late postmenopausal black cohort after adjustment for the number of pregnancies (p=0.07). Weight was positively associated with

SBMAD in the early and late postmenopausal cohort ($p < 0.01$), whereas the number of pregnancies ($p < 0.01$) had a negative impact on SBMAD in the late postmenopausal groups only.

The black subjects in the early and late postmenopausal groups had similar mean SBMAD values ($p = 0.41$), whereas near statistically significantly lower SBMAD was noted in the older white postmenopausal females compared to their younger counterparts ($p = 0.06$). The SBMAD data in the postmenopausal cohort is thus similar to that of the areal SBMD data (section 3.1.2.1).

3.1.2.2.1. SBMAD in normal to low weight and overweight subgroups

Comparison of SBMAD values in the postmenopausal normal weight and overweight subgroups revealed results identical to that of the SBMD data (section 3.1.2.1.2). Results are shown in table 11.

Table 11: Spinal bone mineral apparent density data in postmenopausal subgroups based on BMI

BMAD (g/cm^3)	Postmenopausal females					
	Normal to low BMI subgroup ($\text{BMI} < 25 \text{kg}/\text{m}^2$)			Overweight subgroup ($\text{BMI} \geq 25 \text{kg}/\text{m}^2$)		
	Blacks (n = 23)	Whites (n = 47)	p-value	Blacks (n = 64)	Whites (n = 29)	p-value
SBMAD	0.112* \pm 0.01	0.121 \pm 0.02	0.05	0.128 \pm 0.03	0.126 \pm 0.02	0.30

Values reported are the mean \pm SD; p-values tabulated refers to comparison between blacks and whites within specific weight group * Significantly lower compared with overweight black ($p < 0.01$)

3.2. FEMORAL BONE MINERAL DENSITY

Bone mineral density was measured at various proximal femur sites (femoral neck, trochanter, intertrochanteric, total hip and ward's triangle). This section will primarily report on the analyses of the femoral neck and total hip BMD measurements.

3.2.1. Premenopausal subjects

3.2.1.1. Proximal femoral bone mineral status

The BMC of the femoral neck was similar in the premenopausal black and white subjects.

The mean area of the femoral neck was significantly smaller in the black cohort, which resulted in blacks having higher mean unadjusted femoral neck bone mineral density ($F_N\text{BMD}$) than whites. Weight and height ($p < 0.01$) were found to be significantly associated with $F_N\text{BMD}$. After adjustment for height as a covariate, mean $F_N\text{BMD}$ remained significantly

higher in the premenopausal black cohort whereas the difference in mean F_N BMD between the two cohorts was non-significant after adjustment for weight.

The BMC of the total femoral area tended to be lower in blacks. Mean total femoral area was significantly smaller in blacks, which resulted in a similar mean unadjusted total femoral bone mineral density (F_T BMD) in the two cohorts. Weight ($p < 0.01$) and height ($p = 0.04$) was significantly associated with F_T BMD. After adjustment for weight mean F_T BMD remained similar in the two cohorts, whereas mean F_T BMD was significantly higher in the black compared with the white cohort after adjustment for height.

Unadjusted BMD of the trochanteric and intertrochanteric areas and Ward's triangle were similar in the two ethnic groups (table 12).

Table 12: Comparison of femoral neck BMC, bone area and femoral BMD in the premenopausal black and white females

Femoral bone mineral data	Premenopausal subjects		
	Blacks (n=87)	Whites (n=76)	<i>p-value</i>
Femoral neck			
BMC (g)	4.73 ± 0.78	4.60 ± 0.74	0.5
Bone-area (cm²)	5.27 ± 0.50	5.47 ± 0.42	<0.01
BMD (g/cm²)			
Unadjusted	0.896 ± 0.12	0.842 ± 0.13	<0.01
Adjusted for weight	0.885 ± 0.11	0.855 ± 0.11	0.1
Adjusted for height	0.894 ± 0.13	0.845 ± 0.13	<0.01
Femur Total			
BMC (g)	32.85 ± 5.72	34.55 ± 7.35	0.06
Bone-area (cm²)	33.05 ± 3.35	35.75 ± 4.78	<0.01
BMD (g/cm²)			
Unadjusted	0.993 ± 0.27	0.964 ± 0.12	0.16
Adjusted for weight	0.979 ± 0.12	0.979 ± 0.12	0.98
Adjusted for height	1.005 ± 0.14	0.952 ± 0.14	0.03
Trochanteric BMD (g/cm²)	0.734 ± 0.02	0.738 ± 0.02	0.84
Intertrochanteric BMD (g/cm²)	1.173 ± 0.03	1.125 ± 0.04	0.07
Ward's triangle (g/cm²)	0.751 ± 0.03	0.748 ± 0.04	0.90

Values reported are the mean ± SD

3.2.1.1.1. Correlation of femoral BMD with anthropometric variables

Anthropometric variables i.e. weight, height, BMI and elbow-width correlated significantly with F_N BMD in black and white premenopausal subjects. Similarly, all these variables also correlated significantly with F_T BMD.

3.2.1.1.2. Femoral bone density in normal to low weight and overweight subgroups.

F_NBMD and F_TBMD in normal to low weight and overweight subgroups are shown in table 13. F_NBMD was significantly lower in the premenopausal whites compared to blacks in the normal to low weight group (p=0.05), whereas the F_TBMD was similar. There was a significant difference in age between the black (35 ± 9 years) and white (39 ± 6 years) females in the normal to low weight subgroup; hence BMD was also expressed as Z-scores. The normal to low weight black females had similar Z-scores for the F_NBMD and the F_TBMD compared to the normal to low weight white females, with a non-significant tendency towards lower F_NBMD Z-scores. F_NBMD and F_TBMD were similar between overweight white and black subjects. The difference in F_NBMD between the black and white premenopausal cohorts can thus be mainly attributed to the lower F_NBMD in white subjects with a BMI < 25kg/m².

F_NBMD and F_TBMD values tended to be lower in the normal to low weight compared with overweight blacks, but the difference did not reach statistical significance. Both femoral measurements were significantly lower in the normal to low weight whites compared to their overweight counterparts (p<0.01). The Z-scores differed significantly between the normal to low weight and overweight white females similar to that observed for the absolute femoral BMD values, but differed from the absolute femoral data in that Z-scores were also significantly different between the normal to low weight and overweight black females for both femur neck (p=0.04) as well as the total femoral measurements (p<0.01).

Table 13: Femoral bone mineral density data in premenopausal subgroups based on BMI

BMD (g/cm ²)	Premenopausal groups					
	Normal to low BMI subgroup (BMI < 25kg/m ²)			Overweight subgroup (BMI ≥ 25kg/m ²)		
	Blacks (n=23)	Whites (n =47)	p-value	Blacks (n= 64)	Whites (n= 29)	p-value
F_NBMD						
Absolute value	0.863 ± 0.14	0.814* ± 0.12	0.05	0.909 ± 0.11	0.888 ± 0.11	0.20
Z-score	0.41* ± 1.12	0.03* ± 1.08	0.09	0.89 ± 1.08	0.58 ± 1.05	0.10
F_TBMD						
Absolute value	0.926 ± 0.13	0.934* ± 0.12	0.46	0.984 ± 0.30	1.012 ± 0.12	0.50
Z-score	0.04* ± 0.96	0.15* ± 0.94	0.32	0.87 ± 1.19	0.70 ± 0.97	0.26

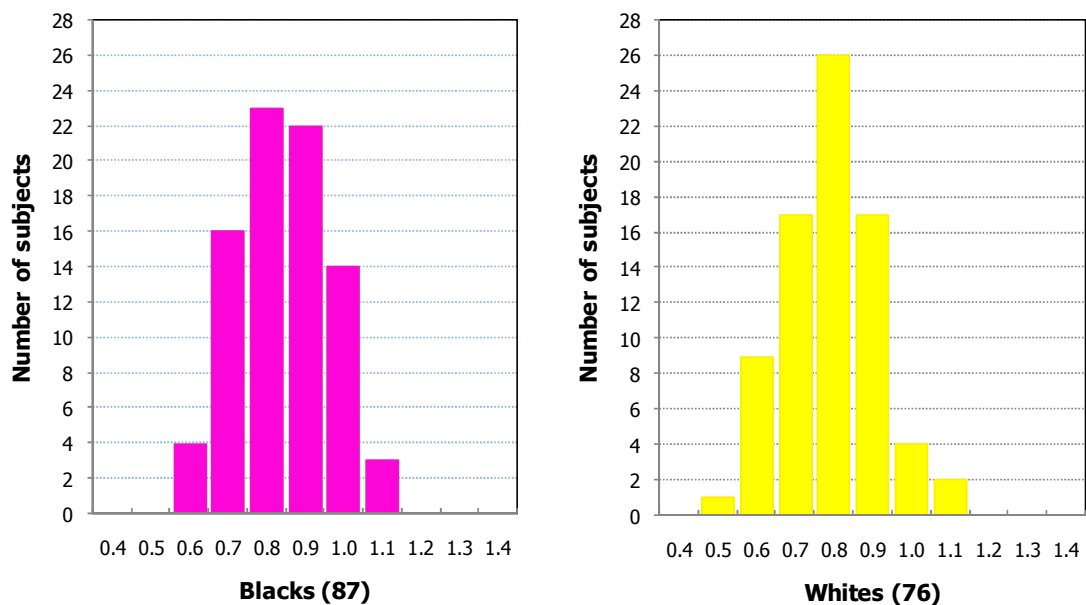
Values reported are the means ± SD; p-values in table refer to comparison between blacks and whites within specific BMI groups. *Significantly lower compared with overweight subjects within the same ethnic group (p<0.05)

3.2.1.1.3. Distribution of femoral BMD in premenopausal cohort.

F_N BMD and F_T BMD Z-scores were normal in the majority of premenopausal females in this study. Measured against a white reference population, 98% of black females had a normal F_N BMD and 92% had a normal F_T BMD. Only 2% (2 females) had osteopenia based on F_N BMD, whereas 8% (7 patients) had a F_T BMD value compatible with osteopenia. None of the black subjects had osteoporosis. A Z-score of 2SD above the reference norm was present in 15% and 11% of blacks based on F_N BMD and F_T BMD measurements respectively. Measured against the DEXA manufacturer's reference values for North-American blacks, 15% (13 females) had osteopenia based on F_N BMD, whereas 18% (16 patients) had a F_T BMD value compatible with osteopenia. None of the subjects had osteoporosis. A Z-score of 2SD above the reference norm was only present in 1% of blacks based on both F_N BMD and F_T BMD measurements.

In the white cohort 12% (9 subjects) had femoral neck osteopenia and 8% had osteopenia based on F_T BMD measurements. None of the white premenopausal subjects had osteoporosis. A Z-score of 2SD above the reference norm was present in 7% and 5% of whites based on F_N BMD and F_T BMD measurements respectively (figure 8 & table 14).

Distribution of F_N BMD



Distribution of F_T BMD

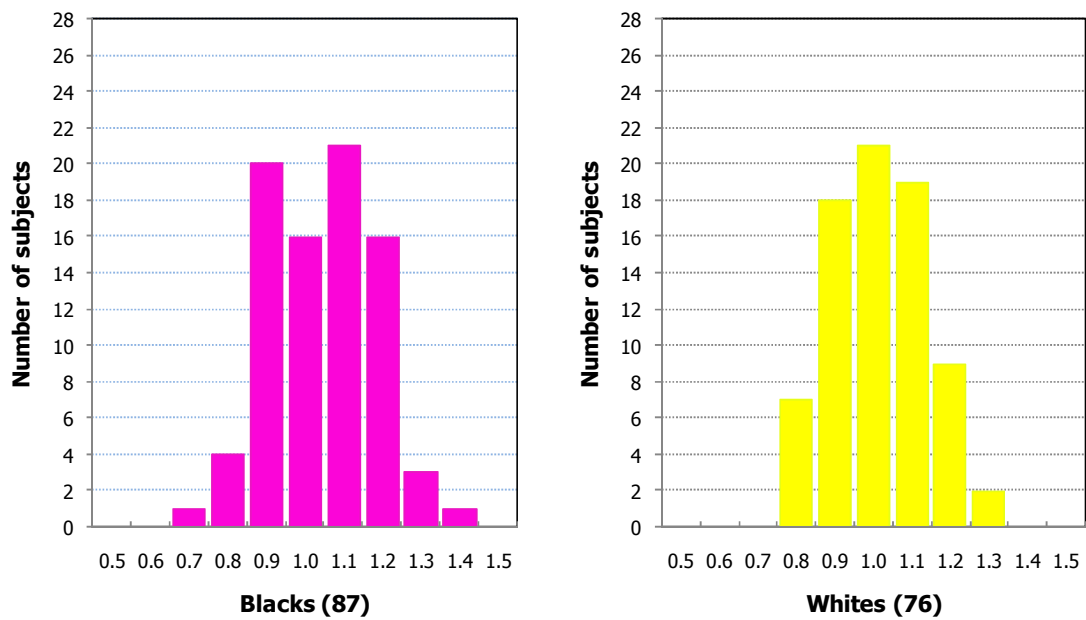


Figure 8: Distribution of F_N BMD and F_T BMD data in premenopausal blacks and whites.

Table 14: Femoral BMD distribution in the premenopausal black and white cohorts based on Z-scores

Z-scores*	Premenopausal subjects			
	F _N BMD		F _r BMD	
	Blacks (n=87) n (%)	Whites (n=76) n (%)	Blacks (n=87) n (%)	Whites (n=76) n (%)
Osteopenia				
White reference	2 (2%)	9 (12%)	7 (8%)	6 (8%)
Black reference	13 (15%)		16 (18%)	
Osteoporosis				
White reference	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Black reference	0 (0%)	0 (0%)	0 (0%)	0 (0%)
BMD > 2 SD				
White reference	13 (15%)	5 (7%)	10 (11%)	4 (5%)
Black reference	1 (1%)		1 (1%)	

* Classification based on Z-scores

3.2.1.1.4. Correlation of femoral BMD with age

F_NBMD and F_TBMD did not show a statistically significant correlation with age in either of the two ethnic groups (table 15).

Table 15: Correlation of femoral BMD with age in premenopausal females

	Premenopausal groups			
	Blacks		Whites	
	<i>r-value</i>	<i>p-value</i>	<i>r-value</i>	<i>p-value</i>
F_NBMD and age	-0.10	0.38	-0.18	0.12
F_TBMD and age	0.07	0.54	-0.1	0.40

3.2.1.2. Femoral neck bone mineral apparent density (F_NBMAD)

Unadjusted F_NBMAD was significantly higher in the black subjects. In addition to ethnicity, age (p=0.06) tended to be negatively associated with F_NBMAD in both the black and white cohorts. After adjustment for age as a covariate, F_NBMAD was still higher in the blacks (table 16).

Table 16: F_NBMAD in the premenopausal cohort

	Premenopausal cohort		
	Blacks (n=87)	Whites (n=76)	<i>p-value</i>
F_NBMAD (g/cm³)			
Unadjusted	0.170 ± 0.03	0.155 ± 0.03	<0.01
Adjusted (for age)	0.170 ± 0.03	0.156 ± 0.03	<0.01

Values reported are the mean ± SD

3.2.1.2.1. F_NBMAD in normal weight and overweight premenopausal subgroups

F_NBMAD was higher in premenopausal blacks compared with whites in both weight subgroups. The ethnic difference was, however, more pronounced in the group with a normal to low BMI (table 17). F_NBMAD was significantly lower in the normal to low weight black (p=0.02) and white (p<0.01) subgroups compared to their overweight counterparts respectively and the difference appeared to be more pronounced in whites.

Table 17: Femoral neck bone mineral apparent density in premenopausal subgroups based on BMI

	Premenopausal females					
	Normal to low BMI subgroup (BMI < 25 kg/m ²)			Overweight subgroup (BMI ≥ 25 kg/m ²)		
F _N BMD (g/cm ³)	Blacks (n = 23)	Whites (n = 47)	p-value	Blacks (n = 64)	Whites (n = 29)	p-value
		0.177* ± 0.03	0.153* ± 0.03	<0.01	0.168 ± 0.03	0.158 ± 0.03

Values reported are the means ± SD; p-values in table refer to comparison between blacks and whites within specific weight groups *Significantly lower compared with overweight subjects within the same ethnic group (p < 0.05)

3.2.2. Postmenopausal females

3.2.2.1. Proximal femoral bone mineral status

Femoral neck and total femoral measurements are depicted in table 18 and illustrated by figure 16. The F_NBMC was similar in all the comparable study groups. F_N-bone area was significantly smaller in the black subjects in both the early and late postmenopausal groups compared with whites. Blacks therefore had higher mean unadjusted F_NBMD than whites in the early and late postmenopausal groups. Likewise, F_TBMC was similar, F_T-bone area was smaller and mean unadjusted F_TBMD thus statistically significantly higher in blacks compared with whites in the early and late postmenopausal groups.

Only weight (p < 0.01) was significantly associated with mean F_NBMD and F_TBMD in the early postmenopausal subjects. Adjustment for weight diminished the difference in mean F_NBMD and F_TBMD between the blacks and whites. Mean F_NBMD, however, remained significantly higher in the black cohort after adjustment, whereas adjustment for weight resulted in similar mean F_TBMD between the two ethnic groups.

In the late postmenopausal cohorts, age, weight, number of pregnancies and number of pack years smoked were all significantly associated with both F_NBMD and F_TBMD. After adjustment for age, number of pregnancies and pack years smoked, mean F_NBMD and F_TBMD remained significantly higher in blacks. Adjustment for weight, however, resulted in similar mean F_NBMD and F_TBMD in the late postmenopausal black and white groups.

F_NBMD and F_TBMD were lower in the late postmenopausal subjects compared with the early postmenopausal subjects of both ethnic groups, but these differences did not reach statistical significance.

Bone density measured in the trochanteric and intertrochanteric areas and Ward's triangle was similar in black and white groups with the exception of a higher intertrochanteric BMD in the older postmenopausal black subjects compared with whites.

Table 18: Proximal femoral bone mineral status in postmenopausal cohorts

Femoral BMD measurements	Postmenopausal cohorts					
	< 60 years			≥ 60 years		
	Blacks (n= 49)	Whites (n=35)	p-value	Blacks (n=48)	Whites (n=31)	p-value
Femoral neck F _N BMC (grams)	4.41 ± 0.80	4.02 ± 0.78	0.07	4.23 ± 0.84	3.95 ± 0.99	0.47
F _N -bone area (cm ²)	5.255 ± 0.37	5.477 ± 0.35	<0.01	5.326 ± 0.37	5.55 ± 0.496	<0.05
F _N BMD(g/cm ²)						
Unadjusted	0.834 ± 0.13	0.736 ± 0.13	<0.01	0.794 ± 0.14	0.698 ± 0.12	<0.01
Adjusted for weight	0.818 ± 0.11	0.762 ± 0.11	0.03	0.770 ± 0.12	0.728 ± 0.12	0.11
Adjusted for age	-	-		0.788 ± 0.13	0.707 ± 0.13	<0.01
Adjusted for nr of pregnancies	-	-		0.802 ± 0.13	0.681 ± 0.14	<0.01
Adjusted for smoking	-	-		0.807 ± 0.13	0.677 ± 0.13	<0.01
Total femur F _T BMC (grams)	34.20 ± 8.08	32.50 ± 6.83	0.16	32.52 ± 7.02	31.25 ± 7.09	0.23
F _T -bone area (cm ²)	35.03 ± 4.19	36.53 ± 3.46	0.05	34.74 ± 3.36	36.56 ± 3.63	0.02
F _T BMD (g/cm ²)						
Unadjusted	0.973 ± 0.16	0.890 ± 0.15	<0.01	0.931 ± 0.15	0.840 ± 0.14	<0.01
Adjusted for weight	0.946 ± 0.11	0.925 ± 0.11	0.42	0.907 ± 0.13	0.877 ± 0.13	0.35
Adjusted for age	-	-		0.926 ± 0.15	0.848 ± 0.15	0.03
Adjusted for no of pregnancies	-	-		0.943 ± 0.15	0.816 ± 0.15	<0.01
Adjusted for smoking	-	-		0.944 ± 0.15	0.812 ± 0.15	<0.01
F-trochanter BMD (g/cm²)	0.706 ± 0.113	0.675 ± 0.109	0.69	0.676 ± 0.12	0.643 ± 0.11	0.15
F-intertroch BMD (g/cm²)	1.138 ± 0.186	1.058 ± 0.189	0.13	1.113 ± 0.19	1.000 ± 0.19	<0.01
F-Ward's BMD (g/cm²)	0.642 ± 0.153	0.597 ± 0.141	0.57	0.552 ± 0.14	0.502 ± 0.14	0.07

Values reported are the mean ±SD; p-values refers to the comparison between blacks and whites within menopausal age-groups

Early postmenopausal cohorts

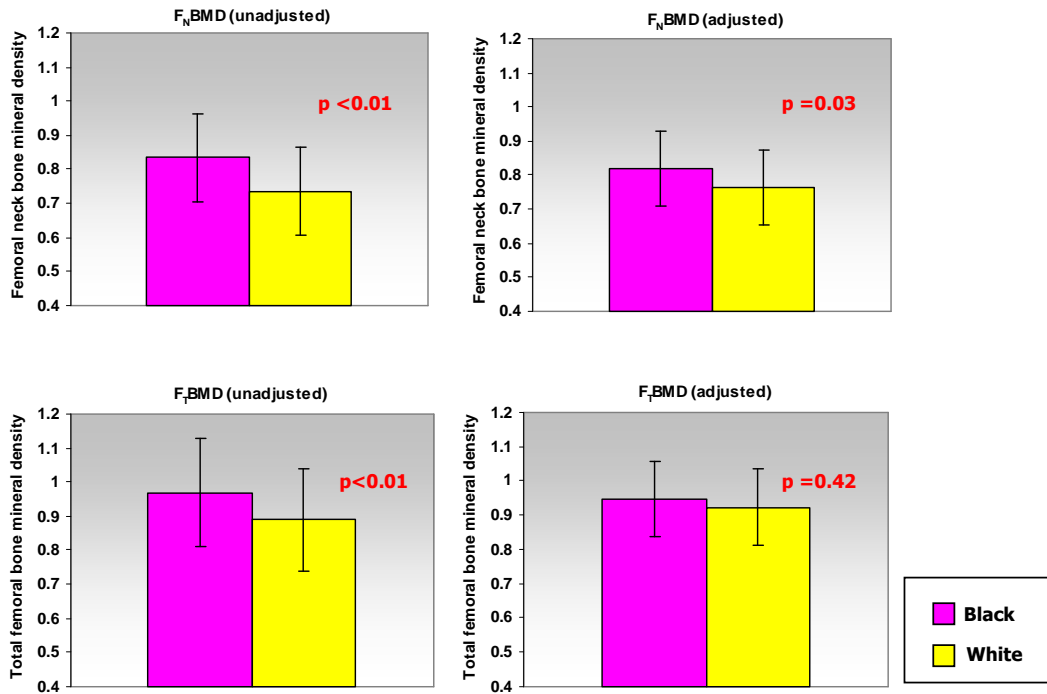


Figure 16a. F_NBMD and F_TBMD before and after adjustment for weight as a covariate in the early postmenopausal cohorts

Late postmenopausal cohorts

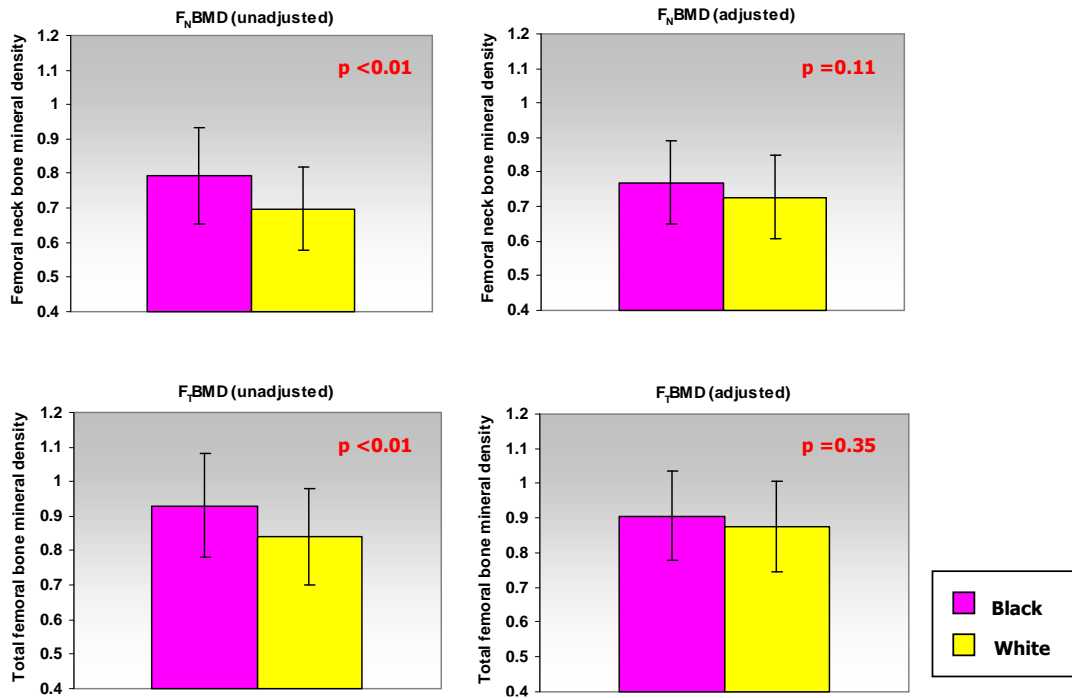


Figure 16b. F_NBMD and F_TBMD before and after adjustment for weight as a covariate in the late postmenopausal cohorts

3.2.2.1.1. Correlation of femoral BMD with anthropometric variables

Weight, BMI and elbow width correlated significantly with F_NBMD and F_TBMD in black and white females in both postmenopausal groups. Weight had the strongest association with F_NBMD and F_TBMD. Height only correlated significantly with F_NBMD and F_TBMD in the older white postmenopausal females.

3.2.2.1.2. Femoral bone density in normal to low weight and overweight subgroups.

Femoral neck and total femoral BMD was higher in blacks compared with whites in the normal to low and overweight subgroups, although significance was not reached for F_TBMD in the normal to low weight subgroup between blacks and whites. This may be partially due to small numbers of both black and white women in this weight subgroup. Both femoral BMD measurements were significantly lower in normal to low weight blacks and whites compared to their respective overweight counterparts (table 19). We did not compare Z-scores as age was comparable in all weight groups studied.

Table 19: Femoral bone mineral density data in postmenopausal subgroups based on BMI

BMD (g/cm ²)	Postmenopausal groups					
	Normal to low BMI subgroup (BMI < 25kg/m ²)			Overweight subgroup (BMI ≥ 25kg/m ²)		
	Blacks (n=22)	Whites (n =27)	p-value	Blacks (n= 75)	Whites (n= 39)	p-value
F_NBMD						
Absolute value	0.766* ± 0.11	0.684* ± 0.11	<0.01	0.829 ± 0.14	0.749 ± 0.13	<0.01
F_TBMD						
Absolute value	0.851* ± 0.13	0.816* ± 0.12	0.17	0.979 ± 0.15	0.910 ± 0.15	0.01

Values reported are the means ± SD; p-values in table refer to comparison between blacks and whites within specific BMI groups. *Significantly lower compared with overweight subjects within the same ethnic group (p<0.05)

3.2.2.1.3. Distribution of femoral bone density in postmenopausal cohorts.

The classification of femoral bone mineral status was based on WHO criteria and results shown in table 20. Measured against a white reference population, 35% of the postmenopausal black subjects had a F_NBMD value in the osteopenic range (34 patients), and 28% had F_TBMD values in keeping with osteopenia (27 patients). None of the postmenopausal blacks met the diagnostic criteria of femoral neck osteoporosis, whereas 3 patients were osteoporotic based on total femoral measurements. Measured against the DEXA manufacturer's reference values for North-American blacks, 51% of the postmenopausal black subjects had a F_NBMD value in the osteopenic range (49 patients) and 35% had F_TBMD values in keeping with osteopenia (34 patients). Three of the black subjects

met the diagnostic criteria for femoral neck osteoporosis (OP) and 5 had a F_TBMD value in keeping with OP.

In the white cohort 61% of females had femoral neck osteopenia (40 patients) and 48% of whites had total femoral values in keeping with osteopenia (32 patients). Seven (11%) of the white subjects met the diagnostic criteria for femoral neck osteoporosis and 2 had a F_TBMD value in keeping with OP.

F_NBMD 2SD above the white reference population was present in only 2 of the black females and 3 of the white subjects. F_TBMD 2SD or more above the normal reference population was present in only 4 of the black patients and 2 of the white subjects. None of the black subjects had a F_NBMD or F_TBMD \geq 2SD above the DEXA manufacturer's black reference range.

Measured against a uniform white reference population, a higher percentage of white postmenopausal females have F_NBMD and F_TBMD compatible with osteopenia. A significant percentage of postmenopausal black females in this study do, however, also have femoral measurements below normal.

Table 20: Distribution of femoral BMD in the total postmenopausal black and white cohorts

Femoral BMD status *	F _N BMD		F _T BMD	
	Blacks (n=97)	Whites (n=66)	Blacks (n=97)	Whites (n=66)
Osteopenia n(%)				
White reference population	34 (35%)	40 (61%)	27 (28%)	32 (48%)
Black* reference population	49 (51%)	-	34 (35%)	-
Osteoporosis n(%)				
White reference population	0 (0%)	7 (11%)	3 (3%)	2 (3%)
Black* reference population	3 (3%)	-	5 (5%)	-
SBMD 2SD above normal n(%)				
White reference population	2 (2%)	3 (5%)	4 (4%)	2 (3%)
Black* reference population	0 (0%)	-	0 (0%)	-

Classification based on WHO criteria^{1,2}

3.2.2.1.4. Correlation of femoral BMD with age and years since menopause

A significant negative correlation was noted between F_NBMD and F_TBMD, and age in the total postmenopausal black group, whereas there was also a tendency towards a negative association between F_NBMD and F_TBMD, and age in the postmenopausal whites. F_NBMD and F_TBMD correlated with years since menopause in postmenopausal blacks only (table 21).

Table 21. Correlation of femoral BMD with age and years post menopause

	Total postmenopausal cohort			
	Blacks		Whites	
	<i>r-value</i>	<i>p-value</i>	<i>r-value</i>	<i>p-value</i>
F_NBMD and age	-0.29	0.01	-0.22	0.08
F_NBMD and yrs since menopause	-0.29	0.01	-0.05	0.68
F_TBMD and age	-0.21	0.05	-0.23	0.07
F_TBMD and yrs since menopause	-0.25	0.02	-0.05	0.69

3.2.2.2. Femoral neck bone mineral apparent density (F_NBMAD)

Unadjusted F_NBMAD was significantly higher ($p < 0.01$) in the black subjects compared to whites in both the early and late postmenopausal cohorts. Weight was the only covariant significantly associated with F_NBMAD in the early postmenopausal subjects and both weight and number of pregnancies were identified as significantly associated with F_NBMAD in the late postmenopausal cohorts. After adjustment for these covariates, F_NBMAD remained significantly higher ($p < 0.01$) in blacks in both early and late postmenopausal groups compared with whites (table 22).

In both black ($p = 0.06$) and white ($p = 0.09$) postmenopausal subjects, a trend towards a lower F_NBMAD was noted in the older (≥ 60 yrs) compared to the younger (< 60 yrs) subgroups (figure 16).

Table 22: F_NBMAD in postmenopausal blacks and whites

F _N BMAD (g/cm ³)	Postmenopausal groups		
	Blacks	Whites	p-value
Early postmenopausal group			
Unadjusted	0.158 ± 0.02	0.134 ± 0.02	<0.01
Adjusted for weight	0.155 ± 0.02	0.138 ± 0.02	<0.01
Late postmenopausal group			
Unadjusted	0.150 ± 0.03	0.127 ± 0.02	<0.01
Adjusted for weight	0.148 ± 0.01	0.130 ± 0.01	<0.01
Adjusted for no of pregnancies	0.151 ± 0.02	0.124 ± 0.02	<0.01

Values reported are the mean ± SD

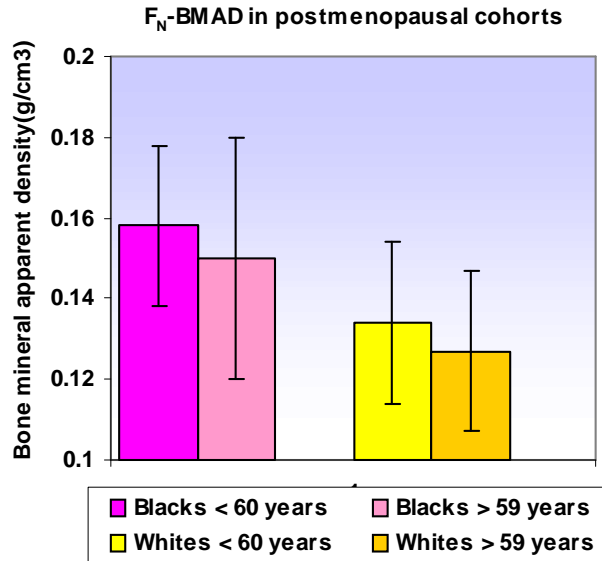


Figure 16: Unadjusted F_NBMAD in the postmenopausal cohort. Higher values noted in the black compared with white females in the early and late postmenopausal groups ($p < 0.01$). F_NBMAD lower in the older blacks and whites compared to their respective younger counterparts ($p = 0.06$ for blacks and $p = 0.09$ for whites).

3.2.2.2.1. F_NBMAD in normal weight and overweight subgroups

F_NBMAD was significantly higher in postmenopausal blacks compared with whites in both weight subgroups (table 23). F_NBMAD tended to be lower in the normal to low weight black ($p = 0.06$) and white ($p = 0.08$) subgroups, but the difference was not statistically significant.

Table 23: Femoral neck bone mineral apparent density in postmenopausal subgroups based on BMI

	Postmenopausal females					
	Normal to low BMI subgroup (BMI < 25 kg/m ²)			Overweight subgroup (BMI ≥ 25 kg/m ²)		
	Blacks (n = 22)	Whites (n = 27)	p-value	Blacks (n = 75)	Whites (n = 39)	p-value
F _N BMAD (g/cm ³)	0.146 ± 0.02	0.127 ± 0.02	<0.01	0.156 ± 0.03	0.135 ± 0.02	<0.01

Values reported are the means ± SD; p-values in table refer to comparison between blacks and whites within specific weight groups

3.3. CORRELATION OF AREAL BMD WITH AGE AND PATTERNS OF BONE LOSS IN THE TOTAL STUDY COHORT

Areal spinal and femoral BMD did not correlate significantly with age when assessed within the different menopausal subgroups, with the exception of a negative correlation noted between age and proximal femoral BMD in the total postmenopausal black group (table 21). A significant negative correlation between age and BMD measurements at all skeletal sites

was however present when evaluated in the larger total black and white cohorts (figure 17). The correlations between age and BMD measurements were lower in blacks compared with whites, the difference reaching statistical significance for spinal ($p=0.02$) and total femoral ($p=0.02$) measurements.

The pattern of bone loss with ageing appeared to differ between the two racial groups, although longitudinal data must be interpreted with caution in this cross-sectional study. The percentage decline in lumbar spine BMD between the premenopausal and early postmenopausal black and white cohorts appeared to be near identical (9% and 10% respectively). Our data, however suggests that postmenopausal black females maintained their lumbar BMD better into old age compared with whites (Table 24), implying a slower rate of postmenopausal decline in spinal bone mineral density. This resulted in improvement of lumbar BMD in blacks compared with whites with ageing with resultant similar spinal BMD values in the late postmenopausal black and white females despite lower peak lumbar spine BMD. The percentage bone loss at the femoral neck and total femoral regions across the menopausal transition i.e. between the premenopausal and early postmenopausal black and white cohorts appeared to be higher in white females (femoral neck region: 13% versus 7%; total femoral region: 8% versus 2%), resulting in higher femoral neck and total femoral BMD measurements in the younger postmenopausal black females compared with whites. Thereafter an apparent similar rate of postmenopausal decline in BMD measurements at the proximal femoral sites was noted in blacks and whites with black females thus maintaining significantly higher mean femoral neck and total femoral BMD values into old age.

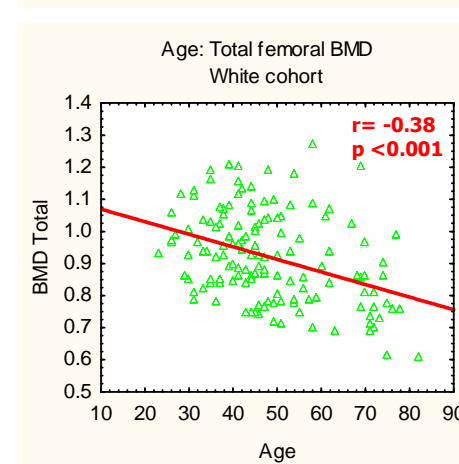
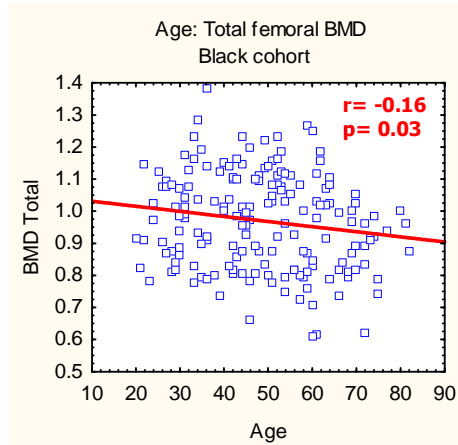
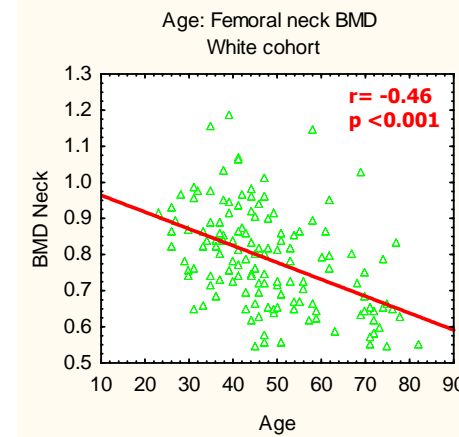
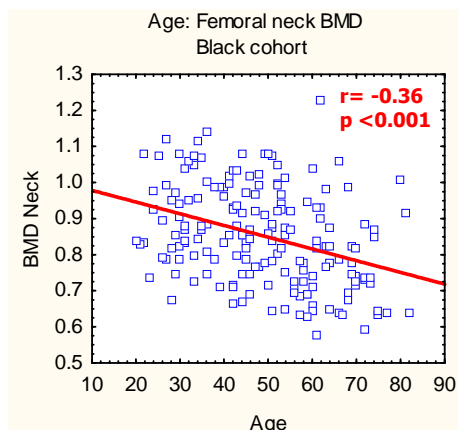
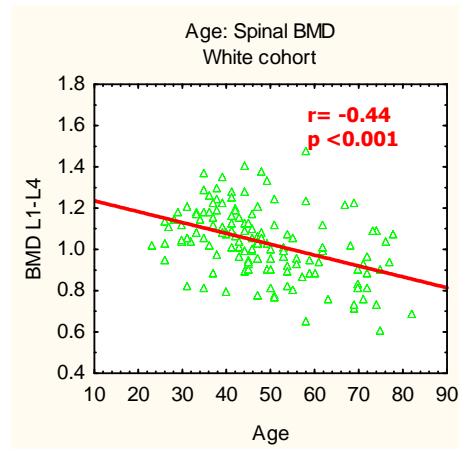
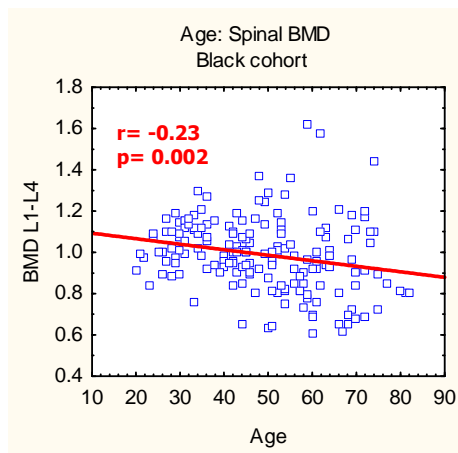


Figure 17. Correlation between age and spinal and proximal femoral BMD in the TOTAL black and white study cohorts. Correlation between age and BMD lower in blacks reaching significance only for spinal ($p=0.02$) and total femoral BMD ($p=0.02$).

Table 24: Bone loss with ageing in black and white cohorts

<i>Ethnicity</i>	<i>Premenopausal</i>	<i>% decline</i>	<i>Early Postmenopausal</i>	<i>% decline</i>	<i>Late postmenopausal</i>
S-BMD					
Blacks	1.047 ± 0.12	9	0.940 ± 0.18	0	0.939 ± 0.21
Whites	1.099 ± 0.13	10	0.988 ± 0.17	6	0.925 ± 0.16
Femoral neck BMD					
Blacks	0.896 ± 0.12	7	0.834 ± 0.13	5	0.794 ± 0.14
Whites	0.842 ± 0.13	13	0.736 ± 0.13	5	0.698 ± 0.12
Femoral total BMD					
Blacks	0.993 ± 0.27	2	0.973 ± 0.16	4	0.931 ± 0.15
Whites	0.964 ± 0.12	8	0.890 ± 0.15	6	0.840 ± 0.14

Values reported are the mean ± SD. Percentage decline noted in red.

4. DISCUSSION

In our study, spinal bone mineral density (SBMD) was lower in premenopausal blacks compared with whites and similar in postmenopausal black and white women. Spinal bone density, expressed as a volumetric calculation, namely spinal bone mineral apparent density (SBMAD), was similar in all menopausal subgroups studied. Correction of both SBMD and SBMAD for marked ethnic differences in anthropometry, i.e. weight and height, did not alter these findings. It is thus not surprising that a similar percentage of black and white pre- and postmenopausal women had spinal osteopenia as measured against a uniform white reference population (53% of postmenopausal blacks and 44% of postmenopausal whites). In the postmenopausal cohort, 14% of both blacks and whites met the diagnostic criteria for osteoporosis.

Significant ethnic differences in bone density of the proximal femur were, however, evident in our study subjects. Femoral neck BMD and total femoral BMD were significantly higher in both younger and older postmenopausal blacks, whereas femoral neck BMD was also significantly higher in premenopausal blacks. The higher femoral BMD values in blacks were, however, mostly accounted for by the marked difference in weight between blacks and whites. Adjustment for weight thus eliminated most of the observed ethnic difference in these measurements. After adjustment of femoral neck and total femoral BMD for weight, a significant ethnic difference was confined to higher femoral neck BMD values in the early black postmenopausal subgroup.

Femoral neck bone mineral apparent density (F_N -BMAD), a volumetric calculation of femoral neck bone mineral content, was higher in blacks in all the subgroups studied. F_N -BMAD

remained significantly higher in blacks after correction for clinical covariates with significant univariate association.

Although a higher percentage of postmenopausal whites were osteopenic at the proximal femoral sites, a significant percentage of postmenopausal blacks also presented with femoral neck (35%) and total femoral (28%) osteopenia. The greatest difference in percentage subjects with proximal femoral osteopenia in postmenopausal blacks and whites was noted for the femoral neck region where osteopenia was present in 35% of blacks and 61% of whites. Osteoporosis as defined by WHO criteria, and measured against a uniform white reference population, was confined to the white group affecting 11% of the postmenopausal population.

The findings of lower or similar spinal BMD and higher femoral neck BMD in blacks versus whites are consistent with the limited data previously reported in other female populations on the African continent. Studies conducted in The Gambia consistently documented lower or similar spinal BMC and spinal BMD in Gambian women compared with British subjects^{6,212}. Other studies in West-African populations also found lower lumbar spine BMD in Africans compared to European females^{218,219}. In the only other previous study employing DEXA in BMD measurement of adult South African black and white females, spinal BMD was similar and femoral BMD significantly higher¹, findings very similar to ours. Our BMD findings differ from the American data, where BMD at all skeletal sites has invariably been found to be higher in blacks than in whites^{135,138,143-145,184-199}.

PEAK BONE MINERAL DENSITY

In our study, ethnic differences in attainment of peak BMD were noted in premenopausal blacks and whites. In blacks significantly lower peak SBMD was observed and this finding was mostly due to significantly lower peak SBMD observed in the premenopausal blacks with normal to low BMI. The black females in the normal to low BMI subgroup were significantly smaller with lower mean weight ($p < 0.01$) and height ($p < 0.01$) compared with the white females. In whites, the observed lower peak femoral neck BMD was mostly due to lower values in the smaller sized whites (normal to low BMI group). Peak spinal and proximal femoral BMD values were similar in the overweight premenopausal subgroups, blacks in this subgroup was significantly heavier with greater BMI's than whites.

The majority of studies indicate that the higher bone mass in adult African-American women is due to the attainment of a greater peak bone mass by early adulthood^{185,186,190-193,196-199}. Recent studies consistently demonstrated greater bone mineral density at the proximal femur in black versus white SA schoolchildren, whereas spinal BMD was either higher or

similar^{215,216}. It is thus plausible that South African blacks, similar to their American counterparts, may have a genetic tendency to greater BMD than whites. This hypothesis is supported by studies that suggest that the South African black population and the African-American population share a common genetic pool as both originated and migrated from West-Africa²¹⁷. The finding of lower peak spinal bone mineral density in our premenopausal blacks compared with whites contrasts that of American data and suggests that SA blacks do not realize their genetic potential at the spine. Although peak bone mass is largely (\pm 70%) genetically determined, it can be substantially affected by environmental factors^{34-42,257,258}.

In our study, significant differences in historical clinical risk profiles between premenopausal blacks and whites were noted especially with regard to phenotype, use of hormonal contraception and calcium-intake.

Weight

Body weight was significantly associated with peak BMD measurements at all skeletal sites in both our blacks and whites. Obesity is associated with increased peak bone mineral density^{193,195,199,238,239} and it is therefore surprising that the heavier young black females in our study had lower peak spinal BMD compared with whites. Analysis of bone mineral densities in premenopausal females in weight subgroups, however, revealed that the lower peak spinal BMD in the black females compared with whites was mainly attributable to lower measurements in the subset of black females with a normal to low weight. Body weight was significantly lower in blacks than whites in the normal to low weight subgroup. This may explain the more marked impact on spinal BMD measurements in blacks in the normal to low BMI subgroup, given the significant association between weight and spinal BMD documented in our study and the fact that low body weight is a well-known risk factor for low bone density^{244,253}. It appears as if a low body weight had a more marked deleterious effect on spinal versus femoral BMD in blacks. Contrary to the lower spinal BMD findings in the normal to low weight subgroup, blacks maintained higher peak proximal femoral BMD values compared with whites in this weight subgroup and similar peak proximal femoral BMD values compared with their overweight white counterparts.

Excess weight exerts its positive skeletal effects mainly via direct mechanical loading, but also has an impact on bone mass via the metabolic effects of adipocyte derived adipokines and androgen aromatization to estrogen in fat cells. The mechanical impact of obesity is most prominent in the weight-bearing sites of the skeleton^{193,239,313} and this may be the main mechanism whereby the heavier premenopausal blacks in our study cohort obtained higher unadjusted proximal femoral BMD measurements than whites. The metabolic/hormonal

impact of obesity in premenopausal females may be less important given the background of normal estrogen status and based on recent work by Gilsanz and colleagues²⁵². In our study, adjustment for weight, resulted in similar femoral measurements between blacks and whites, and the higher peak proximal femoral BMD values in blacks can thus be mainly attributed to the difference in body weight between the two racial groups and not to ethnicity per se.

Height

Greater height is associated with higher spinal and femoral BMD^{115,119}. Blacks in this study were significantly shorter than whites. Height was positively associated with peak spinal and proximal femoral BMD obtained in premenopausal blacks and whites. Adjustment for height as a covariate improved BMD measurements in blacks versus whites as expected. The impact of height on BMD was, however, modest. Adjustment for height did alter observed spinal BMD differences between these two ethnic cohorts i.e. peak spinal BMD was similar in blacks and whites after correction for height, whereas both peak femoral neck and total femoral BMD were higher in blacks compared with whites after correction for height.

Calcium-intake

Calcium-intake in premenopausal black females was substantially lower than that of whites. Calcium nutrition is commonly considered to be important for the attainment of peak bone mass and for optimal maintenance of skeletal mass³⁴⁻³⁷. Most studies assessing the skeletal effects of calcium, both in childhood and in later life, were, however, conducted in white populations and less is known about the impact of calcium nutrition on skeletal health in black population groups. In our study, a significant association between calcium-intake and peak spinal and femoral BMD was not demonstrated in either of the two racial groups.

Hormonal contraception

Oral contraceptives (OCP) were the preferred mode of contraception in white females, whereas depot-medroxyprogesterone acetate (DP) was used most often, and almost exclusively, by the younger black females as discussed in Chapter 4. OCP are mostly regarded as bone-sparing or without BMD effects^{255,256}, although recent studies raised concern that OCP use may have a negative impact on normal physiological bone accretion in adolescents and young females^{263,264,266}. Hypo-oestrogenemia, as a result of DP use, may adversely affect optimal attainment of peak bone mass^{255,257,258-262}. These detrimental effects are particularly apparent in adolescents who have not yet achieved peak bone mass, in current users and it has also been noted that associated low body weight enhances the negative impact of DP²⁶¹. In our study, univariate tests of significance did not identify the different modes of contraception as significantly associated with peak BMD in either of the

two ethnic groups. The majority of our study subjects were, however, past-users of contraception and we furthermore only included premenopausal patients with a regular menstrual cycle, thereby excluding all current DP users with amenorrhea. The presence of a regular cycle in someone on DP may be indicative of ineffective suppression of ovulation and a lesser degree of hypo-oestrogenemia and these patients may thus be expected to have less detrimental effects on the skeleton. Our study, therefore, do not exclude potential adverse skeletal effects of current DP use in premenopausal black females who are amenorrhoeac.

Premenopausal blacks had lower spinal bone mineral density compared with whites and this finding was mostly accounted for by lower SBMD values in blacks with lower body weight. Although poor calcium nutrition and frequent ever use of depot-medroxyprogesterone acetate (DP) were not individually associated with peak BMD in our black premenopausal cohort, a combination of these factors along with a lower body weight may be deleterious to bone health in blacks. Blacks were significantly and markedly heavier than whites and it is possible that the positive impact of higher body weight^{193,195,199,238,239} overshadowed the effects of other clinical and environmental factors in our premenopausal cohort. The modern tendency towards a lower ideal body weight in black urbanized societies may thus increase the likelihood of suboptimal attainment of peak BMD in blacks, especially at the spine, and the presence of other historical clinical risk factors for osteoporosis may potentially enhance the deleterious skeletal effects of a low body weight.

BONE LOSS

In our study, as alluded to before, spinal BMD was similar in postmenopausal blacks and whites, whereas proximal femoral BMD values were consistently higher in blacks. A significant negative correlation between age and both spinal and femoral BMD in the total black and white cohorts was documented. An apparent decrease in BMD at all skeletal sites was observed between the premenopausal and postmenopausal blacks and whites. Although cautious with regard to interpretation of longitudinal changes in this cross-sectional study, our BMD data in blacks and whites do, however, suggest ethnic differences in the pattern of observed bone loss with ageing at both the hip and spine. There appears to be a slower decline in especially femoral BMD during the menopausal transition period in blacks, whereas spinal BMD appears to be better maintained in postmenopausal blacks with ageing (table 24). The slower decline in BMD in blacks compared with whites with ageing at both the spinal and femoral sites favor the aforementioned ethnic group at a time when fracture risk is highest.

The different patterns of bone loss in our black and white female cohorts have also been observed in previous multi-ethnic studies^{1,213}. Our observation of a slower rate of decline in spinal and femoral bone density in black females compared with whites in the peri- or postmenopausal period is consistent with the findings in the nurses' study by Daniels et al¹. The pattern of femoral bone loss in our study was also remarkably similar to that observed by Solomon²¹³ more than 30 years earlier. He noted that black females appeared to reach peak bone mass at a later stage and showed very limited loss in the late premenopausal and perimenopausal periods. A slower rate of cortical and trabecular bone loss, especially in the early postmenopausal period, has also been noted in American blacks compared with whites in some^{139,184,197}, but not all^{144,194,196} studies.

A lower bone turnover in blacks, as shown in most previous studies^{138,142,146,196}, may in part be responsible for the slower postmenopausal decline in trabecular and cortical bone observed in this ethnic group. Previous studies reported that black women have lower bone turnover rates than white women despite higher endogenous PTH-levels and this is ascribed to a relative skeletal resistance to the action of PTH^{138,142,146,196} in blacks.

Significant differences in historical clinical risk profiles between postmenopausal blacks and whites in our study were also noted especially with regard to phenotype, calcium-intake, smoking, physical activity and parity. These clinical risk factors may also influence and impact on BMD and patterns of loss. In the early postmenopausal group, weight was the only clinical covariate with significant BMD associations, whereas, apart from weight; age, parity and the number of pack years smoked significantly correlated with femoral BMD measurements in the older postmenopausal females.

Weight

In our study, the postmenopausal blacks were heavier than whites and they also appeared to maintain their body weight better into old age compared with whites. Weight was positively associated with spinal and femoral BMD in our postmenopausal black and white women; in fact, the observed significant difference in femoral BMD between postmenopausal blacks and whites was fully accounted for by ethnic differences in body weight. Univariate tests of significance identified weight to be significantly correlated with every single areal and volumetric BMD parameter measured in our postmenopausal cohort. The positive impact of increased body weight on BMD is also demonstrated in the postmenopausal weight subgroups where spinal, femoral neck and total femoral BMD are all consistently lower in the low to normal weight blacks and whites compared to the overweight subjects.

Adjusted BMD data (for body size) in this study were different from the data obtained in the SA nurses' study¹. In the nurses' study, femoral neck and total femoral BMD remained significantly higher in blacks even after correction for weight. Our findings also differ from the American data, where BMD before and after adjustment for covariates (including body weight) at all skeletal sites has invariably been found to be higher in blacks than in whites^{135,138,143-145,184-199}. Differences in anthropometric variables, particularly body weight or body mass index, do account for a significant part of the difference in BMD between African-American and Caucasian women^{186,199}. Ettinger et al¹⁸⁶ found that adjustment for a series of anthropometric, lifestyle, and biochemical variables reduced the difference in BMD between black and white premenopausal women by 34%. Finkelstein et al¹⁹⁹ found that adjustment for anthropometric and lifestyle factors, particularly body weight, reduced the magnitude of the difference in lumbar and femoral neck BMD between late premenopausal and early perimenopausal African-Americans and Caucasians, Chinese and Japanese (unadjusted difference lumbar spine BMD 7-12%, adjusted difference 3-6%; unadjusted difference femoral neck BMD 14-24%, adjusted difference 6-9%).

Adiposity may have a role in maintaining BMD in postmenopausal females as reported by other researchers^{239,240,242,247,250,314-316}. After menopause, body mass becomes the main determinant of endogenous estrogen activity, as mentioned before, and excess body mass may be a protective factor for osteoporosis due to increased conversion of androgens to estrogens by fat tissue³¹⁷. This may be particularly relevant in the early postmenopausal period characterized by estrogen withdrawal and increased bone loss. The progressive increase in adiposity with age noted in the black subjects in our study, may thus potentially contribute to the apparent lower rates of postmenopausal decline in spinal BMD and femoral BMD observed in our black cohort.

Calcium-intake

The mean calcium-intake of postmenopausal blacks was significantly lower compare with whites ($p < 0.01$). No significant correlation could be demonstrated between daily calcium-intake and bone mineral density at any of the skeletal sites evaluated.

Physical activity

Physical activity was significantly less well maintained amongst blacks in our study with an impressive 69% of postmenopausal blacks not partaking in any form of out-door activity. Life-long exercise may reduce fracture risk by limiting age related bone loss³¹⁰ and by improving muscle strength (thereby reducing the frequency and severity of falls)³¹¹. A

significant association between physical inactivity and BMD could not be demonstrated in our postmenopausal cohort.

Parity

In our study, older postmenopausal black females had significantly higher parity compared with whites and this clinical variant was significantly and positively associated with femoral BMD measurements in this menopausal subgroup. As mentioned in chapter 4, several previous reports have also confirmed a positive correlation between parity and BMD^{280,281}, although other studies have reported no correlation between parity and BMD²⁸²⁻²⁸⁴ or a negative correlation²⁸⁵. The few studies conducted in very high parity (more or equal to five births) postmenopausal women have not been unanimous regarding beneficial skeletal effects^{281,284,285}.

Smoking

Smoking, especially current smoking, is a known risk factor for osteopenia and subsequent fracture, especially hip fracture^{115,118,119,318}. Our postmenopausal white women smoked more than blacks when expressed as total pack years ($p < 0.01$) and a higher percentage of current smokers was also noted amongst the white postmenopausal cohort. The number of pack years smoked was negatively associated with both femoral neck and total femoral BMD in the late postmenopausal subjects. Correction for this clinical variant, however, did not significantly alter ethnic differences in femoral BMD i.e. after correction for number of pack years smoked femoral BMD values remained higher in blacks.

IMPACT OF BONE SIZE ON BMD MEASUREMENTS

Conventional areal BMD measurements by DEXA introduce a scale artifact that causes small bones to have lower areal BMD than larger bones. When comparing people from different ethnic groups with potential differences in bone size, BMD differences may thus be more apparent than real. Although black women in this study are heavier than white women, their lumbar spine and femoral neck bone areas, as measured by DEXA, are significantly smaller, a finding also observed in African-American women compared with Caucasian women¹⁹⁹. Areal measurements may thus be inappropriately low in the black cohorts due to smaller bone size i.e. may be an underestimate of true volumetric bone density.

This scale artifact is reduced by expressing BMD as BMAD, a calculated three-dimensional variable that helps account for the size of the bones (methodology as described in chapter 3, section 2.2.2). Spinal BMAD was similar in blacks and whites in all the age and menopausal subgroups studied. When analysis was restricted to females of normal to low weight, spinal

BMAD was lower in blacks than whites, similar to that observed for spinal BMD. Spinal BMAD after adjustment for weight as a covariate remained similar in the pre- and postmenopausal blacks and whites. Femoral neck BMAD, before and after adjustment for covariates, was consistently higher in black females in all the comparable groups studied. Partial correction of bone size, via this volumetric calculation, thus increased bone mineral measurements of the black females relative to whites and resulted in similar mean volumetric spinal bone mineral density and significantly higher mean volumetric femoral bone mineral density in pre- and postmenopausal black women.

Numerous previous studies have reported that BMD is a major predictor of fracture risk in postmenopausal women^{12,13,30,106,109,130,135,136,156,180,319-321}. In general, for every SD that BMD is reduced, the risk of fragility fractures doubles¹⁶⁶. Most of these studies have been conducted in white female populations and less is known about the association of BMD with fracture risk in other ethnic populations. In a recent multi-ethnic study by Barrett-Conner et al¹³⁶, women with osteopenia or osteoporosis had an increased risk of fracture in every ethnic group, but the absolute risk of fracture at any given BMD differed among ethnic groups. These findings were confirmed in a prospective study by Cauley et al¹³⁵ who showed that reduced BMD of the total hip and femoral neck is associated with an increased risk of all non-spinal fractures in older black women, but that the absolute fracture incidence was 30 – 40% lower among black women compared with whites - the lower fracture rate in blacks was independent of BMD and other historical clinical risk factors and implied that non-BMD determinants of fracture risk may be responsible for the difference observed. The estimated volumetric apparent bone density of the femoral neck is not regarded as superior to femoral BMD in the prediction of hip fracture in elderly postmenopausal white women³²¹. As women of different racial and ethnic groups have substantially different sizes of femoral neck, BMAD might be a better predictor than BMD of hip fracture in a more diverse population.

BMD DISTRIBUTION AND FRACTURE RISK IN POSTMENOPAUSAL BLACK AND WHITE FEMALES

A significant percentage of postmenopausal black and white females in this study cohort had spinal and/or femoral osteopenia based on WHO criteria and as measured against a uniform white reference population. Spinal osteopenia was noted in a similar percentage of black and white females affecting ~50% of both postmenopausal groups. Spinal osteoporosis was present in 14% of black and white females. Although a higher percentage of white postmenopausal females had femoral osteopenia, a significant percentage of postmenopausal blacks also had femoral BMD measurements compatible with osteopenia (~30%). These data imply that, based on individual BMD measurements, a significant

percentage of postmenopausal black females in this study were also at increased risk of fracture.

The differences in mean BMD at most measured sites, along with the finding of spinal and femoral osteopenia in a significant percentage of both black and white postmenopausal female cohorts cannot explain the apparent marked difference in fracture risk observed in previous studies between black and white SA female populations. The higher mean areal and volumetric BMD at the femoral neck and total femoral sites in blacks may partially explain the finding of lower hip fracture risk in this ethnic group. It is doubtful whether the differences in mean areal and volumetric BMD at the femoral neck and total femoral sites between blacks and whites alone can explain a ten-fold difference in hip fracture risk and other non-BMD determinants of hip fracture risk must be considered as potential contributors such as differences in body size, bone geometry and bone quality.

Lumbar spine BMD was not higher in postmenopausal black women compared with white women and can thus not explain the lower vertebral fracture prevalence previously documented in SA blacks compared with whites²¹¹. Data pertaining to vertebral fracture prevalence in SA black females are, however, limited and old. The abovementioned disparity may thus be explained in more than one way. It may be that the assumed lower vertebral fracture prevalence previously reported in SA black women is not relevant at present and emphasize the need for further studies to clarify this issue. It has, on the other hand, been noted in other African populations that the prevalence of minimal trauma fractures is extremely low despite documented low spinal BMC and spinal BMD compared with British subjects²¹². These fractures do, however, refer mostly to non-spinal fractures and do not include the presence of asymptomatic vertebral deformities. If vertebral fracture prevalence in African blacks is indeed very low, it challenges the concept of bone mineral status as a primary determinant of vertebral fracture risk.

To conclude, we found that peak spinal BMD was lower, but peak femoral BMD similar or higher (depending on the specific proximal femoral site measured) in black South-African females compared with whites. The lower peak spinal BMD was mainly attributed to lower BMD's in the subgroup of black females with normal to low body weight indicating that obesity either protected black females against a low spinal BMD or enhanced optimal attainment of bone mineral. An apparent slower rate of decline in both spinal- and femoral BMD with ageing was noted in the black females compared with whites. This resulted in similar spinal BMD values in postmenopausal blacks and whites, and significantly higher femoral BMD measurements in blacks. The volumetric calculation of bone mineral apparent density at the lumbar spine and femoral neck yielded similar results to that of BMD. Spinal

BMAD was similar in blacks and whites and femoral neck BMAD was consistently higher in all the menopausal subgroups studied.

Weight significantly correlated with peak- and postmenopausal BMD at all sites in the black and white female cohorts. Greater and better maintained body weight may be partially responsible for slower rates of bone loss observed in black postmenopausal females. Most of the observed ethnic difference in BMD was explained by differences in body weight between the two cohorts and not by ethnicity per se. The modern tendency towards a lower ideal body weight in black urbanized societies may increase the likelihood of suboptimal attainment of peak BMD and may impact on bone loss rates with potentially lower BMD in later life in black populations of SA.

The differences in mean BMD at most measured sites, along with the finding of spinal and femoral osteopenia in a significant percentage of both black and white postmenopausal females, cannot explain the marked difference in fracture risk observed in previous studies between black and white SA female populations. The higher proximal femoral BMD results in postmenopausal blacks may increase bone strength in the hip region and protect against fragility fracture, but unlikely to fully account for a ten-fold difference in hip fracture risk. If the present prevalence of vertebral fractures is indeed lower in SA blacks, the lower or similar spinal bone density values in blacks compared with whites suggest that factors other than BMD are important determinants of vertebral bone strength in black South African females. BMD independent determinants of bone strength and fracture risk such as bone quality, bone geometry and fall risk must be considered in an attempt to explain ethnic differences in fracture risk in our study population.

.....

CHAPTER 6

WHICH CLINICAL RISK FACTORS ARE ABLE TO PREDICT *LOW BONE MASS* IN POSTMENOPAUSAL BLACK AND WHITE SOUTH AFRICAN FEMALES?

1.	INTRODUCTION.....	135
2.	PATIENTS AND METHODS	137
3.	RESULTS.....	138
3.1.	CLINICAL RISK FACTORS AND LOW BONE MINERAL DENSITY	138
3.1.1.	<i>Frequency of clinical risk factors by BMD status in the postmenopausal cohorts</i>	138
3.1.2.	<i>Association between individual risk factors and osteopenia</i>	141
3.1.2.1.	<i>Lumbar spine osteopenia.....</i>	141
3.1.2.2.	<i>Total hip osteopenia.....</i>	141
3.1.2.3.	<i>Femoral neck osteopenia</i>	141
3.1.3	<i>Use of Risk Assessment Tools</i>	142
3.1.3.1.	<i>Black cohort</i>	145
3.1.3.2.	<i>White cohort.....</i>	145
4.	DISCUSSION	145

CHAPTER 6

WHICH CLINICAL RISK FACTORS ARE ABLE TO PREDICT LOW BONE MASS IN POSTMENOPAUSAL BLACK AND WHITE SOUTH AFRICAN FEMALES?

1. INTRODUCTION

In recent years, BMD testing has become more widely available. Measuring BMD in all postmenopausal women is, however, logistically impossible, prohibitively expensive and probably unnecessary, since most postmenopausal women will have a normal bone mass and are at low risk of fracture. Targeted testing, i.e. testing persons identified as high risk of having osteoporosis (based on the presence of known clinical risk factors for low bone loss) is an appealing alternative. Assessment of clinical risk factors to identify women likely to benefit from BMD testing has great appeal especially in the primary care setting since it is inexpensive and readily obtainable.

Numerous studies on the ability of clinical risk factors to predict the presence of osteopenia have been reported^{101,115-119,126,128,236}. Large epidemiological and population based studies have noted that current anthropometric and lifestyle factors only explain 20 - 35% of the variance in bone density at different skeletal sites^{115,117}. Most of these studies have been performed in postmenopausal Caucasian females and there are only limited data available regarding risk factor assessment in other population groups^{118,119}.

Numerous simple risk assessment instruments have also been constructed to identify patients who are most likely to have a low BMD warranting a bone density test¹²⁰⁻¹²⁵. These risk instruments have been developed based on data obtained via epidemiological risk factor identification in Asian countries, the US and Europe. The purpose of these risk assessment tools is not to diagnose osteoporosis or low BMD, but to identify women who are more likely to have low BMD and who can then be selectively referred for BMD measurements. It is thus not necessary that a risk assessment tool has both a high sensitivity and specificity.

The Osteoporosis Self-assessment Tool (OST) is based simply on age and weight^{123,124} (table 1). The score is calculated by subtracting age from weight and then multiplying by 0.2¹²³. Lower OST scores are associated with greater likelihood of low BMD, and a score of <2 suggests that BMD be tested. It was developed and tested in women from eight Asian countries and yielded a sensitivity of 91% and a specificity of 45% to identify women with femoral neck osteoporosis (T-score \leq -2.5). It has been validated in several individual Asian countries and has also been validated in five large samples of primarily Caucasian

women^{122,124}. Other risk tools are also based on age and weight, in combination with up to four additional risk factors. These include, amongst others, the Osteoporosis Risk Assessment Instrument (ORAI) and the Osteoporosis Index of Risk (OSIRIS) [table 1]. ORAI differentially score weight and age within certain cut-off ranges and include hormone therapy as a risk index to identify women likely to have either femoral neck or lumbar spine T-scores ≤ -2.0 ¹²¹. Any patient with a score of 9 or higher would be advised to have BMD testing. The development cohort comprised women from the Ontario participants in the Canadian Multicenter Osteoporosis Study (CaMOS) and in this population the sensitivity was 90% and the specificity was 45%. The Osteoporosis Index of Risk (OSIRIS) is based on four variables: age, body weight, current hormone therapy and a history of previous low impact fractures²²⁴. The sensitivity and specificity for the OSIRIS value of +1 were respectively 78.5% and 51.4%. The cohort studied was 1303 postmenopausal Canadian women from an out-patient osteoporosis clinic. The performance of these risk assessment tools in multi-ethnic populations has never been published.

Table 1: Clinical Risk Assessment Instruments – Calculation of the evaluated indices

Factor	Score
ORAI	
Age > 75 years	+ 15
Age 65–74 years	+ 9
Age 55–64 years	+ 5
Body weight < 60 kg	+ 9
Body weight 60–70 kg	+ 3
Oestrogen therapy	+ 2 if not currently using oestrogen
OSIRIS	
Body weight (kg)	+ 0.2 x body weight
Age (years)	- 0.2 x age
History of low impact fracture(s)	- 2
Oestrogen therapy	+ 2
OST	
Body weight (kg)	
Age (years)	0.2 x (body weight-age)

This chapter reports on the ability of historical risk factors to predict low bone mass and on the performance of risk assessment instruments in our population of black and white South African females.

2. PATIENTS AND METHODS

BMD was normal in the majority of premenopausal subjects thus making it near impossible to determine the impact of clinical risk factors in them. The analysis of risk based on the presence of historical risk factor(s) or via the use of risk assessment tools was thus restricted to postmenopausal blacks and whites.

Hormone treated white postmenopausal females were included in the analysis of frequency of individual clinical risk factors by BMD status. Individual risk factors were thus assessed in 100 blacks and 110 whites (clinical characteristics of postmenopausal study cohort as outlined in chapter 4, table 1 & 3).

Risk assessment tools and general discriminant analysis models were evaluated in the non-hormone treated cohorts only, since hormone therapy was used almost exclusively by whites. This cohort thus included 97 blacks and 66 whites, (clinical characteristics of postmenopausal non-hormone treated cohort as outlined in chapter 5, table 1).

The standardization of risk categories are described in detail in chapter 3 (please refer to section 2.1.1.1). Age was also included in this analysis of risk as the postmenopausal group was evaluated in total, and age was regarded as a clinical risk factor if ≥ 65 years.

The frequency for each risk factor (refer to chapter 3, section 2.1.1.1) in patients with normal bone mass (BMD T-score > -1) and in those with osteopenia (BMD T-score ≤ -1 SD) was determined for spinal and femoral sites (tables 2 & 3). The BMD of all patients were measured against a uniform white reference population (in this study we used a white female reference population to calculate T- and Z-scores for both ethnic groups as no normative data for black South African women exist, previously outlined in chapter 3, section 2.2.1.).

General discriminant analysis was used to identify variables able to predict osteopenia in postmenopausal black and white females (table 4). Associations were determined between clinical risk factors and low BMD (T-score ≤ -1 SD as assessed against a uniform white reference population) at the lumbar spine and at the proximal femur (total BMD and femoral neck BMD).

We calculated risk assessment scores based on the OST, OSIRIS and ORAI tools, and evaluated the performance of these tools in identifying non-hormone treated postmenopausal black and white women at risk of osteopenia i.e. a T-score ≤ -1 at various BMD measurement sites (table 5). These risk tools were originally evaluated in terms of their

ability to predict the presence of osteoporosis (T-score ≤ -2.5) or moderate osteopenia (T-score of ≤ -2). Due to very limited numbers of black and white patients with a proximal femoral T-score ≤ -2 , we used ≤ -1 as our cut-off at all skeletal sites, but also evaluated the performance of these risk tools in individuals with a lumbar spine T-score ≤ -2 .

The sensitivity, specificity, positive predictive value and negative predictive value for each of the risk assessment tools within the specific ethnic groups were also calculated.

Cross tabulation and the Chi-square test was used to determine univariate relationships between risk factors and low bone mass. For multivariate prediction of low bone mass in all subsets, linear discriminant analysis was used to pick out the best combinations of predictor variables.

3. RESULTS

3.1. CLINICAL RISK FACTORS AND LOW BONE MINERAL DENSITY

3.1.1. Frequency of clinical risk factors by BMD status in the postmenopausal cohorts

Amongst the black females, the only clinical risk factor that was associated with osteopenia at all skeletal sites was a low weight and BMI. The association between body size, expressed as body weight ($p=0.02$) or BMI ($p<0.01$) was strongest for spinal osteopenia. Only one black female with low body weight and none of the black females with a low BMI had normal spinal BMD. The presence of these anthropometric findings thus indicated a high risk for spinal osteopenia in black females (high specificity 98-100%, positive predictive value 91-100%). The majority of black females with spinal osteopenia were, however, of normal weight (80%) and BMI (88%) and although a significant association was observed between these risk factors and spinal osteopenia, the sensitivity ($<20\%$) and negative predictive value ($\sim 50\%$) were very poor, implying that many normal to overweight black females also have osteopenia. Older age and a low physical activity score were present in a significantly higher percentage of black females with femoral neck osteopenia compared to those with normal femoral neck BMD. The past use of oral contraceptives or Depo Provera did not impact on the presence of osteopenia in the black cohort.

The frequency distribution of clinical risk factors within the white female cohort, based on the presence or absence of osteopenia, is remarkably similar irrespective of the skeletal site affected (tables 2,3). Older age, low body weight and the non-use of hormone therapy was consistently associated with osteopenia at all skeletal sites. The frequency of hormone

therapy use was significantly higher in the normal BMD subgroups for all skeletal sites compared with the osteopenic groups ($p < 0.01$). A normal BMD at the spine and femoral sites was documented in 83% (spinal), 90% (total femoral) and 71% (femoral neck) of white postmenopausal females on hormone therapy. A significant percentage of postmenopausal white females not on hormone therapy, however, also had normal BMD measurements thus limiting the specificity of this factor to predict protection against osteopenia (sensitivity:78%; specificity:53%). Previous oral contraceptive users were evenly distributed in the normal BMD and osteopenic subgroups.

Table 2: Clinical factors that affect risk for spinal bone loss in white and black postmenopausal females

Clinical Risk Factor	BLACK COHORT			WHITE COHORT		
	Normal (n=43)	Osteopenia (n=51)	<i>p-value</i>	Normal (n=74)	Osteopenia (n=36)	<i>p-value</i>
Age (>65yrs)	12 (28)	17 (33)	0.41	13 (18)	13 (36)	0.04
Weight (≤ 60 kg)	1 (2)	10 (20)	0.02	14 (19)	13 (36)	0.07
Height (≤ 156 cm)	13 (30)	13 (25)	0.49	12(16)	9 (25)	0.31
BMI (< 23 kg/m ²)	0 (0)	6 (12)	<0.01	17 (23)	13 (35)	0.18
Daily Ca-intake (< 500 mg/d)	17 (40)	13 (25)	0.15	5 (7)	2 (6)	0.84
Current smoking (Y)	8(19)	7 (14)	0.49	30(41)	8 (22)	0.02
Low PA (score ≤ 2)	25 (58)	38 (75)	0.09	28 (38)	16 (43)	0.51
Alcohol usage (Y)	11 (26)	11 (22)	0.65	27 (36)	17 (46)	0.25
Maternal history of OP (Y)	0 (0)	1 (2)	-	16 (22)	10 (28)	0.51
Oral contraceptive use (Y)	12 (28)	9 (18)	0.23	32 (43)	18 (50)	0.55
Depo Provera use (Y)	10 (23)	7 (14)	0.23	2 (3)	1 (3)	-
Hormone therapy (Y)	2 (5)	0 (0)	-	40 (54)	8 (22)	<0.01
Breastfeeding (Y)	35 (81)	40 (78)	0.72	47 (64)	24 (67)	0.82
High parity (≥ 3)	33 (78)	40 (78)	0.84	43 (58)	20 (56)	0.79

(Y): yes, indicating presence of specific risk factor. Expressed as number of patients, percentage of patients in brackets, *p-value* refers to comparison of specific ethnic cohort and skeletal site measured

Table 3: Clinical factors that affect risk for hip bone loss in white and black postmenopausal females

Clinical Risk Factor	Femur total						Femur neck					
	BLACK COHORT			WHITE COHORT			BLACK COHORT			WHITE COHORT		
	Normal n=69	Osteopenia n=27	<i>p-value</i>	Normal n=74	Osteopenia n=36	<i>p-value</i>	Normal n=62	Osteopenia n=33	<i>p-value</i>	Normal n=57	Osteopenia n=53	<i>p-value</i>
Age (>65 yrs)	20 (30)	8 (30)	<i>0.57</i>	11 (15)	15 (42)	<i>0.02</i>	13 (22)	14 (42)	<i>0.03</i>	7 (12)	19 (36)	<i>0.03</i>
Weight (≤60 kg)	6 (9)	6 (22)	<i>0.73</i>	12 (16)	15 (42)	<i><0.01</i>	5 (8)	7 (21)	<i>0.73</i>	8 (14)	19 (36)	<i>0.05</i>
Height (≤ 156 cm)	18 (26)	9 (33)	<i>0.44</i>	6 (8)	12 (33)	<i>0.01</i>	14 (23)	12 (36)	<i>0.16</i>	7 (12)	14 (26)	<i>0.06</i>
BMI (<23kg/m²)	2(3)	4(15)	<i>0.04</i>	17(23)	113(36)	<i>0.14</i>	2(3)	4(12)	<i>0.09</i>	12(21)	18(34)	<i>0.14</i>
Calcium (<500mg/d)	23(33)	7(26)	<i>0.55</i>	6(8)	1(1)	<i>0.26</i>	20(32)	9(27)	<i>0.61</i>	4(7)	3(6)	<i>0.82</i>
Current smoking	12 (14)	4 (15)	<i>0.79</i>	30 (41)	11 (31)	<i>0.42</i>	12 (19)	4 (12)	<i>0.39</i>	20 (35)	19 (36)	<i>0.96</i>
Low PA (score ≤ 2)	46(67)	18(67)	<i>0.81</i>	31(42)	14(39)	<i>0.39</i>	37(60)	27(82)	<i>0.02</i>	25(44)	18(34)	<i>0.26</i>
Alcohol usage (Y)	14(20)	9(33)	<i>0.16</i>	27(36)	16(44)	<i>0.41</i>	13(21)	9(27)	<i>0.49</i>	20(35)	23(43)	<i>0.21</i>
F/H of OP (Y)	0(0)	1(4)	<i>0.11</i>	16(22)	10(28)	<i>0.44</i>	0(0)	1(3)	-	11(19)	15(28)	<i>0.27</i>
Depo Provera use (Y)	13 (19)	4 (15)	<i>0.69</i>	1 (1)	2 (6)	<i>0.21</i>	14 (23)	4 (12)	<i>0.20</i>	0 (0)	3 (6)	-
OC use (Y)	17(25)	5(19)	<i>0.57</i>	35(47)	15(42)	<i>0.66</i>	17(27)	5(15)	<i>0.17</i>	28(49)	22(42)	<i>0.42</i>
Hormone therapy (Y)	2 (3)	0 (0)	-	43 (58)	5 (14)	<i><0.01</i>	2 (3)	0 (0)	-	34 (60)	14 (26)	<i><0.01</i>
Breastfeeding (Y)	56 (81)	20 (74)	<i>0.65</i>	48 (65)	23 (64)	<i>0.94</i>	49 (79)	27 (82)	<i>0.75</i>	36 (63)	35 (66)	<i>0.76</i>
High parity (≥3)	53 (77)	20 (74)	<i>0.79</i>	40 (54)	23 (64)	<i>0.29</i>	47 (76)	25 (76)	<i>0.55</i>	33 (59)	30 (57)	<i>0.98</i>

(Y): yes, indicating presence of specific risk factor. Values expressed as absolute number with percentage in brackets p-value refers to comparison of specific ethnic cohort and skeletal site measured

3.1.2. Association between individual risk factors and osteopenia

General discriminant analysis identified clinical risk factor subsets best able to identify osteopenia in postmenopausal blacks and whites (table 4).

3.1.2.1. Lumbar spine osteopenia

Discriminant analysis identified 3 variables used for combined prediction of spinal osteopenia in blacks namely *low body weight, low physical activity score and a low calcium intake*. The model was able to correctly identify 74% of blacks with spinal osteopenia. The absence of these risk factors correctly predicted normal bone mass in 71% of black subjects. In the postmenopausal white cohort, 4 variables were identified by discriminant analysis to be associated with osteopenia, *namely low body weight, high parity, breastfeeding and alcohol usage*. This model was able to correctly identify 75% of whites with spinal osteopenia. The absence of these risk factors correctly predicted normal bone mass in 54% of white females.

3.1.2.2. Total hip osteopenia

Variables identified by discriminant analysis for prediction of total femoral osteopenia in blacks included a *low body weight, breastfeeding and smoking* whereas only a *low body weight* was identified in whites. This model was able to correctly identify the presence of a low BMD in 78% of black females and in only 56% of white postmenopausal women. The absence of a low body weight correctly predicted normal total femoral BMD in 69% and 83% of the postmenopausal blacks and whites respectively.

3.1.2.3. Femoral neck osteopenia

Discriminant analysis identified 5 variables used for combined prediction of femoral neck osteopenia in blacks namely *low body weight, low BMI, low physical activity score, high parity and prior use of oral contraception*. The model was able to correctly identify 67% of blacks with femoral neck osteopenia. The absence of these risk factors correctly predicted normal femoral neck BMD in 63% of black subjects. In the postmenopausal white cohort, 2 variables were identified by discriminant analysis, *namely a low body weight and prior use of oral contraceptives*. This model was able to correctly identify only 58% of whites with femoral neck osteopenia. The absence of these risk factors correctly predicted normal femoral neck BMD in 100% of white females.

Table 4: Risk factors identified by general discriminant analysis to predict osteopenia in black and white females

	<i>Risk factor subset</i>	<i>PPV</i>	<i>NPV</i>
LUMBAR SPINE BMD			
Blacks	<i>Low body weight, low PA, low calcium-intake</i>	74%	71%
Whites	<i>Low body weight, high parity, breastfeeding, alcohol usage</i>	75%	54%
TOTAL FEMORAL BMD			
Blacks	<i>Low body weight, breastfeeding, smoking</i>	78%	69%
Whites	<i>Low body weight</i>	56%	83%
FEMORAL NECK BMD			
Blacks	<i>Low body weight, low BMI, low PA, high parity, prior use OC</i>	67%	63%
Whites	<i>Low body weight, prior use of OC</i>	58%	100%

PPV: positive predictive value, NPV: negative predictive value Risk factor subset: risk factors as listed in tables 17 and 18

3.1.3. Use of Risk Assessment Tools

The majority of postmenopausal black and white females included in this study cohort fell into the low risk category for all three risk tools (table 5). Increasing prevalence of osteopenia (T-score ≤ -1 at all sites, T-score ≤ -2 at lumbar spine) with ascending risk category low to moderate was apparent for all three risk tools in both black and white postmenopausal females. Due to the very small percentage of the total patient population in the high risk category, this trend was not universally apparent with ascending risk category from moderate to high risk. An increased prevalence of osteopenia of the lumbar spine in the black cohort and of the femur neck region in whites was, however noted with ascending risk category moderate to high for all three risk tools. The ORAI risk assessment instrument was most sensitive in both ethnic groups and thus identified most women to be at risk (moderate to high risk categories). The prevalence of lumbar spine osteopenia in the black cohort was 44%, 60% and 100% at the low (58% of black women), moderate (37% of black women) and high (5% of black women) ORAI risk levels respectively. In the white cohort, the prevalence of femoral neck osteoporosis was 39%, 72% and 78% at the low (36% of white women), moderate (50% of white women) and high (14% of white women) ORAI risk levels respectively.

The sensitivity, specificity, positive predictive value and negative predictive value for each of the risk assessment tools are tabulated in table 6 (black cohort), table 7 (white cohort) and table 8 (black and white cohort, lumbar spine T-score ≤ -2).

Table 5: Prevalence of low BMD by BMD measurement site and risk category

Risk category	Total n=97 (100%)	Postmenopausal black females				Total n=66 (100%)	Postmenopausal white females			
		Osteopenia: T-score ≤ -1		T-score ≤ -2			Osteopenia: T-score ≤ -1		T-score ≤ -2	
		Hip (28%)	FN (35%)	L1-L4 (53%)	L1-L4 (30%)		Hip (48%)	FN (61%)	L1-L4 (44%)	L1-L4 (23%)
OST										
>1 (low risk)	83%	24%	27%	45%	25%	59%	34%	37%	34%	16%
-3 to 1 (moderate risk)	14%	38%	78%	83%	50%	35%	64%	77%	64%	38%
<-3 (high risk)	3%	33%	33%	100%	67%	6%	75%	100%	50%	40%
<2*	26%	32%	64%	78%	42%	55%	64%	83%	61%	37%
OSIRIS										
>1(low risk)	77%	19%	23%	44%	25%	55%	29%	40%	29%	11%
-3 to 1 (moderate risk)	20%	53%	79%	79%	47%	38%	71%	88%	67%	42%
<-3 (high risk)	3%	33%	33%	100%	67%	8%	80%	100%	60%	40%
$\leq 1^*$	23%	50%	73%	82%	50%	45%	72%	90%	66%	41%
ORAI										
<9 (low risk)	58%	22%	18%	44%	23%	36%	26%	39%	30%	13%
9-17 (moderate risk)	37%	40%	60%	60%	37%	50%	56%	72%	56%	31%
>17 (high risk)	5%	20%	40%	100%	60%	14%	67%	78%	44%	33%
$\geq 9^*$	41%	38%	59%	67%	40%	64%	58%	73%	54%	32%

Hip: Total hip; FN: Femoral neck; L1-L4: Lumbar spine L1 to L4.

*Scores for each Instrument used to recommend BMD testing^{70,72-73}.

Table depicts percentage of patients with osteopenia (defined by a T-score of ≤ -1 or ≤ -2) within different risk categories for the different risk assessment instruments i.e. low risk, moderate risk and high risk at the different skeletal sites i.e. total hip, femoral neck and lumbar spine

Table 6: Performance of the risk indices by BMD measurement site and T-score cut-off (%) in blacks

	Total hip (T-score < -1)				Femoral neck (T-score < -1)				Lumbar spine (T-score < -1)				Any site (T-score < -1)			
	Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV
OST (<2 vs. ≥ 2)	27	80	33	74	42	89	67	74	33	91	81	53	37	100	100	51
OSIRIS (≤ 1 vs. >1)	40	84	50	81	48	88	73	77	36	91	82	56	38	95	91	55
ORAI (< 9 vs. ≥ 9)	52	69	40	78	65	79	63	80	52	80	74	60	53	89	86	53

Table 7: Performance of the risk indices by BMD measurement site and T-score cut-off (%) in whites

	Total hip (T-score < -1)				Femoral neck (T-score < -1)				Lumbar spine (T-score < -1)				Any site (T-score < -1)			
	Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV
OST (<2 vs. ≥ 2)	66	64	64	66	63	71	79	53	72	67	64	75	62	75	85	47
OSIRIS (≤ 1 v.s >1)	68	76	72	71	65	88	90	60	66	71	66	71	63	90	93	54
ORAI (< 9 vs. ≥ 9)	81	55	63	75	78	63	78	63	79	50	56	75	76	65	83	54

Table 8: Performance of the risk indices by BMD measurement site and T-score cut-off of < -2 (%) in blacks and whites

	Lumbar spine -Blacks (T-score < -2)				Lumbar spine- Whites (T-score < -2)			
	Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV
OST (<2 vs. ≥ 2)	33	79	42	72	45	69	37	75
OSIRIS (≤ 1 v.s >1)	38	83	50	75	75	65	34	89
ORAI (< 9 vs. ≥ 9)	55	64	40	77	81	42	32	87

3.1.3.1. Black cohort

All three risk assessment tools had very low sensitivity to identify black individuals with osteopenia at the different skeletal sites. Sensitivities of these risk tools were unacceptably low as screening instruments in blacks with the best performer, the ORAI risk tool, only reaching sensitivities of 50-65% at the different skeletal sites. The specificity of these risk assessment tools in the black cohort was substantially better i.e. these instruments were able to correctly identify 80-100% of the black female cohort with normal BMD at most of the skeletal sites (see table 5). The OSIRIS and OST tools had better specificity at all skeletal sites compared with the ORAI tool.

3.1.3.2. White cohort

The ORAI tool had the highest sensitivity for low BMD at all skeletal sites, similar to that observed in blacks. Risk tools were universally more sensitive to predict osteopenia in whites, with sensitivities of the ORAI risk tool >75% for all skeletal sites in whites. The OSIRIS tool was most specific re low BMD at all skeletal sites with values ranging between 71-90% (most specific for femoral neck osteopenia).

4. DISCUSSION

A low body weight and *advanced age* was identified as by far the most informative individual risk factors for osteopenia in our black and white females, whereas physical inactivity was also identified as an important individual risk factor in blacks only. *A low body weight* was noted more frequently amongst blacks and whites with osteopenia at all skeletal sites measured. Low body weight was, however, only present in a minority of both black and white females (10% of blacks, 20% of whites). The majority of blacks and whites with osteopenia were of normal weight thus resulting in poor sensitivity of low body weight to predict the presence of osteopenia. An *older* age was noted more frequently amongst whites with osteopenia at all skeletal sites and in blacks with femoral neck osteopenia. *Physical inactivity* was significantly associated with femoral neck osteopenia in blacks, whereas the frequency of physical inactivity amongst normal BMD and osteopenic whites was similar for all sites measured. In whites, *hormone therapy* use was significantly higher in the normal BMD group at all skeletal sites compared with the osteopenic groups ($p < 0.01$). The majority of whites on hormone therapy had normal BMD measurements (sensitivity 78%), but many females not on hormone therapy also had normal BMD measurements thus limiting the specificity of this factor to predict protection against osteopenia (58%). The frequency of other risk factors i.e. daily dietary calcium-intake, current smoking, alcohol intake,

breastfeeding, high parity and use of hormonal contraception did not differ significantly between the black and white normal BMD and osteopenic subgroups.

Combinations of clinical risk factors are also useful to identify patients at highest risk of osteopenia. In our study, specific risk factor subsets identified by general discriminant analysis as best able to identify the osteopenic individual, differed between the two ethnic groups and for different skeletal sites. The positive predictive value of these risk factor subsets were similar for the lumbar spine in blacks and whites (~75%), but higher in blacks (67-78%) compared with whites (56-58%) for the proximal femoral sites. The absence of the specific risk factor subsets for the proximal femoral sites in whites (low body weight ± use of oral contraceptives), however, excluded osteopenia in 83-100% of cases.

Risk assessment tools

In our study, the risk assessment tools evaluated i.e. OST, OSIRIS and ORAI, were found to be of limited value to differentiate women with normal BMD from those with osteopenia i.e. T-scores of ≤ -1 at all sites and T-scores of ≤ -2 at the lumbar spine. As alluded to before, these risk tools were originally evaluated in terms of their ability to predict the presence of osteoporosis (T-score ≤ -2.5) or moderate osteopenia (T-score of ≤ -2) in Asian and Caucasian populations^{121-124,224}. Due to very limited numbers of black and white patients with a proximal femoral T-score ≤ -2 , we used ≤ -1 as our cut-off at all skeletal sites, but also evaluated the performance of these risk tools in individuals with a lumbar spine T-score ≤ -2 .

Although increased risk of osteopenia was noted with ascending risk categories for all risk assessment tools evaluated, they were not sensitive enough to effectively identify women with osteopenia who should undergo BMD testing in our study cohort. All these tests depend heavily on body weight i.e. a low body weight determines, to a great extent, categorization into low and high risk groups. Calculations developed for the OST and OSIRIS are identical for incorporation of weight and age into the final score, therefore, in any individual where weight exceeds age, a positive score will be obtained and the patient will thus be categorized as low risk in the absence of fragility fractures. The ORAI tool more specifically scores individuals based on the presence of specific weight ranges and was documented to be the most sensitive tool to depict osteopenia in both our black and white female groups. In the blacks' sensitivities for the ORAI were still unacceptable low (52-65%) at all sites, whereas sensitivities approached 80% in whites. These tools were mainly developed in Asia, Europe and Canada where average body size are significantly smaller than in our study cohort and calculations of these risk tools thus appear to be inappropriate for our heavier study group.

To conclude,

- Low body weight and advanced age were significantly associated with osteopenia at most skeletal sites in our blacks and whites. Low weight (<60 kg) only affected a small subset of our study population with low BMD and therefore, although highly specific, low body weight had poor sensitivity to identify individuals with osteopenia.
- Risk assessment tools, developed and validated in Asian and European populations, demonstrated poor sensitivity for identification of SA women at increased risk of osteopenia. The ORAI showed the best results, with sensitivities to identify osteopenic whites' at most skeletal sites approaching 80% (78% - 81%). A higher percentage of our study population categorized as low risk by the risk assessment instruments had osteopenia compared to the study populations in which these tools were validated. The risk assessment tool scores appear to be inappropriate for our larger sized study cohort, especially our black subjects, thus resulting in incorrect risk stratification and poor test sensitivity.
- *Risk factor subsets* identified for combined prediction of osteopenia were most sensitive in *blacks* at all skeletal sites, whereas the *ORAI* risk tool was more sensitive than discriminant analysis risk models for combined prediction of osteopenia in *whites*. Local risk factor questionnaires should, among others, include all the risk factors identified by our general discriminant analyses i.e. low body weight and BMI, physical inactivity, low calcium intake, current smoking and alcohol intake, high parity and past use of oral contraceptives.
- Larger population based studies are needed in South Africa to better define the role of clinical risk factors and usefulness of risk assessment instruments. Risk assessment instruments and scores more relevant to our population should be developed to ensure improved sensitivity.
- In a developing country with limited resources, where BMD measurement is not feasible in all postmenopausal females, identification of optimal risk factor subsets and development of easy to use risk assessment instruments may help to ensure that BMD resources are allocated to those who are most likely to benefit.

.....

CHAPTER 7

CALCANEAL ULTRASONOGRAPHY IN BLACK AND WHITE SOUTH AFRICAN FEMALES

1.	INTRODUCTION.....	149
2.	PATIENTS AND METHODS	151
3.	RESULTS.....	154
3.1.	Quantitative Ultrasound parameters.....	154
3.1.1.	<i>Premenopausal cohort.....</i>	154
3.1.2.	<i>Postmenopausal cohorts.....</i>	154
3.2.	Correlations of QUS parameters	158
3.2.1.	<i>QUS parameters and DEXA measured lumbar spine and femoral BMD.....</i>	158
3.2.1.1.	<i><u>Premenopausal cohorts</u></i>	158
3.2.1.2.	<i><u>Postmenopausal cohorts</u>.....</i>	159
3.2.2.	<i>QUS parameters and age.....</i>	159
4.	DISCUSSION	163

CHAPTER 7

CALCANEAL ULTRASONOGRAPHY IN BLACK AND WHITE SOUTH AFRICAN FEMALES

1. INTRODUCTION

The most commonly used tool for assessing bone mineral density (BMD) is dual-energy X-ray absorptiometry (DEXA). Although precise, this method provides almost no information about the bone microarchitecture and elasticity. Since microfractures and bone architectural changes may contribute to weakening, a combination of information about bone elasticity, structure and density might be a more sensitive predictor of fracture risk than DEXA, which measures only density. Quantitative ultrasound may be a useful measure of both the quality and quantity of bone. The technology has evolved from the observation that sound waves through porous materials like bone are absorbed, scattered and travel in a manner that reflects the elasticity, stiffness and to a lesser degree the density of the material^{229,323}. Indirect and in-vitro experience has suggested that ultrasonography may give information not only about the bone density, but also about the bone structure, trabecular orientation and micro-architecture²²⁸⁻²³⁰. The speed with which sound travels through bone (SOS) has been shown to be a function of both the elasticity of the bone as well as its density²²⁹. Broadband ultrasound attenuation (BUA) has been found to be related, not only to BMD, but also to architectural characteristics such as trabecular density, spacing and orientation²²⁸⁻²³⁰.

In the past ~ 20 years quantitative ultrasound (QUS) methods have been introduced for the assessment of skeletal status in osteoporosis. QUS is particularly attractive as a measurement tool because it is simple, inexpensive, portable, non-invasive and free of ionizing radiation. As such, QUS has much greater potential for widespread application than traditional X-ray bone densitometry approaches and would thus be a good candidate for screening purposes. The association between QUS and osteoporotic fractures (both non-spinal and vertebral fractures), especially in elderly Caucasian women, has shown promising results in many studies^{226,324-331}. Fracture risk discrimination by means of QUS was about as strong as for absorptiometric techniques such as DEXA. Four independent prospective studies with sample sizes of 400 – 10 000 women showed that QUS results (as measured at the calcaneus) can be used to predict fracture risk in early postmenopausal^{227,321} and older^{226,325} Caucasian women. Two QUS parameters were shown to perform equally well: BUA^{226,227,321} and SOS^{227,325}. Results from two of these studies (EPIDOS³²⁵ and SOF²²⁶ studies) are shown in Figures 1 & 2, demonstrating the increase in non-spine fracture risk. The gradients of risk reported for QUS were similar to those for DEXA.

All the aforementioned studies also reported that QUS parameters predicted fractures independently of BMD^{226,227,321,325}, hence the assumption that QUS also measures bone properties other than BMD. Correlations between QUS measurements and DEXA measured BMD of the spine and the proximal femur have been found to be modest ($r < 0.5$) and QUS results can therefore not be used to predict BMD of the main fracture sites^{332,333}. Whether a combined assessment of QUS and DEXA measured bone density improve fracture risk prediction remains controversial³³⁴ and requires further studies.

Although calcaneal QUS is an independent predictor of OP fractures, the widespread clinical use of QUS has been hampered by the absence of a generally accepted fracture threshold³³⁵, limited normative data, uncertainty regarding its reproducibility (precision) and sensitivity to monitor skeletal changes.

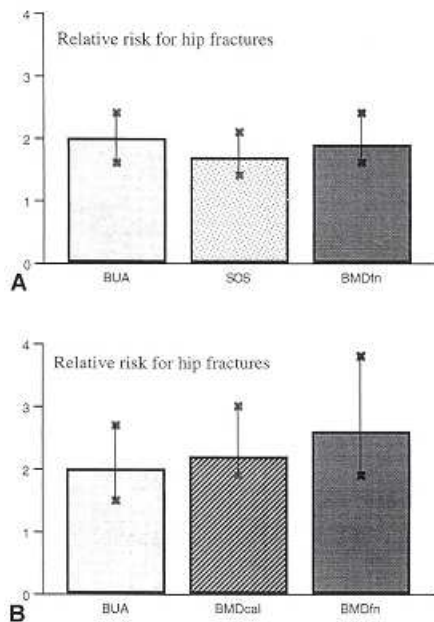


Figure 1: Relative risk of hip fractures as predicted prospectively from QUS (BUA,SOS) of the calcaneus, and BMD calcaneus (BMDcal) and the femoral neck BMD (BMDfn) measured with DEXA. Expressed as relative risk ratios per standard deviation change with 95% confidence intervals. Adapted from the EPIDOS study³²⁵ [A] and the SOF study²²⁶ [B].

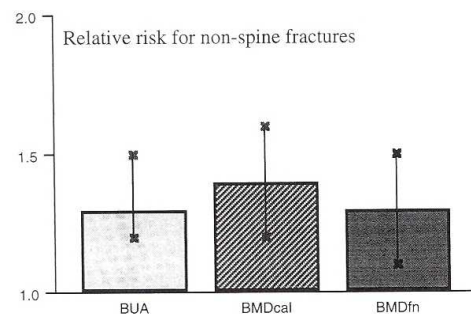


Figure 2: Relative risk of fractures of any type except spine fractures as predicted prospectively from QUS (BUA) of the calcaneus, and BMD calcaneus (BMDcal) and the femoral neck BMD (BMDfn) measured with DEXA. Expressed as relative risk ratios per standard deviation change with 95% confidence intervals. Adapted from the SOF study²²⁶.

Older African-American blacks have greater ultrasonographic BUA and SOS values compared with whites in most^{336,337} but not all studies¹⁸⁹. Most of the ethnic difference in these QUS parameters is, however, eliminated when corrected for weight and DEXA measured BMD. No data are available on racial differences in calcaneal ultrasonography in South African females.

2. PATIENTS AND METHODS

Calcaneal QUS, employing the SAHARA Clinical Bone Sonometer, was performed on 230 pre- and postmenopausal black and white subjects, 97 blacks and 133 whites. This sub-cohort was randomly selected based on test availability.

QUS calcaneal broadband ultrasound attenuation (BUA) and speed of sound (SOS) were measured and the quantitative ultrasound index calculated ($QUI = 0.41 \times SOS + 0.41 \times BUA - 571$). A 'predicted' calcaneal ultrasound BMD value was obtained by a simple re-scaling of the QUI value and is reported as the 'estimated' heel BMD in g/cm^2 . Using the manufacturer's (Sahara) normative range for *Caucasian females*, a BMD T-score was also calculated in both black and white postmenopausal subjects.

Ethnic differences in QUS measurements were analyzed and are reported on in the following patient subgroups:

- Premenopausal black and white subgroups
- Early and late postmenopausal black and white groups as outlined in Chapter 3, section 1.3.

Parameters directly measured by the Sahara Clinical Bone Sonometer i.e. BUA and SOS were compared between the two ethnic groups before and after adjustment for covariates. For the pre- and postmenopausal subjects, covariates included ethnicity, age, weight, height, daily calcium intake, physical activity, pack years of smoking, alcohol usage, age at menarche, hormonal contraceptive use and number of prior pregnancies. In the postmenopausal cohorts years after menopause was also included as covariate. BUA and SOS were also compared between blacks and whites after adjustment for differences in DEXA measured BMD of the spine and proximal femur in both pre- and postmenopausal cohorts in order to demonstrate ethnic differences in QUS parameters independent of DEXA measured BMD.

Correlations between QUS parameters and DEXA measured BMD at the lumbar spine and proximal femur, as well as correlations between QUS parameters and age in the total patient population and the postmenopausal cohort respectively, were determined and are reported on in this chapter.

The baseline clinical characteristics (table 1) of black and white females studied were identical to the total study cohort (refer to chapter 4, tables 1 & 5). Blacks and whites had similar mean ages in all the comparable groups studied. In general, blacks were shorter and

heavier than whites, reached menarche at a later age, preferred injectable hormone contraception, had a larger number of pregnancies and consumed less calcium daily. The white women smoked more, but maintained a higher level of physical activity post menopause. Mean alcohol consumption was low and comparable between the two groups.

Table 1: Baseline characteristics of the ultrasound study cohort

Characteristic	Premenopausal			Postmenopausal					
	Blacks n=39	Whites n=73	p-value	<60 years		≥ 60 years			
				Blacks n=27	Whites n=32	p-value	Blacks n=31	Whites n=28	p-value
Age (yr)	38 ± 7.9	39 ± 6.4	0.41	52 ± 7	52 ± 4.6	0.47	68 ± 6.0	70 ± 5.6	0.09
Height (cm)	161 ± 6	167 ± 6	<0.01	160 ± 7	166 ± 6	<0.01	158 ± 6	160 ± 7	0.16
Weight (kg)	78 ± 19	70 ± 15	<0.01	76 ± 16	71 ± 17	0.11	84 ± 18	71 ± 16	<0.01
BMI (kg/cm ²)	30 ± 7	25 ± 5	<0.01	30 ± 8	26 ± 6	<0.01	34 ± 8	28 ± 5	<0.01
Elbow width (mm)	65.6 ± 5.3	65.5 ± 3.4	0.47	67 ± 3.3	66 ± 4.2	0.28	68 ± 6.1	68.8 ± 4.0	0.43
Age at menarche (yrs)	14.8 ± 2.1	13.2 ± 1.6	<0.01	14 ± 1.8	13 ± 2.0	0.03	15 ± 2.1	13 ± 1.4	<0.01
Age menopause (yrs)				47 ± 5.0	49 ± 3.8	0.02	50 ± 4.9	49 ± 4.7	0.20
YSM (yrs)				6.1 ± 4.1	3.7 ± 3.9	0.02	18.5 ± 8.3	20 ± 6.8	0.19
Ca intake (mg/d)	644 ± 307	882 ± 272	<0.01	572 ± 222	879 ± 237	<0.01	668 ± 338	820 ± 266	0.05
Smoking (pack yrs)	0.6 ± 2.1	1.8 ± 4.7	0.06	1.5 ± 2.7	5.2 ± 11.6	0.05	0.3 ± 1.4	6.8 ± 13.7	<0.01
Alcohol (U/week)	5.7 ± 10.3	4.0 ± 4.8	0.13	5.9 ± 14.0	3.2 ± 5.2	0.1	2.0 ± 5.1	2.0 ± 3.8	0.5
PA score (0-4)	2.7 ± 0.9	2.8 ± 1.0	0.28	2.4 ± 1.1	3.1 ± 0.8	<0.01	1.9 ± 0.8	2.4 ± 0.8	0.01
OCP use (%)	31	71		19	56		26	25	
DP use (%)	38	3		26	3		3	0	
Nr of pregnancies (n)	2.3 ± 1.5	1.8 ± 1.2	0.02	3.6 ± 2.6	1.9 ± 1.5	<0.01	5.0 ± 2.4	3.8 ± 1.6	0.01
Breastfeeding + (%)	70	58		78	62		88	68	

Values reported are the mean ± SD

YSM: years since menopause; PA: physical activity; DP: depo provera; OCP: oral contraceptive

3. RESULTS

3.1. Quantitative Ultrasound parameters

3.1.1. Premenopausal cohort

All QUS parameters were higher in the premenopausal blacks compared to whites, but the ethnic difference only reached significance for SOS and QUI (table 2). In the premenopausal cohort ethnicity was the only clinical covariant significantly associated with BUA and SOS. Ultrasound data thus remained unchanged after adjustment for clinical covariates between the two ethnic groups. Body size, based on weight and height, was significantly associated with densitometric evaluations of the lumbar spine and femoral region in the premenopausal cohorts (chapter 5), but did not have a significant impact on ultrasound parameters.

Table 2: Unadjusted ultrasound findings in the black and white premenopausal cohorts

Ultrasonographic parameters	Premenopausal subjects		
	Blacks n=39	Whites n=73	p-value
Calcaneal BMD (g/cm ²)	0.617 ± 0.15	0.565 ± 0.13	0.06
BUA (dB/MHz)	83.5 ± 22.0	75.2 ± 18.4	0.08
SOS (m/s)	1577 ± 36	1563 ± 33	0.04
QUI (0-150)	109.7 ± 23.1	100.9 ± 20.3	0.04

Values expressed as mean ± SD

Adjustment of BUA and SOS for DEXA measured BMD at the lumbar spine and proximal femoral sites resulted in significantly higher values in blacks compared with whites (table 3).

Table 3: Adjusted ultrasound findings in the black and white premenopausal cohorts

*Adjusted ultrasonographic parameters	Premenopausal subjects		
	Blacks n=39	Whites n=73	p-value
BUA (dB/MHz)	82.5 ± 21	75.2 ± 18	0.02
SOS (m/s)	1576 ± 36	1564 ± 33	0.04

*Ultrasonographic parameters adjusted for DEXA measured BMD at the lumbar spine and proximal femoral sites. Values expressed as mean ± SD

3.1.2. Postmenopausal cohorts

Ultrasound parameters in the postmenopausal cohorts are depicted in table 4 and illustrated in figure 3. Mean calcaneal BMD, BMD T-score, unadjusted SOS and BUA and the calculated

quantitative ultrasound index (QUI) were similar in the early postmenopausal black and white female cohort. Amongst the clinical covariates weight was significantly associated with BUA ($p=0.02$) and height with SOS ($p<0.01$). After appropriate adjustment for clinical variables and DEXA measured BMD, BUA and SOS remained similar in the early postmenopausal blacks and whites. However, all ultrasound parameters were significantly higher in the older postmenopausal black subjects compared with the white subjects with the exception of weight adjusted BUA. In the late postmenopausal cohorts calcium intake was significantly associated with SOS ($p<0.01$), whereas age ($p=0.02$) and weight ($p<0.01$) were both associated with BUA. BUA was still higher in the older blacks after correction for body weight, the difference nearing statistical significance ($p=0.06$). After adjustment for DEXA measured BMD at the lumbar spine and at the proximal femoral sites, BUA and SOS remained higher in the older postmenopausal blacks and whites, reaching statistical significance for BUA only (table 4)

QUS parameters were identical in the younger and older black postmenopausal females. This finding is suggestive of limited decline in QUS measurements with ageing in blacks. In contrast to this observation in blacks, significantly lower values for all QUS parameters was noted in the older versus the younger postmenopausal white females (even after correction of BUA and SOS for DEXA measured BMD) and implies a significant decline in QUS parameters in whites with ageing. This pattern of change in QUS parameters is similar to DEXA measured BMD changes at the spine and proximal femur in ageing blacks and whites (refer to chapter 5, sections 2.2.1 and 3.2.1).

Table 4: Ultrasound findings in postmenopausal black and white females

	Postmenopausal females					
	< 60 years			≥ 60 years		
	Blacks (n=27)	Whites (n=32)	<i>p-value</i>	Blacks (n=31)	Whites (n=28)	<i>p-value</i>
Calcaneal BMD (g/cm²)	0.510 ± 0.16	0.516* ± 0.12	0.47	0.512 ± 0.18	0.413 ± 0.11	0.03
BMD T-score	-0.62 ± 1.4	-0.58* ± 1.0	0.44	-0.61 ± 1.6	-1.51 ± 0.9	0.02
BUA (dB/MHz)						
Unadjusted	69.3 ± 21	71.0* ± 17	0.63	69.3 ± 27	53.1 ± 15	0.01
Adjusted for age	-	-	-	68.1 ± 21	54.4 ± 21	0.01
Adjusted for weight	68.0 ± 25	72.0* ± 25.1	0.41	66.7 ± 21	55.8 ± 21	0.06
Adjusted for DEXA measured BMD**	67.8 ± 22	71.0* ± 17	0.16	69.3 ± 26	53.8 ± 15	0.02
SOS (m/s)						
Unadjusted	1551 ± 39	1551* ± 30	0.73	1551 ± 46	1528 ± 28	0.03
Adjusted for height	1545 ± 35	1557 ± 35	0.23	-	-	-
Adjusted for calcium-intake	-	-	-	1554 ± 36	1520 ± 38	<0.01
Adjusted for DEXA measured BMD**	1549 ± 39	1551 ± 30	0.55	1550 ± 46	1529 ± 28	0.11
QUI (0-150)	93.1 ± 24.0	92.9* ± 19.0	0.49	93.3 ± 29.1	77.4 ± 16.7	0.02

Values expressed as mean ± SD, *p*-values shown in table refer to inter-ethnic differences within younger and older cohort

Unadjusted BUA and SOS values shown in green

* QUS parameter significantly higher in early postmenopausal white cohort compared with late postmenopausal white cohort (*p*<0.05)

** Adjusted for DEXA measured BMD of the lumbar spine and proximal femoral sites

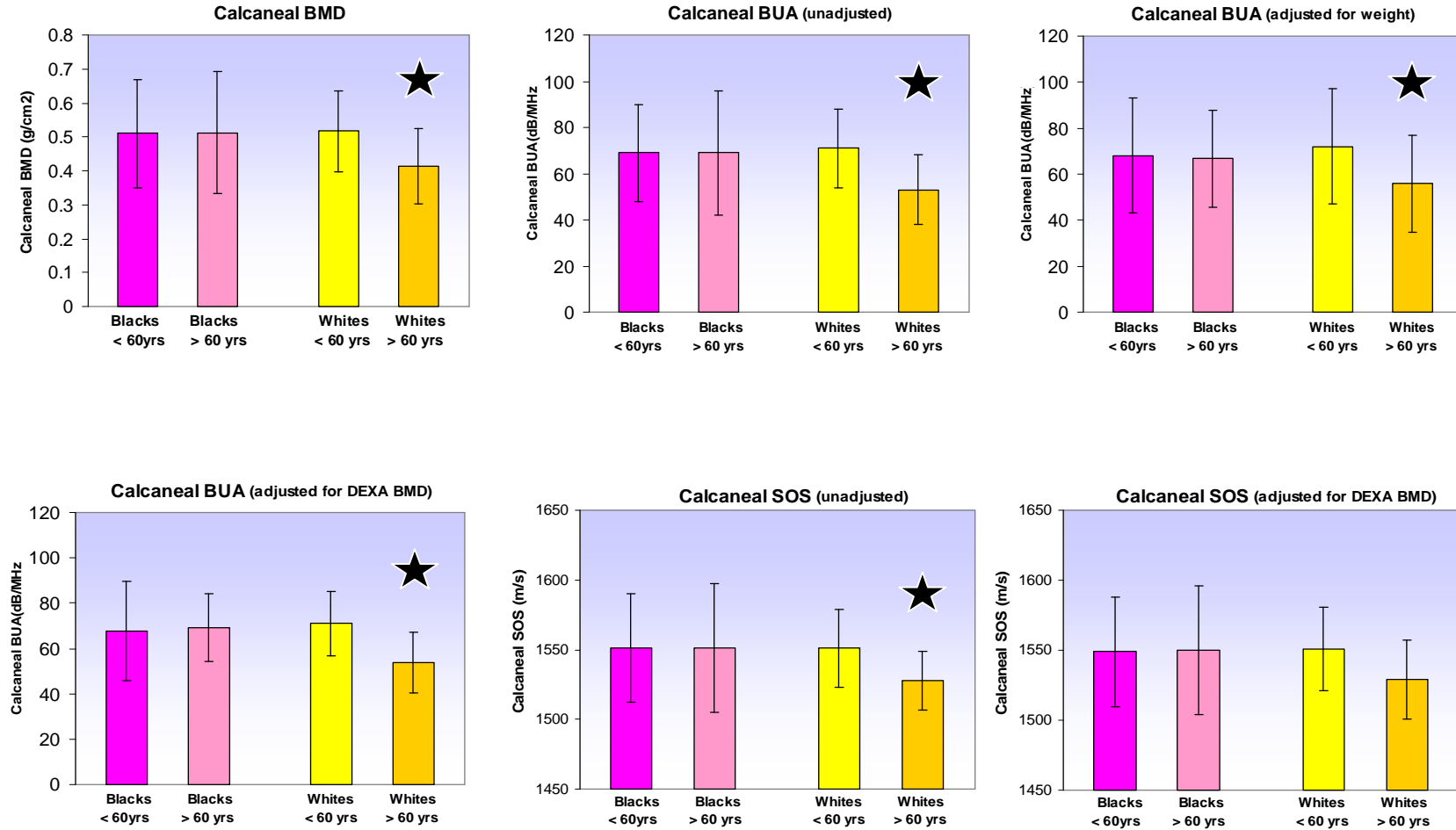


Figure 3: Ultrasound findings in postmenopausal black and white females. Measurements significantly different from others indicated by ★ (p-value < 0.05) .

3.2. Correlations of QUS parameters

3.2.1. QUS parameters and DEXA measured lumbar spine and femoral BMD

3.2.1.1. Premenopausal cohorts

Calcaneal BMD

Calcaneal BMD did not correlate with DEXA measured BMD at the lumbar spine or proximal femur in blacks, whereas significant, albeit weak, correlations were noted between calcaneal BMD and DEXA measured BMD at both the lumbar and proximal femoral sites in whites (table 5).

BUA, SOS and the QUI

A correlation between QUS parameters and DEXA measured BMD in premenopausal blacks was limited to a significant correlation between QUS BUA and total femoral BMD ($r=0.40$; $p=0.02$). In the white cohort significant correlations between DEXA findings at the spine and proximal femur and all these QUS variables was evident with the best correlation noted between QUS BUA and DEXA measured BMD at all sites (table 5). These correlations were, however modest with r -values <0.5 .

Table 5: Correlation between DEXA measured BMD at different skeletal sites and QUS variables in premenopausal black and white females

DEXA measurements	QUS variables							
	BMD (g/cm ²)		SOS (m/sec)		BUA (dB/MHz)		QUI /Stiffness	
	<i>r-value</i>	<i>p-value</i>	<i>r-value</i>	<i>p-value</i>	<i>r-value</i>	<i>p-value</i>	<i>r-value</i>	<i>p-value</i>
<i>Lumbar spine BMD</i>								
Black	0.22	0.20	0.19	0.26	0.26	0.13	0.22	0.20
White	<i>0.32</i>	<i><0.01</i>	<i>0.29</i>	<i>0.01</i>	<i>0.40</i>	<i><0.001</i>	<i>0.34</i>	<i><0.01</i>
<i>Femoral neck BMD</i>								
Black	0.22	0.21	0.16	0.36	0.30	0.08	0.21	0.22
White	<i>0.31</i>	<i><0.01</i>	<i>0.28</i>	<i>0.02</i>	<i>0.37</i>	<i><0.01</i>	<i>0.32</i>	<i>0.01</i>
<i>Total femoral BMD</i>								
Black	0.31	0.07	0.24	0.16	<i>0.40</i>	<i>0.02</i>	0.31	0.07
White	<i>0.29</i>	<i>0.01</i>	<i>0.23</i>	<i>0.05</i>	<i>0.33</i>	<i><0.01</i>	<i>0.28</i>	<i>0.02</i>

Significant correlations noted in italic red

3.2.1.2. Postmenopausal cohorts

Calcaneal BMD

Calcaneal BMD did not correlate significantly with DEXA measured lumbar spine BMD in the early and late postmenopausal blacks, whereas a significant correlation was demonstrated between calcaneal BMD and most of the DEXA measured proximal femoral BMD measurements. In whites significant correlations between calcaneal BMD and DEXA measured BMD at both the lumbar spine and proximal femoral sites were noted in the early postmenopausal cohort, whereas no correlation was noted in the older whites. Significant correlations were, similar to the premenopausal group, modest with r-values of 0.48-0.52.

BUA, SOS and the QUI

Amongst these QUS parameters, BUA correlated best with DEXA measured BMD in both the black and white cohorts. BUA correlated significantly with BMD at most proximal femoral sites in both the early and late black and white cohorts. BUA also correlated significantly with spinal BMD in the late postmenopausal black cohort and in both the early and late postmenopausal white cohorts. QUS SOS correlated significantly only with DEXA measured BMD of the total proximal femur in early and late postmenopausal black cohorts. In whites, significant correlation between QUS SOS and DEXA measured BMD at all sites could be demonstrated in the early postmenopausal cohort only (table 6).

3.2.2. QUS parameters and age

Age was negatively related to all ultrasound parameters in the total black and the white study population (figure 4). In the postmenopausal cohorts, a significant negative correlation between age and QUS parameters was present in whites (figure 5). Due to the apparent minimal decline in all QUS parameters in ageing postmenopausal blacks, the regression lines for all these measurements had an insignificant slope with advancing age.

Table 6: Correlation between DEXA measured BMD at different skeletal sites and QUS variables in postmenopausal black and white females

DEXA measurements	QUS variables							
	BMD (g/cm ²)		SOS (m/sec)		BUA (dB/MHz)		QUI /Stiffness	
	<i>r-value</i>	<i>p-value</i>	<i>r-value</i>	<i>p-value</i>	<i>r-value</i>	<i>p-value</i>	<i>r-value</i>	<i>p-value</i>
Lumbar spine BMD								
<i>EARLY postmenopausal</i>								
Black	0.24	0.23	0.21	0.29	0.24	0.22	0.23	0.25
White	0.50	<0.01	0.44	0.01	0.56	<0.01	0.52	0.01
<i>LATE postmenopausal</i>								
Black	0.33	0.07	0.27	0.14	0.45	0.01	0.34	0.06
White	0.29	0.12	0.20	0.29	0.42	0.02	0.29	0.12
Femoral neck BMD								
<i>EARLY postmenopausal</i>								
Black	0.39	0.04	0.32	0.10	0.45	0.02	0.38	0.05
White	0.48	<0.01	0.41	0.02	0.52	0.03	0.48	0.01
<i>LATE postmenopausal</i>								
Black	0.31	0.09	0.29	0.11	0.32	0.08	0.31	0.09
White	0.24	0.20	0.17	0.37	0.34	0.07	0.24	0.20
Total femoral BMD								
<i>EARLY postmenopausal</i>								
Black	0.57	<0.01	0.50	<0.01	0.52	<0.01	0.52	<0.01
White	0.52	<0.01	0.44	0.01	0.56	<0.01	0.52	0.01
<i>LATE postmenopausal</i>								
Blacks	0.40	0.02	0.37	0.04	0.43	0.02	0.40	0.03
Whites	0.27	0.16	0.19	0.32	0.37	0.04	0.27	0.16

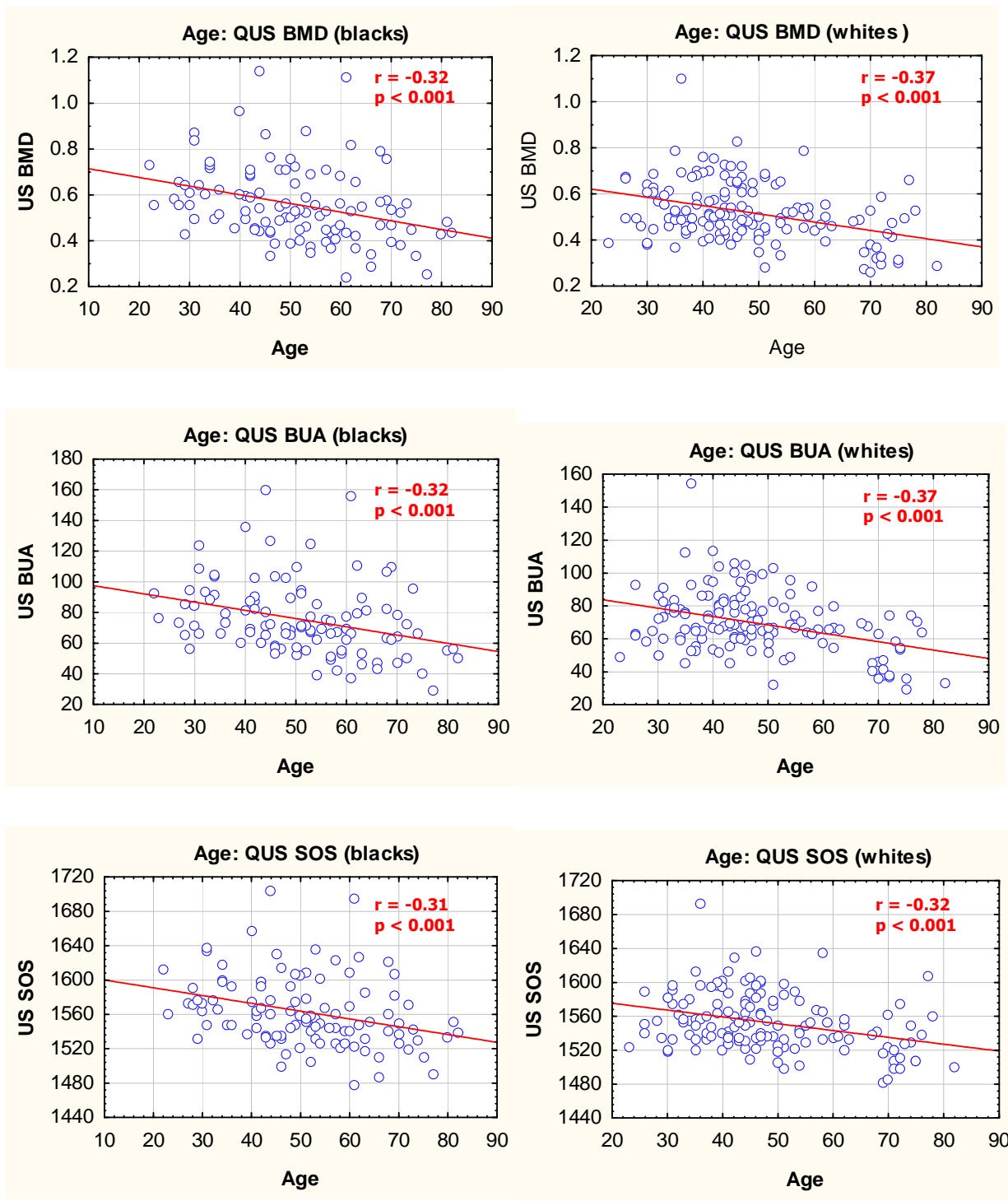


Figure 4: Correlation of age with calcaneal BMD, BUA and SOS in the total black and white study population

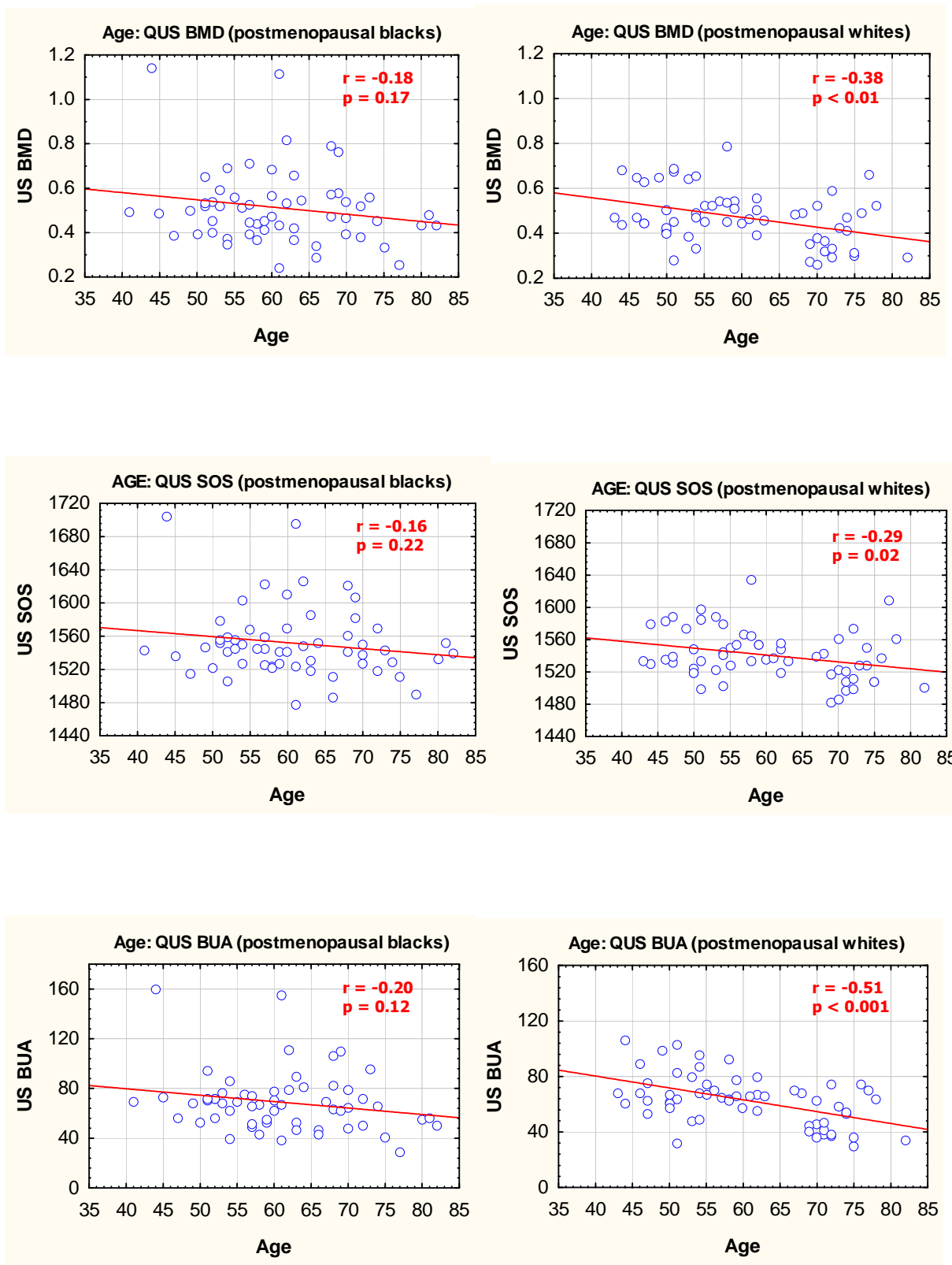


Figure 5: Correlation of age with calcaneal BMD, BUA and SOS in the postmenopausal black and white female cohorts

4. DISCUSSION

As alluded to previously (chapter 5), the lower fracture rates among SA black women relative to Caucasian women could not be readily explained on the basis of a significantly higher DEXA measured bone mineral density at all skeletal sites. Ethnic comparison of calcaneal QUS was thus performed in an attempt to determine why fracture rates vary so much between ethnic groups.

QUS measurements were mostly similar in premenopausal and younger postmenopausal blacks and whites in this study population, but statistically significantly higher in older blacks compared with whites. Taking due cognizance of the limitations inherent to a cross-sectional study, this data do, however, suggest a faster rate of decline in QUS parameters with ageing in whites compared with blacks. Older blacks had similar QUS values compared with younger blacks suggesting an insignificant deterioration with ageing, whereas most QUS measurements were significantly lower in older whites compared with their younger counterparts.

Calcaneal QUS BMD was similar in the premenopausal and early postmenopausal black and white females, but significantly higher in the late postmenopausal black females. Our data, although cross-sectional in nature, thus suggests a slower rate of decline with ageing in blacks. The higher calcaneal BMD in the older black females in our study is consistent with previous reports in American elderly black populations¹⁸⁹ and similar to our DEXA BMD findings. Differing patterns of DEXA measured bone loss were also observed between these two ethnic groups with a slower rate of decline at the spine and proximal femur in postmenopausal blacks compared with whites (refer to chapter 5, sections 2.2.1 and 3.2.1) and are in agreement with data from previous studies regarding bone loss in multi-ethnic populations both locally^{1, 213} and abroad^{139,184,197}. Black females in our study thus appear to preserve BMD (as measured by DEXA and QUS) better into old age.

Inter-ethnic differences in unadjusted calcaneal BUA, SOS and calculated QUI were similar to that observed for calcaneal and DEXA measured BMD i.e. these variables were mostly similar in the younger black and white subgroups (premenopausal and early postmenopausal groups), but consistently and significantly higher in older blacks compared with whites. Weight adjustment attenuated the observed ethnic difference in BUA and although BUA was still higher in older blacks, the difference only neared significance ($p=0.06$).

Correction of BUA and SOS for other clinical covariates (weight excluded) with significant univariate association resulted in modest changes. Adjusted SOS and BUA thus remained

significantly higher in older black females compared with whites. After adjustment of BUA and SOS for DEXA measured spinal and femoral BMD, both QUS parameters remained higher in the older blacks compared with whites, but only the BUA difference reached statistical significance. Greater ultrasonographic BUA and SOS values have been noted in older African-American women compared with whites in most^{336,337} but not all studies¹⁸⁹. Correction for weight and DEXA measured BMD attenuated, but did not eliminate, the ethnic differences in QUS parameters in these studies^{336,337}, findings in accordance with that observed in our study.

BMD-adjusted BUA and SOS values appeared to decline significantly with ageing in postmenopausal whites with lower values recorded in the older versus the younger white postmenopausal women ($p < 0.05$). In contrast to our findings in whites, QUS values were similar in younger and older postmenopausal blacks, thus suggestive of minimal loss in the postmenopausal period. No longitudinal prospective studies comparing changes in BUA and SOS with ageing in postmenopausal women of different ethnicities have been published to date. It is thus not known whether other black populations preserve QUS parameters differently into old age compared with whites.

Prospective studies in postmenopausal Caucasian women have shown that QUS parameters can be used to predict fracture risk independently of BMD^{226,227,321,325}, hence the assumption that QUS measures bone qualitative parameters independently of BMD. Histomorphometric analyses previously carried out on iliac crest bone from 171 South African black and 175 white men and women revealed significant racial differences in trabecular bone architecture with ageing¹³¹. Black females showed no decline in trabecular number and no increase in trabecular separation, whereas whites suffered deterioration of trabecular architecture with regard to trabecular thickness, number and connectivity. The trabecular bone of South African blacks therefore appeared to have a sturdier microstructure, and underwent a less destructive ageing process than that of South African whites. If QUS parameters indeed measure bone qualitative properties independent of BMD, our QUS data support these histomorphometric findings of better bone quality preservation in elderly SA blacks. BUA, specifically, has been proposed to measure, not only BMD, but also architectural characteristics such as trabecular density, spacing and orientation²²⁸⁻²³⁰. In our study, BUA was found to be statistically significantly higher in older blacks compared with whites, even after correction for differences in DEXA measured BMD, and thus supports previously reported histomorphometric findings¹³¹ of better trabecular preservation with ageing in blacks. A reduced absolute fracture risk at any given BMD value, has been documented in blacks^{135,136} compared with whites. This implies that ethnic differences may exist in factors,

other than BMD, which affect bone fragility. Improved bone quality (as determined by QUS) in our elderly blacks may thus help to explain the lower fracture prevalence previously documented in SA blacks compared with whites.

In our study, the correlation between calcaneal BMD and DEXA measured BMD differed in blacks and whites by age and site, and was noticeably poorer in blacks compared with whites (see tabulated summary below). Amongst the QUS measurements, BUA correlated best with DEXA measured spinal and femoral BMD in both blacks and whites. The majority of previous studies assessing correlations between QUS measurements and DEXA determined BMD are limited to evaluation of the association between femoral BMD and QUS variables^{189,325,329} and furthermore often only look at a single QUS parameter such as BUA¹⁸⁹. Correlations between QUS parameters and DEXA measured BMD of the spine and the proximal femur have been found to be modest (range of r-values 0.4 – 0.7), in previous studies^{332,333} and are in accordance with our findings. Most of these studies have, however, been performed in Caucasian populations and very little is known regarding the association between QUS measurements and DEXA measured BMD in other ethnic groups.

SUMMARY: Correlation between DEXA measured BMD and different QUS parameters

DEXA measured BMD	Female subgroups studied		
	Premenopausal	Early postmenopausal	Late postmenopausal
<i>WHITES</i>			
Lumbar	+++	+++	BUA+
Total femoral	+++	+++	BUA+
Femoral neck	+++	+++	NIL
<i>BLACKS</i>			
Lumbar	NIL	NIL	BUA+
Total femoral	BUA+	+++	+++
Femoral neck	NIL	BMD+ // BUA+	NIL

+++ : correlation significant for all QUS parameters, +: as specified, NIL: no correlation with any QUS parameters

The reason(s) for the poorer correlation between BUA and SOS, and DEXA measured BMD at all sites in blacks compared with whites are not known. Previous studies have suggested an increased likelihood of unreliable QUS findings in African Americans compared with whites²²⁸. This may in part be due to larger body size reported to add to technical difficulties with ultrasonography in previous studies²²⁸. Preservation of bone quality, independently of BMD, may also potentially contribute to the limited association between QUS and DEXA measured BMD noted in blacks.

In summary:

- Elderly black SA women have higher calcaneal BMD than white women.
- Significant ethnic differences in absolute values and apparent patterns of decline in BUA and SOS were noted. Higher QUS measurements were documented in our elderly blacks compared with whites, even after correction for differences in DEXA determined BMD at the spine and proximal femoral sites.
- BUA and SOS showed no decline with ageing in blacks, in contrast to a significant deterioration in both parameters in ageing whites.
- If these QUS parameters do measure qualitative properties of bone in our black population, independent of BMD, as has been suggested in previous work in Caucasian populations, the higher values documented in elderly blacks imply better preservation of bone quality and may indeed help to explain the lower fracture prevalence in SA black women previously documented.
- the correlation between calcaneal BMD and DEXA measured BMD at the hip and spine was best in the premenopausal and younger postmenopausal white groups and generally poorer in blacks. At best, these correlations were modest and QUS calcaneal BMD thus unable to predict DEXA measured BMD at clinically important fracture sites.
- BUA was the QUS parameter that correlated best with DEXA measured BMD. A poorer correlation between BUA and SOS and DEXA measured BMD at all sites was, however, noted in blacks compared with whites. This may indicate preservation of QUS measured bone quality in blacks that are not associated and thus independent of DEXA determined BMD.

To conclude, elderly SA black women have significantly higher BUA and SOS measurements (even after correction for differences in DEXA measured spine and hip BMD) compared with whites due to an apparent slower rate of decline with ageing. These results suggest that racial differences in bone quality, as measured by ultrasound attenuation and speed of sound, may contribute to the lower fracture prevalence previously documented in SA blacks. Prospective longitudinal studies are needed to confirm our findings obtained in this cross-sectional work.

.....

CHAPTER 8

BONE TURNOVER, MINERAL HOMEOSTASIS AND CALCIOTROPIC HORMONES IN BLACK AND WHITE SOUTH AFRICAN FEMALES.

1.	INTRODUCTION.....	168
2.	PATIENTS AND METHODS	169
3.	RESULTS.....	171
3.1.	Biochemistry.....	171
3.1.1.	<i>Biochemical assessment of bone turnover.....</i>	171
3.1.1.1.	<i><u>Premenopausal subjects</u></i>	171
3.1.1.2.	<i><u>Postmenopausal subjects</u></i>	172
3.1.2.	<i>Mineral status and calciotropic hormones.....</i>	175
3.1.2.1.	<i><u>Premenopausal subjects</u></i>	175
3.1.2.2.	<i><u>Postmenopausal subjects</u></i>	177
3.1.3.	<i>Correlation between biochemical parameters.....</i>	179
3.1.3.1.	<i><u>Premenopausal subjects</u></i>	179
3.1.3.2.	<i><u>Postmenopausal subjects</u></i>	179
3.1.4.	<i>Correlation between biochemistry and BMD of the spine and hip.....</i>	179
3.1.4.1.	<i><u>Premenopausal subjects</u></i>	179
3.1.4.2.	<i><u>Postmenopausal subjects</u></i>	179
3.1.5.	<i>Densitometry in postmenopausal black and white subgroups based on PTH-tertiles</i>	179
4.	DISCUSSION.....	185

CHAPTER 8

BONE TURNOVER, MINERAL HOMEOSTASIS AND CALCIOTROPIC HORMONES IN BLACK AND WHITE SOUTH AFRICAN FEMALES.

1. INTRODUCTION

Bone strength is a function of both BMD and bone quality. Bone quality describes the set of characteristics that influence bone strength independently of BMD and include structural and material properties. Bone turnover is a function of the bone renewal process in which old or damaged bone is resorbed (bone resorption) and new bone is created (bone formation) to replace it. Under normal circumstances the temporal sequence is always that of resorption followed by formation, with these processes tightly coupled and balanced, to ensure that the amount of bone resorbed and formed within individual bone remodeling units are quantitatively similar. An imbalance of bone turnover may significantly impact on BMD and bone quality with high turnover states generally regarded as deleterious to bone (please refer to chapter 2, section 3.1.2.1).

Ethnic variation in bone formation and/ or bone resorption rates during skeletal development and adult remodeling may help to explain observed ethnic differences in BMD as well as bone strength independent of BMD.

Serum osteocalcin is a marker of bone formation and normal to high levels may indicate adequate bone formation and as such be positively associated with bone strength. Given the normal temporal sequence of events, high osteocalcin levels may also be an indirect marker of increased bone resorption and may as such be negatively associated with BMD and bone strength. Urinary free deoxypyridinoline is a degradation product of the bone resorption process. Elevated levels imply increased bone resorption with expected negative effects on BMD and bone quality.

Histomorphometric studies on racial differences in bone turnover in blacks and whites have yielded conflicting results. Schnitzler et al¹³¹ have reported histomorphometric evidence suggesting that black South Africans have higher rates of bone turnover than whites. The authors, contrary to current belief, hypothesized that the more frequent cycles of renewal would ensure better bone quality and hence, favorably influence fracture rates in blacks. In contrast to this study, Weinstein and Bell¹⁴⁰ reported lower bone turnover in blacks. On the assumption that coupling between resorption and formation is maintained, the authors suggested that a lower rate of bone resorption would help maintain a higher peak bone mass

in blacks. However, the number of subjects in each group was small, and data from men and women were combined in this study. Parisien et al²⁰⁴ found no difference in histomorphometric turnover parameters between black and white premenopausal women, whereas Han and co-workers¹⁴¹ noted a 25% lower mean bone formation rate in both premenopausal and postmenopausal blacks compared with whites.

Most previous studies biochemically assessing bone turnover rates in blacks and whites by looking at serum osteocalcin and urinary pyridinium cross-link excretion have documented either a similar turnover^{144,145}, or lower turnover^{138,142,146,186,196} in blacks. Most studies have reported similar urinary pyridinium cross-link excretion in pre- and postmenopausal Caucasians and African-Americans^{142,144,185,186}. In the only study to date in which bone turnover was assessed biochemically in South African blacks and whites, turnover was similar in blacks and whites⁵. No data is available regarding ethnic differences in biochemical bone turnover markers with ageing.

Lower serum 25-hydroxy-vitamin D, lower urinary calcium excretion rates and higher serum PTH have been documented in African-Americans^{138,145-147,196} and in South African blacks⁵ compared with whites. These biochemical findings, in the presence of similar or lower bone turnover rates and generally higher femoral BMD documented in blacks compared to whites, have prompted the theory of a relative skeletal resistance to the action of PTH in blacks.

2. PATIENTS AND METHODS

We evaluated biochemical bone turnover rates, mineral status and calciotropic hormones in a group of black and white premenopausal and postmenopausal South African females. Please refer to Chapter 3, section 2.6 for details regarding laboratory methodology.

The clinical characteristics of the study cohort are shown in table 1. The premenopausal cohort consisted of 70 black females and 63 white females. The early and late postmenopausal cohorts were identical to those evaluated for BMD (chapter 5, table 1) and included a total of 97 black subjects and 66 white females. Premenopausal women taking oral estrogens or depo provera within the month before blood and urine collections were excluded from this analysis. All premenopausal subjects reported a regular menstrual cycle and the postmenopausal state was confirmed biochemically in all the females classified as postmenopausal (FSH>40mIU/l). None of the subjects sustained a fracture within 12 months before blood or urine collections.

Table 1: Summary of anthropometric, lifestyle and menstrual data of the study cohort

Clinical characteristics	Premenopausal			Postmenopausal					
				< 60 years			≥ 60 years		
	Blacks n=70	Whites n=63	<i>p-value</i>	Blacks n=49	Whites n=35	<i>p-value</i>	Blacks n=48	Whites n=31	<i>p-value</i>
Age (yr)	38 ± 8	39 ± 6	0.14	52 ± 6	52 ± 5	0.43	68 ± 6	70 ± 5	0.49
Height (cm)	159 ± 6	167 ± 6	<0.01	160 ± 7	166 ± 7	<0.01	159 ± 6	160 ± 7	0.16
Weight (kg)	80 ± 21	69 ± 14	<0.01	80 ± 19	71 ± 17	<0.01	86 ± 19	72 ± 15	<0.01
BMI (kg/cm ²)	32 ± 8	25 ± 5	<0.01	32 ± 8	26 ± 6	<0.01	34 ± 8	28 ± 5	<0.01
Waist/Hip ratio (cm)	0.84 ± 0.1	0.78 ± 0.1	<0.01	0.87 ± 0.1	0.79 ± 0.1	<0.01	0.90 ± 0.1	0.88 ± 0.1	0.03
Elbow width (mm)	65 ± 5	66 ± 3	0.78	67 ± 4	66 ± 4	0.15	68 ± 6	68 ± 5	0.23
Age at menarche(yrs)	15 ± 3	13 ± 2	<0.01	14 ± 2	13 ± 2	<0.01	14 ± 2	13 ± 1	<0.01
Menopause age (yrs)				46 ± 5	49 ± 4	0.02	49 ± 5	49 ± 5	0.20
YSM (yrs)				7 ± 5	4 ± 4	0.04	19 ± 8	21 ± 7	0.37
Calcium intake (mg/d)	591 ± 308	901 ± 268	<0.01	597 ± 237	879 ± 230	<0.01	667 ± 304	821 ± 272	<0.01
Smoking (pack yrs)	0.7 ± 2.0	4.1 ± 19.3	0.08	1.6 ± 4.7	5 ± 11	<0.01	0.17 ± 1	8.9 ± 14.1	<0.01
Alcohol (U/week)	4.5 ± 9.6	3.7 ± 4.5	0.28	3.7 ± 11	2.9 ± 5.1	0.17	1.4 ± 4.2	1.8 ± 3.8	0.3
PA score (0-4)	2.8 ± 0.9	2.8 ± 0.9	0.35	2.4 ± 1	3.1 ± 0.9	0.04	1.9 ± 0.9	2.7 ± 0.8	<0.01
Family history (%)	1	25		2	29		0	13	
OCP use (%)	16	68		16	54		29	30	
DP use (%)	39	2		33	6		6	2	
Nr of pregnancies (n)	3 ± 2	2 ± 1	0.03	3 ± 2	2 ± 1	<0.01	6 ± 3	4 ± 2	<0.01
Breastfeeding+ (%)	70	58		78	62		88	68	

Values expressed as mean ±SD except where otherwise stated, *p-values* tabulated refer to comparison between ethnic groups within specific menopausal subgroup

Clinical characteristics of the black and white pre-and postmenopausal cohorts were similar to that of the densitometric study population, with the exception that alcohol intake did not differ significantly between this cohort of premenopausal black and white females (p=0.28).

ANOVA was used to determine significant ethnic differences in biochemical measurements between the various patient subgroups. Spearman correlations were used to determine relationships between certain biochemical measurements (serum osteocalcin, urinary free DPD, serum PTH and serum 25-OH-Vitamin D) as well as between these biochemical measurements and DEXA determined BMD at the spine and proximal femoral sites. Densitometric findings were furthermore compared within the two ethnic groups based on PTH tertiles.

3. RESULTS

3.1. BIOCHEMISTRY

3.1.1. Biochemical assessment of bone turnover

3.1.1.1. Premenopausal subjects

SERUM OSTEOCALCIN

Serum osteocalcin levels were similar in premenopausal black and white females (table 2, figure 1).

URINARY FREE DEOXYPYRIDINOLINE (DPD)

A tendency towards lower urinary DPD was noted in blacks compared with whites, but statistical significance was not reached (table 2, figure 2).

Table 2: Biochemical parameters of bone turnover in premenopausal subjects

Biochemical Parameter	Premenopausal females			Normal values
	<i>Blacks</i> (n=70)	<i>Whites</i> (n=63)	<i>p-value</i>	
<i>Serum</i> Osteocalcin (ng/ml)	7.8 ± 7.8	7.2 ± 6.8	0.33	2.4 - 10.0
<i>Urine</i> Free DPD/creatinine (nmol/mmol)	5.45 ± 4.13	6.80 ± 2.73	0.07	3.0 - 7.4

Values are the mean ± SD, p-values in the table refer to comparison between premenopausal blacks and whites

3.1.1.2. Postmenopausal subjects

SERUM OSTEOCALCIN

Changes in osteocalcin levels with ageing are demonstrated in figure 1 and shown in table 3. An increase in OC levels occurred with ageing in both blacks and whites. This resulted in a significant difference in mean OC levels between pre- and postmenopausal women ($p < 0.01$) of both ethnic groups. The pattern of increase in OC, however, appeared to differ between blacks and whites. In whites most of the increase occurred during menopausal transition resulting in higher levels in the early postmenopausal women compared with the premenopausal women ($p < 0.01$). In blacks this increase occurred later, with highest OC levels documented in the late postmenopausal subgroup. Mean OC levels were thus highest and near identical in the early postmenopausal whites and in the late postmenopausal blacks. Due to these different patterns of change a tendency towards lower OC levels in the younger postmenopausal blacks compared with whites ($p = 0.08$) and higher OC levels in the older blacks compared with whites ($p = 0.06$) were noted. In the total postmenopausal cohorts unadjusted OC-levels were similar between blacks and whites ($p = 0.48$).

URINARY FREE DEOXYPYRIDINOLINE

Changes in urinary DPD levels with ageing are shown in table 3 and demonstrated in figure 2. Urinary DPD remained unchanged in blacks with ageing. There was not the expected increase from the pre- to the postmenopausal state and no change with further ageing in blacks. In whites a slight increase in mean urinary DPD was noted between pre- and early postmenopausal women. With further ageing a near significant decrease in DPD levels was observed in whites ($p = 0.08$). The pattern of change in DPD in whites is thus very similar to that noted for OC except that the changes are less marked. In the total postmenopausal black and white cohorts, urinary DPD was similar.

Table 3: Biochemical parameters of bone turnover in early and late postmenopausal cohorts

Biochemical Parameter	Postmenopausal subjects						Normal values
	< 60 years			≥ 60 years			
	Blacks (n= 48)	Whites (n=35)	p-value	Blacks (n= 49)	Whites (n= 31)	p-value	
<i>Serum</i> Osteocalcin (ng/ml)	10.2 ± 8.8	14.3 ± 13	0.08	14.04 ± 11	9.2 ± 5.8	0.06	2.4 - 10.0
<i>Urine</i> DPD/creatinine (nMI/mMI)	5.37 ± 4.4	7.16 ± 6.2	0.08	5.42 ± 4.2	4.89 ± 2.8	0.30	3.0 - 7.4

Values expressed as mean ± SD, p-values in the table refer to comparison between blacks and whites within specific subgroups

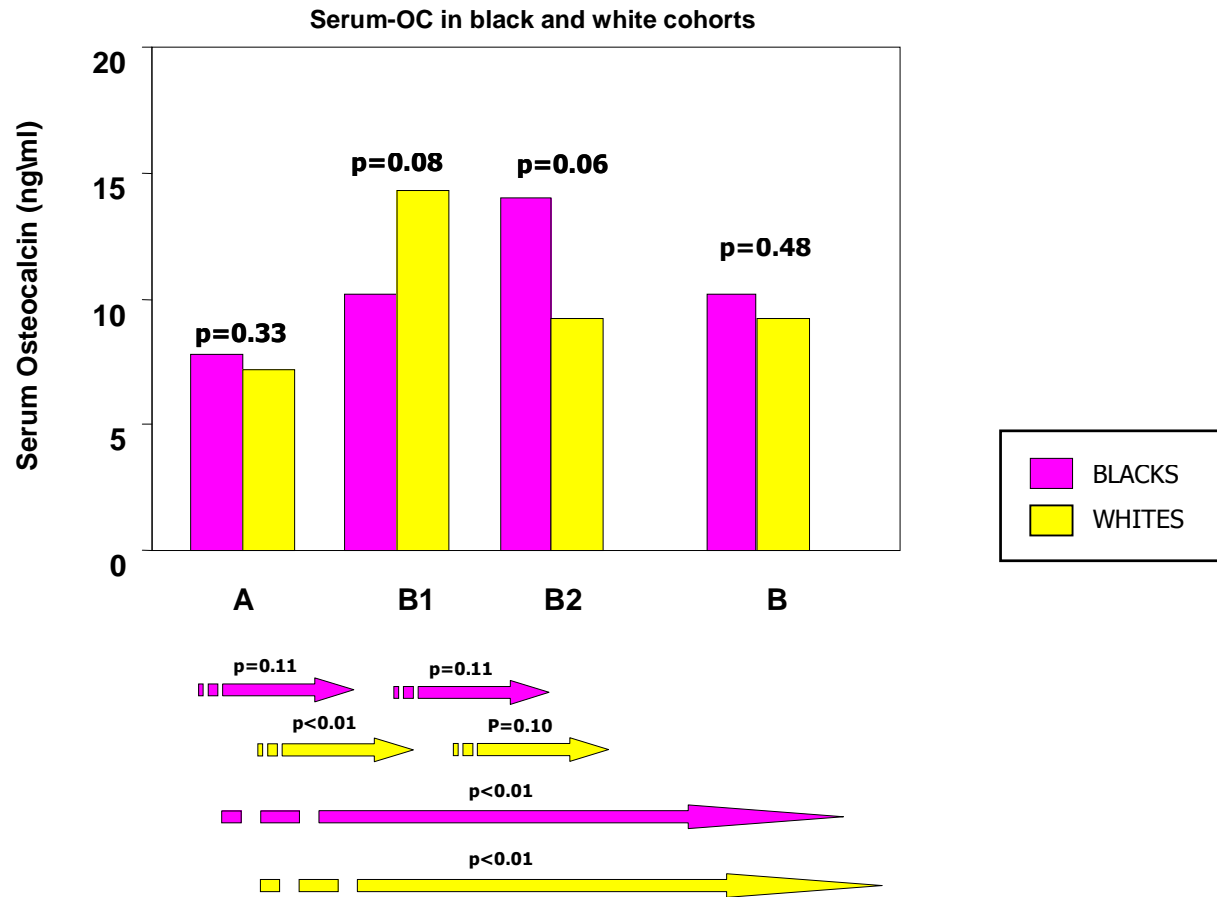


Figure 1: Mean (\pm SD) unadjusted serum OC levels of A: premenopausal blacks and whites; B1: early postmenopausal blacks and whites; B2: late postmenopausal blacks and whites; B:: total postmenopausal black and white cohort. OC levels increased significantly from the premenopausal state to the early postmenopausal period in whites only. OC shows tendency towards lower values in the early postmenopausal blacks compared with whites, whereas mean OC value tends to be higher in the older postmenopausal blacks vs. whites. No significant difference between early and late postmenopausal black and white groups respectively, p-values as indicated above arrows

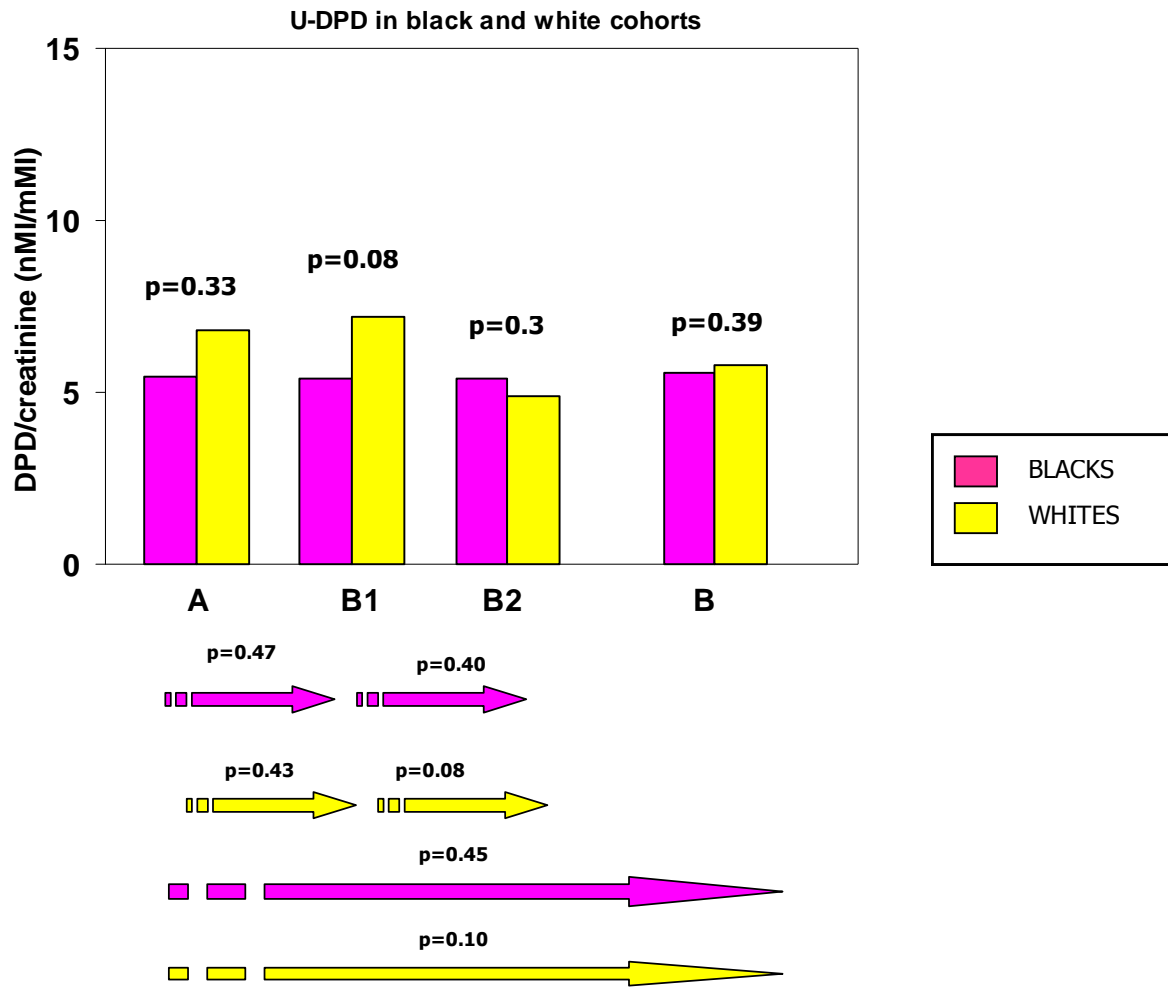


Figure 2: Mean (\pm SD) unadjusted urine DPD levels of A: premenopausal blacks and whites; B1 early postmenopausal blacks and whites; B2: late postmenopausal blacks and whites; B: total postmenopausal black and white cohort. DPD levels did not increase significantly from the premenopausal state to the early postmenopausal period in blacks and whites. U-DPD levels shows tendency towards higher values in the early postmenopausal whites compared with older whites and with blacks, p-values as indicated

3.1.2. Mineral status and calciotropic hormones

3.1.2.1. Premenopausal subjects

Blacks had similar albumin corrected serum calcium than whites. Serum total alkaline phosphatase (ALP) levels were significantly higher in the black females. We did not obtain iso-enzymes of ALP and are thus unable to comment on the relative contribution of bone and liver to the total ALP value obtained (table 4).

25-OH-Vitamin D levels were low in blacks and whites, but tended to be lower in blacks. A tendency towards higher PTH-levels was noted in blacks, although statistical significance was not reached. Significantly higher serum phosphate levels and better renal phosphate re-absorption, when expressed as a function of creatinine clearance (TmP/GF), were present in blacks. The higher renal phosphate re-absorption, in the presence of near significantly higher serum PTH levels in blacks, suggests a relative renal resistance to the action of PTH. Blacks conserved calcium better compared with whites despite a significantly higher urinary sodium loss (table 4).

The higher serum phosphate levels in premenopausal blacks was not explained by higher dietary intake of either protein or phosphate as determined by dietary recall and analyzed by the Foodfinder program (see chapter 3, section 2.1.2). Sodium-intake was comparable between blacks and whites ($p=0.31$) and not the reason for the higher sodium excretion in blacks.

Table 4: Biochemical data for premenopausal subjects

Biochemical Parameter	Premenopausal females			
	Blacks (n=70)	Whites (n=63)	p-value	Normal reference values
<i>Serum</i>				
Total albumin corrected calcium (mmol/l)	2.21 ± 0.13	2.17 ± 0.12	0.05	2.10 - 2.60
Phosphate (mmol/l)	1.13 ± 0.16	1.05 ± 0.16	<0.01	0.80 - 1.40
Magnesium (mmol/l)	0.86 ± 0.13	0.90 ± 0.10	<0.05	0.75 - 1.00
Creatinine (umol/l)	78 ± 13	81 ± 13	0.12	80 - 120
Alkaline phosphatase (IU/l)	64 ± 19	49 ± 12	<0.01	30 - 85
25-(OH)D (ng/ml)	16.5 ± 5.8	17.9 ± 4.6	0.07	>18
PTH (pmol/l)	6.1 ± 4.5	5.1 ± 3.5	0.09	1.3 – 7.6
<i>Urine</i>				
Calcium/creatinine (mmol/mmol)	0.19 ± 0.17	0.25 ± 0.17	<0.05	
Ca/100ml GF	0.01 ± 0.01	0.02 ± 0.01	<0.01	
TRP (%)	90 ± 15	89 ± 7	0.27	85 - 95
TmP/GF	1.15 ± 0.27	1.07 ± 0.26	0.04	1.00 – 1.68
Sodium/creatinine (mmol/mmol)	21.6 ± 11.3	15.6 ± 8.6	<0.001	

Values are the mean ± SD, p-values in the table refer to comparison between premenopausal blacks and whites

3.1.2.2. Postmenopausal subjects

Blacks and whites in the early and late postmenopausal group had similar mean albumin corrected serum calcium values (table 5), whereas serum phosphate levels was higher in the early postmenopausal black cohort. Total alkaline phosphatase levels were significantly higher in blacks compared with whites in both postmenopausal cohorts and was also noted to be significantly higher in older compared with younger postmenopausal blacks ($p=0.04$).

Significantly lower 25-OH-Vitamin D levels were noted in blacks compared with whites in both postmenopausal cohorts (table 5). Vitamin D levels appeared to decline significantly with ageing in the black females only ($p<0.01$). PTH-levels were similar in the younger postmenopausal black and white subjects, but a tendency towards higher PTH was noted in the older blacks compared with whites. Tubular phosphate handling was similar in the early postmenopausal blacks and whites as expected given similar PTH values. In the older blacks, with higher PTH levels, no PTH-induced renal phosphaturic effect was noted, suggesting resistance to the biological actions of this hormone. In fact, late postmenopausal black females had higher mean phosphate re-absorption despite higher PTH values. Urinary calcium excretion was significantly lower in the younger postmenopausal black females, but similar in the older black and white subjects. Higher mean urinary sodium loss was noted in both black postmenopausal groups, similar to that observed in the premenopausal subjects.

Dietary intake of protein was similar in postmenopausal blacks and whites in both the early ($p=0.46$) and the late ($p=0.30$) group. Phosphate intake tended to be lower in younger postmenopausal blacks ($p=0.06$), whereas phosphate intake was similar in the older blacks and whites. Sodium intake varied between the two ethnic groups with a tendency towards higher intake in the younger postmenopausal blacks ($p=0.05$) and lower intake in the older blacks compared with whites ($p=0.02$). Dietary intake of phosphate and sodium were thus unable to explain neither the observed renal conservation of phosphate nor the higher sodium loss in blacks.

Table 5: Biochemical data for early and late postmenopausal cohorts

Biochemical Parameter	Postmenopausal subjects						Normal reference values
	< 60 years			≥ 60 years			
	Blacks (n= 48)	Whites (n=35)	p-value	Blacks (n= 49)	Whites (n= 31)	p-value	
<i>Serum</i>							
Alb corrected calcium (mmol/l)	2.25 ± 0.12	2.24 ± 0.10	0.24	2.31 ± 0.16	2.26 ± 0.09	0.06	2.10-2.60
Phosphate (mmol/l)	1.15 ± 0.19	1.07 ± 0.16	0.02	1.06 ± 0.15	1.02 ± 0.16	0.1	0.80-1.40
Magnesium (mmol/l)	0.87 ± 0.09	0.89 ± 0.11	0.12	0.87 ± 0.11	0.92 ± 0.1	0.02	0.75-1.00
Creatinine (umol/l)	87 ± 16	87 ± 30	0.48	92 ± 16	94 ± 29	0.40	80-120
Alkaline phosphatase (IU/l)	79 ± 23*	71 ± 18	0.03	90 ± 36	71 ± 31	<0.01	30-85
25-(OH)D (ng/ml)	15 ± 6.5*	18 ± 5.4	0.02	11 ± 4.9	18 ± 6.4	<0.01	>18
PTH (pmol/l)	7.5 ± 5.1	6 ± 6.2	0.12	7.8 ± 4.2	6.4 ± 2.5	0.05	1.3 – 7.6
<i>Urine</i>							
Calcium/creatinine (mM/mM)	0.21 ± 0.15	0.43 ± 0.30	<0.01	0.27 ± 0.29	0.30 ± 0.21	0.29	
Ca/100ml GF	0.018 ± 0.01	0.03 ± 0.02	<0.01	0.024 ± 0.02	0.025 ± 0.02	0.29	
TRP (%)	87 ± 7	87 ± 7	0.41	88 ± 7	84 ± 8	0.01	85-95
TmP/GF	1.14 ± 0.27	1.1 ± 0.23	0.07	1.06 ± 0.21	0.93 ± 0.21	<0.01	1.00–1.68
Sodium/creatinine (mM/mM)	25.4 ± 18.3	17.3 ± 10.9	0.01	24.0 ± 16	18 ± 12	0.05	

Values expressed as mean ± SD, p-values in the table refer to comparison between blacks and whites within specific subgroups

*p-value <0.05 younger postmenopausal blacks versus older postmenopausal blacks

3.1.3. Correlation between biochemical parameters

3.1.3.1. Premenopausal subjects

Correlations between OC, DPD, PTH and 25-OH-Vitamin D were determined in the premenopausal cohort. The only near significant correlation was noted between serum osteocalcin and urinary DPD in blacks ($r=0.37$, $p=0.06$).

3.1.3.2. Postmenopausal subjects

Significant correlation between the different biochemical parameters were confined to the late postmenopausal groups. In blacks, a significant positive correlation was noted between U-DPD and serum PTH ($r=0.30$, $p=0.02$), and in whites a significant negative correlation was documented between serum PTH and serum 25-OH-Vitamin D ($r=-0.47$, $p=0.01$).

3.1.4. Correlation between biochemistry and BMD of the spine and hip

3.1.4.1. Premenopausal subjects

S-Osteocalcin (OC) correlated significantly with spinal measurements in blacks ($r=-0.41$; $p<0.01$ for BMD; $r=-0.35$, $p=0.01$ for BMAD) and whites ($r=0.35$; $p<0.01$ for BMD; $r=0.29$, $p=0.03$ for BMAD). PTH correlated significantly with femoral neck BMAD in blacks only ($r=-0.24$, $p=0.04$). The correlation between OC and spinal BMD in blacks was negative and in contrast with the positive correlations noted in whites. No correlation was noted between U-DPD or 25-OH- Vitamin D, and any of the densitometric data in premenopausal women.

3.1.4.2. Postmenopausal subjects

Correlations between biochemistry and BMD of the spine and hip are shown in table 6 and 7. In the early postmenopausal females, significant correlations between biochemical parameters and BMD were confined to blacks, with a negative correlation noted between OC and all femoral measurements (table 6). In the older women, significant correlations between PTH and 25-OH-Vitamin D and BMD/BMAD at all the proximal femoral sites were noted in blacks and whites (correlation negative for PTH, positive for 25-OH-Vitamin D). In addition, in whites, OC showed a positive correlation with spinal BMD and spinal BMAD (table 7).

3.1.5. Densitometry in postmenopausal black and white subgroups based on PTH-tertiles

Densitometric findings in postmenopausal blacks and whites based on PTH tertiles are demonstrated in tables 8 and 9. Ages were comparable in the low, middle and high PTH tertile subgroups in blacks, whereas whites in the high PTH tertile were significantly older than those in the low PTH tertile. The mean serum PTH value was significantly higher in the high PTH tertile in blacks compared with whites. A significant negative impact of high PTH on proximal femoral BMD was demonstrated in postmenopausal blacks, especially at the femoral neck region. BMD was comparable in all the PTH tertile subgroups in whites.

Table 6: Correlation between DEXA measured BMD/BMAD at different skeletal sites and biochemical variables in early postmenopausal black and white females.

DEXA measurements	Biochemical parameters								
	OC		DPD		PTH		25-OH-Vitamin D		
	r-value	p-value	r-value	p-value	r-value	p-value	r-value	p-value	
Lumbar spine BMD									
Black	-0.22	0.26	-0.2	0.25	0.08	0.63	0.03	0.82	
White	-0.17	0.37	-0.19	0.28	-0.14	0.42	0.09	0.62	
Lumbar spine BMAD									
Black	-0.32	0.14	-0.18	0.35	0.08	0.63	0.08	0.66	
White	-0.24	0.24	-0.15	0.42	-0.15	0.41	0.09	0.64	
Femoral neck BMD									
Black	-0.38	0.05	-0.10	0.58	0.18	0.25	0.10	0.51	
White	-0.15	0.43	-0.26	0.14	-0.11	0.54	0.09	0.96	
Femoral neck BMAD									
Black	-0.35	0.07	-0.15	0.40	0.02	0.89	0.08	0.62	
White	-0.26	0.19	-0.27	0.13	-0.09	0.62	-0.09	0.58	
Total femoral BMD									
Black	-0.43	0.02	-0.2	0.23	0.07	0.64	-0.01	0.97	
White	-0.17	0.39	-0.29	0.09	-0.03	0.88	-0.38	0.83	

Table 7: Correlation between DEXA measured BMD/BMAD at different skeletal sites and biochemical variables in late postmenopausal black and white females.

DEXA measurements	Biochemical parameters								
	OC		DPD		PTH		25-OH-Vitamin D		
	r-value	p-value	r-value	p-value	r-value	p-value	r-value	p-value	
Lumbar spine BMD									
Black	0.09	0.60	0.02	0.90	-0.16	0.31	-0.04	0.77	
White	0.55	0.05	0.07	0.76	-0.10	0.61	0.15	0.47	
Lumbar spine BMAD									
Black	0.04	0.82	-0.10	0.59	0.23	0.16	0.01	0.99	
White	0.52	0.09	-0.01	0.96	-0.26	0.24	0.17	0.42	
Femoral neck BMD									
Black	0.13	0.43	-0.01	0.99	-0.38	0.01	0.19	0.20	
White	0.14	0.62	0.22	0.33	-0.39	0.04	0.43	0.02	
Femoral neck BMAD									
Black	0.20	0.23	-0.01	0.94	-0.35	0.02	0.24	0.12	
White	0.33	0.29	0.02	0.95	-0.53	0.01	0.58	<0.01	
Total femoral BMD									
Black	0.20	0.22	0.16	0.35	-0.20	0.04	0.35	0.02	
White	0.09	0.76	0.24	0.29	-0.35	0.07	0.47	0.01	

Table 8: Densitometric findings in postmenopausal black subgroups based on PTH tertiles

	Postmenopausal black subgroups based on PTH tertiles				
	Low PTH tertile 1	Middle PTH tertile 2	High PTH tertile 3	p-value(1 vs 3)	p-value (2 vs 3)
Age	60.3 ± 9.6	59.6 ± 10.1	59.9 ± 9.4	0.42	0.47
S-PTH	4.1 ± 0.68	6.8 ± 0.96	12.5 ± 5.2	<0.01	<0.01
SBMD					
Absolute	0.903 ± 0.18	0.983 ± 0.21	0.914 ± 0.17	0.47	0.07
T-score	-1.19 ± 1.7	-0.61 ± 1.96	-1.16 ± 1.48	0.47	0.09
Z-score	0.13 ± 1.63	0.88 ± 1.99	0.18 ± 1.78	0.48	0.06
F-neck BMD					
Absolute	0.831 ± 0.13	0.832 ± 0.12	0.766 ± 0.13	0.02	0.02
T-score	-0.19 ± 1.15	-0.15 ± 1.08	-0.77 ± 1.21	0.02	0.01
Z-score	1.09 ± 1.29	1.17 ± 0.90	0.53 ± 1.05	0.02	<0.01
F-total BMD					
Absolute	0.938 ± 0.13	0.991 ± 0.16	0.914 ± 0.16	0.20	0.02
T-score	-0.06 ± 1.06	0.40 ± 1.31	-0.24 ± 1.34	0.22	0.02
Z-score	0.41 ± 1.11	0.18 ± 1.20	0.26 ± 1.20	0.19	0.01

Values expressed as mean ± SD.

p-value (1 vs 3): refers to comparison between low and high PTH tertile; p-value (2 vs 3): refers to comparison between middle and high PTH tertile;

Table 9: Densitometric findings in postmenopausal white subgroups based on PTH tertiles

	Postmenopausal white subgroups based on PTH tertiles				
	Low PTH tertile 1	Middle PTH tertile 2	High PTH tertile 3	p-value(1 vs 3)	p-value (2 vs 3)
Age	55 ± 9.4	61 ± 9.8	63.6 ± 11.7	0.07	0.20
S-PTH	3.5 ± 0.74	5.3 ± 0.49	8.2 ± 1.81	<0.01	<0.01
SBMD					
Absolute	0.989 ± 0.16	0.966 ± 0.17	0.914 ± 0.19	0.09	0.18
T-score	-0.44 ± 1.56	-0.71 ± 1.53	-1.21 ± 1.69	0.07	0.17
Z-score	0.52 ± 1.46	0.71 ± 1.52	0.46 ± 1.69	0.45	0.32
F-neck BMD					
Absolute	0.726 ± 0.12	0.728 ± 0.12	0.678 ± 0.14	0.12	0.12
T-score	-1.10 ± 1.045	-1.08 ± 1.09	--1.58 ± 1.25	0.09	0.09
Z-score	-0.04 ± 1.1	0.27 ± 1.1	-0.05 ± 1.26	0.49	0.20
F-total BMD					
Absolute	0.867 ± 0.13	0.876 ± 0.16	0.826 ± 0.16	0.19	0.15
T-score	-0.61 ± 1.06	-0.54 ± 1.31	-0.95 ± 1.34	0.19	0.15
Z-score	0.17 ± 1.1	0.501 ± 1.2	0.25 ± 1.2	0.41	0.26

Values expressed as mean ± SD.

p-value (1 vs 3): refers to comparison between low and high PTH tertile; p-value (2 vs 3): refers to comparison between middle and high PTH tertile;

4. DISCUSSION

Our data demonstrated that bone turnover, as assessed biochemically, were similar in the pre-and postmenopausal black and white cohorts. Although longitudinal changes must be interpreted with caution given the cross-sectional nature of our study, our data do, however, suggest differing patterns of bone turnover with ageing between the two racial groups.

A marked increase in serum osteocalcin levels was noted in whites at the time of the menopausal transition, whereas the difference in serum OC levels between premenopausal and early postmenopausal blacks were non-significant. The percentage increase in OC levels was 50% in whites compared with a 14% increase in blacks. Serum osteocalcin is a marker of bone formation, but as the processes of bone formation and bone resorption is normally tightly coupled, serum osteocalcin levels also reflect bone turnover. The relative contribution of bone formation and bone resorption to the ultimate bone turnover rate cannot be determined. This may result in varying associations between serum osteocalcin levels and BMD status, albeit positive or negative. The association between OC levels and BMD data in the early postmenopausal blacks and whites were consistently negative, with significant associations confined to that between serum OC and femoral measurements in blacks. This may imply that, in our study, the raised serum OC levels in early menopause reflect a general increase in bone turnover and not only an increase in bone formation, with resultant detrimental effects on BMD status. Bone formation is so highly correlated with bone resorption that a value for either process usually correlates very well with bone loss³³⁸. OC has been suggested to be the best single biochemical marker for estimating the rate of bone loss in untreated postmenopausal women^{339,340}.

Neither of the two racial groups demonstrated a significant increase in urinary DPD from the premenopausal to the early postmenopausal state. The reason why the increased bone turnover is not reflected by an associated significant increase in urinary DPD levels is uncertain, but may be partially explained by the limitations of a single evaluation of a biochemical parameter known to have a significant day-to-day variation²³³. Vesper et al²³³ reviewed the literature and noted the reported day-to day variation in U-DPD averaged 17.4% (range, 5-24%). We did try to minimize the pre-analytical variability of urine DPD as outlined in chapter 3 section 2.6.2.

Due to these apparent differing patterns of change in biochemical parameters of bone turnover, a tendency towards lower serum OC and urinary DPD was noted in our early postmenopausal blacks compared with whites ($p=0.08$).

There was no difference in biochemical markers of bone turnover including osteocalcin and urinary DPD in a relatively young postmenopausal South African black and white female group (mean age 45-64 yrs) studied by Daniels et al⁵. Our findings are, however, consistent with data obtained by Finkelstein et al¹⁴² who noted significantly lower serum OC levels in early perimenopausal African-Americans compared with Caucasians, but failed to show significantly different urinary NTX levels between these two ethnic groups. Our findings are further supported by other previous studies showing lower OC levels in African Americans^{138,146,196} and studies reporting similar urinary pyridinium cross-link excretion in postmenopausal Caucasians and African-Americans^{142,144,185,186}.

In our study, the percentage bone loss at the proximal femoral regions at the time of the menopausal transition appeared to be lower in blacks compared with whites (chapter 5, table 20) and this may be partially explained by the observed lower bone turnover at this time in our blacks. Our observation of an apparent slower rate of decline in femoral bone density in black females compared with whites in the peri- and early postmenopausal period is consistent with the findings in the nurses' study by Daniels et al¹. This pattern of femoral bone loss was also remarkably similar to that observed by Solomon²¹³ more than 30 years earlier. He noted that South African black females appeared to reach peak bone mass at a later stage than whites and showed that black females had very limited bone loss in the late premenopausal and perimenopausal periods. A slower rate of cortical and trabecular bone loss, especially in the early postmenopausal period, has also been noted in American blacks compared with whites in some^{139,184,197}, but not all^{144,194,196} studies.

During the latter part of menopause (early to late menopause) apparent differences in bone turnover rates were again observed between blacks and whites. An increase in bone formation/turnover as assessed by serum OC levels was noted in ageing blacks, whereas a tendency towards lower bone formation/turnover was observed in ageing whites (percentage change OC: blacks – 28% increase; whites – 36% decrease). Urinary DPD levels remained unchanged in blacks from the early to the late postmenopause, whereas a decrease of 32% was shown in whites.

Daily dietary calcium-intake was statistically significantly lower in postmenopausal blacks compared with whites in the early and late postmenopausal cohorts ($p < 0.01$, table 1). The 25-OH-Vitamin D levels were also consistently lower in postmenopausal blacks compared with whites and decreased with ageing. Lower urinary calcium excretion in blacks, especially in the younger postmenopausal subjects was also noted, and this would support the concept of a more negative calcium balance in blacks compared with whites. Since metabolic balancing studies were, however, not performed, the ability of black subjects to conserve

calcium more stringently regardless of PTH status cannot be ruled out. The lower calcium excretion in blacks was noted despite significantly higher urinary sodium loss. Although renal sodium loss is directly proportional to dietary sodium intake, higher dietary intake of sodium were not consistently noted in our blacks and were thus unable to explain the observed higher renal sodium loss in blacks.

This negative calcium balance in blacks compared with whites evoked a more marked increase in PTH-levels in blacks with ageing, with resultant near significantly higher PTH levels in older postmenopausal blacks ($p=0.05$). The observed increased bone turnover in ageing postmenopausal blacks may thus be explained, at least in part, by the associated increase in PTH-levels in blacks and this would argue against the belief that black skeletons are markedly PTH resistant^{138,144,146,196}. Similar and significant associations were also noted between 25-OH-Vit D (positive) and PTH (negative) and all proximal femoral BMD measurements in both blacks and whites, once again contesting the idea that blacks do not suffer the detrimental bony effects due to secondary hyperparathyroidism. The PTH sensitivity of the black skeleton is furthermore demonstrated by the finding of lower femoral neck densitometric measurements in the tertile of postmenopausal blacks with the highest PTH levels compared to the tertile with lowest PTH levels (table 10 & table 11). The absence of any association between BMD and ascending PTH-tertiles in whites may be due to a more modest increase in PTH-levels from the low to the high tertile, with values in the highest tertile varying from high normal to only slightly elevated.

Some degree of resistance to the biological action of PTH was, however, noted at a renal level in postmenopausal blacks (higher renal phosphate re-absorption despite higher PTH-levels). Our study data do not exclude some degree of skeletal resistance to PTH in blacks, but cautions against the belief that PTH will have no adverse skeletal effects in blacks.

A study by Harris et al in low income, elderly black and white individuals with secondary hyperparathyroidism (HPT) also contested the belief that this is a benign condition with no deleterious skeletal effects in blacks¹⁴⁵. Although bone turnover has repeatedly been shown to be lower or similar in black versus white groups, bone turnover was noted to be higher and BMD lower in the subgroups of patients with secondary HPT in both black and white ethnic groups¹⁴⁵ (see chapter 2, figure 12).

The tendency towards higher PTH-levels in older blacks, and the observed significant negative associations between PTH and proximal femoral BMD measurements, did not result in a higher percentage decline in femoral BMD in older blacks (transition from the early to the late postmenopausal phase) compared with whites. The percentage decline in BMD at

proximal femoral sites in our older study population appeared to be similar in blacks and whites. Better preservation of femoral BMD was, however, observed at the time of the menopausal transition in blacks compared with whites (chapter 5, table 20), implying that femoral BMD loss increased in blacks relative to whites in later years. This may be ascribed, at least in part, to the presence of secondary hyperparathyroidism in older blacks. Protective mechanisms independent of bone turnover and the presence of secondary hyperparathyroidism appear to protect the black skeleton, especially at the femoral sites, into old age.

To conclude,

- Bone turnover, as assessed biochemically, was similar in the total pre- and postmenopausal black and white cohorts.
- Bone turnover rates appeared to differ with ageing between the two racial groups.
- A lower bone turnover rate was noted in blacks at the time of the menopausal transition and is consistent with the finding of a lower percentage bone loss at the femoral sites at this time in blacks compared with whites.
- Bone turnover increased in ageing postmenopausal blacks only. This could be ascribed, at least in part, to the more pronounced secondary hyperparathyroidism noted in blacks.
- Deleterious effects of secondary hyperparathyroidism on bone mineral density at the proximal femoral sites were demonstrated in our postmenopausal blacks and contest the idea of an absolute skeletal resistance to the action of PTH in blacks.
- The increase in bone turnover and the presence of secondary hyperparathyroidism may thus potentially aggravate bone loss in ageing blacks, especially at the proximal femoral sites.

.....

CHAPTER 9

BONE GEOMETRY IN BLACK AND WHITE SOUTH AFRICA FEMALES

1.	INTRODUCTION	190
2.	PATIENTS AND METHODS	191
3.	RESULTS.....	192
3.1.	Geometric measurements.....	192
3.2.	Correlations of Geometric measurements.....	192
4.	DISCUSSION	194

CHAPTER 9

BONE GEOMETRY IN BLACK AND WHITE SOUTH AFRICAN FEMALES

1. INTRODUCTION

The role of BMD and micro-architectural (bone quality) properties in the pathophysiology of skeletal fracture has previously been alluded to. Bone mineral density (BMD) is an excellent predictor of bone strength and fracture risk at all skeletal sites²⁶⁻³⁰. The relationship between low BMD and the risk of subsequent hip fracture is strongest for measurements of femoral bone density³⁴¹, but many women who present with hip fracture have BMD higher than that usually associated with osteoporosis³⁴². Bone mineral density is thus not the sole factor influencing whether a fracture occurs. Based on engineering principles, geometric measurements of femoral size should be related to femoral strength and the risk for hip fracture. Differences in the length, width and angle of the femoral neck may affect hip fracture risk¹⁶⁰⁻¹⁶⁶, whereas differences in vertebral body size may influence vertebral fracture risk^{167,343}.

Numerous studies have confirmed the relationship between *hip axis length* (HAL) and risk of hip fracture, independent of bone mineral density status^{160-166,344,345}. Analyses of results obtained in the study by Faulkner et al¹⁶⁶ showed a near doubling of the risk of hip fracture with every SD increase in hip axis length.

The *femoral neck-shaft angle* was also shown in some¹⁶¹ but not all studies¹⁶⁶ to affect hip fracture, whereas most studies^{161,166} failed to show a significant association between the *neck width* and risk of hip fracture. Identifying women at high risk of hip fracture is likely to be substantially enhanced by combining bone density with data on the structural geometry of the hip, especially HAL.

Vertebral strength is also influenced by the geometry of the vertebrae. *Vertebral size* has been documented to be reduced in women predisposed to vertebral fractures^{167,343}.

Most studies of hip geometry have documented a shorter HAL in African-Americans compared with Caucasians^{3,4}. A shorter HAL was also documented in SA black female nurses compared with whites⁵ and Gambians had shorter mean HAL compared with British subjects⁶. Although American blacks are heavier than whites, their lumbar spine and femoral neck areas are actually smaller¹⁶⁷. Neck width has been reported to be smaller in blacks^{3,4,346} along with documentation of thicker cortices^{4,346}. Blacks also have shorter trunk lengths

compared with whites which imply reduced vertebral height²⁰³. Vertebral size in adult South African blacks and whites has not been studied previously.

2. PATIENTS AND METHODS

To assess previous observations of racial differences in skeletal geometry, the hip axis length (HAL) and the femoral neck width was determined directly from the DEXA-scan printouts as defined in figure 1¹⁶⁶. The femoral DEXA measurements were all performed using a Hologic QDR-1000 scan and all geometric measurements were conducted by one investigator. Employing standard DEXA software, HAL was defined as the length along the femoral neck axis, from below the lateral aspect of the greater trochanter, through the femoral neck, to the inner pelvic brim. Femoral neck width was defined as the shortest distance within the femoral neck region of interest (as defined by the DEXA analysis software) perpendicular to the femoral neck axis. Vertebral size was also determined directly from the DEXA-scan printouts and expressed as the total vertebral cross-sectional area and the calculated mean area of individual vertebrae L1-L4. (please refer to chapter 3, section 2.4 for a more detailed outline of methodology).

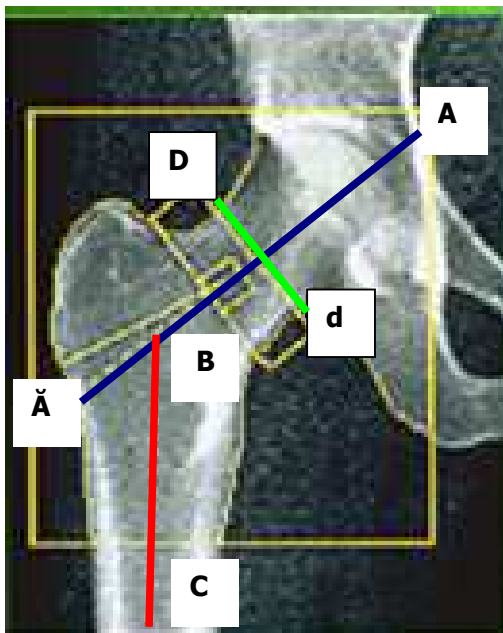


Figure 1 Definition of geometric measurements from femoral DEXA scan printout.

AA: hip axis length, defined as the length along the femoral neck axis as defined by the DEXA analysis software, from below the lateral aspect of the greater trochanter, through the femoral neck, to the inner pelvic brim

Dd: neck width, defined as the shortest distance within the femoral neck region of interest, as defined by the DEXA analysis software, perpendicular to the femoral neck axis *Adapted from Faulkner et al. 1993, J Bone Miner Res; 8(10): 1211-1217¹⁶⁶*

Geometric assessments were performed on the total study cohort who included 187 blacks and 186 whites (see Chapter 4, section 3.1.1 & 3.1.3 for detail regarding clinical characteristics).

Ethnic differences were determined and are reported on in the following patient subgroups:

- Premenopausal black and white subgroups
- Early and late postmenopausal black and white groups as outlined in section 1.3.

ANOVA was used to determine significant ethnic differences in geometry between the various patient subgroups. Spearman correlations were used to determine relationships between geometric measurements and anthropometry (i.e. weight and height) as well as between certain femoral geometric measurements (HAL and femoral neck width) and between certain anthropometric measurements (weight and height).

3. RESULTS

3.1. Geometric measurements

Mean hip axis length (HAL) and mean femoral neck width was significantly shorter in premenopausal and postmenopausal black females compared with whites. A marked difference of $\pm 1SD$ in hip axis length between blacks and whites in all the different subgroups studied was noted. The mean cross-sectional area of the lumbar vertebral bodies and the mean of the average of the cross-sectional areas of individual lumbar vertebrae L1-L4 of the black females in this study were significantly smaller than whites in all the subgroups studied (table 1).

3.2. Correlations of Geometric measurements

Correlations between anthropometry and geometry are shown in table 2 and correlations between weight and height and between the different femoral geometric measurements are depicted in table 3.

Height was strongly and positively associated with all geometric measurements i.e. HAL, femoral neck width and vertebral bone area in blacks and whites. Weight correlated with femoral neck width in both blacks and whites, but correlated with vertebral bone area and HAL in whites only (table 2).

Weight and height correlated significantly in whites in all the subgroups and only in premenopausal blacks. The absent correlation between weight and height in the postmenopausal blacks is consistent with the finding of increasing weight and unchanged height with ageing in blacks only. A correlation between weight and geometric

measurements was absent in the postmenopausal black subgroups where height and weight did not correlate (table 3).

A significant association between hip axis length and femoral neck width was noted in both blacks and whites. The association tended to be stronger in whites.

Table 1: Femoral and vertebral geometry in the premenopausal and postmenopausal blacks and whites

Geometric measurements	Premenopausal			Postmenopausal					
				< 60 years			≥ 60 years		
	Blacks n=87	Whites n=76	<i>p-value</i>	Blacks n=52	Whites n=63	<i>p-value</i>	Blacks n=48	Whites n=47	<i>p-value</i>
HAL (mm)	62.5 ± 4.1	66.8 ± 4.3	<0.01	61.9 ± 3.8	66.8 ± 4.2	<0.01	62.5 ± 4.2	66.1 ± 4.0	<0.01
F- neck width (mm)	19.2 ± 1.8	19.7 ± 2.1	0.07	19.1 ± 1.6	20.1 ± 1.4	<0.01	19.0 ± 2.0	19.7 ± 1.3	0.04
Vertebral BA (cm ²)									
Total	56.6 ± 5.6	60.4 ± 5.2	<0.01	56.1 ± 6.1	60.2 ± 5.6	0.01	57.0 ± 5.2	59.8 ± 6.7	0.02
Mean of L1-L4	14.1 ± 1.4	15.1 ± 1.3	<0.01	14.0 ± 1.5	15.1 ± 1.4	<0.01	14.2 ± 1.3	15.0 ± 1.7	0.02

Values reported are the mean ±SD. HAL: hip axis length; F-neck: femoral neck; BA: bone area

Table 2: Correlation between Anthropometry and Geometric measurements in black and white females

Anthropometry and racial group	Geometric measurements					
	HAL (mm)		FEMORAL NECK WIDTH (mm)		VERTEBRAL BONE AREA (cm2)	
	<i>r-value</i>	<i>p-value</i>	<i>r-value</i>	<i>p-value</i>	<i>r-value</i>	<i>p-value</i>
WEIGHT (kg)						
<i>Premenopausal</i>						
Black	0.11	0.34	0.36	<0.01	0.22	0.06
White	0.28	0.02	0.46	<0.01	0.30	0.11
<i>EARLY postmenopausal</i>						
Black	0.09	0.58	0.30	0.05	0.17	0.31
White	0.32	0.01	0.42	<0.01	0.55	<0.01
<i>LATE postmenopausal</i>						
Black	0.27	0.06	0.29	0.05	0.09	0.56
White	0.30	0.05	0.34	0.02	0.39	0.01
HEIGHT (cm)						
<i>Premenopausal</i>						
Black	0.44	<0.01	0.32	<0.01	0.65	<0.01
White	0.57	<0.01	0.25	0.03	0.63	<0.01
<i>EARLY postmenopausal</i>						
Black	0.60	<0.01	0.34	0.03	0.47	<0.01
White	0.62	<0.01	0.52	<0.01	0.71	<0.01
<i>LATE postmenopausal</i>						
Black	0.66	<0.01	0.15	0.29	0.61	<0.01
White	0.56	<0.01	0.58	<0.01	0.48	<0.01

Table 3: Additional correlation between weight and height and between HAL and femoral neck width in black and white females

Anthropometry and racial group	Geometric measurements			
	HEIGHT (cm)		FEMORAL NECK WIDTH (mm)	
	<i>r-value</i>	<i>p-value</i>	<i>r-value</i>	<i>p-value</i>
WEIGHT (kg)				
<i>Premenopausal</i>				
Black	0.32	<0.01		
White	0.36	<0.01		
<i>EARLY postmenopausal</i>				
Black	0.03	0.83		
White	0.34	<0.01		
<i>LATE postmenopausal</i>				
Black	0.06	0.71		
White	0.39	<0.01		
HAL (mm)				
<i>Premenopausal</i>				
Black			0.39	<0.01
White			0.45	<0.01
<i>EARLY postmenopausal</i>				
Black			0.34	0.03
White			0.60	<0.01
<i>LATE postmenopausal</i>				
Black			0.35	0.02
White			0.55	0.02

4. DISCUSSION

In our study population significant differences in skeletal morphology were noted between blacks and whites and these differences were consistent throughout all the subgroups evaluated. Hip axis length and femoral neck width was significantly shorter in the black females compared with whites. Vertebral size based on assessment of lumbar vertebral bone area was significantly smaller in blacks. Height was strongly and positively associated with geometric measurements in both blacks and whites.

A markedly lower hip fracture rate has been documented in South African and African black populations compared with whites^{20,212}. The HAL findings in our black study group will be expected to enhance femoral strength independent of femoral BMD¹⁶⁰⁻¹⁶⁶. An approximate 1 SD difference in hip axis length between blacks and whites in all the different subgroups studied was noted. In the study by Faulkner et al¹⁶⁶ a hip axis length of 1 standard deviation longer than average was associated with an almost twofold increase in the risk of subsequent hip fracture, after age adjustment. Although increased height is associated with increased BMD^{115,119}, probable mostly due to associated increased body weight, tallness had been previously identified as a risk factor for hip fracture¹⁰⁹. Given the very strong association between height and HAL it is plausible that the increased hip fracture risk in tall individuals are due, at least in part, to an increased HAL.

The precise mechanism by which the hip axis length is associated with fracture risk is not known. A longer hip axis might cause the greater trochanter to extend beyond the pelvis to a larger degree, thus creating a more vulnerable target for impact.

We demonstrated a significant positive association between hip axis length and femoral neck width in both blacks and whites in our study population, as has been previously documented in African-Americans and Caucasians elsewhere. Most studies^{161,166} failed to show a significant association between the neck width and risk of hip fracture or ability of neck width to predict the risk of fracture in the hip region independent of BMD and HAL. The association between hip fracture risk and femoral neck width is thus most likely circumstantial due to the association of femoral neck width with HAL.

Vertebral size was noted to be smaller in our black females. A study in SA schoolchildren found that the black children had shorter lumbar vertebral heights for the same bone area, before and after correction for differences in height, suggesting that the vertebrae in the black children are wider^{191,216}. We documented significantly smaller vertebral bone area in our adult black females compared with whites. This may be accounted for primarily by

differences in vertebral height and do not necessarily imply differences in vertebral transverse diameter. We did not specifically calculate vertebral heights in our black cohort and can therefore not comment on the height or width of individual vertebrae.

A vertebral body's strength, similar to femoral bone strength, is determined predominantly by the BMD of the area, but is also influenced by geometrical properties. The major mechanical role of the vertebral body is to withstand compressive loads. The surface area of the vertebral endplates determines the compressive stress concentration imparted to the cancellous bone and explains why smaller vertebral cross-sectional dimensions may enhance the risk of vertebral compression fractures. Smaller vertebral size has been documented in women predisposed to vertebral fractures^{167,343}.

To conclude, shorter, adult black women have a significantly shorter hip axis length than whites. This geometric feature has been documented to protect against hip fracture^{160-166,344,345}. The approximately one standard deviation difference in HAL between our blacks and whites may definitely contribute to the significantly lower hip fracture rate previously reported in South African black females compared with whites²⁰. Average vertebral size was, however, smaller in black females and fail to explain the apparent lower vertebral fracture risk previously reported in this population. Racial differences in vertebral dimensions (height, width) and/or other qualitative bone properties as has been suggested by our QUS data may, however, account for different vertebral fracture rates in white and black women – that is, if such a difference in fact exists.

.....

CHAPTER 10

FALL RISK IN BLACK AND WHITE SOUTH AFRICAN FEMALES

1.	INTRODUCTION.....	201
2.	PATIENTS AND METHODS	201
3.	RESULTS.....	205
3.1.	Fall results in the total study population	205
3.2.	Falling and bone mineral density in the postmenopausal cohort	205
3.2.1.	<i>Blacks</i>	207
3.2.2.	<i>Whites</i>	207
3.3.	Elderly study population (age ≥ 65 yrs)	207
3.4.	Hormone therapy and falls.....	208
4.	SENSORY AND NEUROMUSCULAR FUNCTION	208
4.1.	Body Sway	208
4.1.1.	<i>Total study cohort.....</i>	208
4.1.2.	<i>Postmenopausal females</i>	208
4.1.3.	<i>Fallers versus non-fallers</i>	209
4.2.	Reaction Time.....	209
4.2.1.	<i>Total study cohort.....</i>	209
4.2.2.	<i>Postmenopausal females</i>	209
4.2.3.	<i>Fallers versus non-fallers</i>	209
4.3.	Visual Contrast Sensitivity (Melbourne Edge Test).....	212
4.3.1.	<i>Total study cohort.....</i>	212
4.3.2.	<i>Postmenopausal females</i>	212
4.3.3.	<i>Fallers versus non-fallers</i>	212
4.4.	Quadriceps Strength.....	212
4.4.1.	<i>Total study cohort.....</i>	212
4.4.2.	<i>Postmenopausal females</i>	212
4.4.3.	<i>Fallers versus non-fallers</i>	212

5.	25-OH VITAMIN D STATUS, FALLS AND NEUROMUSCULAR TESTING.....	213
5.1.	Vitamin D status and recent falls in postmenopausal blacks and whites	213
5.2.	Vitamin D status and physical performance tests in postmenopausal blacks and whites.....	213
6.	DISCUSSION	214

CHAPTER 10

FALL RISK IN BLACK AND WHITE SOUTH AFRICAN FEMALES

1. INTRODUCTION

Fall risk contributes significantly to fracture risk, especially in the elderly. Bone density at the age of 75 yrs is only about 4% lower than at the age of 65 yrs¹⁰⁹. The incidence of hip fracture, however, is about four times as great at 75 years as at 65 years, and 12 times as great at 85 years. This increase is not primarily due to further loss of bone, but rather to a large increase in the risk of falling at more advanced ages.

Hip fractures occur almost exclusively after a fall, spontaneous hip fractures without prior falling is extremely rare¹⁶⁸. A history of recent falls is a major contributing factor to the occurrence of symptomatic fractures in postmenopausal women, independent of and additive to the risk attributable to age and osteoporosis^{169,170,347}.

Some^{206,207}, but not all studies^{208,209}, suggest that Caucasians may fall as much as 50-60% more often than African-Americans or other ethnic groups. However, in a study by Faulkner and co-workers²⁰⁹ the frequencies of falling between older Caucasian and African-Americans were similar, but the circumstances during which a fall occurred differed which might partially explain ethnic differences in fracture risk. No data regarding possible differences in the propensity to fall between black and white South Africans exist.

Epidemiological data have revealed that some 50% of mostly white osteoporotic patients have muscle loss/weakness ("sarcopenia"), 30% have postural hypotension and many have poor visual acuity or problems with depth perception, cognitive dysfunction or use drugs that may predispose to falls¹⁷³⁻¹⁷⁶. Low 25-OH Vitamin D levels are associated with sarcopenia and neuromuscular dysfunction especially in the elderly^{176,348,349}, and poor vitamin D status has been shown to be independently associated with an increased risk of falling in the elderly³⁵⁰.

2. PATIENTS AND METHODS

A history of falls and an assessment of sensory and neuromuscular function were obtained in all study subjects. Detailed methodologies are discussed in Chapter 3 (refer to section 2.1.3).

We analyzed and report on fall data and sensory and neuromuscular function tests results in different patient subgroups as follows:

- A total study population comprised of pre- and postmenopausal black and white females and included women who were currently using hormone therapy (blacks: n=3; whites: n=43). The baseline clinical characteristics of the total postmenopausal study population are outlined in Chapter 4 (section 2.2 & 2.4) and were noted to be near identical to the baseline clinical characteristics of the postmenopausal black and white women not using hormone therapy (chapter 5, table 1). The baseline clinical characteristics of the white postmenopausal hormone never-users and current hormone users are summarized in table 1. Anthropometric variables, reproductive factors and lifestyle risk factors, with the exception of age at menarche and smoking, were comparable between the two cohorts. The women currently on hormone therapy (HT+) reached menarche at an earlier mean age (p=0.03) and they smoked more (p=0.04) compared with the never-users. A positive family history of osteoporosis was present in 21% and 26% of the users and the never-users respectively.
- A postmenopausal cohort only including postmenopausal black and white females not using hormone therapy.
- An additional subgroup of elderly blacks and whites (age \geq 65yrs), included due to the known significant contribution of falling to fracture risk especially in the elderly¹⁰⁹. The baseline clinical characteristics of this subgroup are shown in table 2.
- We also analyzed data separately in postmenopausal white females currently on hormone therapy and compared data between hormone never-users and current hormone users.
- Results of sensory and neuromuscular function tests are also compared between postmenopausal fallers and non-fallers.

One way analysis of variance was used to determine differences between the various ethnic subgroups with regard to falls and sensory and neuromuscular function tests. Cross tabulation was used to summarize categorical variables. Analysis of covariance was performed to assess the association between serum 25-OH Vitamin D status and fall risk in postmenopausal females. Partial correlations between Vitamin D status and physical performance tests i.e. quadriceps strength, AP-sway and lateral sway were drawn after correction for co-factors namely age, weight, BMI, exercise, smoking, alcohol intake and serum creatinine levels in postmenopausal females.

Table 1. Baseline characteristics of the white postmenopausal hormone never-users (HT-) and hormone users (HT+)

Characteristic	White postmenopausal women		
	Hormone never-users (n=60)	Current hormone users (n=43)	<i>p-value</i>
Age (yr)	59 ± 9	56 ± 7	0.06
Height (cm)	163 ± 17	160 ± 26	0.18
Weight (kg)	71.6 ± 15	69 ± 11	0.20
BMI (kg/cm ²)	27 ± 5	26 ± 4	0.14
Elbow width (mm)	67 ± 4	67 ± 4	0.34
Age (yrs) at menarche	13.2 ± 1.8	12.6 ± 1.7	0.03
Years since menopause	10.9 ± 8.7	10.5 ± 7.0	0.39
Calcium intake (mg/d)	855 ± 250	855 ± 255	0.28
Smoking (pack yrs)	5.9 ± 14.4	11.0 ± 16.1	0.04
Alcohol (U/week)	2.4 ± 4.0	1.7 ± 3.2	0.20
Physical activity score (0-4)	2.8 ± 0.9	2.7 ± 0.8	0.24
Number of pregnancies	2.7 ± 1.6	2.6 ± 1.4	0.38
Past OC use n (%)	25 (38)	24 (52)	
Past Depo Provera use n(%)	2 (3)	0 (0)	
Positive family history n (%)	14 (21)	12 (26)	

Values are reported as average ± SD except where otherwise stated

Table 2: Baseline clinical characteristics of the elderly black and white postmenopausal females

Postmenopausal females ≥ 65 years			
Characteristic	Blacks (n= 28)	Whites (n= 28)	p-value
Age (yr)	72 ± 4	72 ± 4	0.26
Height (cm)	158 ± 7	158 ± 7	0.43
Weight (kg)	83 ± 17	70 ± 15	<0.01
BMI (kg/cm²)	33.5 ± 8	27.4 ± 5	<0.01
Waist/Hip ratio (cm)	0.87 ± 0.1	0.87 ± 0.1	0.45
Elbow width (mm)	67 ± 5	68 ± 5	0.24
Age at menarche(yrs)	14 ± 2	13 ± 2	0.01
Menopause age (yrs)	49 ± 5	48 ± 4	0.02
YSM (yrs)	23 ± 6	23 ± 5	0.45
Calcium intake (mg/d)	616 ± 168	745 ± 207	0.01
Smoking (pack yrs)	0	6 ± 11	<0.01
Alcohol (U/week)	0.83 ± 3.9	1.96 ± 4.0	0.15
PA score (0-4)	1.7 ± 1	2.6 ± 0.9	<0.01
Family history (%)	0%	7%	
OCP use (%)	21%	18%	
DP use (%)	7%	4%	
Nr of pregnancies (n)	5 ± 3	4 ± 2	<0.01
Breastfeeding+ (%)	86%	79%	

3. RESULTS

3.1. Fall results in the total study population

A recent fall (within 12 months) occurred in 73 of the study subjects, 29 blacks and 44 whites.

Fall subjects thus represented 16% and 24% of the two ethnic groups respectively. The majority of these falls occurred in postmenopausal females and affected 22% of blacks and 29% of whites. A similar percentage of white postmenopausal hormone users (28%) and non-users sustained a recent fall (30%).

A recent fall resulted in non-spine fractures in two postmenopausal white females (one Colle's fracture, one rib fracture). In patients with recent falls, non-spine fractures occurred following prior fall(s) in a further 6 patients.

Reliable information regarding the direction of the fall was only available in 42 subjects. Twenty-three subjects reported a forward fall, 10 fell sideways and 9 backwards. The only 2 documented fractures at the time of a recent fall were sustained following a lateral fall (table 3). Although numbers are very limited, 90% of lateral falls occurred in the postmenopausal females.

3.2. Falling and bone mineral density in the postmenopausal cohort

Bone mineral density data pertaining to the postmenopausal fallers and non-fallers amongst blacks and whites is depicted in table 4 (please refer to chapter 3, section 2.2.1 for definitions of osteopenia and osteoporosis used in this study).

Table 3. Falls in the total study population

	Black cohort		White cohort			
	Premenopausal (n=87)	Postmenopausal (n=100)	Premenopausal (n=76)	Postmenopausal (n=110)		
				Total (n=110)	Non-hormone users(n=64)	Hormone users(n=46)
FALLS:						
Total	7	22	12	32	19	13
Multiple	1	4	0	4	2	2
DIRECTION:						
Uncertain	6	11	3	11	7	4
Forwards	1	7	6	9	5	4
Backwards	0	1	2	6	3	3
Lateral	0	3	1	6	4	2
FRACTURES*						
Recent fall	0	0	0	2	1	1
Past fall(s)	1	3	0	4	3	0

* Historical fractures as reported by subjects

3.2.1. Blacks

A higher percentage of black females with a recent fall had documented proximal femoral osteopenia compared to those without falls. Lumbar osteopenia was present in a similar percentage of blacks with and without a history of a recent fall. Osteoporosis at any skeletal site was noted in 23% (5/22) of fallers and in 12% (9/78) of non-fallers.

3.2.2. Whites

In whites a somewhat higher percentage of lumbar osteopenia was noted in fallers compared to non- fallers, whereas femoral osteopenia occurred in a similar percentage of whites with and without recent falls. Documented osteoporosis at any skeletal site was present in 16% (5/32) and 9% (7/78) of fallers and non-fallers respectively.

Table 4 Bone mineral density at different skeletal sites in postmenopausal females with and without recent falls

Postmenopausal Population	Regional bone mineral density					
	Lumbar spine BMD		Femoral neck BMD		Total femoral BMD	
	Normal BMD n(%)	Osteopenic n(%)	Normal BMD n(%)	Osteopenic n(%)	Normal BMD n(%)	Osteopenic n(%)
Black cohort						
Falls (n=22)	12 (55)	10 (45)	10 (45)	12 (55)	13 (59)	9 (41)
No falls (n=78)	39 (50)	39 (50)	58 (74)	20 (26)	62 (79)	16 (21)
White cohort						
Falls (n=32)	19 (59)	13 (41)	18 (56)	14 (44)	22 (69)	10 (31)
No falls (n=78)	54 (69)	24 (31)	38 (49)	40 (51)	52 (67)	26 (33)

Values expressed as total number with percentage in brackets

3.3. Elderly study population (age ≥65yrs)

Twenty-nine black females and twenty-eight white postmenopausal females were 65 years and older. Twenty-one of the 80 recent falls occurred in these elderly women. About one third of females older than 65 years reported a recent fall - 10 falls occurred in blacks (34%) and 11 falls in whites (39%). None of these falls occurred in the five elderly white women on hormone therapy. In blacks 8 of the 10 falls (80%) occurred in patients with osteopenia at one or more skeletal site, whereas 10 of the 11 white females (91%) who reported a recent fall had osteopenia. A significant percentage of elderly females without a recent fall was also osteopenic at one or more skeletal sites in blacks and whites representing 68% and 71% of the two ethnic groups respectively. Osteoporosis at any skeletal site was present in 36% of white fallers and in 40% of black fallers. In the non-fallers, 18% (3/17) of whites and 21% (4/19) of blacks had osteoporosis at one or more skeletal sites (table 5).

Table 5 Bone mineral density at different skeletal sites in elderly postmenopausal females (≥ 65 years) with and without recent falls

Elderly postmenopausal population (≥ 65 years)	Regional bone mineral density				
	<i>Lumbar spine BMD</i>	<i>Femoral neck BMD</i>	<i>Total femoral BMD</i>	<i>Any site</i>	
	Osteopenic n(%)	Osteopenic n(%)	Osteopenic n(%)	Osteopenic n(%)	Osteoporotic n(%)
<i>Black cohort</i>					
Falls (n=10)	6 (60)	8 (80)	5 (50)	8 (80)	4 (40)
No falls (n=19)	11 (58)	7 (37)	3 (16)	13 (68)	4 (21)
<i>White cohort</i>					
Falls (n=11)	7 (64)	9 (82)	7 (64)	10 (91)	4 (36)
No falls (n=17)	6 (35)	11 (65)	8 (59)	12 (71)	3 (18)

Values expressed as total number with percentage in brackets

3.4. Hormone therapy and falls

As mentioned before, a similar percentage of white postmenopausal hormone users (28%) and non-users sustained a recent fall (30%). None of the five elderly white women on hormone therapy reported a recent fall.

4. SENSORY AND NEUROMUSCULAR FUNCTION

4.1. Body Sway

4.1.1. Total study cohort

Body sway was objectively assessed in all study subjects. A significantly greater mean anterior-posterior sway, but similar mean lateral sway was documented in white premenopausal females compared with blacks. Early and late postmenopausal blacks and whites had similar mean anterior-posterior sway, but a greater mean lateral sway was noted in blacks compared with whites. No increase in AP sway was noted with ageing in either racial group, whereas increased lateral sway was present in the late postmenopausal women compared to the younger subgroups (table 6).

4.1.2. Postmenopausal females

Body sway data in the early and late postmenopausal groups not using hormone therapy was near identical to that of the total cohorts (table 7). Black and white women had similar mean anterior-posterior sway, whereas lateral sway was greater in blacks compared with whites. Hormone therapy in whites had very little impact on body sway in the younger

postmenopausal group. Near-significant reduction in lateral sway was however noted in the older white hormone users compared with the non-users ($p=0.05$) [table 8].

4.1.3. Fallers versus non-fallers

Black females had similar mean body sway in the group of fallers and non-fallers, whereas the white fallers had a significantly greater anterior-posterior body sway compared to non-fallers (table 9).

4.2. Reaction Time

4.2.1. Total study cohort

Mean reaction time was significantly longer in premenopausal and postmenopausal blacks compared with whites. Reaction time increased with ageing in both blacks and whites (table 6).

4.2.2. Postmenopausal females

Mean reaction time in the early and late postmenopausal blacks and whites not on hormone therapy was near identical to that of the total cohorts (table 7). Mean reaction time in the white females with and without hormone therapy was similar in the early and late postmenopausal groups (table 8).

4.2.3. Fallers versus non-fallers

In the postmenopausal blacks, the reaction time in females who reported a recent fall was near identical to non-fallers. In whites there was a tendency towards a longer mean reaction time in the postmenopausal white female fallers compared with the non-fallers, but this did not reach statistical significance (table 9).

Table 6. Sensory and neuromuscular function tests in premenopausal and the total postmenopausal black and white cohorts

Function	Premenopausal females			Postmenopausal females					
				<60 years			≥ 60 years		
	<i>Blacks</i> (n=87)	<i>Whites</i> (n=76)	<i>p-value</i>	<i>Blacks</i> (n=52)	<i>Whites</i> (n=63)	<i>p-value</i>	<i>Blacks</i> (n=48)	<i>Whites</i> (n=47)	<i>p-value</i>
Body sway (mm)									
Anterio-posterior	17.6 ± 6.3	20.4 ± 7.2	<0.01	19.4 ± 7.0	19.0 ± 5.9	0.35	20.9 ± 7.6	20.0 ± 8.3	0.29
Lateral	13.9 ± 8.2	13.6 ± 9.4*	0.39	14.8 ± 9.1	10.7 ± 5.9	<0.01	20.1 ± 8.6**	12.8 ± 9.6	<0.01
Reaction time (ms)	391 ± 171	262 ± 39*	<0.01	428 ± 152	275 ± 42**	<0.01	529 ± 189**	320 ± 78	<0.01
Visual contrast	18.0 ± 3.2*	19.4 ± 2.8*	<0.01	15.4 ± 4.4	18.1 ± 2.2**	<0.01	14.7 ± 2.4	15.8 ± 2.5	0.01
Quadriceps strength (kg)	26.6 ± 9.3	32.6 ± 6.2	<0.01	24.5 ± 9.0	32.5 ± 8.1**	<0.01	21.3 ± 7.7**	26.1 ± 6.9	<0.01

Values reported are the mean ± SD. *p-values* tabulated refers to the comparison between blacks and whites within each age-group

* *p-value* <0.05 compared with early postmenopausal cohort of same racial group

** *p-value* <0.05 compared with late postmenopausal cohort of same racial group

Table 7. Sensory and neuromuscular function tests in postmenopausal blacks and whites not using hormone therapy

Function	Postmenopausal females					
	<60 years			≥ 60 years		
	<i>Blacks</i> (n=49)	<i>Whites</i> (n=35)	<i>p-value</i>	<i>Blacks</i> (n=48)	<i>Whites</i> (n=31)	<i>p-value</i>
Body sway (mm)						
Anterio-posterior	18.9 ± 7.2	19.2 ± 5.9	0.42	21.6 ± 8.0	22.2 ± 7.0	0.37
Lateral	15.2 ± 9.3	10.9 ± 6.1	0.01	20.1 ± 8.6	15.3 ± 11.2	<0.01
Reaction time (ms)	433 ± 153	274 ± 48	<0.01	529 ± 189	325 ± 86	<0.01
Visual contrast	15.3 ± 4.5	18.5 ± 1.9	<0.01	14.7 ± 2.6	16.0 ± 2.4	0.01
Quadriceps strength (kg)	24.1 ± 9.2	34.2 ± 7.9	<0.01	21.3 ± 7.7	25 ± 7.0	0.02

Values reported are the mean ± SD

Table 8. Sensory and neuromuscular function tests in white postmenopausal hormone non-users (HT-) and users (HT+)

Function	Postmenopausal females					
	<60 years			≥ 60 years		
	<i>Whites (HT-)</i> <i>(n=35)</i>	<i>Whites (HT+)</i> <i>(n=28)</i>	<i>p-value</i>	<i>Whites (HT-)</i> <i>(n=31)</i>	<i>Whites (HT+)</i> <i>(n=18)</i>	<i>p-value</i>
Body sway (mm)						
Anterio-posterior	19.2 ± 5.9	19.4 ± 5.1	0.46	22.2 ± 7.0	23.6 ± 8.3	0.10
Lateral	10.9 ± 6.1	10.7 ± 5.7	0.45	15.3 ± 11.2	10.5 ± 5.7	0.05
Reaction time (ms)	274 ± 48	276 ± 33	0.42	325 ± 86	307 ± 57	0.22
Visual contrast	18.5 ± 1.9	17.7 ± 2.3	0.09	16.0 ± 2.4	15.9 ± 2.4	0.46
Quadriceps strength (kg)	34.2 ± 7.9	30.6 ± 8.1	0.04	25 ± 7.0	28.5 ± 6.3	0.05

Values expressed as mean ± SD

Table 9. Sensory and neuromuscular function tests in postmenopausal black and white female fallers and non-fallers

Function	Postmenopausal females					
	<i>Black fallers</i> <i>(n= 22)</i>	<i>Black non-fallers</i> <i>(n=78)</i>	<i>p-value</i>	<i>White fallers</i> <i>(n=32)</i>	<i>White non-fallers</i> <i>(n=78)</i>	<i>p-value</i>
Body sway (mm)						
Anterio-posterior	22.0 ± 9.0	19.6 ± 9.9	0.12	22.4 ± 7.5	19.3 ± 5.2	0.01
Lateral	17.3 ± 7.7	17.4 ± 6.1	0.42	11.9 ± 9.3	12.0 ± 6.9	0.49
Reaction time (ms)	475 ± 184	480 ± 177	0.48	306 ± 81	288 ± 53	0.09
Visual contrast	14.4 ± 3.0	15.2 ± 3.7	0.19	17.3 ± 2.6	17.2 ± 2.5	0.38
Quadriceps strength (kg)	22.9 ± 8.6	23.1 ± 8.6	0.35	27.3 ± 8.1	31.0 ± 8.0	0.02

Values expressed as mean ± SD

4.3. Visual Contrast Sensitivity (Melbourne Edge Test)

4.3.1. Total study cohort

Visual acuity was assessed by the Melbourne Edge test. Whites scored significantly better than blacks in all the different subgroups of the total cohort. Visual contrast sensitivity decreased with ageing in both blacks and whites (table 6).

4.3.2. Postmenopausal females

Visual acuity results remained better in whites compared with blacks when hormone users were excluded and as expected no significant impact of hormone therapy on visual contrast sensitivity could be demonstrated in whites (table 8).

4.3.3. Fallers versus non-fallers

Visual contrast studies yielded similar results in black and white fallers and non-fallers respectively (table 9).

4.4. Quadriceps Strength

4.4.1. Total study cohort

Significantly higher mean quadriceps muscle strength was documented in the whites compared with blacks in all the subgroups of the total study cohort. Reduced quadriceps strength was noted with ageing in postmenopausal blacks and whites (table 6).

4.4.2. Postmenopausal females

Mean quadriceps strength remained significantly higher in the postmenopausal whites compared with blacks when only hormone non-users were analyzed (table 7). In whites, greater quadriceps strength was documented in the older postmenopausal women on hormone therapy compared with non hormone users, but statistical significance was not reached (table 8).

4.4.3. Fallers versus non-fallers

Mean quadriceps strength was similar in postmenopausal black fallers and non-fallers, but significantly weaker in the white fallers compared with non-fallers (table 9).

5. 25-OH VITAMIN D STATUS, FALLS AND NEUROMUSCULAR TESTING

5.1. Vitamin D status and recent falls in postmenopausal blacks and whites

Analysis of covariance was performed to assess the association between serum 25-OH Vitamin D status and fall risk in postmenopausal females. Two main factors i.e. race and Vitamin D, were included to assess the combined effect on fall risk as signified by recent falls within the last twelve months. The influence of co-factors namely age, weight, BMI, exercise, smoking, alcohol intake and serum creatinine levels were corrected for. A non-significant interaction between race and fall risk was demonstrated thus implying that a difference between fallers and non-fallers regarding Vitamin D status was the same irrespective of race. This allowed pooling of data obtained in the two race groups in order to determine possible differences in serum 25-OH Vitamin D status between fallers and non-fallers. Our results indicated no significant difference in this parameter between fallers and non-fallers. As reported in Chapter 8, serum 25-OH Vitamin D levels were significantly lower in blacks compared with whites in this study ($p < 0.01$).

5.2. Vitamin D status and physical performance tests in postmenopausal blacks and whites

Partial correlations between Vitamin D status and physical performance tests i.e. quadriceps strength, AP-sway and lateral sway were drawn after correction for co-factors namely age, weight, BMI, exercise, smoking, alcohol intake and serum creatinine levels in postmenopausal females. A significant association between quadriceps strength and Vitamin D status was noted in blacks whereas a weaker, non-significant tendency to correlate was also noted in whites. No correlation was noted between serum 25-OH Vitamin D status and AP-sway or between serum 25-OH Vitamin D status and lateral sway in neither blacks nor whites (table 10).

Table 10. Partial correlations between 25-OH-Vitamin D status and physical performance in postmenopausal blacks and whites

Parameters correlated	Postmenopausal blacks		Postmenopausal whites	
	r-value	p-value	r-value	p-value
25-OH-Vit D and quadriceps strength	0.3	0.01	0.23	0.12
25-OH-Vit D and AP-sway	-0.09	0.41	-0.16	0.28
25-OH-Vit D and lateral sway	-0.03	0.78	-0.05	0.75

Parameters correlated after correction for age, weight, BMI, exercise, smoking, alcohol intake and serum creatinine levels.

6. DISCUSSION

FALLS

In our study population of ambulatory community dwelling females, a similar percentage of black and white females sustained a recent fall (16% black; 24% white). The majority of falls occurred in older postmenopausal females. Thirty-nine percent of blacks and 36% of whites over the age of 65 years sustained a recent fall, values similar to those reported in the literature³⁵¹. Although numbers are limited, the fall direction appeared to be different in blacks and whites, with whites documented to more often fall laterally and backwards than blacks. It has been suggested in some studies^{206,207} that African Americans fall less than whites. In other studies^{208,209} the frequency of falling was similar, but the fall circumstances differed i.e. whites were significantly more likely to fall outdoors versus indoors and laterally versus forward²⁰⁹. It has been documented that the nature of the fall determines the type of fracture i.e. that women with wrist fractures were more likely to have fallen backward than those who fell without a fracture, whereas women who suffered hip fractures were more likely to have fallen sideways or straight down¹⁷⁴. Falls per se, especially in the elderly, contribute significantly to the occurrence of symptomatic fractures^{169,170,319}. Fall frequency was similar in our blacks and whites, but whether fall circumstances differ significantly between these two ethnic groups will have to be confirmed in a larger population sample.

No significant correlation between 25-OH Vitamin D status and fall risk could be demonstrated in our postmenopausal blacks and whites. Patient numbers were, however, small and may account for the lack of such a correlation. No studies assessing the impact of low 25-OH Vitamin D status on fall risk in blacks have been published, whereas the positive association between low 25-OH Vitamin D status and fall risk in Caucasian populations have been documented previously^{176,350}. Given the absence of any significant association, it will, therefore, be interesting to assess 25-OH-Vitamin D status in a larger black and white South African population to verify whether any association does exist with fall risk.

Femoral osteopenia was present in a higher percentage of black fallers compared to those who did not fall, whereas white fallers and non-fallers were similarly affected. Osteoporosis at any skeletal site was noted in a higher percentage of black and white fallers compared with non-fallers in the total postmenopausal groups (black: 23% vs. 13%; whites: 16% and 9%) and in the older subgroup (black: 40% vs. 22%; whites: 36% and 18%). A higher fall risk has been noted in older women with osteoporosis compared with their age-matched counterparts without osteoporosis³⁵² and is ascribed in part to associated sarcopenia in up to

50% of osteoporotic patients¹⁷³⁻¹⁷⁶. This highlights the importance of fall risk screening and fall risk reduction to prevent fractures in women with osteoporosis.

NEUROMUSCULAR AND VISUAL ASSESSMENT

Neuromuscular and visual assessment based on postural sway, reaction time, visual contrast sensitivity studies and quadriceps strength yielded consistently better results in whites than blacks. We conducted a cross-sectional study with a single patient contact visit. As test outcomes were heavily dependent on patient understanding, results might have been suboptimal in our black cohort due to the language barrier in some of the subjects. Premenopausal, as well as postmenopausal black females, had significantly weaker quadriceps strength with greater lateral sway, along with poorer vision and slower reaction time. Our black females were also less active than whites especially into old age (see Chapter 4, section 3.1.3) which may partially explain their poorer performance with regard to neuromuscular testing. Poor 25-OH Vitamin D status has been associated with poor physical performance and sarcopenia in older white populations^{176,348,349}. 25-OH Vitamin D levels were significantly lower in blacks in our study ($p < 0.01$). A modest association between 25-OH Vitamin D status and quadriceps strength in blacks and whites was documented in this study, reaching significance only in the black population. Low 25-OH Vitamin D status may thus contribute to the finding of weaker quadriceps strength in blacks. Based on neuromuscular and visual studies, and a more inactive cohort with ageing, one might have expected more falls in our blacks, but this was not the case. Similar fall histories were documented in blacks and whites in this study, but numbers are limited and may as such mask significant differences. Previous studies have documented poorer muscle strength and less physical activity, but similar fall histories, in African American females compared with whites²⁰⁸, findings similar to ours.

Neuromuscular impairment and poor vision have been shown to be independent predictors of hip fracture risk in numerous studies^{178,319,342,351}. Neuromuscular impairment may have two distinct roles in the occurrence of hip fractures: it may not only increase the risk of falling, but also influence an individual's speed, coordination and protective responses during a fall and as such may increase the risk of fracture independently of fall frequency. No difference in neuromuscular parameters and visual test results between black fallers and non-fallers was documented in this study, whereas a larger AP-sway and weaker quadriceps strength were noted in the white fallers compared with the white subjects who did not fall. These tests of neuromuscular function and visual contrast sensitivity have been shown to be able to identify individuals in the community at risk of falls and fall related fractures^{178,319,342,351}. Most of these studies were conducted in postmenopausal white females and little is known

regarding the ability of these functional and visual tests to predict fall and fracture risk in blacks. In our white cohort, quadriceps weakness and a slower reaction time was noted in the group of fallers and may in part explain why these individuals did sustain a recent fall. The finding of similar neuromuscular function and visual contrast sensitivity in black fallers and non-fallers may be explained in more than one way. These tests may be a true reflection of function and may indicate that these modalities do not significantly contribute to falls in our black female population. As alluded to before, we conducted a cross-sectional study with a single patient contact visit. Outcome of these tests are heavily dependent on patient understanding and co-operation and might have been compromised in our black cohort due to a suboptimal grasp of the English language in some of the subjects. These differences in neuromuscular function tests between blacks and whites should therefore be interpreted with caution.

HORMONE THERAPY

The use of hormone therapy in whites had an impact on falls in the elderly. A significantly lower percentage of falls occurred amongst the older postmenopausal white females using hormone therapy compared with non-users (11% versus 45%) and none of the white female hormone users over the age of 65 years sustained a recent fall. Current hormone therapy reduced lateral sway and improved quadriceps strength in older white females in this study which may partially explain why older white female hormone users fell less than those without hormone therapy.

To conclude, the percentage fallers in our black and white cohorts was similar and in both ethnic groups the risk of falling increased with age. There is a suggestion that the nature of falls in our black and white postmenopausal females may differ, but numbers are limited. Fallers in our postmenopausal study population were more likely than non-fallers to have osteoporosis. Postmenopausal blacks in our study demonstrated poorer outcomes regarding neuromuscular function, Vitamin D status and visual contrast testing and were shown to be more inactive with ageing compared with whites. This, however, did not result in an increased fall tendency amongst the black females. Quadriceps weakness and slower reaction time indicated an increased fall risk amongst whites, but were unable to distinguish black female fallers from non-fallers. Hormone therapy improved quadriceps strength and reduced lateral sway and significantly reduced fall risk in older white females. Data regarding fall tendencies, risk factors for falling and the association with reduced BMD amongst South African black and white females are limited at present and further studies are clearly needed to better define these important issues.

.....

CHAPTER 11

VERTEBRAL FRACTURE PREVALENCE IN BLACK AND WHITE SOUTH AFRICAN FEMALES

1.	INTRODUCTION.....	218
2.	PATIENTS AND METHODS	219
3.	RESULTS.....	220
3.1.	VERTEBRAL FRACTURE PREVALENCE	220
3.1.1.	Comparison between black and white fracture subjects.....	220
3.1.2.	Comparison between subjects with and without vertebral fracture	223
3.1.2.1.	<i>Postmenopausal blacks</i>	223
3.1.2.2.	<i>Postmenopausal whites</i>	223
4.	DISCUSSION.....	226

CHAPTER 11

VERTEBRAL FRACTURE PREVALENCE IN BLACK AND WHITE SOUTH AFRICAN FEMALES

1. INTRODUCTION

In South Africa, osteoporosis related fractures occur more frequently in whites. The only documented fracture data in South Africa, however, date back to the 1970's when Solomon et al noted that the urban Black population of the Johannesburg Metropolitan Area had a more than ten fold lower hip fracture rate compared to that seen in Western European populations, and that black males and females were affected equally²⁰. In 1968 Dent and co-workers published their data on spinal osteoporosis in rural and urban black females, and white females residing in the Durban area. They noted severe osteoporosis of the spine (as defined by structural abnormalities of the vertebrae on conventional X-rays of the lumbar spine) in 14% of Whites compared to a 3% and 2% prevalence in the rural and urban blacks respectively²¹.

In West Africa, a very low incidence of minimal trauma fractures of the hip and wrist has also been observed²¹². This clinical impression is supported by the experience of the UK Medical Research Council (MRC) field station in Keneba, The Gambia, where there have been no reported cases of osteoporosis-related fractures during the past 40 years.

Most studies evaluating risk factors for vertebral fracture in women have been conducted in Caucasian populations. The Study of Osteoporotic Fractures (SOF) identified a low BMD at peripheral or central sites³⁵³, prevalent vertebral fractures³⁵⁴, low estradiol levels^{355,356} and depression³⁵⁷ as risk factors for incident vertebral fracture in a prospective cohort of women ≥ 65 years of age, followed for an average of 3.8 years. In this same cohort, Nevitt et al³⁰⁵ recently reported that low BMD at all sites measured, previous non-spine fracture, falls in the last year, increased age, smoking, and low body mass index increased risk for a first vertebral fracture, whereas physical activity and estrogen use were associated with decreased risk. In contrast, The European Osteoporosis study (EPOS)³⁵⁸ found that smoking and physical inactivity did not increase risk of incident vertebral fracture in women or men, 50-79 years of age, after 4 years of follow-up. The Rotterdam study³⁵⁹, with a slighter longer duration of follow-up (6.3 years), found that prevalent vertebral fracture and low BMD were associated with an increased incidence of vertebral fracture in women and men, whereas increased age and smoking increased risk in women only. Long-term risk of incident vertebral fractures was assessed in middle-aged persons as part of the Framingham Study¹⁵⁸.

Prevalent vertebral fracture was identified as the only factor able to predict long-term incidence of fractures in these women. Age, height, weight, grip strength, physical activity and estrogen use had little or no influence on cumulative incidence of vertebral fractures. In the Chingford study³⁶⁰ spinal bone density was similar for fracture and non-fracture cases.

In a single study by Vokes et al³⁶¹, risk factors for prevalent vertebral fractures in black and white females were assessed and included age, height loss, history of non-vertebral fractures, BMD and corticosteroid use. Among whites all risk factors evaluated were significantly associated with vertebral fractures, whereas only age and corticosteroid use were found to be significant predictors of vertebral fracture presence in blacks.

The purpose of this chapter is to describe the prevalence of vertebral fractures in this group of community-dwelling and otherwise healthy black and white South African women and to examine the relationship between parameters of bone strength (clinical and lifestyle factors, BMD, geometry, ultrasonography, biochemistry and falls and fall tendency) and vertebral fracture in blacks and whites.

2. PATIENTS AND METHODS

Conventional radiology of the thoraco-lumbar vertebrae was obtained randomly in as many of the study subjects as possible. Patients were referred for radiological evaluation whenever possible, but due to financial constraints and logistical difficulties the total cohort was not examined. Two hundred and eighty nine of the subjects underwent conventional radiology and included 116 blacks (55 premenopausal and 61 postmenopausal subjects) and 173 whites (69 premenopausal and 104 postmenopausal subjects of whom 42 were on hormone therapy). The evaluation was thus performed in 77% of the total study cohort. We used a fixed percentage reduction in vertebral height to define incident deformities. A vertebral fracture was defined as vertebral height loss of 20% or more²³² and all radiographs were evaluated and interpreted by a single specialist radiologist (please refer to chapter 3, section 2.5 for a more detailed outline of methodology). Analysis of vertebral compression fractures reported here was restricted to the premenopausal and non-hormone treated postmenopausal cohorts.

One way analysis of variance (ANOVA) was used to compare black and white fracture cases as well as females with and without prevalent vertebral fractures with regard to clinical characteristics, densitometry, ultrasonography, geometry and biochemically determined bone turnover and fall tendency within the two ethnic groups.

Clinical characteristics of the study population evaluated for vertebral fractures are summarized in table 1 and was similar to the total study cohort (refer to Chapter 4, section 3.1.1 and 3.1.2). Blacks and whites had similar mean ages in the comparable groups studied except for older age noted in the older white postmenopausal females. In general, blacks were shorter and heavier than whites, reached menarche at a later age, preferred injectable hormone contraception, had a larger number of pregnancies and consumed less calcium daily. The white women smoked more but maintained a higher level of physical activity post menopause. Mean alcohol consumption was low and comparable between the two groups.

3. RESULTS

3.1. VERTEBRAL FRACTURE PREVALENCE

3.1.1. Comparison between black and white fracture subjects

A total of 13 patients with vertebral compression fractures were identified and included 8 black patients and 5 white patients. Characteristics of the subjects with vertebral fracture(s) are summarized in table 2 and illustrated in figure 1. Blacks with fracture were younger than whites and the difference neared statistical significance ($p=0.05$). Mean weight, height and BMI were comparable between the black and white fracture groups. The subjects with vertebral fractures were all postmenopausal (with the exception of one black female with a single vertebral fracture) and represented 11.5% and 8.1% of postmenopausal blacks and whites respectively. Vertebral osteopenia was present in 6/7 (86%) black postmenopausal females with fracture, vertebral osteoporosis in 2/7 (29%), and femoral osteopenia in 6/7 (86%). In whites, vertebral osteopenia was present in 3/5 (60%) of fracture cases, vertebral osteoporosis in one patient, femoral osteopenia in 5/5 cases (100%) and femoral osteoporosis in 2/5 cases (40%). It thus appears as if vertebral and femoral BMD-values are of similar value to predict vertebral fractures in blacks, but that femoral BMD is better in the white cohort.

Table 1: Baseline characteristics of the study cohort in which vertebral fractures were assessed

	Premenopausal females			Postmenopausal females					
				< 60 years			≥ 60 years		
	Blacks n=55	Whites n=69	<i>p-value</i>	Blacks n=31	Whites n=32	<i>p-value</i>	Blacks n=30	Whites n=30	<i>p-value</i>
Age (yr)	37 ± 8	39 ± 7	0.05	52 ± 5	51 ± 5.0	0.42	67 ± 5	70 ± 5	0.02
Height (cm)	160 ± 6	167 ± 6	<0.01	161 ± 6	165 ± 7	<0.01	159 ± 6	160 ± 7	0.36
Weight (kg)	80 ± 21	69 ± 15	<0.01	81 ± 17	72 ± 17	0.02	89 ± 19	72 ± 15	<0.01
BMI (kg/cm²)	31 ± 7.6	25 ± 5.0	<0.01	31 ± 7.1	26 ± 5.6	<0.01	35 ± 8.1	28 ± 5.3	<0.01
Elbow width (mm)	64.6 ± 5.6	65.3 ± 3.4	0.22	67.1 ± 3.8	66.0 ± 4.1	0.19	69.6 ± 6.4	67.8 ± 4.9	0.22
Age at menarche (yrs)	15 ± 2.2	13 ± 1.6	<0.01	14 ± 1.8	13 ± 2.0	0.09	15 ± 2.0	13 ± 1.4	<0.01
Age at menopause (yrs)				46 ± 4.4	49 ± 3.9	<0.01	49 ± 5.0	49 ± 4.4	0.47
YSM (yrs)				6.3 ± 4.4	4.0 ± 4.1	0.03	18 ± 7.4	21 ± 7.1	0.09
Nr of pregnancies (n)	2.2 ± 1.6	1.8 ± 1.3	0.03	3.7 ± 2.6	1.9 ± 1.4	<0.01	5.8 ± 2.3	3.7 ± 1.6	<0.01
Calcium intake (mg/d)	592 ± 312	882 ± 278	<0.01	556 ± 217	865 ± 230	<0.01	665 ± 272	802 ± 264	0.04
Smoking (pack yrs)	0.6 ± 1.9	4.1 ± 18.6	0.08	1.1 ± 2.4	4.4 ± 11.1	0.06	0.28 ± 1.3	6.5 ± 13.1	<0.01
Alcohol (U/week)	4.8 ± 10.3	4.1 ± 5.5	0.34	3.8 ± 10	3.0 ± 5.2	0.34	0.8 ± 2.8	2.0 ± 3.9	0.1
PA score (0-4)	2.8 ± 1.0	2.8 ± 1.0	0.44	2.5 ± 1.1	3.1 ± 0.9	<0.01	1.7 ± 1.0	2.4 ± 0.8	<0.01
OCP use (%)	18%	75%	-	13%	52%	-	33%	24%	-
DP use (%)	45%	1%	-	33%	6%	-	7%	0%	-
Breastfeeding + (%)	64%	54%	-	80%	61%	-	90%	79%	-

Values expressed as mean ± SD, YSM: years since menopause; PA: physical activity; DP: Depo Provera; OCP: oral contraceptive

Table 2: Characteristics of the study subjects with vertebral fractures

Characteristics	Patients		
	Black n=8	White n=5	<i>p-value</i>
Age (yrs)	57 ± 8	67 ± 14	0.05
Weight (kg)	75 ± 14	70 ± 18	0.40
Height (cm)	160 ± 4	161 ± 12	0.43
BMI (kg/cm ²)	30 ± 6	27 ± 6	0.33
Fractures:			
Site			
Thoracic	6	5	
Lumbar	1	0	
Both	1	0	
Single	5	2	
Multiple	3	3	
% of postmenopausal cohort	11.5%	8.1%	
Spinal bone mineral status:			
Osteopenia n (% of fracture group)	6 (86%)	3 (60%)	
Osteoporosis n (% of fracture group)	2 (29%)	1 (20%)	
Femoral bone mineral status:			
Osteopenia n (% of fracture group)	6 (86%)	5 (100%)	
Osteoporosis n (% of fracture group)	0	2 (40%)	

Values expressed as mean ± SD unless otherwise specified

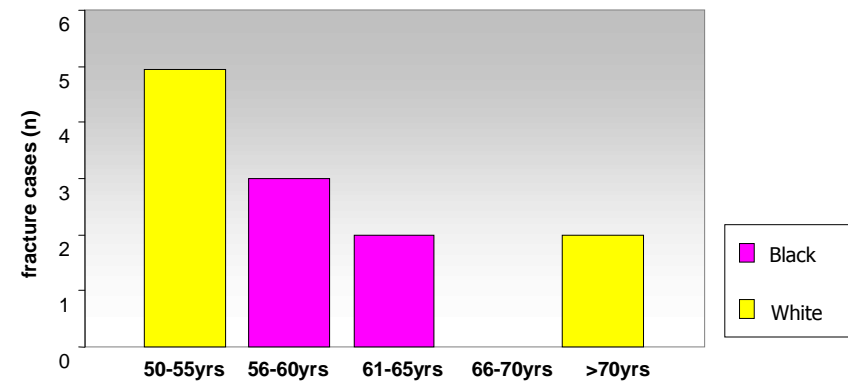


Figure 1: Number of fracture cases in black and white postmenopausal females within specified age groups

3.1.2. Comparison between subjects with and without vertebral fracture

Postmenopausal females with prevalent vertebral fractures and those with normal vertebral morphometry were compared with regard to clinical characteristics, densitometry, ultrasonography, geometry and biochemically determined bone turnover and fall tendency (table 3 and 4). We limited our comparison to postmenopausal females as, with the exception of one black female with vertebral fracture, all other vertebral fractures occurred in postmenopausal women.

3.1.2.1. Postmenopausal blacks

Proximal femoral BMD, as determined by DEXA, was consistently lower in blacks who fractured compared with the non-fracture group. This included the areal and 'volumetric' measurement of femoral neck bone mineral status and the total areal femoral BMD expressed as both absolute and T-score values. The densitometric evaluations of the spine (BMD: $p=0.05$ and BMAD: $p=0.06$) also appeared to be lower in the black fracture group. Clinical characteristics were similar in the black fracture and non-fracture cases, although a tendency towards lower weight and BMI was noted in the fracture group. The average BMI, however, was still in the overweight range. Macro-geometry, ultrasonography, biochemical bone turnover parameters, 25-OH-Vit D status, falls and neuromuscular assessment were similar in blacks with and without fractures.

3.1.2.2. Postmenopausal whites

Proximal femoral BMD, as determined by DEXA, was similar to the findings in blacks and consistently lower in whites who fractured compared with the non-fracture group. Densitometric evaluations of the spine were similar between the white fracture and non-fracture groups. A higher percentage of whites who fractured were physically inactive, and a significantly higher alcohol intake was noted in these subjects. Weight and BMI in whites were similar in the absence or presence of fractures. HAL, a known independent predictor of hip fracture risk, was significantly greater in the fracture group. Vertebral bone area was similar in white fracture and non-fracture cases.

A lower 25-OH-Vit D level, along with significantly weaker quadriceps strength, greater lateral sway, and reduced visual contrast sensitivity were present in the fracture group compared with those who had not sustained a fracture.

Table 3: Comparison between black subjects with and without vertebral fracture

<i>COMPARATORS</i>	Postmenopausal blacks		
	Fracture cases (n = 7)	Non-fracture cases (n = 53)	p-value
<i>CLINICAL CHARACTERISTICS</i>			
Age (yrs)	57 ± 7.5	60.0 ± 8.0	0.19
Weight (kg)	75 ± 14.1	86 ± 18.7	0.06
Height (cm)	160 ± 3.9	160 ± 6.4	0.48
BMI (kg/cm ²)	30 ± 6.1	34 ± 7.9	0.07
Family History + (%)	0%	3%	-
Age at menarche (yrs)	14.3 ± 2.7	14.2 ± 1.8	0.47
YSM (yrs)	14 ± 1.8	12 ± 8.3	0.28
Nr of pregnancies (n)	5 ± 3	4.7 ± 3	0.40
Calcium intake (mg/d)	692 ± 249	599 ± 252	0.18
Low PA (PA score ≤ 2) (%)	55%	70%	-
Alcohol intake (U/week)	3.8 ± 5.3	2.2 ± 7.5	0.29
<i>DENSITOMETRY</i>			
SBMD (g/cm ²)	0.852 ± 0.18	0.989 ± 0.21	0.05
SBMAD(g/cm ³)	0.115 ± 0.02	0.131 ± 0.03	0.06
SBMD T-score	-1.6 ± 1.6	-0.46 ± 1.96	0.06
FN-BMD (g/cm ²)	0.717 ± 0.06	0.848 ± 0.14	<0.01
FN-BMAD (g/cm ³)	0.135 ± 0.01	0.160 ± 0.03	0.01
FN-BMD T-score	-1.22 ± 0.59	-0.04 ± 1.23	<0.01
FT-BMD (g/cm ²)	0.808 ± 0.06	0.985 ± 0.16	<0.01
FT-BMD T-score	-1.13 ± 0.49	+0.33 ± 1.27	<0.01
<i>GEOMETRY</i>			
HAL (mm)	62 ± 2.3	62 ± 3.7	0.42
Femur-width (mm)	19 ± 0.4	19 ± 1.9	0.24
Vertebral BA (cm ²)	55 ± 6.9	57 ± 5.7	0.2
<i>ULTRASONOGRAPHY</i>			
Calcaneal BMD (g/cm ²)	0.47 ± 0.1	-0.52 ± 0.2	0.19
Calcaneal BMD-T-score	-1.03 ± 0.89	-0.55 ± 1.38	0.18
Calcaneal BUA (dB/MHz)	63 ± 16	71 ± 22	0.16
Calcaneal SOS (m/s)	1539 ± 23	1552 ± 40	0.20
<i>BIOCHEMISTRY</i>			
S-ALP (IU/l)	88 ± 45	88 ± 30	0.49
S-PTH (pg/ml)	5.4 ± 3.2	7.6 ± 5.4	0.14
S-Osteocalcin (ng/ml)	15.0 ± 8.8	11.9 ± 8.0	0.19
Free U-DPD/ creatinine (nmol/mmol)	8.2 ± 6.3	5.8 ± 4.2	0.10
S-25OH Vitamin D (ng/ml)	16 ± 5	13 ± 7	0.10
<i>FALLS AND FALL TENDENCY</i>			
Recent falls (%)	43%	23%	-
Quadriceps strength (kg)	24.3 ± 9.2	23.8 ± 9.9	0.45
Lateral sway (mm)	12.9 ± 8.0	16.6 ± 8.9	0.14
AP sway (mm)	16.5 ± 6.2	19.6 ± 8.0	0.17
Reaction time (ms)	466 ± 160	464 ± 187	0.49
Visual contrast sensitivity	14.4 ± 4.3	15.0 ± 4.0	0.35

Table 4: Comparison between white subjects with and without vertebral fracture

<i>COMPARATORS</i>	Postmenopausal whites		
	Fracture cases (n = 5)	Non-fracture cases (n = 57)	p-value
<i>CLINICAL CHARACTERISTICS</i>			
Age (yrs)	67 ± 14	60 ± 10	0.07
Weight (k)	70 ± 19	71 ± 19	0.44
Height (cm)	161 ± 12	163 ± 7	0.30
BMI (kg/cm ²)	27 ± 6	27 ± 6	0.50
Family History + (%)	20%	23%	-
Age at menarche (yrs)	13.4 ± 2.3	13.3 ± 1.7	0.43
YSM (yrs)	17.1 ± 13.6	11.4 ± 9.5	0.11
Nr of pregnancies (n)	3 ± 3	2.7 ± 1.6	0.37
Calcium intake (mg/d)	908 ± 470	833 ± 228	0.28
Low Physical activity (PA score ≤ 2)	80%	33%	-
Alcohol intake (U/week)	7 ± 10	2 ± 4	0.01
<i>DENSITOMETRY</i>			
SBMD (g/cm ²)	0.895 ± 10.2	0.960 ± 0.17	0.21
SBMAD(g/cm ³)	0.110 ± 0.01	0.124 ± 0.02	0.07
SBMD T-score	-1.38 ± 1.32	-0.76 ± 1.59	0.20
FN-BMD (g/cm ²)	0.606 ± 0.05	0.726 ± 0.13	0.02
FN-BMAD (g/cm ³)	0.106 ± 0.01	0.133 ± 0.02	<0.01
FN-BMD T-score	-2.2 ± 0.46	-1.12 ± 1.13	0.02
FT-BMD (g/cm ²)	0.742 ± 0.10	0.876 ± 0.15	0.03
FT-BMD T-score	-1.64 ± 0.78	-0.54 ± 1.20	0.03
<i>GEOMETRY</i>			
HAL (mm)	69 ± 6.1	66 ± 3.6	0.04
Femur-width (mm)	21 ± 2.5	20 ± 1.2	0.02
Vertebral BA (cm ²)	57.69 ± 5.8	59.3 ± 5.4	0.27
<i>ULTRASONOGRAPHY</i>			
Calcaneal BMD (g/cm ²)	0.417 ± 0.10	0.472 ± 0.12	0.12
Calcaneal BMD-T-score	-1.56 ± 0.93	-0.98 ± 1.08	0.12
Calcaneal BUA (dB/MHz)	55 ± 14	63 ± 18	0.17
Calcaneal SOS (m/s)	1524 ± 28	1541 ± 31	0.12
<i>BIOCHEMISTRY</i>			
S-ALP (IU/l)	80 ± 19	70 ± 24	0.19
S-PTH (pg/ml)	7.6 ± 4.0	6.6 ± 5.1	0.24
S-Osteocalcin (ng/ml)	24.4 ± 9.4	11.4 ± 11	0.10
Free U-DPD/ creatinine (nmol/mmol)	8.6 ± 4.7	6.3 ± 5.3	0.21
S-25OH Vitamin D (ng/ml)	13 ± 7	18 ± 6	0.02
<i>FALLS AND FALL TENDENCY</i>			
Recent falls (%)	40%	30%	-
Quadriceps strength (kg)	20 ± 8.2	30.3 ± 8.4	0.01
Lateral sway (mm)	24.1 ± 17.7	11.9 ± 7.2	<0.01
AP sway (mm)	23.4 ± 10.4	20.3 ± 6.2	0.16
Reaction time (ms)	345 ± 147	294 ± 62.8	0.07
Visual contrast sensitivity	14.8 ± 3.6	17.5 ± 2.3	0.01

4. DISCUSSION

This cross-sectional study of healthy free-living postmenopausal black and white females found that the prevalence of morphometric vertebral fractures was *not higher* in postmenopausal white females compared with blacks. In our study population, vertebral fractures occurred in 11.5% of black postmenopausal females compared with 8.1% of whites. Taking due cognizance of the small patient numbers employed in the present study, our data none the less appears to differ from the only other vertebral fracture study performed on a South African multi-ethnic population by Dent and co-workers in 1968²¹¹. Lateral X-rays of only the lumbar vertebrae were obtained in 100 rural blacks, 100 urbanized blacks and 100 women of European origin. Significant vertebral compression was noted in 3 rural blacks, 2 urbanized black subjects and 14 white subjects. The urbanized black females were all domestic workers, indicating a work entailing significant physical activity, and not necessarily representative of present urbanized black individuals' occupations.

World-wide very little has been published on vertebral fracture prevalence in black populations. Mui et al¹⁵⁷ found a 25% prevalence of vertebral fractures in inner-city, multi-ethnic postmenopausal women that included 40% blacks in the age group 55-89 yrs (mean age 65), whereas Vokes et al³⁶¹ documented a prevalence of 21% in both black and white patients aged 64 ± 13 yrs who were referred for densitometry. Based on data obtained from hospital records of vertebral fracture discharges, Jacobsen et al³⁸⁰ suggested that the vertebral fracture incidence is higher in white women compared with blacks. Vertebral fracture prevalence in blacks have not been adequately documented and researched. The presumed lower vertebral fracture prevalence in blacks on the African continent compared with whites is largely based on old studies and clinical experience. Our study, although limited by its cross-sectional nature and small numbers, did not show lower vertebral fracture prevalence in blacks. Larger population studies are needed to determine the exact prevalence of vertebral fractures in the different ethnic populations of South Africa.

Weight, height and BMI were comparable between the black and white fracture groups. With the exception of one case, all the black females with vertebral fractures had spinal and femoral osteopenia (86%). Femoral osteopenia was present in 100% of whites with vertebral fractures, whereas vertebral osteopenia was only present in 3/5 cases (60%). White fracture cases tended to be older than blacks, a finding similar to that observed by Dent et al²¹¹. Age may influence the presence of concomitant degenerative/ sclerotic changes that may impact on the accuracy of vertebral BMD measurements by DEXA, especially in the older whites, and

may thus explain why femoral BMD more accurately predicted vertebral fractures in our whites.

In our study, racial differences could be documented in the occurrence of risk factors known to predispose to the development of vertebral fracture. A low femoral BMD was the only bone strength parameter that was consistently associated with fracture in both black and white cohorts. In blacks, a tendency towards lower body weight in those who fractured was also observed. In whites' alcohol intake, physical activity, quantifiable physical performance parameters and 25-OH-Vitamin D levels were also noted to be significantly different between fracture and non-fracture cases. A longer HAL was also noted in whites with fractures and may indicate, in addition to vertebral fracture risk, also an increase in hip fracture risk in this group of patients. Vertebral BA was non-significantly lower in both black and white fracture cases.

As alluded to, low BMD at the proximal femoral sites was identified as the only risk factor for fractures in *both* blacks and whites in this study. A tendency towards lower lumbar spine BMD was also noted in black fracture cases, whereas lumbar spinal BMD was similar for white fracture and non-fracture groups. In the SOF³⁵³ and Rotterdam³⁵⁹ studies, BMD at both spinal and proximal femoral sites were associated with an increased risk of vertebral fractures, whereas other studies³⁶⁰ have also noted similar spinal BMD in fracture and non-fracture cases in agreement with our findings. Concomitant degenerative changes may explain these apparent discrepancies.

In our study, several clinical and lifestyle factors, including age, weight, height, BMI, family history of OP or fractures, age at menarche, parity, calcium intake, physical inactivity and alcohol intake did not differ between fracture and non-fracture cases in blacks. An association between clinical and lifestyle factors and fracture risk was similarly absent in whites except for physical inactivity and alcohol intake where a higher prevalence was noted in our fracture cases.

The Rotterdam Study³⁵⁹, EPOS³⁵⁸ and Framingham Vertebral fracture Study¹⁵⁸ found no association between physical activity and incident vertebral fracture in Caucasian women, similar to our findings in blacks, whereas physical activity was identified as a protective factor against first vertebral fracture in the SOF³⁵³ study as noted in our white women.

Skeletal geometry, ultrasonography, biochemistry, falls and fall tendency assessed in the present study were similar in black fracture and non-fracture cases. In whites, significant

differences were documented in skeletal geometric measurements, 25-OH-Vit D levels and neuromuscular function tests.

Serum 25-OH-Vitamin D levels were significantly lower in white women with fractures compared with non-fracture cases. White fracture cases also showed evidence of poor physical performance i.e. weaker quadriceps strength, greater lateral sway and reduced visual contrast sensitivity, and in addition a higher percentage of white women with fractures were physically inactive (80% versus 33%) and consumed more alcohol. Despite these findings, fall risk was not clearly different between the white fracture and non-fracture groups (40% versus 30%).

Low 25-OH-Vitamin D levels have been documented in previous studies to be associated with poorer physical performance (tests of muscle strength, reaction time and postural body sway)^{176,348,349} and have been independently associated with an increased risk of falling in the elderly, particularly those aged 65-75yrs³⁵⁰. In our study, 25-OH-Vitamin D status was not significantly associated with fall risk or postural sway, and only a modest correlation with quadriceps strength was observed (see chapter 10, section 5). The number of recent falls in our postmenopausal blacks and whites was similar, despite significantly lower 25-OH-Vitamin D levels and poorer physical performance in blacks. Previous studies have noticed less muscle strength and less activity, but similar fall histories, in African American females compared with whites²⁰⁸, findings similar to ours. The association between 25-OH-Vitamin D status and physical performance is particularly noted in those above 65yrs of age. The average age of our black fracture cases was 57±8yrs, i.e. not a single one above 65yrs of age, and may therefore partly explain this lack of association.

A history of recent falls is a major contributing factor to the occurrence of symptomatic non-spinal fractures in postmenopausal women, independent of and additive to the risk attributable to age and osteoporosis^{169,170}. Hip fractures occur almost exclusively after a fall and spontaneous hip fractures without prior falling is extremely rare¹⁶⁸. The exact role and significance of falls with regard to vertebral fractures is less well defined. Of the 13 subjects in our study with radiological evidence of vertebral fracture, five subjects (38%) reported a recent fall (3 blacks, 2 whites). None of these subjects were aware that they sustained a back injury at the time of the fall.

To conclude, despite the small patient numbers and other limitations of the present study, it does argue against the widely held belief that SA blacks have a lower vertebral fracture prevalence compared with whites. Vertebral fractures occurred in a similar percentage of postmenopausal blacks and whites in our study (11.5% and 8.1% respectively). Proximal

femoral BMD best identified black and white vertebral fracture cases in this study. Quite a number of other risk factors i.e. physical inactivity, alcohol-intake, poorer physical performance test results and a longer HAL were more frequent in the white fracture cases and could therefore serve as markers of increased fracture risk, although not necessarily implicated in the pathophysiology of OP or falls. However, in blacks, only femoral BMD served as risk factor. Similar risk factors for blacks and whites cannot therefore be assumed and is deserving of further study. White fracture cases did not fall more despite lower 25-OH-Vitamin D, poorer physical performance and lower activity levels than non-fracture cases. Calcaneal ultrasonography and biochemical parameters of bone turnover were similar in fracture and non-fracture cases in both ethnic groups.

Our study data on vertebral fractures in this cohort of urbanized blacks thus cautions against the belief that blacks are not at risk to sustain vertebral compression fractures and emphasize the need for further studies to better define fracture prevalence in the different ethnic populations of SA.

.....

CHAPTER 12

THE IMPACT OF HORMONE THERAPY ON BONE MINERAL DENSITY, CALCANEAL ULTRASONOGRAPHY, BONE TURNOVER AND FALL RISK IN WHITE POSTMENOPAUSAL SOUTH AFRICAN FEMALES

1.	INTRODUCTION.....	231
2.	PATIENTS AND METHODS	231
3.	RESULTS.....	233
3.1.	BONE MINERAL DENSITY	233
3.1.1.	<i>Spinal bone mineral status.....</i>	<i>233</i>
3.1.2.	<i>Femoral bone mineral status.....</i>	<i>233</i>
3.2.	BONE TURNOVER STATUS	235
3.3.	ULTRASONOGRAPHIC MEASUREMENTS.....	236
3.4.	FALL RISK	236
3.4.1.	<i>History of recent fall(s).....</i>	<i>236</i>
3.4.2.	<i>Sensory and neuromuscular tests.....</i>	<i>237</i>
3.5.	FRACTURES	237
4.	DISCUSSION	237

CHAPTER 12:

THE IMPACT OF HORMONE THERAPY ON BONE MINERAL DENSITY, CALCANEAL ULTRASONOGRAPHY, BONE TURNOVER AND FALL RISK IN WHITE POSTMENOPAUSAL SOUTH AFRICAN FEMALES

1. INTRODUCTION

Hormone therapy in white females protects against bone loss during the menopausal transition and sustains this protective effect with continuous use. Observational data^{285,286} and several recent meta-analyses²⁸⁸⁻²⁹⁰ have documented the efficacy of hormone therapy in the reduction of fractures in postmenopausal women. The anti-fracture efficacy of hormone therapy was confirmed by the Women's Health Initiative (WHI)^{291,292,293} a large randomized double-blinded clinical trial designed to determine the effects of estrogen plus progestin or unopposed estrogen compared with placebo on a number of chronic diseases of older women. Combination and unopposed estrogen hormone therapy increased BMD at the hip and spine and reduced the risk of fractures at the hip, vertebrae and wrists in healthy postmenopausal white and black women, the majority of whom had normal BMD at study entry (only 4% of women in the estrogen-plus-progestin group and 6% of women in the placebo group had osteoporosis at the total hip at baseline). All types of hormone therapy appear to confer benefit. In a prospective, cohort study of over a million women³⁶² (the Million Women Study), current users of hormone therapy had a significantly lower risk of fracture than non-users. The protective effect was seen for all types of hormone therapy (unopposed estrogen, combined estrogen-progestin, different estrogen and progestin formulations, different routes of administration [oral versus transdermal], and different patterns of administration [cyclic versus continuous]).

One of the major advantages of hormone therapy in the prevention of fractures lies in the ability of this treatment modality to reduce fracture risk in non-osteoporotic patients. The bisphosphonate trials showed a reduction in risk of hip and spine fractures in women with osteoporosis, but not in women without osteoporosis³⁶³⁻³⁶⁵.

2. PATIENTS AND METHODS

In our study population, hormone therapy was used almost exclusively by the white females. We did not include white females currently using hormone therapy when differences in BMD, ultrasonography and bone turnover between blacks and whites were assessed in previous chapters and also analyzed fall data separately due to the fact that use was confined to one

ethnic group and because of the fact that long-term use of HT is currently not recommended primarily for bone protection.

In this chapter, data regarding BMD, ultrasonography, biochemically determined bone turnover, fall risk and the radiological presence of vertebral fractures are compared between current users of hormone therapy [duration of at least 12 months] (n=43) and never-users (n=60) in the white postmenopausal cohort. The mean duration of hormone therapy in current users was 8.3 ± 5.5 years (range 1-18 years). One way analysis of variance was used to determine differences between current hormone users and never-users regarding abovementioned variables. Cross tabulation was used to summarize categorical variables.

Anthropometric variables, reproductive factors and lifestyle risk factors, with the exception of age at menarche and smoking, were comparable between the two cohorts (table 1). The women on hormone therapy (HT+) reached menarche at an earlier mean age ($p=0.03$) and smoked more ($p=0.04$) compared with the never-users.

Table 1: Baseline characteristics of the white postmenopausal hormone never-users (HT-) and hormone users (HT+)

Characteristic	Postmenopausal (HT-) (n=60)	Postmenopausal (HT+) (n=43)	<i>p-value</i>
Age (yr)	59 ± 9	56 ± 7	0.06
Height (cm)	163 ± 17	160 ± 26	0.18
Weight (kg)	71.6 ± 15	69 ± 11	0.20
BMI (kg/cm ²)	27 ± 5	26 ± 4	0.14
Elbow width (mm)	67 ± 4	67 ± 4	0.34
Age (yrs) at menarche	13.2 ± 1.8	12.6 ± 1.7	0.03
Years since menopause	10.9 ± 8.7	10.5 ± 7.0	0.39
Calcium intake (mg/d)	855 ± 250	855 ± 255	0.28
Smoking (pack yrs)	5.9 ± 14.4	11.0 ± 16.1	0.04
Alcohol (U/week)	2.4 ± 4.0	1.7 ± 3.2	0.20
Physical activity score (0-4)	2.8 ± 0.9	2.7 ± 0.8	0.24
Number of pregnancies	2.7 ± 1.6	2.6 ± 1.4	0.38
Past OC use n (%)	25 (38)	24 (52)	
Past Depo Provera use n(%)	2 (3)	0 (0)	
Positive family history n (%)	14 (21)	12 (26)	

Values are reported as average ± SD except where otherwise stated

3. RESULTS

3.1. BONE MINERAL DENSITY

3.1.1. Spinal bone mineral status

The mean S-BMC, SBMD and SBMAD were significantly higher in hormone users (table 2, figure 1) compared with never-users. The BMD expressed as a T-score as well as a Z-score (to compensate for the tendency towards lower mean age in the hormone users, $p=0.06$) was also statistically significantly different between the groups, with lower deviations from the norm noted in the group receiving hormone therapy.

3.1.2. Femoral bone mineral status

The mean F_N BMC, F_N BMD, F_N BMAD and F_T BMD were all significantly higher in the group of hormone users. The femoral BMD expressed as T- and Z-scores were also significantly different between the two groups with lower deviations from the norm noted in the hormone users (table 3 and figure 2).

Table 2: Spinal bone mineral status of white postmenopausal hormone never-users (HT-) and hormone users (HT+)

Spinal bone mineral status	Postmenopausal (HT-) (n=60)	Postmenopausal (HT+) (n=43)	p-value
BMC	57.63 ± 12.6	62.01 ± 9.79	0.02
BMD			
Total	0.948 ± 0.16	1.060 ± 0.13	<0.01
T-score	-0.79 ± 1.50	0.11 ± 1.15	<0.01
Z-score	0.51 ± 1.43	1.31 ± 1.16	<0.01
BMAD	0.123 ± 0.02	0.136 ± 0.02	<0.01

Values expressed as average ± SD

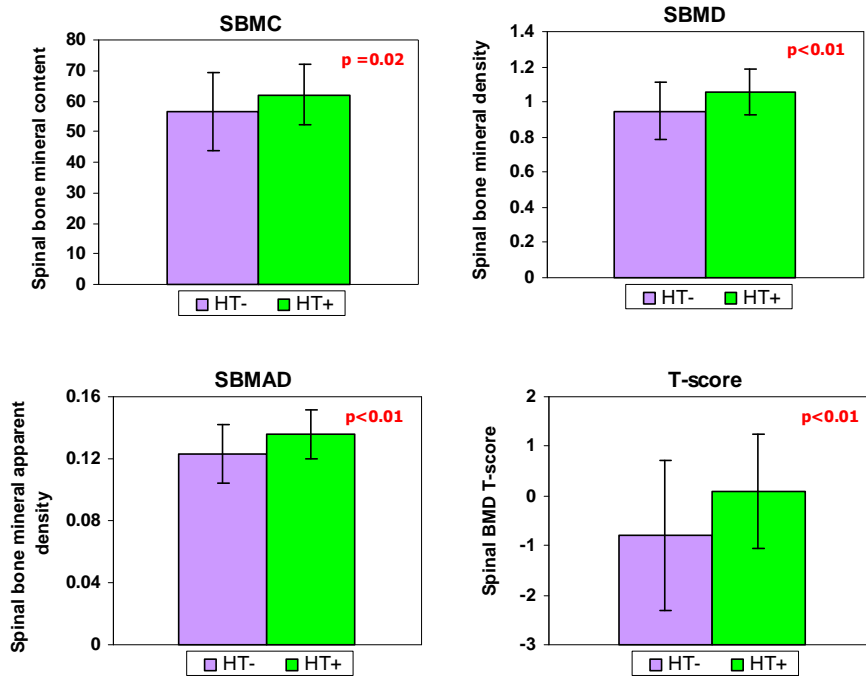


Figure 1: Spinal bone mineral status in the white postmenopausal hormone therapy never-users (HT-) and users (HT+). Bone mineral status significantly better in the cohort on hormone therapy (p-values as illustrated).

Table 3: Femoral bone mineral status of white postmenopausal hormone never-users (HT-) and users (HT+)

Bone mineral status	Postmenopausal (HT-) (n=60)	Postmenopausal (HT+) (n=43)	p-value
<i>Femoral neck</i>			
BMC	3.99 ± 0.77	4.30 ± 0.50	0.03
BMD			
Total	0.718 ± 0.12	0.800 ± 0.12	<0.01
T-score	-1.18 ± 1.13	-0.470 ± 0.99	<0.01
Z-score	0.109 ± 1.12	0.641 ± 0.96	<0.01
BMAD	0.131 ± 0.02	0.147 ± 0.03	<0.01
<i>Femur Total</i>			
BMC	31.88 ± 6.10	33.68 ± 4.50	0.08
BMD			
Total	0.865 ± 0.143	0.957 ± 0.12	<0.01
T-score	-0.60 ± 1.14	0.05 ± 0.89	<0.01
Z-score	0.38 ± 1.14	0.88 ± 0.96	0.01

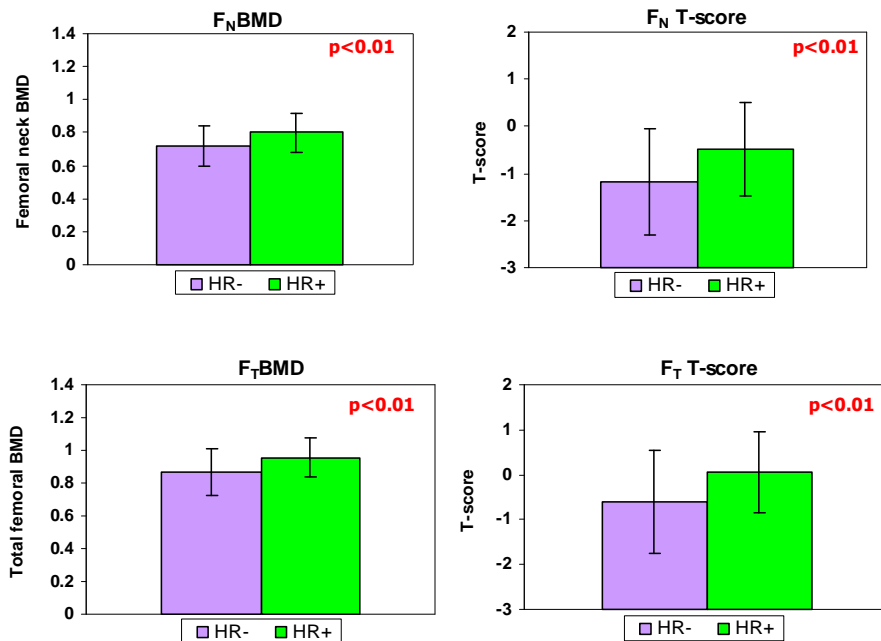


Figure 2: Femoral bone mineral status in the white postmenopausal hormone therapy never-users (HT-) and users (HT+). Bone mineral status significantly better in the cohort on hormone therapy (p-values as illustrated).

3.2. BONE TURNOVER STATUS

Bone turnover status in these two cohorts was evaluated biochemically via determination of serum-osteocalcin (OC) levels and urine-deoxypyridinoline (DPD). OC was significantly lower

in the hormone users compared with never-users. No significant difference was, however, noted in DPD between the two groups (table 4).

Table 4: Biochemical evaluation of bone turnover status in white postmenopausal hormone never-users (HT-) and users (HT+)

Biochemical parameter	Postmenopausal (HT-) (n=60)	Postmenopausal (HT+) (n=43)	p-value
Serum Osteocalcin	12.5 ± 9.9	6.95 ± 5.3	<0.01
Urinary free DPD/creatinine	6.4 ± 4.6	6.0 ± 3.5	0.37

Values expressed as mean ± SD

3.3. ULTRASONOGRAPHIC MEASUREMENTS

All QUS measured parameters of bone (US BMD, US BMD T-scores, SOS, BUA and QUI) were significantly higher in the hormone users compared with those who had never used hormone therapy (table 5). QUS SOS and BUA remained higher in the hormone treated group after correction for DEXA determined BMD at the spine and proximal femur. The difference in BMD adjusted QUS SOS remained significantly higher in the HT group, whereas the difference in QUS BUA levels neared statistical significance.

Table 5: Ultrasound measurements in white postmenopausal hormone never-users (HT-) and users (HT+)

Ultrasound measurement	Postmenopausal (HT-) (n=60)	Postmenopausal (HT+) (n=43)	p-value
Calcaneal BMD (g/cm ²)	0.457 ± 0.12	0.573 ± 0.11	<0.01
Calcaneal BMD T-score	-1.11 ± 1.04	-0.04 ± 0.97	<0.01
SOS (m/s)			
Unadjusted	1537 ± 29	1567 ± 30.1	<0.01
Adjusted (for DEXA BMD)	1538 ± 29	1566 ± 31	<0.01
BUA (dB/MHz)			
Unadjusted	61.5 ± 18	76.1 ± 15.0	<0.01
Adjusted (for DEXA BMD)	62.5 ± 18	75.4 ± 17	0.05
QUI (0-150)	83.9 ± 18.4	102.6 ± 17.5	<0.01

Values expressed as mean ± SD

3.4. FALL RISK

3.4.1. History of recent fall(s)

A history of a recent fall was present in 13 (30%) of the hormone users and in 19 (32%) never-users. Hormone therapy had an impact on falls only in the older (≥ 60 years) postmenopausal females and especially in those over the age of 65 years. Less falls occurred amongst the older postmenopausal females using hormone therapy (11%) compared with

non-users (45%) and none of the hormone users over the age of 65 years sustained a recent fall.

3.4.2. Sensory and neuromuscular tests

Current hormone therapy reduced lateral sway and improved quadriceps strength in older females only (table 6). Near significant differences in lateral sway and quadriceps strength were thus found between hormone non-users and users in the late postmenopausal group ($p=0.05$).

Table 6: Sensory and neuromuscular function tests in white postmenopausal hormone never-users (HT-) and users (HT+)

Function	Postmenopausal females					
	<60 years			≥ 60 years		
	Whites (HT-) n=35	Whites (HT+) n=25	p-value	Whites (HT-) n=31	Whites (HT+) n=18	p-value
Body sway (mm)						
Anterio-posterior	19.2 ± 5.9	19.4 ± 5.1	0.46	22.2 ± 7.0	23.6 ± 8.3	0.10
Lateral	10.9 ± 6.1	10.7 ± 5.7	0.45	15.3 ± 11.2	10.5 ± 5.7	0.05
Reaction time (ms)	274 ± 48	276 ± 33	0.42	325 ± 86	307 ± 57	0.22
Visual contrast	18.5 ± 1.9	17.7 ± 2.3	0.09	16.0 ± 2.4	15.9 ± 2.4	0.46
Quadriceps strength (kg)	34.2 ± 7.9	30.6 ± 8.1	0.04	25 ± 7.0	28.5 ± 6.3	0.05

Values expressed as mean ± SD

3.5. VERTEBRAL FRACTURES

Only one patient amongst the hormone users (2%) had radiological evidence of vertebral fractures compared with four patients (6%) amongst the never-users.

4. DISCUSSION

Parameters of bone strength parameters evaluated in the present study were significantly greater among current users of hormone therapy compared with never users. Bone mineral density at the hip and spine, and all QUS parameters were higher among current hormone users. Hormone therapy furthermore resulted in reduced bone turnover based on determination of serum osteocalcin levels. Urinary DPD levels were, however, similar between current hormone users and never users. Fall risk was significantly lower in older postmenopausal hormone users along with a tendency towards reduced lateral sway and improved quadriceps strength. Although numbers are very limited, the positive impact of hormone therapy in our healthy postmenopausal white cohort appeared to culminate in reduced vertebral fracture prevalence amongst the hormone users (2% vs. 6% in never users).

It has been recognized for more than 50 years that bone loss in women is unequivocally accelerated by estrogen deficiency. Estrogen halts or slows bone loss – probably for as long as it is continued in the majority of women. The Postmenopausal Estrogen/progestin Interventions (PEPI) trial³⁸¹ showed sustained increases in bone mineral density when conjugated equine estrogen (CEE) was used alone or in combination with medroxyprogesterone acetate or micronized progesterone. The positive impact of hormone therapy was also confirmed in the more recent Women’s Health Initiative (WHI) trial²⁹¹⁻²⁹³. After 3 years of combination hormone treatment, the percentage difference in favor of hormone therapy was greater, with mean differences of 4.5% and 3.6% at the lumbar spine and total hip respectively. In our study, the difference between hormone users and never-users was 10.6% for the lumbar spine, 9.7% for the total hip and 10.3% for the femoral neck. The mean duration of hormone therapy was 8.3 years ranging from 1-18 years. The positive impact of hormone therapy on BMD at the hip and spine observed in our study are thus consistent with the findings from the PEPI³⁸¹ and WHI trial²⁹¹⁻²⁹³ as well as observational data obtained from numerous previous epidemiological studies^{286,287,344}. The increase in BMD at the lumbar spine and proximal femur documented in our hormone treated subjects were very similar – this differs from the WHI trial which showed a more marked increase at the lumbar spine, a site that contains a large proportion of metabolically active trabecular bone, which is more likely to reflect acute or short-term permutations. The difference in BMD at the hip and spine was also greater in our study, compared with the results of the WHI trial. These differences can probably be accounted for by the significantly longer duration of hormone therapy used by our study subjects, compared with the 3 year observation period of the WHI.

QUS parameters can be used to predict fracture risk independently of BMD^{226,227,321,325}, hence the assumption that QUS BUA and SOS measures bone qualitative parameters independently of BMD. All QUS variables, including BUA, SOS and the calculated calcaneal BMD and QUI were significantly higher in our hormone users. Correction of BUA and SOS for DEXA BMD at the spine and proximal femoral sites attenuated the difference in BUA values only ($p=0.05$), with SOS values remaining statistically significantly higher in the hormone users. In agreement with our data, numerous previous studies³⁶⁷⁻³⁶⁸ have also documented higher QUS measurements in hormone users compared with non-users. Hormone therapy thus appears to prevent deterioration in BUA and SOS as measured by QUS at the calcaneus in ageing postmenopausal women, an effect similar to that observed for DEXA BMD. If these QUS parameters do indeed measure qualitative properties of bone independent of BMD, as has been suggested in previous work²²⁸⁻²³⁰, the higher values documented in hormone users

imply better preservation of bone quality compared with non-users and may indeed contribute to a lower fracture prevalence in hormone treated postmenopausal white women.

Menopause is associated with adverse changes in bone turnover, and bone biochemical markers have been suggested to reflect postmenopausal high bone turnover. Both bone resorption and bone formation increase. When bone resorption exceeds formation, bone loss and osteoporosis will occur. According to the results of previous studies, hormone therapy decreases the concentration of serum OC in postmenopausal women³⁶⁹⁻³⁷². OC has been suggested to be the best single biochemical marker for estimating the rate of bone loss in untreated postmenopausal women^{339,340}. Its value as a follow-up marker during preventative medication i.e. hormone therapy of osteoporosis has also been established. Several studies have shown a positive correlation between lowering of biochemical markers and BMD changes in women receiving HT^{368,372-375}. Owing to a close coupling between osteoblasts and osteoclasts, the lowering of bone formation markers in serum during hormone therapy is most likely a consequence of decreased bone resorption. In our study, OC was significantly lower in the hormone users compared with never-users. No significant difference was, however, noted in urinary DPD between the two groups. This may be partially explained by the greater variations/lower sensitivity of urinary as opposed to serum biomarkers as well as the limitations of a single measurement of a biochemical parameter known to have a significant day-to-day variation²³³ (see in chapter 8).

It may be that treatment with estrogen also reduces fractures in women without osteoporosis through a reduction in falls and improvement in muscle strength, although the evidence for this is sparse and conflicting³⁷⁶⁻³⁷⁸. In our study the fall frequency was significantly reduced in older postmenopausal hormone users, along with a tendency towards reduced lateral sway and improved quadriceps strength. Neuromuscular impairment and poor vision have been shown to identify individuals in the community at risk of falls and fall related fractures^{178,319,342,351}. Falls per se, especially in the elderly, contribute significantly to the occurrence of symptomatic fractures^{169,170,319}. It has also been documented that the nature of the fall determines the type of fracture and that women who suffered hip fractures were more likely to have fallen sideways or straight down¹⁷⁴. Hormone therapy significantly reduced fall frequency in our elderly females, in part due to improved quadriceps strength and a tendency towards reduced lateral sway and may thus potentially reduce hip fracture risk in these women.

To conclude, in our study hormone therapy in postmenopausal white women improved bone strength parameters and reduced fall risk. In hormone treated whites compared with non-hormone users:

- Higher BMD at the spine and proximal femur as determined by DEXA was documented.
- All QUS measurements were significantly higher.
- The bone turnover rate as reflected by lower serum osteocalcin levels was lower.
- The fall frequency was lower in the older hormone treated women (≥ 60 yrs) and greater quadriceps strength and reduced lateral sway was noted.

This may have contributed to the fact that only one patient amongst the hormone users (2%) had radiological evidence of vertebral fractures, compared with four patients (6%) amongst the never-users. Our subject numbers were, however, limited and this data needs to be confirmed in a larger population study. Moreover, the impact of hormone therapy also needs to be assessed in black postmenopausal females.

.....

CHAPTER 13

FINAL CONCLUSIONS AND REFLECTIVE SUMMARY

The major goal of this study was to define bone strength parameters in black (Xhosa) and white South African women in an attempt to assess ethnic differences in fracture risk. Although limited by its cross-sectional nature and small patient numbers, the study has nonetheless provided potentially valuable information.

A significantly lower hip fracture rate has previously been documented in SA black females compared with whites. Evidence obtained in the present study suggests higher bone strength in the femoral region in blacks, especially with ageing and at a time when hip fracture risk is highest. Older postmenopausal black females was documented to have higher densitometric determined bone mineral density of the femoral region, higher ultrasonographic measures of qualitative bone properties and significantly shorter hip axis length compared with whites. Ethnic differences in proximal femoral bone mineral density could be ascribed to higher peak BMD, but also to an apparent better maintenance of BMD with ageing. The higher proximal femoral bone strength in blacks, in the presence of documented similar fall frequencies in blacks and whites, is in accordance with previously documented lower hip fracture rates in SA black females compared with whites.

A similar vertebral fracture rate was, however, documented in black and white females in our study and is in keeping with the finding of similar spinal BMD measurements in postmenopausal blacks and whites. Ethnic differences in vertebral dimensions and qualitative bone properties, as has been suggested by our quantitative ultrasound data, may impact on vertebral fracture risk, but was found to be similar in our fracture and non-fracture cases.

Westernization and urbanization may alter risk factor profiles for osteopenia in black females. A trend towards a lower ideal body weight may significantly impact on optimal BMD attainment and may attenuate, and even eliminate, the apparent better maintenance of BMD in blacks with ageing - in fact - most of the observed ethnic difference in BMD in this study was explained by differences in body weight between the two cohorts and not by ethnicity per se.

Although cautious with regard to interpretation of longitudinal changes in this cross-sectional study, an apparent better preservation of vertebral and femoral bone mineral density as well as quantitative ultrasound parameters i.e. BUA and SOS were noted in aging black females compared with whites. In fact, most of the observed higher femoral bone mineral density and QUS measurements in older blacks compared with whites appeared to be due to an

attenuated decline in these parameters rather than higher peak values obtained in premenopausal black females. The apparent ethnic differences in bone mineral and bone qualitative changes with ageing observed and documented in this study, however, needs to be verified in prospective population based studies. Following completion of this dissertation, my future research objectives thus include a prospective follow-up evaluation of the majority of the black and white study subjects who participated in this cross-sectional evaluation.

Larger, prospective studies are also clearly needed to identify appropriate risk factor subsets for our SA female population to ensure that BMD resources are allocated to those who are most likely to benefit, and to better define the current vertebral- and hip fracture prevalence in the different ethnic populations of South Africa.

.....

ADDENDUM I

TELEPHONIC QUESTIONNAIRE

1. AGE

2. ETHNIC GROUP

3. JOB

CURRENT

PAST

4. ANY KNOWN SYSTEMIC AILMENT/ILLNESS?

OSTEOPOROSIS

OSTEOMALACIA

HYPERPARATHYROIDISM

RENAL BONE DISEASE

PAGETS

ENDOCRINE DISEASE: CUSHINGS

PROLACTINOMA

THYROID DISEASE

ACROMEGALY

OVARIAN FAILURE (Not menopause related)

MALABSORPTION (Gastric disease, chronic diarrhoea)

MALIGNANCY

KNOWN RENAL/HEPATIC DISEASE

ALCOHOL ABUSE (> 4U/day, impact on daily functioning)

5. HAVE YOU TAKEN ANY THERAPY DURING THE PAST SIX MONTHS?

PLEASE NAME THEM:

VITAMIN D, BISPHOSPHONATES, ANTIACIDS, CORTICOSTEROIDS

SEX HORMONES Estrogen/Testosterone, ANTICONVULSANTS Epanutin/Tegretol....

ADDENDUM II

PATIENT QUESTIONNAIRE: OSTEOPOROSIS STUDY

PATIENT NUMBER:

AGE:

ETHNIC GROUP:

JOB:

CURRENT:

PAST:

HISTORY		
A. BONE COMPLAINTS <ul style="list-style-type: none">• PAIN• DEFORMITY	YES	NO
B. FRACTURES IF YES: <ul style="list-style-type: none">• POSITION• NUMBER• DATES• ASSOCIATED TRAUMA	YES	NO
C. RISK FACTOR ANALYSIS FAMILY HISTORY <ul style="list-style-type: none">• OSTEOPOROSIS<ul style="list-style-type: none">• Affected family member• RENAL STONES• OTHER BONE DISEASES RENAL DISEASE	YES	NO
GYNAECOLOGICAL HISTORY AGE AT MENARCHE MENSTRUAL CYCLE: <ul style="list-style-type: none">• REGULAR/ IRREGULAR• CYCLE LENGTH (DAYS)		

<ul style="list-style-type: none"> • USE OF CONTRACEPTIVE (Y/N) <ul style="list-style-type: none"> • TYPE • DURATION OF USAGE • CURRENT/PAST <p>MENOPAUSE:</p> <ul style="list-style-type: none"> • AGE AT MENOPAUSE • SPONTANEOUS/SURGICAL • SURGICAL: OOPHERECTOMY- Y/N • DURATION OF MENOPAUSE (YRS) • HRT, YES OR NO <ul style="list-style-type: none"> • DATE COMMENCED • MENOPOUSAL YEARS WITHOUT HRT • DURATION OF USAGE • COMPLIANCE • CURRENT/PAST <p>PREGNANCIES</p> <ul style="list-style-type: none"> • TOTAL NUMBER • WHEN • GRAVIDA <p>BREASTFEEDING</p> <ul style="list-style-type: none"> • YES / NO • DURATION 	
<p>MEDICATION (including Ca-supplements)</p> <ol style="list-style-type: none"> 1. <ul style="list-style-type: none"> • TYPE • DOSAGE • DURATION OF USAGE 2. <ul style="list-style-type: none"> • TYPE • DOSAGE • DURATION OF USAGE 3. <ul style="list-style-type: none"> • TYPE • DOSAGE • DURATION OF USAGE 	
<p>EXERCISE</p> <ul style="list-style-type: none"> • TYPE • INTENSITY <ul style="list-style-type: none"> • DAILY IN-HOUSE (1-2) • ADDITIONAL <ul style="list-style-type: none"> • MODERATE (3) • STRENUOUS (4) • DURATION • IMMOBILIZATION 	

<p>DIETARY ANALYSIS</p> <ul style="list-style-type: none"> • CALCIUM • PROTEIN • PHOSPHATE • MAGNESIUM • SALT • CALORIES • EATING DISORDER YES/NO 	
<p>TOXINS</p> <p>ALCOHOL</p> <ul style="list-style-type: none"> • PREVIOUS/PRESENT • AMOUNT • TYPE • DURATION <p>NICOTINE</p> <ul style="list-style-type: none"> • PREVIOUS/PRESENT • AMOUNT/DAY • DURATION 	
<p>OTHER KNOWN SYSTEMIC ILLNESSES</p> <p>1.</p> <p>3.</p>	
<p>D. FALL-TENDENCY</p> <ul style="list-style-type: none"> • ANY FALLS Y/N (within last year) <ul style="list-style-type: none"> • WHEN • NUMBER • WHERE • DIRECTION • INJURIES 	

PHYSICAL EXAMINATION

<p>ANTROPOMETRIC DATA</p> <ul style="list-style-type: none"> • LENGTH (cm) <ul style="list-style-type: none"> • Arm span • Leg length • Sitting length • WEIGHT (KG) • BMI • WHR • SKINFOLDS <ul style="list-style-type: none"> • Triceps • Subscapular 	
--	--

CARDIOVASCULAR <ul style="list-style-type: none"> • BP <ul style="list-style-type: none"> • Sitting • PULSE • HEART 	
LUNGS	
GASTRO-INTESTINAL	
NEUROLOGICAL SYSTEM	
VASCULAR SYSTEM	
GENITO-URINARY SYSTEM	
MUSCULO-SKELETAL SYSTEM <ul style="list-style-type: none"> • DEFORMITIES <ul style="list-style-type: none"> • Type • Location OTHER	
GENERAL	

BIOCHEMISTRY

INVESTIGATION	COMPLETED (✓)
A. SERUM	
CALCIUM Serum Total (Corrected)	
PO4	

Mg	
ALBUMIN	
CREATININE	
ALP	
PTH	
LH	
INVESTIGATION	COMPLETED (✓)
FSH	
E2	
TESTOSTERONE	
SHBG	
T4	
TSH	
CORTISOL	
25OH VITD	
OSTEOCALCIN	

DEOXYPIRODINOLINE	
GGT	
GENETIC STUDIES	
INVESTIGATION	COMPLETED (✓)
B. URINE	
2 ND VOIDED URINE DEOXIPIRODINOLINE,CREAT	
2HR HYDRATED URINE CA,CREATININE,NA	

RADIOLOGY

INVESTIGATION	DONE (✓)
THORACICO-LUMBAR VERTEBRAE	
DEXA	
ULTRASOUND	

FALL TESTS

A SIMPLIFIED FOOD FREQUENCY QUESTIONNAIRE

FOOD ITEM	FREQUENCY	AMOUNT
Sweets		
Chocolate		
Cake/Tarts		
Biscuits		
Fruits		
Fruit Juice		
Dried fruit		
Can fruit		
Chips		
Peanuts		
Pudding		
Ice-cream		
Sugar		
Jam		
Rusks		
Yoghurt		
Popcorn		
Egs		
Milo/ Horlicks / Ovaltine		
Sodas		
Milk		
Cheese		
Alcohol		

Adapted from: Department of Nutrition, Tygerberg Hospital

ADDENDUM IV

SENSORY AND NEUROMUSCULAR TESTS												
MELBOURNE EDGE TEST	DB											
QUADRICEPS STRENGTH	kg											
REACTION TIME - HAND (msec)	1 5 9 13 17	2 6 10 14 18	3 7 11 15 19	4 8 12 16 20								
SWAY TEST	<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; text-align: center;">Sway on floor- Anterior-Posterior</td> <td style="text-align: center;">mm</td> </tr> <tr> <td style="text-align: center;">Lateral</td> <td style="text-align: center;">mm</td> </tr> <tr> <td style="text-align: center;">Sway on floor-Anterior-Posterior</td> <td style="text-align: center;">mm</td> </tr> <tr> <td style="text-align: center;">Lateral</td> <td style="text-align: center;">mm</td> </tr> </table>				Sway on floor- Anterior-Posterior	mm	Lateral	mm	Sway on floor-Anterior-Posterior	mm	Lateral	mm
Sway on floor- Anterior-Posterior	mm											
Lateral	mm											
Sway on floor-Anterior-Posterior	mm											
Lateral	mm											

REFERENCES

1. Daniels ED, Pettifor JM, Schnitzler CM, Russell SW, Patel DN. Ethnic Differences in Bone Density in Female South African Nurses. *J Bone Miner Res* 1995; 10(3): 360-367
2. Gluer CG, Genant HK. Ultrasound parameters and bone structure. *Calcif Tissue Int* 1994; 55:46-52
3. Mikhail MB, Vaswani AN, Aloia JF. Racial differences in femoral dimensions and their relation to hip fracture. *Osteoporos Int*. 1996; 6(1):22-24
4. Theobald TM, Cauley JA, Gluer CC, Bunker CH, Ukoli FA, Genant HK. Black-white differences in hip geometry. Study of Osteoporotic Fractures Research Group. *Osteoporos Int* 1998; 8(1):61-67
5. Daniels ED, Pettifor JM, Schnitzler CM, Zachen, et al. Differences in Mineral Homeostasis, Volumetric Bone Mass and Femoral Neck Axis length in Black and White South African Women. *Osteoporos Int* 1997; 7:105-112
6. Dibba B, Prentice A, Laskey MA, Stirling DM, Cole TJ. An investigation of ethnic differences in bone mineral, hip axis length, calcium metabolism and bone turnover between West African and Caucasian adults living in the United Kingdom. *Annals of Human Biol* 1999; 26(3):229-242
7. White BL, Fisher WD, Laurin CA. Rate of mortality for elderly patients after fracture of the hip in the 1980's. *J Bone Joint Surg* 1987; 69:1335-1340
8. Cooper C, Atkinson EJ, Melton LJ et al. Population-based study of survival after osteoporotic fractures. *Am J Epidemiol* 1993; 137:1001-1005
9. Forsen L, Sogaard AJ, Kopjar B et al. Survival after hip fracture: short- and long-term excess mortality according to age and gender. *Osteoporos Int* 1999; 10:73-78
10. Davidson CW, Merrilees MJ, Gilcrist NC. Hip fracture mortality and morbidity – can we do better? *NZ Med J* 2001; 114:329-332
11. Kanis JA, Oden A, Oglesby AK et al. The components of excess mortality after hip fracture. *Bone* 2003; 5:468-473
12. WHO Study Group. Assessment of fracture risk and its application to screening for post-menopausal osteoporosis. *Osteoporos Int* 1994; 4:368-381
WHO Study Group: Consensus Development Statement. *Osteoporos Int* 1997; 7:1-6

13. Gullberg B, Johnell O and Kanis JA. World-wide Projections for Hip Fracture. *Osteoporos Int.* 1997; 7:407-413
14. Nordin BEC, Need AG. How can we prevent osteoporosis? *Osteoporosis* 1987. Christiansen C, Johansen JS, Riis BJ (eds). Copenhagen, Horhaven A/S, 1987; 1204-1210
15. US Department of Health and Human Services. Bone Health and Osteoporosis: A report of the Surgeon General, Rockville, Md: US Dept of Health and Human Services; 2004
16. Cooper C, Campion G, Melton LG III. Hip fractures in the elderly: a world-wide projection. *Osteoporos Int* 1992; 2:85-89
17. World Health Organization. Assessment of Fracture Risk and Application to Screening for Postmenopausal Osteoporosis. Geneva: WHO Technical Report Series. 1994
18. Cooper C, Atkinson EJ, O'Fallon WM, Melton LJ III. Incidence of clinically diagnosed vertebral fractures: A population-based study in Rochester, Minnesota, 1985-1989. *J Bone Miner Res* 1992; 7:221-227
19. Solomon L. Osteoporosis and fracture of the femoral neck in the South African Bantu. *J Bone and Joint Surgery* 1968; 50(B):2-12
20. Gallagher JC, Melton LJ, Riggs BL, et al. Epidemiology of fractures of the proximal femur in Rochester, Minnesota. *Clin Orthop* 1980; 150:163-171
21. Melton LJ III, Kan SH, Frye MA et al. Epidemiology of vertebral fractures in women. *Am J Epidemiol* 1989; 129:1000-1011
22. Effors L. Osteoporotic fractures due to osteoporosis. Impacts of a frailty pandemic in an aging world. *Aging (Milano)* 1998; 10:191-204
23. Osteoporosis Prevention, Diagnosis, and Therapy. NIH Consensus Statement 2000; March 27-29, 17(1):1-36.
24. Nicholson PH, Lowet G, Cheng XG, Boonen S, van der Perre G, Dequeker J. Assessment of the strength of the proximal femur in vitro: relationship with ultrasonic measurements of the calcaneus. *Bone* 1997; 20(3):219-224.
25. Lochmuller EM, Zeller JB, Kaiser D, Eckstein F, Landgraf J, Putz R, Steldinger R. Correlation of femoral and lumbar DXA and calcaneal ultrasound measured in situ with intact soft tissues, with the in-vitro failure loads of the proximal femur. *Osteoporos Int* 1998; 8(6):591-598

26. Hansson T, Roos B, Nachemson A. The bone mineral content and ultimate strength of lumbar vertebrae. *Spine* 1980; 5(1):46–55.
27. Cheng XG, Nicholson PH, Boonen S, Dequeker J. Prediction of vertebral strength in vitro by spinal bone densitometry and calcaneal ultrasound. *J Bone Miner Res* 1997; 12(10):1721-1728
28. Granhed H, Jonson R, Hansson T. Mineral content and strength of lumbar vertebrae. A cadaver study. *Acta Orthop Scand* 1989; 60:105–9.
29. Cummings SR, Black DM, Nevitt MC, Vogt TM, et al. Appendicular bone density and age predict hip fracture in women. *JAMA* 1990; 263:665-668
30. Nelson HD, Helfand M, Woolf SH, Allan JD. Screening for postmenopausal osteoporosis: a review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2002; 137:529-541
31. Hanlon JT, Landerman LR, Fillenbaum GG et al. Falls in African-American and White community dwelling elderly residents. *J Gerontol A Biol Sci Med Sci.* 2002; 57A:473-478
32. Nevitt MC, Cummings SR, Kidd S et al. Risk factors for recurrent non-syncopal falls. *JAMA* 1989; 261:2663-2668
33. Halioua L, Anderson JJB. Lifetime calcium intake and physical activity habits: independent and combined effects on the radial bone of healthy premenopausal Caucasian women. *Am J Clin Nutri* 1989; 49:534-541
34. Sandler RB, Slemenda C, La Porte RE et al. Postmenopausal bone density and milk consumption in childhood and adolescence. *Am J Clin Nutr* 1985; 42:270-274
35. Soroko S, Holbrook TL, Edelstein S, Barrett-Connor E. Lifetime milk consumption and bone mineral density in older women. *Am J Public Health* 1994; 84:1319-1322
36. Welten DC, Kemper HCG, Post GB, Van Staveren WA. A meta-analysis of the effect of calcium intake on bone mass in young and middle-aged females and males. *J Nutr* 1995; 125:2802-2813
37. Wallace BA, Cumming RG. Systematic review of randomized trials of the effect of exercise on bone mass in pre- and postmenopausal women. *Calcif Tissue Int* 2000; 67:10-18
38. Morris FL, Naughton GA, Gibbs JL, et al. Prospective ten-month exercise intervention in pre-menarcheal girls: positive effects of bone and lean mass. *J Bone Miner Res* 1997; 12:1453-1462

39. Bradney M, Pearce G, Naughton G, et al. Moderate exercise during growth in prepubertal boys: changes in bone mass, size, volumetric density, and bone strength: a controlled prospective study. *J Bone Miner Res* 1998; 13:1814-1921
40. Finkelstein JS, Klibanski A, Neer RM. A longitudinal evaluation of bone mineral density in adult men with histories of delayed puberty. *J Clin Endocrinol Metab* 1996; 81:1152-1155
41. Schoenau E. A longitudinal evaluation of bone mineral density in adult men with histories of delayed puberty. *J Clin Endocrinol Metab* 1996; 81:3812-3813
42. Lindberg JS, Fears WB, Hunt HM. Exercise induced amenorrhoea and bone density. *Ann Intern Med* 1984; 101:647-649
43. Meyerson M, Gutin B, Warren MP et al. Total body bone density in amenorrhoeic runners. *Obstet Gynecol* 1992; 79:973-978
44. Fruth SJ, Worrell TW. Factors associated with menstrual irregularities and decreased bone mineral density in female athletes. *J Orthop Sports Phys Ther* 1995; 22:26-38
45. Marcus R, Cann C, Madvig D. Menstrual function and bone mass in elite women distance runners. *Ann Intern Med* 1985; 102:158-163
46. Myburgh KH, Bachrach LK, Lewis B et al. Low bone mineral density at axial and appendicular sites in amenorrhoeic athletes. *Med Sci Sports Exerc* 1993; 25:1197-1202
47. Davies KM, Pearson PH, Huseman CA et al. Reduced bone mineral in patients with eating disorders. *Bone* 1990; 11:143-147
48. Bachrach LK, Katzman DK, Litt IF, Marcus R. Decreased bone density in adolescent girls with anorexia nervosa. *Pediatrics* 1990; 86:440-447
49. Klibanski A, Neer RM, Beitins IZ et al. Decreased bone density in hyperprolactinemic women. *N Engl J Med* 1980; 303:1511-1514
50. Koppelman MCS, Kurtzs DW, Morrish KA et al. Vertebral body bone mineral content in hyperprolactinemic women. *J Clin Endocrinol Metab* 1984; 59:1050-1053
51. Falahiti-Nini A, Riggs BL, Atkinson EJ, et al. Relative contributions of testosterone and estrogen in regulating bone resorption and formation in elderly men. *J Clin Invest* 2000; 106:1533-1560

52. Khosia S, Melton LJ III, Atkinson EJ et al. Relationship of sex steroid levels to longitudinal changes in bone density in young versus elderly men. *J Clin Endocrinol Metab* 2001; 86:3555-3561
53. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly; consequences of bone loss and fractures and therapeutic implications. *Endocr Rev* 2001; 22:477-501
54. Chambers TJ. Regulation of the differentiation and function of osteoclasts. *J Pathol* 2000; 192:4-13
55. Khosia S. The OPG/RANK system. *Endocrinology* 2001; 142:5050-5055
56. Fuller K, Murphy C, Kirstein B, et al. TNF-alpha potentially activates osteoclasts, through a direct action independent of and strongly synergistic with RANKL. *Endocrinology* 2002; 143:1108-1118
57. Li X, Okada Y, Pilbeam CC et al. Knockout of the murine prostaglandin EP2 receptor impairs osteoclastogenesis in vitro. *Endocrinology* 2000; 141:2054-2061
58. Pfeilschfter J, Koditz R, Pfohl M et al. Changes in pro-inflammatory cytokine activity after menopause. *Endocr Rev* 2002; 23:90-119
59. Kimble RB, Srivastava S, Pacifici R. Estrogen deficiency increases the ability of stromal cells to support osteoclastogenesis via an IL-1 and TNF mediated stimulation of M-CSF production. *J Biol Chem* 1996; 271:2890-2897
60. Lorenzo J. Mice lacking the type 1 Interleukin-1 receptor do not lose bone mass after ovariectomy. *Endocrinology* 1998; 139:3022-3025
61. Lee SK, Lorenzo JA. Parathyroid hormone stimulates TRANCE and inhibits osteoprotegerin messenger ribonucleic expression in murine bone marrow cultures: correlation with osteoclast-like cell formation. *Endocrinology* 1999; 140:3552-3561
62. Miura M Tanaka K, Komutsa Y et al. A novel interaction between thyroid hormones and 1,25(OH)₂D₃ in osteoclast formation. *Biochem Biophys Res Commun* 2002; 291:987-994
63. Dempster D, Hughes-Begos CE, Lindsay R. Normal human osteoclasts formed from peripheral blood monocytes express PTH type 1 receptors and are stimulated by PTH in the absence of osteoblasts. *J of Cellular Biochemistry* 2005; 95:139-148
64. Hirayama T, Sabokhar A and Athanasou NA. Effect of corticosteroids on human osteoclast formation and activity. *J of Endocrinol* 2002; 175(1):155-163

65. Hofbauer LC, Hosia S, Dunstan CR et al. Estrogen stimulates gene expression and protein production of osteoprotegerin in human osteoblastic cells. *Endocrinology* 1999; 140(9):4367-70
66. Hughes DE, Dai A, Tiffée JC et al. Estrogen promotes apoptosis of murine osteoclasts mediated by TGF-beta. *Nat Med* 1996; 2:1132-1136
67. Cornish J, Callon KE, Bava U, Kamona SA, Cooper GJS, Reid IR. Effects of calcitonin, amylin and calcitonin gene-related peptide on osteoclast development. *Bone* 2001; 29(2):162-168
68. Boonen S, Mohan S, Dequeker J et al. Down-regulation of the serum stimulatory components of the insulin-like growth factor (IGF) system (IGF-I, IGF-II, IGF binding protein (BP) and IGFBP-5) in age-related (type II) femoral neck osteoporosis. *J Bone Miner Res* 1999; 14:2150-2158
69. Langlois JA, Rosen CJ, Visser M, et al. Association between insulin-like growth factor I and bone mineral density in older women and men: the Framingham Heart Study. *J Clin Endocrinol Metab* 1998; 83:4257-4262
70. Seck T, Scheppach B, Scharia S, et al. Concentration of insulin-like growth factor (IGF)-1 and -II in iliac crest bone matrix from pre- and postmenopausal women: relationship to age, menopause, bone turnover, bone volume, and circulating IGF's. *J Clin Endocrinol Metab* 1998; 83:2331-2337
71. Tuominen JT, Impivaara O, Puukka P, Ronnema T. Bone mineral density in patients with type 1 and type 2 diabetes. *Diabetes Care* 1999; 22:1196-1200
72. J Chow, J H Tobias, K W Colston, and T J Chambers. Estrogen maintains trabecular bone volume in rats not only by suppression of bone resorption but also by stimulation of bone formation. *J Clin Invest* 1992; 89(1): 74-78.
73. Bain SD, Bailey MC, Celino DL, Lantry MM, Edwards MW. High-dose estrogen inhibits bone resorption and stimulates bone formation in the ovariectomized mouse. *J Bone Miner Res.* 1993; 8(4):435-42.
74. Raisz LG, Wiita B, Artis A, Bowen A, Schwartz S, Trahiotis M, Shoukri K and Smith J. Comparison of the effects of estrogen alone and estrogen plus androgen on biochemical markers of bone formation and resorption in postmenopausal women. *J Clin Endocrinol Metab* 1996; 81:37-43
75. Hofbauer LC and Khosla S. Androgen effects on bone metabolism: recent progress and controversies. *European Journal of Endocrinology* 1999; 140(4):271-286

76. Thomas T, Gori F, Khosla S, Jensen MD, Burguera B and Riggs BL. Leptin acts on human marrow stromal cells to enhance differentiation to osteoblasts and to inhibit differentiation to adipocytes. *Endocrinology* 1999; 140:1630–1638.
77. Holloway WR, Collier FM, Aitken CJ, Myers DE, Hodge JM and Malakellis M et al. Leptin inhibits osteoclast generation, *J Bone Miner Res* 2002; 17:200–209.
78. Blain H, Vuillemin A, Guillemin F, Jeandel C et al. Serum Leptin is a predictor of bone mineral density in postmenopausal women. *J Clin Endocrinol Metab* 2002; 87(3):1030-1035
79. Rauch F, Blum WF, Klein K, Allolio B and Schonau E. Does leptin have an effect on bone in adult women? *Calcif Tissue Int* 1998; 63:453–455.
80. Pasco JA, Henry MJ, Kotowicz MA, Collier GR, Ball MJ and Ugoni AM et al. Serum leptin levels are associated with bone mass in nonobese women. *J Clin Endocrinol Metab* 2001; 86:1884–1887.
81. Roux C, Arabi A, Porcher R and Garnero P. Serum leptin as a determinant of bone resorption in healthy postmenopausal women. *Bone* 2003; 33:847–852.
82. Ruhl CE and Everhart JE. Relationship of serum leptin concentration with bone mineral density in the United States population. *J Bone Miner Res* 2002; 17:1896–1903.
83. Sato M, Takeda N, Sarui H, Takami R, Takami K and Hayashi M et al. Association between serum leptin concentrations and bone mineral density, and biochemical markers of bone turnover in adult men. *J Clin Endocrinol Metab* 2001; 86:5273–5276.
84. Blum M, Harris SS, Must S, Naumova EN, Phillips SM and Rand WM. Leptin, body composition and bone mineral density in premenopausal women. *Calcif Tissue Int* 2003; 73:27–32.
85. Urisi MK. Bone formation by autoinduction. *Science* 1965; 150:893-899
86. Cheng H, Jiang W, Frank BA, Phillips M, He T et al. Osteogenic Activity of the Fourteen Types of Human Bone Morphogenetic Proteins (BMPs). *J Bone and Joint Surgery (American)* 2003; 85:1544-1552

87. Leboy PS. Regulating Bone Growth and Development with Bone Morphogenetic Proteins. *Ann. N.Y. Acad. Sci.* 2006; 1068(1):14-18.
88. Jackson SM, Demer LL. Peroxisome proliferator-activated receptor activators modulate the osteoblastic mutation of MC3T3-E1 preosteoblasts. *FEBS Lett* 2000; 471:119-124
89. Christian JC, Yu PL, Slemenda CW, et al. Heritability of bone mass: a longitudinal study in aging male twins. *Am J Hum Genet* 1989; 44:429-433
90. Pocock NA, Eisman JA, Hopper JL, et al. Genetic determinants of bone mass in adults: a twin study. *J Clin Invest* 1987; 80:706-710
91. Gueguen R, Jouanny P, Guillemin F, et al. Segregation analysis and variance components analysis of bone mineral density in healthy families. *J Bone Miner Res* 1995; 12:2017- 2022
92. Arden NK, Baker J, Hogg C, et al. The heritability of bone mineral density, ultrasound of the calcaneus and hip axis length: a study of postmenopausal twins. *J Bone Miner Res* 1996; 11:530-534
93. Morrison NA, Qi JC, Tokita A et al. Prediction of bone density from Vitamin D receptor alleles. *Nature* 1994; 367:274-287
94. Fleet JC, Harris SS, Wood RJ. The BsmI vitamin D receptor restriction fragment length polymorphism (BB) predicts low bone density in premenopausal black and white women. *J Bone Miner Res* 1995; 10:985-990
95. Yamagata Z, Miyamura T, Iijima S et al. Vitamin D receptor gene polymorphism and bone mineral density in healthy Japanese women. *Lancet* 1994; 334(8928):1027
96. Gross C, Ecclesholl TR, Malloy PJ et al. The presence of a polymorphism at the translation initiation site of the vitamin D receptor gene is associated with low mineral density in postmenopausal Mexican women. *J Bone Miner Res* 1996; 11:1850-1855
97. Riggs BL, Nguyen TV, Melton LJ III et al. The contribution of vitamin D receptor gene alleles to the determination of bone mineral density in normal and osteoporotic women. *J Bone Miner Res* 1995; 10:991-996
98. Harris SS, Ecclesholl TR, Gross C. The vitamin D receptor start codon polymorphism (Fok I) and bone mineral density in premenopausal American black and white women. *J Bone Miner Res* 1997; 12:1043-1048
99. Ecclesholl TR, Garreo P, Gross C et al. Lack of correlation between start codon polymorphism of the vitamin D receptor gene and bone mineral density in premenopausal French Women. The OFELY study. *J Bone Miner Res* 1998; 13:31-35

100. Vandevyver C, Wylin T, Cassiman JJ et al. Influence of the vitamin D receptor gene alleles on bone mineral density in postmenopausal and osteoporotic women. *J Bone Miner Res* 1997; 12:241-247
101. Cooper GS, Umbach DM. Are Vit D receptor polymorphisms associated with bone mineral density? A meta-analysis. *J Bone Miner Res* 1996; 11:1841-1849
102. Uitterlinden AG, Ralston SH, Brandi ML, Carey AH, Ionnidis et al; APOSS Investigators; EPOS Investigators; EPOLOS Investigators; FAMOS Investigators; LASA Investigators; Rotterdam Study Investigators; GENOMOS Study. The association between common vitamin D receptor gene variations and osteoporosis: a participant-level meta-analysis. *Ann Intern Med* 2006; 145(4):255-264
103. MacDonald HM, McGuigan FEA, New SA, Campbell MK, Golden MHN, Ralston SH, Reid DM. COLIA 1 Sp1 polymorphism predicts early perimenopausal spinal bone loss. *J Bone Miner Res* 2001; 16:1634-1643
104. Beavan S, Prentice A, Dibba B, Yan L, Cooper C, Ralston SH. Polymorphism of the collagen type 1 α gene and ethnic differences in hip-fracture rates. *N Engl J Med* 1998; 339:351-352
105. McGuigan FE, Armbrecht G, Smith R, Felsenberg D, Reid DM, Ralston SH. Prediction of osteoporotic fractures by bone densitometry and COLIA 1 genotyping: a prospective, population-based study in men and women. *Osteoporos Int* 2001; 12(2):91-96
106. Ralston SH. Genetic Control of Susceptibility to Osteoporosis. *J Clin Endo Metab* 2002; 87(6):2460-2466
107. Kelly PJ, Nguyen T, Hopper J, Pocock N, Sambrook P, Eisman J. Changes in axial bone density with age: a twin study. *J Bone Miner Res* 1993; 8:11-17
108. Cummings SR, Nevitt MC, Browner WS, et al. Risk factors for hip fracture in white women: Study of Osteoporotic Fractures Research Group. *N Eng J Med* 1995; 332:767-773
109. Harris M, Nguyen TV, Howard GM, et al. Genetic and environmental correlations between bone formation and bone mineral density: a twin study. *Bone* 1998; 22:141-145
110. Lemenda CW, Turner CH, Peacock M, et al. The genetics of proximal femur geometry, distribution of bone mass and bone mineral density. *Osteoporos Int* 1996;6:178-182

111. Kaprio J, Rimpela A, Winter T, et al. Common genetic influences on BMI and age at menarche. *Hum Biol* 1995; 67:739-753
112. Aden NK, Spector TD. Genetic influences on muscle strength, lean body mass, and bone mineral density: a twin study. *J Bone Miner Res* 1997; 2:2076-2081
113. Snieder H, MacGregor AJ, Spector TD. Genes control the cessation of a woman's reproductive life: a twin study of hysterectomy and age at menopause. *J Clin Endocrinol Metab* 1998; 83:1875-1880.
114. Orwoll ES, Bauer DC, Vogt TM, et al. Axial bone mass in older women: The Study of Osteoporotic Fractures Research Group. *Ann Intern Med* 1996; 124:187-196
115. Bauer DC, Browner WS, Cauley JA, et al. Factors associated with appendicular bone mass in older women. The Study of Osteoporotic Fractures Research Group. *Ann Intern Med* 1993; 118:657-665
116. Kröger H, Tuppurainen M, Honkanen R, Alhava E, Saarikoski S. Bone mineral density and risk factors for osteoporosis – a population-based study of 1600 perimenopausal women. *Calcif Tissue Int* 1994; 55(1):1-7
117. Broussard DL, Magnus JH. Risk assessment and screening for low bone mineral density in a multi-ethnic population of women and men: does one approach fit all? *Osteoporos Int* 2004; 5:349-360
118. Blaauw R, Albertse EC, Hough FS et al. Risk factors for the development of osteoporosis in a South African population. *SAMJ* 1993; 84:328-332
119. Lydick E, Cook K, Turpin J, Melton M, Stine R, Byrnes C. Development and validation of a simple questionnaire to facilitate identification of women likely to have low bone density. *Am J Man Care* 1997; 4:37-48
120. Cadarette SM, Jaglal SB, Kreiger N, McIsaac WJ, Darlington GA Tu JV. Development and validation of the Osteoporosis Risk Assessment Instrument to facilitate selection of women for bone densitometry. *Can Med Assoc J* 2000; 162:1289-1294
121. Richy F, Gourlay M, Ross PD, En SS, Reginster JY et al. Validation and comparative evaluation of the osteoporosis self-assessment tool (OST) in a Caucasian population from Belgium. *J Med* 2004; 97:39-46
122. Koh LKH, Ben Sedrine W, Torralba TP et al. A simple tool to identify Asian women at increased risk of osteoporosis. *Osteoporos Int* 2001; 12:699-705

123. Geusens PP, Hochberg MC, van der Voort DM et al. Performance of risk indices for identifying low bone density in postmenopausal women. *Mayo Clinic Proc* 2002; 77:629-637
124. Wehren LE, Siris ES. Beyond bone mineral density: can existing clinical risk assessment instruments identify women at risk of osteoporosis. *J of Intern Med* 2004;256(5):375-380
125. Wildner M, Peters A, Siebert U et al. Superiority of age and weight as variables in predicting osteoporosis in postmenopausal white women. *Osteoporos Int* 2003; 14:950-956
126. Looker AC, Johnston CCJ, Wahner HW et al. Prevalence of low femoral bone density in older U.S. women from NHANES III. *J Bone Miner Res* 1995; 10:796-802
127. Caplan GA, Scane AC, Francis RM. Pathogenesis of vertebral crush fractures in women. *JR Soc Med* 1994; 87:200-202
128. Baillie SP, Davison CE, Johnson FJ, Francis RM. Pathogenesis of vertebral crush fractures in men. *Age Ageing* 1992; 21:139-141
129. Cummings SR, Bates D, Black DM. Clinical use of bone densitometry: scientific review. *JAMA* 2002; 288:1889-1897
130. Schnitzler CM, Pettifor JM, Mesquita JM, Bird MDT, Schnaid E, Smyth AE. Histomorphometry of iliac crest bone in 346 normal black and white South African adults. *Bone Miner* 1990; 10(3):183-199
131. Mosekilde Li. Sex differences in age-related loss of vertebral trabecular bone mass and structure-biomechanical consequences. *Bone* 1989; 10:425-432
133. Seeman E, Hopper JL, Bach LA, et al. Reduced bone mass in daughters of women with osteoporosis. *N Engl J Med* 1989; 320:554-558
134. Seeman E, Tsalamandris C, Formica C, et al. Reduced femoral neck density in the daughters of women with hip fractures: the role of low peak bone density in the pathogenesis of osteoporosis. *J Bone Miner Res* 1994; 9:739-743
135. Cauley JA, Lui LY, Cummings SR et al. Bone Mineral Density and the Risk of Incident Non-spinal Fractures in Black and White Women. *JAMA* 2005; 293(17):2102-2108
136. Barrett-Connor E, Siris ES, Wehren LE, Sherwood LM, et al. Osteoporosis and Fracture Risk in Women of Different Ethnic Groups. *J Bone Miner Res* 2005; 20(2):185-194

137. Han Z-H, Palnitkar S, Rood S, Nelson D, Parfitt AM. Effect of ethnicity and age or menopause on the structure and geometry of iliac bone. *J Bone Miner Res* 1996; 11:1967-1975
138. Kleerekoper M, Nelson DA, Peterson EL, Wilson P, et al. Reference Data for Bone Mass, Calcitropic Hormones, and Biochemical Markers of Bone Remodeling in Older (55-75yrs) Postmenopausal White and Black Women. *J Bone Miner Res* 1994; (9)8:1267-1276
139. Cauley JA, Lui LY, Stone KL, et al. Longitudinal study of changes in hip bone mineral density among Caucasian and African-American Women. *J Am Geriatr Soc* 2005; 53:183-189
140. Weinstein RS, Bell N H. Diminished rates of bone formation in normal black adults. *N Engl J Med* 1988; 319:1698-1701
141. Han ZH, Palnitkar S, Rao DS, Nelson D, Parfitt AM. Effects of ethnicity and age or meno-pause on the remodeling and turnover of iliac bone: implications for mechanisms of bone loss. *Bone Miner Res* 1997; 12(4):498-508
142. Finkelstein JS, Sowers M, Ettinger B, et al. Ethnic variation in bone turnover in Pre-and early Perimenopausal Women: effects of Anthropometric and Lifestyle Factors. *J Clin Endocrinol Metab* 2002; 87(7):3051-3056
143. Meier DE, Luckey, Wallenstein S, Clemens TL, Orwoll ES and Waslien CI. Calcium, Vitamin D, and Parathyroid Hormone Status in Young White and Black Women: Association with Racial Differences in Bone Mass. *J Clin Endocrinol Metab* 1991; 72(3):703-710
144. Horace M. Perry III, Horowitz H, Morley JE, Sundarum M, et al. Aging and Bone Metabolism in African American and Caucasian Women. *J Clin Endocrinol Metab* 1996; 81(3):1108-1116
145. Harris SS, Soteriades E, Dawson-Hughes B. Secondary hyperparathyroidism and bone turnover in elderly Blacks and Whites. *J Clin Endocrinol Metab* 2001; 8:3801-3804
146. Bell NH, Greene A, Epstein S, Oexmann MJ, Shaw S, Shary J. Evidence for Alteration of the Vitamin D-Endocrine System in Blacks. *J Clin Invest* 1985; 76:470-473
147. Cosman F, Shen V, Morgan D, Lindsay R, et al. Biochemical Responses of Bone Metabo-lism to 1,25-Dihydroxyvitamin D Administration in Black and White Women. *Osteoporos Int* 2000; 11:271-277

148. Recker RR, Barger-Lux MJ. Bone remodeling findings in osteoporosis. In: Marcus R, Feldman D, Kelsey J, editors. Osteoporosis, 2nd edition.
149. Mosekilde L. Age-related changes in bone mass, structure and strength—effects of loading. *Z Rheumatol* 2000; 59(Suppl 1):1-9
150. Parfitt AM. Use of bisphosphonates in the prevention of bone loss and fractures. *Am J Medicine* 1991; 91(Suppl 5B):42S-46S
151. Mashiba T, Hirano T, Turner CH, Burr DB et al. Suppressed Bone Turnover by Bisphosphonates Increases Microdamage Accumulation and Reduces Some Biomechanical Properties in Dog Rib. *J Bone Miner Res.* 2000; 15(4):613-620.
152. Mashiba T, Turner CH, Hirano T, Burr DB et al. Effects of Suppressed Bone Turnover by Bisphosphonates on Microdamage Accumulation and Biomechanical Properties in Clinically Relevant Skeletal Sites in Beagles. *Bone* 2001; 28(5):524-531.
153. Odvina CV, Zerwekh JE, Rao DS, Pak CYC et al. Severely Suppressed Bone Turnover: A Potential Complication of Alendronate Therapy. *J Clin Endocrinol Metab.* 2005; 90(3):1294-1301.
154. Ott SM. Editorial: Long-Term Safety of Bisphosphonates. *J Clin Endocrinol Metab.* 2005; 90(3):1897-1899.
155. Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, prevention and treatment. *J Oral Maxillofac Surg* 2005; 63(11):1567-1575
156. Nevitt MC, Ross PD, Palermo L, Thompson DE et al. Association of prevalent vertebral fractures, bone density, and alendronate treatment with incident vertebral fractures: effect of number and spinal location of fractures. The Fracture Intervention Trial Research Group. *Bone* 1999; 25(5):613-619
157. Mui LW, Haramati LB, Alterman DD, Haramati N, Zelefsky MN, Hamerman D. Evaluation of vertebral fractures on lateral chest radiographs of inner-city postmenopausal women. *Calcif Tissue Int* 2003 Dec; 73(6):550-4
158. Samuelson EJ, Hannan MT, Zhang Y, Genant HK, Felson DT, Kriel DP. Incidence and Risk Factors for Vertebral Fracture in Women and Men: 25-Year Follow-Up Results from the Population-Based Framingham Study. *J Bone Miner Res* 2006; 21(8):1207-1214

159. Marcus R, Wong M, Stock JL et al. Antiresorptive treatment of postmenopausal osteoporosis: comparison of study designs and outcomes in large clinical trials with fracture as an endpoint. *Endocrin Rev* 2002; 23:16-37
160. Peacock M, Turner CH, Liu G, Manatunga AK, Timmerman L, Johnston Jr. Better discrimination of hip fracture using bone density, geometry and architecture. *Osteoporos Int* 1995; 5(3):167-173
161. Gnudi S, Malavolta N, Testi D, Viceconti M. Differences in proximal femur geometry distinguishes vertebral from femoral neck fractures in osteoporotic women. *Br J Radiol*, 2004; 77(915):219-223
162. Brownbill RA, Lindsey C, Cracevic-Orlic Z, Ilich JZ. Dual hip bone mineral density in post- menopausal women: geometry and effect of physical activity. *Calcif Tissue Int* 2003; 73 (3): 217-224
163. Bergot C, Bousson V, Meunier A, Laval-Jeantet M, Laredo JD. Hip fracture risk and proximal femur geometry from DXA scans. *Osteoporos Int* 2002; 13(7):542-550
164. Crabtree NJ, Kroger H, Martin A, Pols HA, Reeve J, et al. Improving risk assessment: hip geometry, bone mineral distribution and bone strength in hip fracture cases and controls. The EPOS study. *European Prospective Osteoporosis Study. Osteoporos Int* 2002; 13(1): 48-54
165. Center JR, Nguyen TV, Pocock NA, Noakes KA, Kelly PJ, Eisman JA, Sambrook PN. Femoral neck axis length, height loss and risk of hip fracture in males and females. *Osteoporosis Int* 1998; 8(1):75-81
166. Faulkner KG, Cummings SR, Black D, Palermo L, Gluer CG, Genant HK. Simple measurement of Femoral Geometry Predicts Hip Fracture: The Study of Osteoporotic Fractures. *J Bone Miner Res* 1993; 8(10):1211-1217
167. Duan Y, Parfitt A, Seeman E. Vertebral bone mass, size, and volumetric density in women with spinal fractures. *J Bone Miner Res* 1999; 14:1796-1802
168. Nevitt MC, Cummings SR for the Study of Osteoporotic Fractures Research Group. Falls and fractures in older women. In: Vellas B, Toupet M, Rubenstein L, Albarede JL, Christen Y, eds. *Falls, balance and gait disorders in the elderly*. Paris: Elsevier, 1992:69-80

169. Kaptoge S, Benevolenskaya LI, Bhalla AK, Cannata JB, Boonen S, Reeve J, et al. Low BMD is less predictive than reported falls for future limb fractures in women across Europe: results from the European Prospective Osteoporosis Study. *Bone* 2005; 36:387-398
170. Geusens P, Autier P, Boonen S, Vanhoof J, Declerck K, Raus J. The Relationship Among History of Falls, Osteoporosis and Fractures in Postmenopausal Women. *Arch Phys Med Rehabil* 2002; 83(7):903-906
171. Ensrud KE, Ewing SK, Taylor BC, Fink HA, Stone KL, Cauley JA, Tracy JK, Hochberg MC, Rodondi N, Cawthon PM; for the Study of Osteoporotic Fractures Research Group. Frailty and risk of falls, fracture, and mortality in older women: the study of osteoporotic fractures. *J Gerontol A Biol Sci Med Sci* 2007 Jul; 62(7):744-51
172. Whooley MA, Kip KE, Cauley JA, Ensrud KE, Nevitt MC, Browner WS. Depression, falls and risk of fracture in older women. Study of Osteoporotic Fractures Research Group. *Arch Intern Med* 1999; Mar 8, 159(5):484-490
173. Lord SR, Sambrook PN, Gilbert C et al. Postural stability, falls and fractures. Results from the Dubbo Osteoporosis Epidemiology study. *Med J Australia* 1994; 160:684-691
174. Nevitt M, Cummings SR. Type of fall and risk of hip and wrist fractures: The Study of Osteoporotic Fractures. *J Am Geriatr Soc* 1993; 41:1226-1234
175. Nguyen T, Sambrook PN, Kelly P et al. Prediction of osteoporotic fractures by postural in-stability and bone density. *Br Med J* 1993; 307:1111-1115
176. Dhesi JK, Bearne LM, Moniz C, Hurley MV, Jackson SHD, Swift CG and Allain TJ. Neuro-muscular and psychomotor function in elderly subjects who fall and the relationship with vitamin D status. *J Bone Miner Res* 2002; 17(5):891-897
177. Lord SR, Dayhew J. Visual risk factors for falls in older people. *J Am Geriatr Soc* 2001; 49(5): 508-515
178. Dargent-Molina P, Favier F, Grandjean H, Breant G et al, for EPIDOS group. Fall related factors and risk of hip fracture: the EPIDOS prospective study. *Lancet* 1996; 348:145-149
179. Magaziner J, Simonsick EM, Kashner TM, Hebel JR, Kenzora JE. Survival experience of aged hip fracture patients. *Am J Public Health* 1989; 79:274-278(abstract)
180. De Lact CEDH, van der Klits M, et al. Osteoporosis in men and women: a story about bone mineral density thresholds and hip fracture risk. *J Bone Miner Res* 2002;17:2231-2236

181. Melton LJ, Atkinson EJ, O'Connor MK, et al. Bone density and fracture risk in men. *J Bone Miner Res* 1998; 13:1915-1923
182. Brinkley NC, Schmeer P, Wasnich RD et al. International Society for Clinical Densitometry Position Development Panel and Scientific Advisory Committee. What are the criteria by which a densitometric diagnosis of osteoporosis can be made in males and non-Caucasians? *J Clin Densitom* 2002; 5(3):19-27
183. Lewlecki EM, Watts NB, McClung MR, Downs RW et al, Jr the International Society for Clinical Densitometry. *J Clin Endocrinol Metab* 2004; 89(8):3651-3655
184. Luckey MM, Wallenstein S, Lapinski R and Meier DE. A Prospective Study of Bone Loss in African-American and White Women – A Clinical Research Center Study. *J Clin Endocrinol Metab* 1996; 81(3):2948-2956
185. Henry Y M, Eastell R. Ethnic and Gender Differences in Bone Density and Bone in Young Adults: Effect of Bone Size. *Osteoporos Int* 2000; 11:512-517
186. Ettinger B, Sidney S, Cummings SR, Steiger P, et al. Racial Differences in Bone Density between Young Adult Black and White Subjects Persist after Adjustment for Anthropometric, Lifestyle and Biochemical Differences. *J Clin Endocrinol Metab* 1997; 82(2):429-434
187. Luckey MM, Meier DE, Mandeli JP, DaCosta MC, Hubbard ML, Goldsmith SJ. Radial and vertebral bone density in white and black women: evidence for racial differences in pre-menopausal bone homeostasis. *J Clin Endocrinol Metab* 1989; 69:762-770
188. Fielding KT, Backrach LK, Hudes ML, Crawford PB, Wang MC. Ethnic differences in bone mass of young women vary with method of assessment. *J Clin Densitom* 2002; 5(3):229-238
189. Cauley J A, Danielson M E, Gregg E W, Vogt M T, Zmuda J, Bauer C. Calcaneal Ultrasound Attenuation in Older African-American and Caucasian–American Women. *Osteoporos Int* 1997; 7:100-104
190. Gilsanz V, Roe TF, Mora S, Costin G, Goodman WG. Changes in Vertebral bone density in Black girls and White girls during childhood and puberty. *N Engl J Med* 1991; 325(23):1597-1600
191. Gilsanz V, Skaggs D L, Kovanlikaya A, Sayre J, Loro M L, Kaufman F, Korenman S G. Differential Effect of Race on the Axial and Appendicular Skeletons of Children. *J Clin Endocrin Metab* 1998; 83(5):1420-1427

192. Looker AC, Johnston CC Jr, Wahner HW, Dunn WL, Calvo MS, Harris TB, Heyse SP, Lindsay RL. Prevalence of Low Femoral Bone Density in Older U.S. Women from NHANES III. *J Bone Miner Res* 1995; 10(5):796-802
193. Liel Y, Edwards J, Shary J, Spicer KM, Gordon L, Bell NH. The Effects of Race and Body Habitus on Bone Mineral Density of the Radius, Hip and Spine in Premenopausal Women. *J Clin Endocrinol Metab* 1988; (66)6:1247-1250
194. Trotter M, Broman GE, Peterson RR. Densities of Bones of White and Negro Skeletons. *J Bone Joint Surg* 1960; 42-A(1):50-58
195. DeSimone DP, Stevens J, Edwards J, Shary J, Gordon L, Bell NH. Influence of Body Habitus and Race on Bone Mineral Density of the Midradius, Hip and Spine in Aging Women. *J Bone Miner Res* 1989; (4)6:827-830
196. Aloia JF, Vaswani A, Yeh JK, Flaster E. Risk for Osteoporosis is Black Women. *Calcif Tissue Int* 1996; 59:415-423
197. Aloia JF, Vaswani A, Mikhail M, Badshah M, Flaster E. Cancellous Bone of the Spine is Greater in Black Women. *Calcif Tissue Int* 1999; 65:29-33.
198. Bachrach LK, Hastie T, Wang May-Choo, Narasimhan B, Marcus R. Bone Mineral Acquisition in Healthy Asian, Hispanic, Black and Caucasian Youth: A Longitudinal Study. *J Clin Endocrinol Metab* 1999; (84)12:4702-4712
199. Finkelstein JS, Lee M-L T, Sowers M, Ettinger B, Greendale GA, et al. Ethnic Variation in Bone Density in Premenopausal and Early Perimenopausal Women: Effects of Anthropometric and Lifestyle Factors. *J Clin Endocrinol Metab* 2002; 87(7):3057-3067
200. Carter DR, Bouxsein ML, Marcus R. New Approaches for Interpreting Projected Bone Densitometry Data. *J Bone Miner Res* 1992; 7(2):137-145
201. Katzman DK, Bachrach LK, Carter DR, Marcus R. Clinical and Anthropometric correlates of bone mineral acquisition in healthy adolescent girls. *J Clin Endocrinol Metab* 1991; 73:1332-1339
202. Woodson Grattan C. Risk factors for osteoporosis in postmenopausal African-American women. *Current Medical Research and Opinions* 2004; 20(10):1681-1687
203. Seeman E. Growth in Bone Mass and Size – Are Racial and Gender Differences in Bone Mineral Density More Apparent than Real? *J Clin Endocrinol Metab* 1998; (83)5:1414-1419

204. Parisien M, Cosman F, Morgan D, Dempster DW et al. Histomorphometric Assessment of Bone Mass, Structure and Remodeling: A Comparison Between Healthy Black and White Premenopausal Women. *J Bone Miner Res* 1997; 12(6):948-957
205. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. *N Engl J Med* 1988; 319:1701-1707
206. Nevitt MC, Cummings SR, Kidd S et al. Risk factors for recurrent non-syncopal falls. *JAMA* 1989; 261:2663-2668
207. Hanlon JT, Landerman LR, Fillenbaum GG et al. Falls in African-American and white community dwelling elderly residents. *J Gerontol A Biol Sci Med Sci* 2002; 57A:473-478
208. Means KM, O'Sullivan PS, Rodell DE. Balance, mobility and falls among elderly African American women. *Am J Phys Med Rehabil.* 2000; 79:30-39
209. Faulkner KA, Cauley JA, Zmuda JM, Redfern MS et al. Ethnic Differences in the Frequency and Circumstances of Falling in Older Community-Dwelling Women. *JAGS* 2005; 53(10):1774-1779
210. Tracy JK, Meyer WA, Grigoryan M, Hochberg MC et al. Racial differences in the prevalence of vertebral fractures in older men: the Baltimore Men's Osteoporosis Study. *Osteoporos Int* 2006; 17(1):99-104
211. Dent CE, Engelbrecht HE, Godfrey RC 1968. Osteoporosis at lumbar vertebrae and calcification of abdominal aorta in women living in Durban. *BMJ* 1968; 4:76-79
212. Aspray TJ, Prentice A, Cole TJ, Sawo Y, Reeve J, Francis RM. Low Bone Mineral Content is Common, but Osteoporotic Fractures are Rare in Elderly Rural Gambian Women. *J Bone Miner Res* 1996; 11(7):1019-1025
213. Solomon L. Bone Density in ageing Caucasian and African populations. *Lancet* 1979; 57(B)2:1326-1329
214. Patel DN, Pettifor JM, Leschner K, et al. The Effect of Ethnic Group on Appendicular Bone Mass in Children. *J Bone Miner Res* 1992; 7(3):263-272
215. McVeigh JA, Norris SA, Cameron N, Pettifor JM. Association between physical activity and bone mass in black and white South African children at age 9 yr. *J Applied Physiol* 2004; 97(3):1-11
216. Vidulich L, Norris SA, Cameron N, Pettifor JM. Differences in bone size and bone mass between black and white 10-year-old South African children. *Osteoporos Int* 2006; 17:433-440

217. Excoffier L, Pelligrini B, Sanchez-Mazas A, Simon C, Langaney A. Genetics and history of sub-Saharan Africa. *Yearbook Phys Anthropology* 1987; 30:151-194
218. Melton LJ III, Marquez MA, Achenbach SJ, Riggs BL. Variations in bone density among Persons of African Heritage. *Osteoporos Int* 2002; 13:551-559
219. Bererhi H, Constable A, Lindell AE, Coutino J, Kharousi W. A study of bone mineral density vs age in Omani women - a comparison with normal British women. *Nucl Med Commun* 1994; 15:99-103
220. Gong G, Haynatzki G, Haynatzki V, Wilson MR et al. Bone mineral density of recent African immigrants in the United States. *J Natl Med Assoc* 2006; 98(5):746-752
221. Einhorn TA. Bone strength: The bottom line. *Calcif Tissue Int.* 1992; 51:333-339
222. Prentice A, Shaw J, Laskey AN, Cole TJ, Fraser DR. Bone mineral content of British and rural Gambian women aged 18-80+ years. *J Bone Miner Res* 1991; (12):201-214
223. Kahn HS. A major error in nomograms for estimating body mass index. *Am J Clin Nutr* 1991; 54:435-437
224. Sedrine WB, Chevallier T, Zegels B, Kvasz A, Micheletti MC, Gelas B, Reginster JY. Development and assessment of the Osteoporosis Index of Risk (OSIRIS) to facilitate selection of women for bone densitometry. WHO Collaborating Center for Public Health Aspects of Rheumatic Diseases, Liège, Belgium
225. Kuczmarski R J, Flegal K M. Criteria for definition of overweight in transition: background and recommendations for the United States. *Am J Clin Nutr* 2000; 72:1074-81
226. Bauer DC, Gluer CC, Cauley JA, Vogt TM, Ensrud KE, Genant HK, Black DM. Broadband ultrasound attenuation predicts fractures strongly and independently of densitometry in older women. A prospective study. Study of Osteoporotic Fractures Research Group. *Arch Intern Med* 1997; Mar 24,157(6):629-34
227. Huopio J, Kröger H, Honkanen R, Jurvelin J, Saarikoski S, Alhava E. Calcaneal ultrasound predicts early postmenopausal fractures as well as axial BMD. A prospective study of 422 women. *Osteoporos Int* 2004; 15:190-195
228. Tylavsky FA, Carbone LD, Bush AJ. Effects of ethnicity and gender on reliable measurements using the Sahara Ultrasonometer. *J Clin Densitom* 2002; 5(4):411-419
229. Langton CM, Palmer SB, Porter RW. The measurement of broadband ultrasonic attenuation in cancellous bone. *Eng Med* 1984; 13:89-91

230. Langton CM, Evans GP. Dependence of ultrasonic velocity and attenuation on the material properties of cancellous bone. *Osteoporos Int* 1991; 1:194
231. Hans D, Arlot ME, Schott AM, Roux GP, Kotzki PO, Meunier PJ. Do ultrasound measurements on the os calcis reflect more the micro-architecture of bone than the bone mass? A two dimensional histomorphometric study. *Bone* 1995; 16:295-300
232. Dennis M Black, Lisa Palermo, Michael C Nevitt, Harry K Genant, Lisa Christensen, Steven R Cummings for the Study of Osteoporotic Fractures Research Group. *J Bone Miner Res* 1999; 14(1):90-101
233. Vesper H W, Demers L M, Estell R, Garnero P, Kleerekoper M, Robins S P, Srivastava AK, Warnick G R, Watts N, Myers G L. Assessment and Recommendations on Factors Contributing to Pre-analytical Variability of Urinary Pyridinoline and Deoxypyridinoline. *Clinical Chemistry* 2002; 48(2):220-235
234. Shephard GS, Carlini SM, Hanekom C, Labradarios D. Analysis of 25-hydroxyvitamin D in plasma using solid phase extraction. *Clinica Chemica Acta* 1987; 167:231-236
235. Prediction of falls. Training video by Eli Lilly Australia Pty. Ltd. in conjunction with Dr Stephen Lord, Prince of Wales, Medical Research Centre, Sydney, Australia.
236. Espallargues M, Sampietro-Colom L, Estrada MD, et al. Identifying bone mass-related risk factors for fracture to guide bone densitometry measurements: a systematic review of the literature. *Osteoporos Int* 2001; 12:811-822
237. Barrett JA, Baron JA, Karagas MR, Beach ML. Fracture risk in the US Medicare population. *J Clin Epidemiol* 1999; 52:243-249
238. Albala C, Yanez M, Devoto E, Santos JL et al. Obesity as a protective factor for postmenopausal osteoporosis. *Int J Obes Relat Metab Disord* 1996; 20(11):1027-1032
239. Glauber HS, Vollmer WM, Nevitt MC, Orwoll ES et al. Body weight versus body fat distribution, adiposity, and frame size as predictors of bone density. *J Clin Endocrinol Metab* 1995; 80:1118-1123
240. Sowers MR, Clarke MK, Jannausch ML, Wallace RB. Body size, estrogen use and thiazide diuretic use affect 5-year radial bone loss in postmenopausal women. *Osteoporos Int* 1993; 3:314-321
241. Grisso JA, Kelsey JL, Stom BL, Hoffman S, et al. for Northeast Hip Fracture Study Group. Risk Factors for Hip Fracture in Black Women. *N Engl J Med* 1994; 330:1555-2559

242. Nelson DA, Kleerekoper M, Peterson E, Parfitt AM. Skin color and body size as risk factors for osteoporosis. *Osteoporos Int* 1993; 3:18-23
243. Cummings SR, Black DM, Rubin SM. Lifetime risks of Hip, Colles or Vertebral fracture and Coronary Heart Disease among White Postmenopausal Women. *Arch Intern Med* 1989; 149:2445-2448
244. Burger H, de Laet CE, van Daele PL, Pols HA et al. Risk factors for increased bone loss in an elderly population: the Rotterdam Study. *Am J Epidemiol* 1998; 147(9):871-879
245. Pruzansky ME, Turano M, Luckey M, Senie R. Low body weight as a risk factor for hip fracture in both black and white women. *J Orthopaedic Res* 1989; 7(2):192-197
246. Kontogianni MD, Dafni UG, Routsias JG, Skopouli FN. Blood Leptin and Adiponectin as Possible Mediators of the Relation Between Fat Mass and BMD in Perimenopausal Women. *J Bone Miner Res* 2004; 19(4):546-551
247. Dennison E, Eastell R, Fall CHD, Kellingray S, Wood PJ, Cooper C. Determinants of bone loss in elderly men and women: a prospective population-based study. *Osteoporos Int* 1999; 10:384-391
248. Frumar AM, Meldrum DR, Geola F, et al. Relationship of fasting urinary calcium to circulating estrogen and body weight in postmenopausal women. *J Clin Endocrinol Metab* 1980; 50:70-75
249. Jacobsen SJ, Cooper C, Gottlieb MS, Goldberg J, Yahnke DP, Melton LJ 3rd. Hospitalization with vertebral fracture among the aged: a national population-based study 1986-1989. *Epidemiology* 1992; 3(6):515-518
250. Reid IR, Ames R, Evans MC, Sharpe S, Cundy TF. Determinants of total body and regional mineral density in normal postmenopausal women – a key role for fat mass. *J Clin Endocrinol Metab* 1992; 75:45-51
251. Zhao L-J, Liu Y-J, Liu P-Y, Hamilton J, Recker R R, Deng H-W. Relationship of Obesity with Osteoporosis. *J Clin Endocrinol Metab* 2007; 92(5):1640-1646
252. Janicke A, Wren TAL, Sanchez MM, Gilsanz V et al. Fat mass is not beneficial to bone in adolescents and young adults. *J Clin Endocrinol Metab* 2007; 92(1):1143-1147
253. Ensrud KE, Ewing SK, Stone KL, Cauley JA, Cummings SR et al. for the Study of Osteoporotic Fractures Research Group. Intentional and unintentional weight loss increase bone loss and hip fracture risk in older women. *J Am Geriatr Soc* 2003; 51:1740-1747

254. Ensrud KE, Cauley J, Lipschutz R, Cummings SR. Weight change and fractures in older women. Study of Osteoporotic Fractures Research Group. *Arch Intern Med* 1997; 157(8):857-863
255. Pettiti DB, Piaggio G, Meirik O et al. Steroid hormone contraception and bone mineral density: a cross-sectional study in an international population. The WHO Study of Hormonal Contraception and Bone Health. *Obstet Gynecol* 2000; 95(5):736-744
256. Kleerekoper M, Brienza RS, Shultz LR, Johnson CC. Oral contraceptive use may protect against low bone mass. *Arch Intern Med* 1991; 151:1971-1976
257. Clark MK, Sowers MR, Nichols S, Levy B. Bone mineral density changes over two years in first-time users of depot medroxyprogesterone acetate. *Fertil Steril* 2004; 82(6):1580-1586
258. Cromer BA, Stager M, Bonny A, Debanne SM et al. Depot medroxyprogesterone acetate, oral contraceptives and bone mineral density in a cohort of adolescent girls. *J Adolesc Health* 2004; 35(6):427-429
259. Curtis KM, Martins SL. Progestogen-only contraception and bone mineral density; a systematic review. *Contraception* 2006; 73(5):470-487
260. Albertazzi P, Bottazzi M, Steel SA. Bone mineral density and depot medroxyprogesterone acetate. *Contraception* 2006; 73:577-583
261. Piava LC, Pinto-Neto AM, Faundes A. Bone density among long-term users of medroxyprogesterone acetate as a contraceptive. *Contraception* 1998; 58:351-355
262. Scholes D, LaCroix AZ, Ichikawa LE, Barlow NWE, Ott SM. Change in bone mineral density among adolescent women using and discontinuing depot medroxyprogesterone acetate contraception. *Arch Pediatr Adolesc Med* 2005; 159(2):139-144
263. Polatti F, Perotti F, Filippa N, Gallina D, Nappi RE. Bone mass and long-term monophasic oral contraceptive treatment in young women. *Contraception* 1995; 51:221-224
264. Elgan C, Dykes AK, Samsioe G. Bone mineral density changes in young women: a two year study. *Gynecol Endocrinol* 2004; 19:169-177
265. Prior JC, Kirkland SA, Joseph L, Tenenhouse A, et al. for the CaMOS Research Group. Oral contraceptive use and bone mineral density in premenopausal women: cross-sectional, population based data from the Canadian Multicenter Osteoporosis Study. *Canadian Med Association J* 2001; 165(8):1023-1029

266. Hartard M, Kleinmond C, Wiseman M, Erben RG et al. Detrimental effect of oral contraceptives on parameters of bone mass and geometry in a cohort of 248 young women. *Bone* 2007; 40(2):444-450
267. Turner RT, Colvard DS, Spelsberg TC. Estrogen inhibition of periosteal bone formation in rat long bones: down-regulation of gene expression for bone matrix proteins. *Endocrinology* 1990; 127:1346-51
268. Petit MA, Beck TJ, Lin HM, Bentley C, Legro RS, Lloyd T. Femoral bone structural geometry adapts to mechanical loading and is influenced by sex steroids: the Pennsylvania State Young Women's Health Study. *Bone* 2004; 35:750-9
269. Ott SM, Scholes D, LaCroix AZ, Ichikawa LE, Yoshida CK, Barlow WE. Effects of contraceptive use on bone biochemical markers in young women. *J Clin Endocrinol Metab* 2001; 86:179-85
270. Wiegatz I, Kutschera E, Lee JH, Moore C, Winkler UH, et al. Effect of four different oral contraceptives on various sex hormones and serum-binding globulins. *Contraception* 2003; 67:25-32
271. Orr-Walker BJ, Evans MC, Reid IR et al. The effect of past use of the injectable contraceptive depot medroxyprogesterone acetate on bone mineral density in normal postmenopausal women. *Clin Endocrinol (Oxf)* 1998; 49(5):615-618
272. Murphy S, Khaw KT, Compston JE. Lack of relationship between hip and spine bone mineral density and oral contraceptive use. *Eur J Clin Invest* 1993; 23(2):108-111
273. Tuppurainen M, Kroger H, Saarikoski S, Honkanen R, Alhava E. The effect of previous oral contraceptive use on bone mineral density in perimenopausal women. *Osteoporos Int.* 1994; 4(2):93-98
274. Fortney JA, Feldblum PJ, Talmage RV, Zhang J, Godwin SE. Bone mineral density and history of oral contraceptive use. *J Reprod Med* 1994; 39(2):105-109
275. Cooper C, Hannaford P, Croft P, Kay CR. Oral contraceptive pill use and fractures in women: a prospective study. *Bone* 1993; 14(1):41-45
276. Vessey M, Mant J, Painter R. Oral contraception and other factors in relation to hospital referral for fracture. Findings in a large cohort study. *Contraception* 1998; Apr, 57(4):231-235
277. Cobb KL, Kelsey JL, Sidney S, Ettinger B, Lewis CE. Oral contraceptives and bone mineral density in white and black women in CARDIA. *Osteoporos Int* 2002; 13:893-900

278. Department of Health South Africa. Medical Research Council and Measure DHS (2002). South African demographic and health survey 1998, full report. Pretoria (South Africa): Department of Health; 2002
279. Beksinska ME, Smit JA, Kleinschmidt I, Farley TMM, Mbatha F. Bone mineral density in women aged 40-49 years using depot-medroxyprogesterone acetate, norethisterone enanthate or combined oral contraceptive for contraception. *Contraception* 2005; 71:170-175
280. Nguyen T, Jones G, Sambrook P, Eisman J et al. Effects of estrogen exposure and reproductive factors on bone mineral density and osteoporotic fractures. *J Clin Endocrinol Metab* 1995; 80:2709-2714
281. Cure-Cure C, Cure-Ramirez, Lopez-Jaramillo P. Bone mass peak in multiparity and reduced risk of bone fractures in menopause. *Int J Gynaecol Obstet* 2002; 76:285-291
282. Kritz-Silverstein D, Barrett-Connor E, Hollenbach K. Pregnancy and lactation as determinants of bone mineral density in postmenopausal women. *Am J Epidemiol* 1992; 136:1052-1059
283. Bererhi H, Kolhoff N, Nielsen S. Multiparity and bone mass. *Br J Obstet Gynecol* 1996; 159:318-322
284. Streeten EA, Ryan KA, Mitchell BD et al. The relationship between parity and bone mineral density in women characterized by a homogeneous lifestyle and high parity. *J Clin Endocrinol Metab* 2005; 90(8):4536-4541
285. Gur A, Nas K, Cevik R, Sarac AJ, Karakoc M. Influence of number of pregnancies on bone mineral density in postmenopausal women of different age groups. *J Bone Miner Res* 2003; 21:234-241
286. Weiss NS, Ure CL, Ballard JH, Williams AR, Daling JR. Decreased risk of fractures of hip and lower forearm with postmenopausal use of estrogen. *N Engl J Med* 1980; 303:1195-1198
287. Eiken P, Kolthoff N, Nielsen SP. Effect of 10 years' hormone replacement therapy on bone mineral content in postmenopausal women. *Bone* 1996; Nov,19(5 Suppl):191S-193S
288. Wells G, Tugwell P, Shea B, et al. Meta-analysis of the efficacy of hormone replacement therapy in treating and preventing osteoporosis in postmenopausal women. *Endocr Rev* 2000; 23:529-539

289. Torgerson DL, Bell-Syer SE. Hormone replacement therapy and prevention of non-vertebral fractures. *JAMA* 2002; 285:2891-2897
290. Nelson HD, Humphrey LL, Nuygren P, Teutsch SM, Allan JD. Postmenopausal hormone replacement therapy. *JAMA* 2002; 288:872-881
291. Cauley JA, Robbins J, Chen Z, Watts NB et al. for the Women's Health Initiative Investigators. Effects of Estrogen Plus Progestin on Risk of Fracture and Bone Mineral Density. The Women's Health Initiative Randomized Trial. *JAMA* 2003; 290:1729-1738
292. Rossouw JE, Anderson GL, Prentice RL et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; 288(3):321-333
293. Anderson GL, Limacher M, Assaf AR et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004; 291:1701-1712
294. Winzenberg T, Shaw K, Fryer J, Jones G. Effects of calcium supplementation on bone density in healthy children: meta-analysis of randomized controlled trials. *BMJ* 2006; 14(7572)333:775
295. Reid IR, Mason B, Horne A, Ames R, Reid HE, Bava U, Bolland MJ, Gamble GD. Randomized Controlled Trial of Calcium in Healthy Older Women. *Clinical Research Study. Am J Med* 2006; 119:777-785
296. Dawson-Hughes B, Dallal GE, Krall EA et al. A controlled trial of the effect of calcium supplementation on bone density in postmenopausal women. *N Engl J Med* 1990; 23:878-883
297. Prince RL, Smith M, Dick IM et al. Prevention of postmenopausal osteoporosis. A comparative study of exercise, calcium supplementation and hormone-replacement therapy. *N Engl J Med* 1991; 325:1189-1195
298. Reid IR, Ames RW, Evans MC, et al. Effect of calcium supplementation on bone loss in postmenopausal women. *N Engl J Med* 1993; 328:460-464
299. Reid IR, Ames RW, Evans MC, Gamble GD, Sharpe SJ. Long-Term Effects of Calcium Supplementation on Bone Loss and Fractures in Postmenopausal Women: A Randomized Controlled Trial. *Am J Med* 1995; 98:331-335
300. Dawson-Hughes B, Harris SS, Krall EA, Dallal G. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med* 1997; Sept:670-676

301. Grant AM, Anderson FH, Avenell A, et al. Oral vitamin D₃ and calcium for secondary prevention of low-trauma fractures in elderly people (Randomized Evaluation of Calcium Or Vitamin D, RECORD) a randomized placebo-controlled trial. *Lancet* 2005; 365:1621-1628
302. Prince RL, Devine A, Dhaliwal SS, Dick IM. Results of a 5 year double blind, placebo controlled trial of calcium supplementation: clinical fracture outcomes. *J Bone Min Res* 2004; 19:suppl 1:S3
303. Shea BJ, Adachi JD, Cranney A, Griffith L, Guyatt G, Hamel C, Ortiz Z, Peterson J, Robinson VA, Tugwell P, Wells G, Zutaruk N. Calcium supplementation on bone loss in postmenopausal women (Review). *The Cochrane Library* 2005, Issue 4:1-19
304. Bensen R, Adachi JD, Bensen W et al. Evaluation of easily measured risk factors in the prediction of osteoporotic fractures. *BMC Musculoskelet Disord* 2005; 6:47
305. Nevitt MC, Cummings SR, Stone KL, Palermo L, Cauley JA et al. Risk factors for a first-incident radiographic vertebral fracture in women \geq 65 years of age: The Study of Osteoporotic Fractures. *J Bone Miner Res* 2005; 20:131-140
306. Welton DC, Kemper HC, Post GB, Teule GJ et al. Weight-bearing activity during youth is a more important factor for peak bone mass than calcium intake. *J Bone Miner Res* 1994; 9(7):1089-1096
307. Cooper C, Cawley M, Bhalla A, Barker D et al. Childhood growth, physical activity, and peak bone mass in women. *J Bone Miner Res* 1995; 10(6):940-947
308. Parfitt AM. The two faces of growth: Benefits and risks to bone integrity. *Osteoporos Int* 1994; 4:382-398
309. Pocock NA, Gwinn T, Sambrook PN, Yeates MG. Muscle strength, physical fitness and weight, but not age predict femoral bone mass. *J Bone Miner Res* 1998; 4:441-448
310. Dennison E, Eastell R, Fall C, Cooper C. Determinants of bone loss in elderly men and women: a prospective population-based study. *Osteoporos Int* 1999; 10:384-391
311. Nelson ME, Fiatarone MA, Morganti CM, Evans WJ et al. Effects of high-intensity strength training on multiple risk factors for osteoporotic fractures. *JAMA* 1994; 272:1909-1914
312. Danielson ME, Cauley JA, Baker CE, Kuller LH et al. Familial resemblance of bone mineral density (BMD) and calcaneal ultrasound attenuation: the BMD in mothers and daughters study. *J Bone Miner Res* 1999; 14(1):102-110

313. Liel Y, Edwards J, Shary J, Bell NH et al. The effects of race and body habitus on bone mineral density of the radius, hip, and spine in premenopausal women. *J Clin Endocrinol Metab* 1988; 66:1247-1250
314. Holbrook TL, Barrett-Connor E. The association of lifetime weight and weight control patterns with bone mineral density in an adult community. *J Bone Miner Res* 1993; 20:141-149
315. Jones G, Nguyen T, Sambrook P, Kelly PJ, Eisman JA. Progressive loss of bone in the femoral neck in elderly people: longitudinal findings from the DUBBO osteoporosis epidemiology study. *BMJ* 1994; 309:691-695
316. Reid IR, Ames RW, Evans MC, Sharpe SJ, Gamble GD. Determinants of the rate of bone loss in normal postmenopausal women. *J Clin Endocrinol Metab* 1994; 79:950-954
317. Meldrum DR, Davidson BJ, Taturyn IV, Judd HL. Changes in circulating steroids with aging in postmenopausal women. *Obstet Gynecol* 1981; 57:624-629
318. Kanis JA, Johnell O, Johansson H, Tenenhouse A et al. Smoking and fracture risk: a meta-analysis. *Osteoporos Int.* 2005; 16(2):155-162
319. Nguyen ND, Pongchaiyakul C, Center JR, Eisman JA, Nguyen TV. Identification of high-risk individuals for hip fracture: a 14-year prospective study. *J Bone Miner Res* 2005; 20(11):1921-1928
320. Stone KL, Seeley DG, Lui LY, Cauley JA, Cummings SR et al: Osteoporotic Fractures Research Group. BMD at multiple sites and risk of fracture of multiple types: long-term results from the Study of Osteoporotic Fractures. *J Bone Miner Res* 2003; 18(11):1947-1954
321. Stewart A, Kumar V, Reid DM. Long-term fracture prediction by DXA and QUS: a 10-year prospective study. *J Bone Miner Res* 2006; 21(3):413-418
322. Waud CE, Lew R and Baran DT. The relationship between ultrasound and densitometric measurements of bone mass at the calcaneus in women. *Calcific Tissue International* 1992; 51(6):415-418
323. Kaufmann JJ, Einhorn TA. Perspectives: Ultrasound assessment of bone. *J Bone Miner Res* 1993; 8:517-525
324. Schott AM, Weill-Engerer S, Hans D et al. Ultrasound discriminates patients with hip fracture equally well as dual energy X-ray absorptiometry and independently of bone mineral density. *J Bone Miner Res* 1995; 10:243-249

325. Hans D, Dargent-Molina P, Schott AM, Meunier PJ et al, for the EPIDOS prospective study group. Ultrasonographic heel measurements to predict hip fracture in elderly women: the EPIDOS prospective study. *Lancet* 1996; 348:511-514
326. Hartl F, Tyndall A, Kraenzlin M, Theiler R et al. Discriminatory Ability of Quantitative Ultrasound Parameters and Bone Mineral Density in a Population-based Sample of Postmenopausal Women With Vertebral Fractures: Results of the Basel Osteoporosis Study. *J Bone Miner Res* 2002; 17(2):321-330
327. Bauer DC, Gluer CC, Genant HK, Stone K. Quantitative ultrasound and vertebral fracture in postmenopausal women. Fracture Intervention Trial Research Group. *J Bone Miner Res* 1995; 10:353-358
328. Pfeifer M, Pollaehne W, Minne HW. Ultrasound analyses of the calcaneus predict relative risk of the presence of at least one vertebral fracture and reflect different physical qualities of bone in different regions of the skeleton. *Horm Metab Res* 1997; 29:76-79
329. He YQ, Fan B, Hans D, Genant K et al. Assessment of a New Quantitative Ultrasound Calcaneus Measurement: Precision and Discrimination of Hip Fractures in Elderly Women compared with Dual X-ray Absorptiometry. *Osteoporos Int* 2000; 11(4):354-360
330. Marin F, Gonzalez-Macias J, Diez-Perez A, Palma S, Delgado-Rodriguez M. Relationship between bone quantitative ultrasound and fractures: a meta-analysis. *J Bone Miner Res* 2006; 21(7):1126-1135
331. Mautalen C, Vega E, Gonzales D et al. Ultrasound and dual X-ray absorptiometry densitometry in women with hip fracture. *Calcif Tissue Int* 1995; 57:165-168
332. Faulkner KG, McClung MR, Coleman LJ, Kingston-Sandahl E. Quantitative ultrasound of the heel: Correlation with densitometric measurements at different skeletal sites. *Osteoporos Int* 1994; 4:42-47
333. Massie A, Reid DM, Porter RW. Screening for osteoporosis: Comparison between dual energy X-ray absorptiometry and broadband ultrasound attenuation in 1000 perimenopausal women. *Osteoporos Int* 1993; 3:107-110
334. Frost ML, Blake GM, Fogelman I. Does the combination of quantitative and dual-energy X-ray absorptiometry improve fracture discrimination? *Osteoporos Int* 2001;12(6):471-7

335. Frost ML, Black GM, Fogelman I. Can the WHO criteria for diagnosing osteoporosis be applied to calcaneal quantitative ultrasound? *Osteoporos Int* 2000; 11(4):321-330
336. Evans EM, Ross KM, Heinrichs KL, McAuley E, Rosengren KS. Ultrasound of the calcaneus and bone mineral density differs in older black and white women, but is not impacted by current physical activity. *Osteoporos Int*. 2005; 16(12):1755-1760
337. Hinkley HJ, Drysdale IP, Walters NJ, Bird D. Normative data for ultrasound measurement of the calcaneus within different ethnic groups. *Br J Radiol* 2004; 77(921):740-744
338. Garnero P, Shih W J, Gineyts E, Karpf D B, Delmas P D. Comparison of New Biochemical Markers of Bone Turnover in Late Postmenopausal Osteoporotic Women in Response to Alendronate Treatment. *J Clin Endo Metab* 1994; 79(6):1693-1700
339. Rosenquist C, Bonde M, Fledelius C, Qvist P. A simple-enzyme-linked immunosorbent assay of human osteocalcin. *Clin Chem* 1994; 40:1258-1264
340. Johansen JS, Riis BJ, Delmas PD, Christiansen C. Plasma BGP: an indicator of spontaneous bone loss and the effect of oestrogen treatment in postmenopausal women. *Eur J Clin Invest* 1986; 18:191-195
341. Cummings SR, Black DM, Nevitt MC, Vogt TM. Bone density at various sites for prediction of hip fractures. *Lancet* 1993; 341:72-75
342. Wainwright SA, Marshall LM, Ensrud KE, Cauley JA, Orwoll ES et al. for the Study of Osteoporotic Fractures Research Group. Hip fracture in women without osteoporosis. *J Clin Endocrinol Metab* 2005; 90(5):2787-2793
343. Gilsanz V, Boechat MI, Gilsanz R, Loro ML, Roe TF, Goodman WG. Gender differences in vertebral sizes in adults: Biomechanical implications. *Radiology* 1994; 190: 678-682
344. Cauley JA, Seeley DG, Ensrud K, Ettinger B. Black D, Cummings SR. Estrogen replacement therapy and fractures in older women. *Ann Intern Med* 1995; 122:9-16
345. El-Kaissi S, Pasco JA, Henry MJ, Panahi S, Nicholson JG, Nicholson GC, Kotowicz MA. Femoral neck geometry and hip fracture risk: the Geelong osteoporosis study. *Osteoporos Int* 2005; Oct, 16(10):1299-1303
346. Nelson DA, Pettifor JM, Barondess DA, Cody DD, Uusi-Rasi K, Beck TJ. Comparison of cross-sectional geometry of the proximal femur in white and black women from Detroit and Johannesburg. *J Bone Miner Res* 2004; 19(4):560-565
347. Mazess RB, Barden HS, Ettinger M et al. Spine and femur density using dual photon absorptiometry in US white women. *J Bone Miner Res* 1987; 2:211-219

348. Visser M, Deeg DHJ, Lips P. Low Vitamin D and High Parathyroid Hormone Levels as Determinants of Loss of Muscle Strength and Muscle Mass (Sarcopenia): The Longitudinal Aging Study Amsterdam. *J Clin Endocrinol Metab* 2003; 88(12):5766-5772
349. Wicherts IS, van Schoor NM, Boeke AJP, Visser M, Deeg DJH, Smit J, Knol DL, Lips P. Vitamin D Status Predicts Physical Performance and Its Decline in Older Persons. *J Clin Endocrinol Metab* 2006; 92(6):2058-2065
350. Snijder MB, van Schoor NM, Pluijm SMF, van Dam RM, Visser M, Lips P. Vitamin D Status in Relation to One-Year Risk of Recurrent Falling in Older Men and Women. *J Clin Endocr Metab* 2006; 91(8):2980-2985
351. Cummings SR, Nevitt MC, Browner WS, Voght TM et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. *N Engl J Med* 1995; 332(12):767-773
352. Liu Ambrose T, Eng JJ, Khan KM, Carter ND, McKay HA. Older women with osteoporosis have increased postural sway, and weaker quadriceps strength than counterparts with normal bone mass: overlooked determinants of fracture risk? *J Gerontol A Biol Sci Med* 2003; 58(9):862-866
353. Stone KL, Seeley DG, Lui LY, Cummings SR, et al. BMD at multiple sites and risk of fracture of multiple types: Long-term results from the Study of Osteoporotic Fractures. *J Bone Miner Res* 2003; 18:1947-1954
354. Black DM, Arden NK, Palermo L, Pearson J, Cummings SR, et al. Prevalent vertebral deformities predict hip fractures and new vertebral deformities but not wrist fractures. Study of Osteoporotic Fractures Research Group. *J Bone Miner Res* 1999; 14:821-828
355. Cummings SR, Browner WS, Bauer D, Ettinger B, et al. Endogenous hormones and the risk of hip and vertebral fractures among older women. Study of Osteoporotic Fractures Research Group. *N Engl J Med* 1998; 339:733-738
356. Ettinger B, Pressman A, Sklarin P, Bauer DC, Cauley JA, Cummings SR. Associations between low levels of serum estradiol, bone density, and fractures among elderly women: The study of osteoporotic fractures. *J Clin Endocrinol Metab* 1998; 83:2239-2243
357. Whooley MA, Kip KE, Cauley JA, Ensrud KE, Nevittt MC, Browner WS. Depression, falls and risk of fracture in older women. Study of Osteoporotic Fractures Research Group. *Arch Intern Med* 1999; 159:484-490

358. Roy DE, O'Neill TW, Finn JD, Lunt M, Silman AJ, Reeve J, et al. Determinants of incident vertebral fracture in men and women: Results from the European Prospective Osteoporosis Study (EPOS). *Osteoporos Int* 2003; 14:19-26
359. Van der Klift M, de Laet CE, McCloskey EV, Johnell O, Kanis JA, Hofman A, Pols HA. Risk factors for incident vertebral fractures in men and women: The Rotterdam Study. *J Bone Miner Res* 2004; 19:1172-1180
360. Spector TD, McCloskey EV, Doyle DV, Kanis JA. Prevalence of vertebral fracture in women and the relationship with bone density and symptoms: the Chingford Study. *J Bone Miner Res* 1993; Jul, 8(7):817-22
361. Vokes TJ, Gillen DL, Pham AT, Lovett JM. Risk factors for prevalent vertebral fractures in black and white female densitometry patients. *J Clin Densitom* 2007; Jan-Mar, 10(1):1-9
362. Banks E, Beral V, Reeves G et al. Fracture incidence in relation to the pattern of the use of hormone therapy in postmenopausal women. *JAMA* 2004; 291:2212
363. Black DM, Cummings SR, Karpf DB et al. Randomized trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet* 1996; 348:1535-1541
364. Harris St, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and non-vertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. *JAMA* 1999; 282:1344-1352
365. McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. *N Engl J Med* 2001; 344:333-340
366. Hays J, Ockene JK, Brunner RL, et al. Effects of estrogen plus progestin on health-related quality of life. *N Engl J Med* 2003; 348:1839-1854
367. Hadji P, Hars O, Schuler M, Emons G, Schulz K D. Assessment by quantitative ultrasonometry of the effects of hormone replacement therapy on bone mass. *Am J Obstet Gynecol* 2000; 182:529-34
368. Heikkinen A-M, Parviainen M, Niskanen L, Komulainen M, Tuppurainen M T, Kröger H, Saarikoski S. Biochemical Bone Markers and Bone Mineral Density during Postmenopausal Hormone Replacement Therapy with and without Vitamin D₃: A Prospective, Controlled, Randomized Study. *J Clin Endocrin Metab* 1997; 82(8):2476-2482

369. Hasling C, Eriksen E F, Melkko J, et al. Effects of a combined estrogen-progestogen regimen on serum levels of carboxy-terminal propeptide of human type 1 procollagen in osteoporosis. *J Bone Miner Res* 1991; 6:1295-1300
370. Seibel M J, Cosman F, Shen V, et al. Urinary hydroxypyridinium crosslinks of collagen as markers of bone resorption and estrogen efficacy in postmenopausal osteoporosis. *J Bone Miner Res* 1993; 8:881-889
371. Cicinelli E, Galantino P, Pepe V, et al. Bone metabolism changes after transdermal estradiol dose reduction during estrogen replacement therapy: a 1-year prospective study. *Maturitas* 1994; 19:133-139
372. Leino A, Järvisalo J, Impivaara O, Kaitsaari M. Ovarian hormone status, lifestyle factors, and markers of bone metabolism in women aged 50 years. *Calcif Tissue Int* 1994; 54:262-267
373. Hall G M, Spector TD, Delmas PD. Markers of bone metabolism in postmenopausal women with rheumatoid arthritis. *Arthritis Rheum* 1995; 38:902-906
374. Akesson K, Ljunghall S, Jonsson B, et al. Assessment of biochemical markers of bone metabolism in relation to occurrence of fracture: a retrospective and prospective population-based study of women. *J Bone Miner Res* 1995; 10:1823-1829
375. Cosman FM, Nieves J, Wilkinson C, Schnering D, Shen V, Lindsay R. Bone density changes and biochemical indices of skeletal turnover. *Calcif Tissue Int* 1996; 58:236-243
376. Cauley JA, Petrini AM, LaPorte RE, et al. The decline of grip strength in the menopause: relationship to physical activity, estrogen use and anthropometric factors. *J Chronic Dis* 1987; 40:115-120
377. Brown BW, Birge SJ, Kohrt WM. Hormone replacement therapy does not augment gains in muscle strength or fat-free mass in response to weight-bearing exercise. *J Gerontol A Biol Sci Med* 1997; 52:B166-170
378. Seeley DG, Cauley JA, Grady D, Browner WS, Nevitt MC, Cummings SR. Is postmenopausal estrogen therapy associated with neuromuscular function or falling in elderly women? *Arch Intern Med* 1995; 155:293-299
379. Tremollieres FA, Pouilles J, Ribot C. Vertebral postmenopausal bone loss is reduced in overweight women: A longitudinal study in 155 early postmenopausal women. *J Clin Endocrinol Metab* 1993; 77:683-686

380. Jacobsen SJ, Cooper C, Gottlieb MS, Goldberg J, Yahnke DP, Melton LJ 3rd. Hospitalization with vertebral fracture among the aged: a national population-based study 1986-1989. *Epidemiology* 1992; 3(6):515-518
381. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. *JAMA* 1995; 18, 273(3):199-208

.....

ACKNOWLEDGEMENTS

I wish to express my sincere appreciation and heartfelt thanks to the following:

1. my promotor, Professor Stephen Hough, for his intellectual input, guidance and inspiration as well as his exceptional and unique research insight;
2. for financial assistance and support I gratefully acknowledge Eli Lilly Women's Health Initiative, Indianapolis and the South African Medical Research Council;
3. the Provincial Administration of the Western Cape for their appreciation of ongoing career development and creating the opportunity for me to complete this dissertation;
4. my colleagues and staff of the Endocrine and Metabolic Unit at Tygerberg Hospital for their friendship and support;
5. Riana Eagar, my dear friend and colleague, for her unconditional help and contribution to this project;
6. my sister Helene for final formatting of my manuscript and her constant interest and appreciation of my academic endeavours;
7. my exceptionally wonderful, loving husband Jacques and children Tonie, Kristie and Henri who not only make my life possible, but joyful and happy - I am blessed to have you;
8. my parents for providing me with an education and encouraging me to always do my best; and
9. to the best grandparents my kids could hope for, Hennie and Babs Conradie, Tonie and Ursula du Toit.... for everything.