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Risk factors for the development of osteoporosis in a South African population

A prospective analysis

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Abstract Despite the vast number of risk factors that apparently predispose to the development of osteoporosis (OP), they have not been accurately identified and given relative priority. In order to analyse possible risk factors prospectively in a local patient population with overt OP (histomorphometrically confirmed and characterised) and compare it with an appropriately matched non-OP control group (with normal bone mass on dual-energy X-ray absorptiometry), a detailed general history, risk factor analysis, dietary history and anthropometric data were obtained from 56 OP and 125 non-OP subjects. In females a positive family history of OP ($P = 0,002$), a fair complexion ($P = 0,009$), lower body mass ($P = 0,02$) and height ($P = 0,03$), no breast-feeding of babies ($P = 0,006$), a history of smoking ($P = 0,001$) and fat distribution around the waist ($P = 0,009$) were identified as risk factors. In males lack of exercise ($P = 0,008$), a history of smoking ($P = 0,01$), lower body mass ($P = 0,04$) and height ($P = 0,04$), a preference for salty food ($P = 0,02$) and fat distribution around the waist ($P = 0,002$) appeared to predispose. Dietary calcium, phosphorus, protein and caffeine intakes were similar in OP and control subjects, but alcohol consumption was clearly higher in both OP males ($P = 0,001$) and females ($P = 0,01$).

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Osteoporosis (OP) and associated fractures are endemic in Western societies, with prevalence rates approximating 50% among elderly white women, a mortality rate of 12 - 25% in patients with hip fractures, and annual costs of some \$7 billion in the USA alone.¹ Although it clearly constitutes a major health problem, the exact incidence and magnitude of the OP syndrome in South Africa is as yet unknown.

Since OP usually becomes manifest at a late stage when the patient has lost more than 50% of his/her skeletal mass, early detection and implementation of prophylactic measures are essential. This is, however, complicated by the fact that bone loss is undetectable by routine radiographs until at least 30 - 40% of the bone mass has been lost. Moreover, the more reliable and accurate methods of measuring bone mass, such as dual-energy X-ray absorptiometry (DEXA), are expensive and not readily available.² Ideally, the identification of historical risk factors of a person's predisposition to develop OP, followed by DEXA examination of those at risk, should be undertaken.

Although a large number of possible risk factors for the development of OP are known, studies to date have generally been unsuccessful in identifying and giving relative priority to those risk factors that are most important in a specific community. Moreover, since OP is a heterogeneous syndrome and not a single disease entity, different risk factors may pertain to different subsets of OP.

This study aimed to analyse possible risk factors prospectively in a local patient population with overt primary OP and to compare it with an appropriately matched non-OP control group.

Subjects and methods

Subjects

All the subjects in the OP group had proven idiopathic ('primary') OP, detected by DEXA as well as clinical examination, a skeletal survey, quantitative histomorphometric examination of undecalcified bone biopsies and a full biochemical work-up. The group consisted of 56 subjects, consecutively admitted to our metabolic

unit, of whom 17 were male and 39 female. The mean age (\pm SD) of the males was 49 ± 15 years and that of the females 61 ± 11 years.

Absence of osteopenia in the control group was confirmed by DEXA. This group consisted of 125 age- and sex-matched subjects of whom 27 were males and 98 females. The mean age of the males was 52 ± 16 years and that of the females 60 ± 10 years. All the subjects were white and resided in the Cape Province.

Methods

A dietary history was obtained from every subject by means of a quantified food frequency questionnaire, covering current and past intakes.³ A detailed general history and a risk factor questionnaire were completed by all the subjects. Anthropometric data were also obtained from every subject and included weight, height, skinfold measurements, mid-upper arm, middle and hip circumferences and elbow breadth determination. The following methods were employed: (i) the subjects were weighed, wearing the minimum of clothes, to the nearest 0,1 kg;⁴ (ii) height was measured with a sliding headpiece to increase the accuracy of the readings, which were taken to the nearest 0,1 cm;⁴ (iii) skinfolds were measured using a Harpenden caliper (all measurements were taken on the right side of the body to the nearest 0,1 mm, as follows: biceps — over the biceps muscle, at the midpoint of the muscle; triceps — over the triceps muscle, midway between the acromial process of the scapula and the olecranon; subscapular — just below the tip of the scapula, at 45° to the vertical; supra-iliac — just above the iliac crest on the mid-axillary line);⁴ (iv) mid-upper arm circumference was measured at the same position as the triceps skinfold;⁴ (v) middle circumference was determined in the erect position, around the waist through a point one-third of the distance between the xiphoid process and the umbilicus;⁵ (vi) hip circumference was assessed in the erect position, around the hips through a point 4 cm below the superior anterior iliac spine;⁵ and (vii) elbow breadth was measured with a sliding caliper to the nearest 0,1 cm, at the point of greatest breadth across the joint.⁶ All the measurements were done by the same researcher in triplicate, and the results averaged.

Investigation of subjects with OP comprised a physical examination; urinalysis; a full blood count; a biochemical profile, including serum calcium, phosphate and alkaline phosphatase (measured with a Technicon SMAC II AutoAnalyzer), C-terminal parathyroid hormone (radio-immunoassay⁷), cortisol (Clinical Assays, RIA Kit), thyroid-stimulating hormone (Serona RIA Kit) and free thyroxine and free tri-iodothyronine (Amersham M, RIA Kit); protein electrophoresis; a radiological skeletal survey; and quantitative histomorphometric examination of undecalcified bone biopsy specimens after time-spaced tetracycline labelling,² to confirm the diagnosis of primary OP and rule out other causes of osteopenia and/or secondary OP.

Axial bone mass was measured by DEXA (Hologic QDR-1000) in all subjects. This included the lumbar spine (L1-L4) and hip (neck, trochanter, intertrochanteric region, Ward's triangle and total). OP was diagnosed if the bone mineral density (BMD) was found to be decreased by more than 1,5 SD in subjects younger than 40 years, or by more than 2,0 SD in those over 40 years of age, compared with the BMD of young normal subjects.⁸

Statistical analysis was performed by means of the Wilcoxon signed-ranks test, the Spearman correlation coefficient and the Cochran-Mantel-Haenszel test to determine odds ratios (ORs) and to obtain 95% confidence intervals (95% CI) for this statistic.⁹

Results and discussion

Table I sets out the BMD values of the lumbar spine and hip regions of the OP and the control groups as performed by DEXA. As expected, the values of the OP men and women were significantly lower than that of the controls throughout.

Dietary data

In all subjects, not a single nutrient (current and past intakes) was consumed in quantities less than the recommended daily allowances (RDA).¹⁰ There was also no significant difference between the intakes of the OP and the control groups.

The mean calcium intake of all the subjects was adequate compared with the RDA and was comparable in the two groups. The average intakes of the men ranged between 810 and 860 mg/d and that of the women between 800 and 815 mg/d. The RDA of calcium for adults is set at 800 mg/d in the USA and the RSA.¹⁰ Lindsay¹¹ and others^{12,13} have shown that lactating or pregnant premenopausal women and postmenopausal women need much more calcium (1 000 - 1 500 mg) to prevent a negative calcium balance. A negative calcium balance greater than 40 mg/d will result in bone loss of 1,5% per year.¹⁴

Although severe calcium deprivation causes OP in animals, and lower fracture rates have been reported in areas of high calcium intake,¹⁵ the role of dietary calcium in the causation of OP in humans is still controversial. Advances have, however, recently been made in unravelling the calcium controversy. It is now accepted that low calcium intake can definitely limit the achievement of genetically programmed peak bone mass,^{16,17} but the role of dietary calcium in later life is less clear. Before the menopause oestrogen-replete women are able to conserve calcium efficiently, and calcium intake at this time exhibits little relationship to bone mass. Menopausal bone loss is mainly due to oestrogen withdrawal and it is now well established that exogenous calcium will not replace endogenous oestrogen in peri- or postmenopausal subjects. It is not surprising that most

TABLE I.
BMD values (g/cm³)(mean \pm SD) for OP and control subjects

Measurements	Men			Women		
	OP	Controls	Significance	OP	Controls	Significance
Spine						
L1-L4	0,72 \pm 0,13	1,15 \pm 0,13	P = 0,0078	0,72 \pm 0,10	1,11 \pm 0,17	P = 0,0001
Hip						
Neck	0,64 \pm 0,12	0,95 \pm 0,08	P = 0,0078	0,60 \pm 0,09	0,88 \pm 0,13	P = 0,0001
Troch.	0,54 \pm 0,08	0,80 \pm 0,06	P = 0,0078	0,50 \pm 0,10	0,76 \pm 0,09	P = 0,0001
Total	0,74 \pm 0,12	1,09 \pm 0,06	P = 0,0078	0,64 \pm 0,20	1,02 \pm 0,13	P = 0,0001
Ward's	0,39 \pm 0,16	0,69 \pm 0,10	P = 0,0078	0,39 \pm 0,11	0,71 \pm 0,17	P = 0,0001

of the negative studies of calcium intake relative to age-related bone loss have in fact been performed during this early menopausal period. Conversely, most of the positive studies on calcium intake and bone loss have concentrated on older postmenopausal women. A definitive large-scale study by Dawson-Hughes *et al.*¹⁸ has demonstrated that calcium supplementation improves bone mass in older women (> 6 years postmenopausal) with a dietary intake under 400 mg/d. Similar results were reported by others.^{19,20} It is also important to note that the absorption and bio-availability of calcium is markedly influenced by other dietary constituents (including phosphorus, protein, sodium, fibre, phytates), calcitropic and sex hormones, lactose intolerance and local factors in the gut.²¹

An increased protein intake results in hypercalcaemia and a negative calcium balance.²¹ The calciuric effect of protein is, however, diminished if the protein source is also high in phosphorus, e.g. meat.²¹ It is therefore difficult to assess whether a high protein intake *per se* should be regarded as a risk factor for OP, since diets containing protein also contain other nutrients, making it impossible to determine the effect of protein alone.¹ In the present study, protein and phosphorus intakes were similar in OP and control subjects, where the men averaged 95 g and 1 500 mg respectively and the women 75 g and 1 250 mg. These values compare favourably with RDA recommendations.¹⁰

Zarkadas *et al.*²² have shown that as little as 3 g sodium chloride results in a significant rise in urinary calcium excretion in postmenopausal women. An increased sodium intake was also shown to increase parathyroid hormone secretion and bone resorption. Although it has been suggested²³ that a significant amount of postmenopausal bone resorption may be sodium-dependent and may respond to dietary salt restriction, further studies are required. In our study, the OP males had a significantly ($P = 0,02$) greater inclination towards salty food than control males, with the chance of an OP male adding extra salt to his food being 4,7 times that of a control male (95% CI: 1,252 - 17,857). No significant difference was found between the women.

Heaney and Recker²⁴ recently reported that a high caffeine intake (especially > 1 g/d) results in a negative calcium balance as a consequence of increased urinary calcium losses.²⁴ Other studies have failed to support these observations.¹ The mean per capita intake of caffeine in the USA is estimated at 200 mg/d, equivalent to approximately 2 cups of coffee per day.²⁵ The mean intake in this study ranged from 360 to 420 mg/d, equivalent to 4 - 5 cups of coffee per day. There was, however, no significant difference between the caffeine intakes of OP and control subjects.

Marked differences were found between the alcohol consumption of both OP males ($P = 0,001$) and OP females ($P = 0,01$) when compared with matched controls in the present study (Fig. 1). Numerous studies have reported that excessive use of alcohol results in bone loss and an increased incidence of fractures.^{26,27} Alcohol has a direct toxic effect on osteoblasts and suppresses bone formation.²⁸ It may also promote bone loss as a consequence of poor nutrition,²⁹ malabsorption,²⁹ liver damage,²⁹ alcohol-induced calcium diuresis,²⁹ reduced physical activity and body weight,³⁰ and/or hypercortisolaemia.³¹ Regular use of alcohol may also increase the fracture rate by predisposing to falls. Kelsey¹ found that the risk for hip fractures doubled if more than 8 tots of alcohol were consumed per week — an amount that was grossly exceeded by both OP men (21 tots) and OP women (12 tots) in the present study.

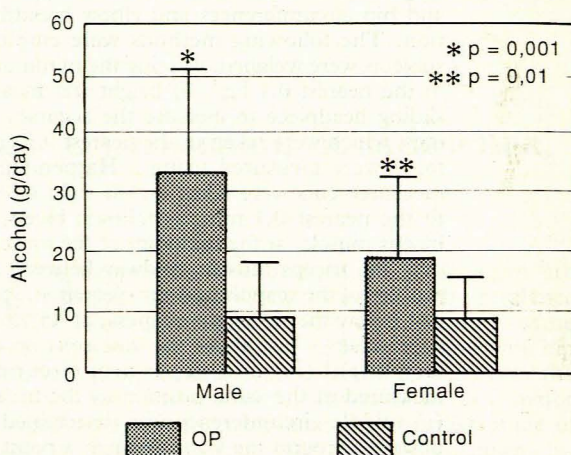


FIG. 1. Alcohol intake of OP v. control subjects.

Anthropometric data

Short individuals are at risk (less total bone) and thin subjects, including those with a low skinfold thickness, are at even greater risk of developing OP fractures — observations that have been ascribed to decreased peripheral conversion of circulating androgens to oestrogens by adipose tissue and to less mechanical loading.^{30,28} Table II depicts all the anthropometric data of the subjects. The OP men and women were significantly ($P = 0,04$) shorter and of a lower body mass than controls. The OP group also had significantly lower elbow breadth values (an indicator of frame size) than the con-

TABLE II. Anthropometric data (mean \pm SD) for OP and control subjects

Measurements	Men			Women		
	OP	Controls	Significance	OP	Controls	Significance
Body mass (kg)	70 \pm 12	77 \pm 12	$P = 0,04$	64 \pm 12	69 \pm 12	$P = 0,02$
Height (cm)	1,71 \pm 0,07	1,77 \pm 0,08	$P = 0,04$	1,62 \pm 0,06	1,64 \pm 0,07	$P = 0,03$
Elbow breadth (cm)	7,1 \pm 0,3	7,4 \pm 0,4	$P = 0,007$	6,4 \pm 0,8	6,7 \pm 0,4	$P = 0,03$
Biceps (mm)	5,6 \pm 2,9	6,5 \pm 2,5	$P = 0,10$	12,0 \pm 5,7	12,6 \pm 5,9	$P = 0,69$
Triceps (mm)	10,7 \pm 5,3	13,2 \pm 2,9	$P = 0,01$	20,0 \pm 6,4	23,4 \pm 6,3	$P = 0,01$
Subscapular (mm)	12,3 \pm 4,6	16,4 \pm 6,4	$P = 0,03$	16,3 \pm 6,7	16,8 \pm 7,1	$P = 0,96$
Supra-iliac (mm)	13,1 \pm 5,5	16,6 \pm 5,3	$P = 0,07$	18,2 \pm 8,5	19,9 \pm 9,0	$P = 0,52$
Mid-upper arm circumf. (cm)	29,2 \pm 2,0	31,4 \pm 3,0	$P = 0,008$	29,0 \pm 4,3	31,1 \pm 3,6	$P = 0,0005$
Middle circumf. (cm)	85,6 \pm 12,2	90,9 \pm 9,6	$P = 0,18$	84,9 \pm 15,3	83,9 \pm 10,7	$P = 0,91$
Hip circumf. (cm)	89,3 \pm 12,3	100,9 \pm 6,5	$P = 0,001$	97,9 \pm 13,4	103,9 \pm 10,3	$P = 0,01$
WHR	0,96 \pm 0,06	0,89 \pm 0,06	$P = 0,002$	0,87 \pm 0,11	0,81 \pm 0,05	$P = 0,0009$

WHR = waist-to-hip ratio.

trols, although mean values for both groups fell in the range of medium frame size. The OP group had significantly lower skinfold and circumference values for most of the measurements, although the majority of subjects in both groups fell within the 15 - 85th percentile.

An increased risk for the development of chronic degenerative diseases such as atherosclerosis, hypertension and diabetes mellitus is indicated if the waist-to-hip ratio exceeds 1,0 in men and 0,8 in women.³² Despite their lower body mass, both the OP women ($P = 0,009$) and the OP men ($P = 0,002$) had significantly higher waist-to-hip ratios than corresponding controls (Table II). The odds that an OP man had a middle fat distribution was 8 times higher than the odds for a control man (95% CI: 1,037 - 61,731), whereas the odds for OP women were 1,6 times higher (95% CI: 0,751 - 3,538). In women, upper body segment obesity is associated with decreased sex hormone binding globulin levels, an increase in the percentage of free testosterone and a decrease in oestrogen.³³ Conversely, elevated levels of oestrone and both free and total oestradiol, and subnormal levels of free testosterone and lutenising hormone, which in combination represent a state of mild hypogonadotropic hypogonadism, have been described in obese men.³⁴ Whatever the underlying pathogenesis, this novel finding suggests that OP should now be added to the list of chronic degenerative diseases associated with a middle fat distribution.

Risk factor analysis

The development of skeletal failure and OP fractures depend on both peak adult bone mass and rate of bone loss. *Genetic factors* are thought to have a strong influence on the attainment of peak bone mass.² An interesting finding in our study was that the OP women had a 4,3 times greater chance (95% CI: 1,729 - 10,920) of having a positive family history of OP than the control women ($P = 0,02$). No such difference was noted in males, suggesting that the genetic predisposition to develop OP was sex (females)-linked. A *fair complexion*, assessed on the basis of hair/eye colour, was also found to be a risk factor in women ($P = 0,009$), with an OR of 3 in favour of the OP women (95% CI: 1,314 - 6,879).

Exercise against gravitation stimulates new bone formation and decreases the rate of bone loss.³⁵ A direct effect of muscle-pull on bone,³⁵ as well as higher circulating levels of calcitonin, have been proposed to explain this finding.³⁶ This study revealed that OP men had a significantly ($P = 0,008$) greater chance of not currently participating in exercise than control men. No difference was found between the women.

It is well known that women who experience a *premature menopause* are at risk, but the roles of *parity*, age at *menarche* and *breast-feeding* as risk factors are poorly defined.³⁰ No difference was found between the two groups of women regarding the number of pregnancies or age at menopause (44,2 years for OP women and 45,5 years for control women ($P = 0,387$)). Thirteen per cent of the OP women and 11% of the control women had not reached the menopause. These differences were not statistically significant. However, whereas 47% of OP women did not breast-feed and only 13% breast-fed for more than 3 months, 42% of control women breast-fed for more than 3 months and a mere 9% never breast-fed at all. The OR that an OP woman did not breast-feed her baby was 4 times higher (95% CI: 1,545 - 12,581) than that for a control woman ($P = 0,006$). It was previously believed that lactation resulted in a severe negative calcium balance ('drainage effect') and bone loss.³⁰ More recent data suggest that long-term lactation may in fact protect against bone loss because lactation stimulates bone remodelling.³⁷ Our data would support this hypothesis.

Women who *smoke* have lower serum oestrogen levels, a lower body mass, undergo menopause at an earlier age, and generally have a lower bone mass than women who do not smoke.² All subjects in our study decreased their smoking habits over the preceding 10 years. Significantly more OP men than control men were current smokers ($P = 0,01$; OR 5,75; 95% CI: 1,425 - 32,256), while OP women with a previous smoking history also outnumbered control women ($P = 0,001$; OR 5,38; 95% CI: 2,481 - 11,627).

Conclusion

Since OP usually becomes manifest at a late stage, early identification of those at risk is essential if rational prevention regimens are to be implemented successfully. Mass screening of BMD is expensive, impractical and not recommended by leaders in the field, including the National Osteoporosis Foundation of the USA.⁸ Although it is generally stated that the predictive value of a risk factor analysis for OP is limited and in the order of 40 - 60%,⁸ we believe that this can be improved upon as newer data become available (the calcium controversy is a case in point), and if this information is applied in the evaluation of specific patient populations. The present study attempted to identify risk factors for the development of OP in such a local population, and these are summarised in Table III. Clearly the study group was too small to give relative priority to these risk factors or to assess ORs for various combinations of risk factors. Moreover, given the clinical, biochemical and histological heterogeneity of the OP syndrome,² it is to be expected that risk factors at different ages, in different ethnic groups and for different types of OP (spine v. hip; high- v. low-turnover OP) could differ markedly. Further studies are required if a scientific and cost-effective approach to the effective management of OP is to be realised.

TABLE III.
Risk factors for the development of OP

Females	
Family history of OP	
Fair complexion	
No breast-feeding	
Males	
Lack of exercise	
Preference for salty food	
Both sexes	
Lower body weight	
Lower height	
Smoking history	
High alcohol intake	
Fat distribution around the waist	

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Guidelines for the management of asthma in adults in South Africa

Part II. Acute asthma

STATEMENT BY A WORKING GROUP OF THE SOUTH AFRICAN PULMONOLOGY SOCIETY

The morbidity and mortality caused by asthma can be attributed to three factors: underassessment of severity, failure on the part of both patients and their medical attendants to initiate treatment promptly, and undertreatment of exacerbations. Moreover, most exacerbations can be prevented by use of appropriate long-term treatment (*S Afr Med J* 1992; **81**: 319-322). The present guidelines are for the care of acute asthma ('asthma attacks') and are intended to encourage a uniform approach to the management of exacerbations, whether of rapid or gradual onset, mild or severe. They have been developed on the basis of the best available evidence on the efficacy and safety of asthma drugs, and efforts have been made to ensure that recommendations are cost-effective and affordable, and may with little modification be applied in all locations: the home (as initial self-management), the clinic with modest facilities, doctors' surgeries, emergency departments and hospitals. The guidelines stress (i) assessment of severity; (ii) recognition of risk; and (iii) stepwise treatment based upon these assessments. Primary therapies are the repeated use of high doses of β_2 -agonists and early introduction of corticosteroids.

Specific goals of treatment are to: (i) relieve airway obstruction; (ii) relieve hypoxaemia; (iii) restore lung function to normal as rapidly as possible by reducing airway irritability; (iv) provide a suitable plan to avoid future relapse; and (v) provide a written plan of action to be followed early in future attacks.

Simplified management schemes for different locations are provided as addenda for ease of reference.

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Definition and general comment

Acute asthma (the 'acute asthma attack') is usually an exacerbation of chronic asthma, and is characterised by worsening shortness of breath, cough, wheeze and chest tightness, or combinations of these symptoms, often with apparent non-responsiveness to usual bronchodilator treatment. It may range from mild to life-threatening and is always associated with a fall in expiratory airflow measured as peak expiratory flow (PEF) rate or forced expiratory volume in 1 second (FEV₁). The latter serve as more reliable indicators of severity of airflow obstruction than the severity of symptoms.