

**ABNORMALITIES OF BONE AND MINERAL METABOLISM IN PATIENTS
WITH EATING DISORDERS**

By

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**Thesis presented in partial fulfilment of the requirements for the degree of
Master of Science in Medical Sciences (Medical Physiology)
at the University of Stellenbosch.**

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Declaration

I the undersigned hereby declare that the work contained in this thesis is my own original work and has not previously, in its entirety or in part, been submitted at any university for a degree.

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Date: _____

Abstract

Osteopenia is a well documented complication of anorexia nervosa (AN). The pathogenesis of this bone loss is presently poorly defined in the literature. Pathogenetic mechanisms that have been implicated include certain nutritional factors, exercise abuse, hypogonadism, hypercortisolism and/or vitamin D deficiency.

We studied, 59 Caucasian eating disorder patients aged 15-45yr. The eating disorder was classified by a single, qualified psychiatrist according to DSM IV R criteria as either anorexia nervosa (AN: n =25), bulimia nervosa (BN: n = 17) or eating disorder not otherwise specified (EDNOS: n = 17). All patients were subjected to a detailed dietary and general history. We assessed the prevalence and severity (DEXA), the nature (osteocalcin, deoxypyridinoline) and site (vertebral versus hip) of osteopenia in these patients. The role of nutritional factors (energy intake, weight, height, BMI, plasma albumin, lipids), physical activity, hypercortisolemia (plasma and urinary free cortisol), vitamin D deficiency (plasma 25OHD) and hypogonadism (amenorrhoea, E₂, LH, FSH) in the pathogenesis of bone loss were also evaluated.

Mild osteopenia (BMD decreased by more than 1SD below age-matched controls) was documented in 46% of the total study population, with more marked osteopenia (Z-Score < -2 SD) present in 15%. Both vertebral and hip osteopenia were documented. In the study population those patients with AN (Lumbar BMD (g/cm²) = 0.869 ± 0.121) were most likely to develop osteoporosis, although a significant percentage of patients with BN (Lumbar BMD (g/cm²) = 0.975 ± 0.16) and EDNOS (Lumbar BMD (g/cm²) = 0.936 ± 0.10) were also osteopenic (29% and 35% respectively). Twenty four percent (24%) of the total patient population had a history of fragility fractures. These fractures were reported more commonly amongst patients with AN and EDNOS (28% and

29.4%). Fracture prevalence was however similar in patients with normal and low bone mass.

Conventional risk factors were similar in patients with normal and low bone mass, except for a significantly longer duration of amenorrhoea ($p = 0.009$), a lower BMI ($p = 0.0001$) and greater alcohol consumption ($p = 0.05$) in the osteopenic patients. Nutritional parameters (S-albumin, protein, Ca, and PO_4 intakes), physical activity, as well as 25(OH) vitamin D levels were similar in AN and BN subjects, as well as in patients with a low versus normal BMD. Plasma and urine cortisol levels were also similar in these subgroups.

With the exception of two patients with borderline osteopenia, significant bone loss was only documented in those patients with a past or current history of amenorrhoea. In the total patient population the duration of amenorrhoea was significantly ($p < 0.009$) longer in patients with osteopenia versus those with a normal bone mass. A significant negative correlation between BMD (Z-Score) and duration of amenorrhoea was also documented in the total patient population ($r = -0.4$, $p = 0.001$) as well as in all three eating disorder groups (AN $r = -0.4$, $p = 0.03$; BN $r = -0.6$, $p = 0.008$; EDNOS $r = -0.6$, $p = 0.005$).

In the total patient population, those patients with amenorrhoea, had lower BMD and BMI values and lower estrogen levels compared to those with a normal menstrual cycle.

We conclude that osteopenia commonly attends AN, as well as BN and EDNOS. Nutritional (with the exception of alcohol consumption) and mechanical factors as well as hypercortisolemia did not appear to contribute significantly to bone loss in this study population. Hypogonadism appeared to be the main cause of the bone loss observed in these patients.

Abstrak

Osteopenie is 'n welbekende komplikasie van anorexia nervosa (AN). Die patogene van hierdie beenverlies is swak in die huidige literatuur omskryf en nutriele faktore, 'n vitamien D gebrek, oormatige oefening, hiperkortisolemie en hipogonadisme word onder andere geïmpliseer.

Vir die doel van die studie is 'n totaal van 59 Kaukasier eetsteurnis pasiënte volledig ondersoek. Die tipe eetsteurnis is deur 'n enkel gekwalifiseerde psigiater volgens die DSM IV R kriteria geklassifiseer as anorexia nervosa (AN: n = 25) of bulimia nervosa (BN: n = 17) of eetsteurnis nie anders gespesifiseer (EDNOS: n = 17). Elke pasiënt is ook aan 'n gedetailleerde dieet en algemene risikofaktor vraelys vir osteoporose onderwerp. Die voorkoms en graad (DEXA), die aard (osteokalsien, deoksipiridinolien) asook die tipe (werwelkolom/heup) osteopenie is ondersoek. Die rol van nutriele faktore (totale kalorie-inname, gewig, lense LMI, plasma albumien, lipiede) en vitamien D gebrek, oefening, hiperkortisolemie (plasma en urinêre kortisol) en hipogonadisme (amenoree, plasma E2, LH,FSH) in die patogene van die beenverlies is ook evalueer.

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Pasiënte met 'n lae beenmassa was gekenmerk deur 'n betekenisvolle laer LMI ($p = 0.0001$), hoër alkoholverbruik ($p = 0.05$) en langer duurt van amenoree

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Betekenisvolle beenverlies (met die uitsondering van twee pasiënte met grenslyn osteopenie) het slegs voorgekom in pasiënte met 'n huidige of 'n vorige geskiedenis van amenoree. In die totale pasiëntpopulasie was die duurte van amenoree ($p < 0.009$) betekenisvol langer in die pasiënte met osteopenie. 'n Betekenisvolle negatiewe korrelasie tussen BMD (Z-Telling) en die duurte van amenoree in die toale pasiënt populasie ($r = -0.4$; $p = 0.001$) asook in al drie eetsteurnis groepe (AN: $r = -0.4$; $p = 0.03$; BN: $r = -0.06$; $p = 0.008$; EDNOS: $r = -0.6$, $p = 0.005$) is aangetoon. In die groep as 'n geheel, het die amenoree pasiënte 'n laer LMI, E_2 vlakke en BMD gehad in vergelyking met die pasiënte met normale menses.

Opsommend dus, kom osteopenie algemeen in pasiënte met AN, asook BN en EDNOS voor. 'n Betekenisvolle bydrae van nutrisieële (met die uitsondering van alkoholiname) en meganiese faktore asook hiperkortisolemie tot been verlies, kon nie in hierdie studie populasie gedemonstreer word nie. Hipogonadisme is as die hooforsaak van osteopenie in dié pasiënte geïdentifiseer.

Vir MA

**om baie dankie te sê vir jou onvoorwaardelike liefde, aanmoediging en
ondersteuning oor al die jare.**

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LIST OF ABBREVIATIONS

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AN	anorexia nervosa
BMD	bone mineral density
BMI	body mass index
BN	bulimia nervosa
Cr	creatinine
DEXA	dual energy X-ray absorptiometry
DPD	deoxypyridinoline
E ₂	estrogen
EDNOS	eating disorder not otherwise specified
FSH	follicle stimulating hormone
GH	growth hormone
IGF 1	insulin-like growth factor 1
IRMA	immunoradiometric assay
LH	luteinizing hormone
NIH	National Institute of Health
PTH	parathyroid hormone
RDA	recommended daily allowance
SHBG	sex hormone binding globulin
T ₄	thyroxine
TRP%	tubular reabsorption of phosphate (%)
T-Score	bone mineral density compared to the young reference mean
TSH	thyroid stimulating hormone
Z-Score	bone mineral density compared to age and sex matched controls

ADDENDA

- I. Risikofaktor Vraelys
- II. Risk Factor Questionnaire
- III. Dieet Inligting
- IV. Diet Information

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ADDENDA

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- II. Risk Factor Questionnaire
- III. Dieet Inligting
- IV. Diet Information

CHAPTER 1

RESEARCH OBJECTIVES

The eating disorder, Anorexia Nervosa (AN) predisposes to low bone mineral density, with osteopenia occurring in up to 50% of affected patients. This association between AN and osteopenia was first reported in the literature in the early 1980^s (*Rigotti et al, 1984*) and consistently confirmed in follow up studies (*Brotmen and Stern, 1985; Rigotti et al, 1991; Salisbury and Mitchell, 1991; Hay et al, 1992*). A higher fracture risk has also been documented in this condition. (*Verbruggen et. al, 1993; Kaplan et al, 1986*). Data regarding the association between bone mass status and other eating disorders i.e. Bulimia Nervosa (BN) and Eating Disorder Not Otherwise Specified (EDNOS) are limited and conflicting.

The pathogenesis of bone loss in eating disorder patients remains incompletely understood and appears to be complex. Mechanisms implicated in this disease process include nutritional factors, exercise abuse, associated hypogonadism and more recently, chronic stress and hypercortisolemia.

This comparative study amongst the three eating disorder groups (i.e. AN, BN, EDNOS) specifically aimed to:

1. Determine the - prevalence,
 - biochemical nature (i.e. low versus high turnover) and
 - clinical type (i.e. vertebral versus hip)of osteopenia in the study populations.
2. Compare the presence of clinical risk factors previously shown to predispose Caucasian women to osteoporosis.
 - In the three different eating disorder groups and
 - in subgroups with a normal and low bone mineral density (BMD).
3. Gain insight into the pathogenesis of osteopenia in this study population, specifically with regard to:

- Nutritional factors
- Mechanical factors including physical exercise
- Hypogonadism
- Hypercortisolemia

CHAPTER 2

GENERAL BACKGROUND

A. OSTEOPOROSIS

1. Introduction

Osteoporosis is a progressive systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture (*Kanis et al, 1997*). It is a major health problem through its association with fractures, which typically occur at the hip, vertebra and wrist.

2. Epidemiology

Uncomplicated osteoporosis does not cause symptoms. Patients with osteoporosis do not seek medical aid until complications occur, generally a fracture, loss of height or back pain. Osteoporosis occurs in all population groups although it is more common in Caucasoids. Recent evidence indicates that the incidence of osteoporosis is increasing. This disease affects more than one-third of Caucasian women over age 50 and nearly half of all individuals over age 70 (*Kanis, 1994*).

The prevalence of osteoporosis of the femoral neck increases from 5.1% at 50-54 years, to over 60% at age 85 or more. Spinal osteoporosis is 6 times and hip fractures 2-3 times more common in women than in men (*Hiller and Cooper, 1997*). Osteoporotic fractures of the spine and the forearm are associated with significant morbidity, but the most serious consequences arise in patients with hip fractures, which is associated with a significant increase in mortality (15-20%), particularly in the elderly (*Kanis et al, 1997*).

3. Pathogenesis of osteoporosis

3.1. Bone composition and structure

Bone is a metabolically active living tissue, which is continually formed and resorbed by bone cells. Activity of these bone cells is modified by many factors, including normal growth, the external environment as well as endocrine- and nutritional factors, physical activity and local growth factors. Two types of bone are found in the body, namely cortical and trabecular bone. Cortical bone predominates in the shafts of the long bones and trabecular bone is concentrated in the vertebrae, in the pelvis and other flat bones and in the ends of long bones. Trabecular bone, with its greater surface area, is metabolically much more active than cortical bone and therefore more responsive to changes in mineral homeostasis (*Riggs and Melton, 1986*).

3.2. Bone remodeling (Figure 1)

Bone formation and bone resorption do not occur randomly throughout the skeleton. Rather, they follow a programmed sequence at discrete foci called bone-remodeling units. Remodeling is the process of bone resorption followed by bone formation and provides a mechanism for self-repair and adaptation to stress. Activation is the process by which the quiescent bone surface is prepared for resorption. Osteoclasts appear on a previously inactive surface and, over a period of about two weeks construct a tunnel in cortical bone or a lacuna on the surface of trabecular bone. The osteoclasts are replaced by osteoblasts, which fill in the resorption cavity with

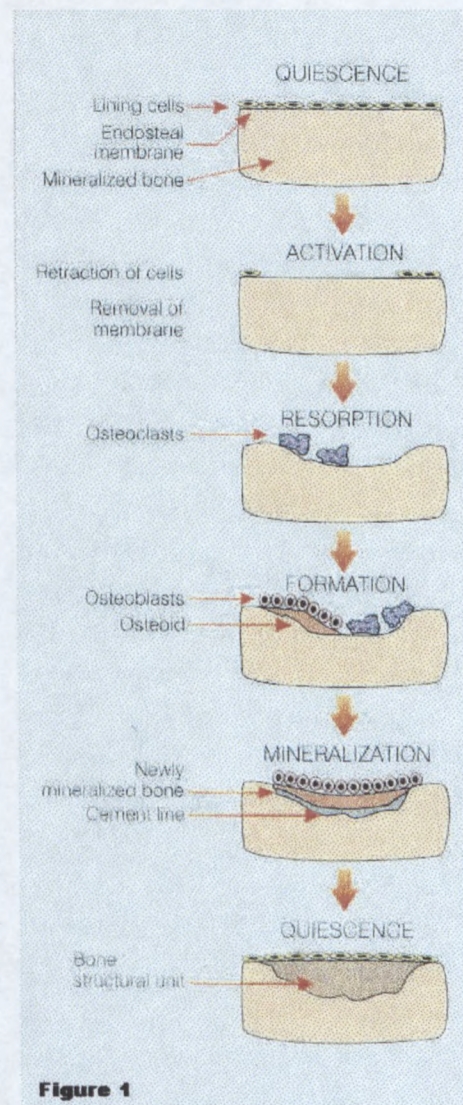


Figure 1

Diagram to illustrate the process of bone remodeling
Adapted from: Compston, 1997

immature unmineralised bone over a period of three to four months. The latter is subsequently mineralised to create a new structural unit of bone. The rate of one turnover cycle is determined mainly by the frequency of activation of new bone-remodeling units. In normal young adults, the resorption and formation phases are tightly coupled and bone mass is maintained. This is accomplished by a variety of chemical factors (e.g. hormones, minerals) as well as physical influences (e.g. exercise) which affect the activity of the bone cells.

3.3. Life time changes in bone mass

Bones grow in size during the first two decades of life, with a spurt during adolescence. This is followed by a period of consolidation. Peak adult bone mass is reached at about the age of 30 years for cortical bone and a little earlier for trabecular bone. After age 35, bone resorption exceeds bone formation, resulting in a progressive decline in bone mass (age-related bone loss) (*Riggs and Melton, 1986*).

3.4. Pathophysiology of bone loss

Bone loss implies an uncoupling of the phases of bone remodeling, with a relative or absolute increase in resorption and /or inadequate formation. There are two basic mechanisms of bone loss, namely increased activation frequency and remodelling imbalance. Increased activation frequency implies an increase in the number of remodelling units on the bone surface. This leads to increased resorption and bone turnover. Remodelling imbalance occurs within the remodelling units and implies an imbalance between formation and resorption, favouring the latter.

Menopausal bone loss in women is associated with both increased activation frequency and remodelling imbalance. Age related bone loss in males and females however, are the result of remodelling imbalance only.

4. Risk factors for the development of osteoporosis

The most important clinical endpoint of osteoporosis is a bony fracture. A combination of skeletal fragility and the risk of sustaining a fall determine the risk of fracture. Differences in bone mineral density (BMD) account for 60-90% of the variation in bone fragility and are the most commonly used method of assessing a subject's risk of fracture (*Arden, 1997*). An individual's bone mass is a function of peak bone mass attained and subsequent losses. Osteoporosis may arise from abnormalities at all stages of skeletal life and it is therefore more useful to consider osteoporosis as a multifactorial disease, largely determined by genetic, life-style and ageing factors as well as a variety of medical diseases.

4.1. Genetic factors

A number of studies suggest that peak bone mass and to a lesser extent involutional bone loss are genetically determined. Recent studies suggest that, in some countries, approximately 50% of the apparent heritability may be associated with polymorphisms in the genes coding for the vitamin D receptor, the estrogen receptor, growth factors, or collagen (*Arden, 1997*).

Body mass is an important determinant of peak bone mass. It is also an essential factor in the development and maintenance of BMD at all ages. Although it is obvious that large people have larger bones, body weight is a more important factor than stature per se. Excessive leanness ($BMI < 19\text{kg/m}^2$) is undoubtedly an important risk factor for the development of osteoporosis (*Kanis et al, 1997*).

4.2. Life-style

4.2.1. Reproductive history

Estrogen is an important anti-resorptive agent. All causes of hypogonadism, including the natural menopause, cause loss of skeletal mass. Examples of reversible premature gonadal dysfunction include anorexia nervosa, exercise

induced gonadal failure and pituitary tumours including prolactinomas. The natural menopause is by far the most common cause of hypogonadal osteoporosis. Accelerated postmenopausal bone loss puts women at substantially higher risk of osteoporotic fractures than men. An early menopause (<age 45 years) increases this risk.

4.2.2. Smoking

Cigarette smoking has an adverse influence on bone mineral density. Several mechanisms have been described whereby smoking may reduce BMD. These include lower body mass and reduced circulating estrogen levels in females (*Aden, 1997*).

4.2.3. Alcohol

Alcohol abuse appears to be a significant risk factor for osteoporosis. The association between moderate alcohol consumption and bone density is less clear. A direct toxic effect of alcohol on bone has been described, resulting in reduced rates of bone formation. A high intake of alcohol is also associated with marked dietary disturbances such as protein undernutrition, liver disease, hypogonadism and other changes in lifestyle such as smoking and a lack of exercise (*Bikle, 1993*). Alcohol abuse further increases fracture risk by enhancing the propensity to a fall. Premenopausal women and men appear to be at particular risk, while postmenopausal females with moderate alcohol consumption may in fact have a decreased risk of fracture (*Bikle, 1993; Arden, 1997*).

4.2.4. Physical activity

Physical activity may be beneficial or harmful to bone. Exercise, especially if weight bearing, has been shown to stimulate bone formation whereas excessive exercise adversely influences bone health. Physical loading of bone is essential for the normal growth and development of the skeleton and is very important to ensure attainment of optimal peak bone mass. Bone responds rapidly to any

loss of physical loading (e.g. weightlessness in space, immobilisation). The type of activity may also be significant (weight bearing i.e. running, non-weight bearing i.e. swimming). Ordinary daily activity and moderate exercise may have little or no effect on BMD in healthy young women (*Kanis, 1994*).

4.2.5. Nutrition

Undernutrition has many causes such as poverty, famine, ignorance, anorexia and depression. An adequate calcium intake is required to attain genetically determined peak bone mass and to maintain this (*Kanis et al, 1997*). Adequate calcium nutrition is especially important in the elderly - when accompanied by vitamin D deficiency, secondary hyperparathyroidism or even frank osteomalacia may occur. Protein-calorie malnutrition leads to weak muscles and poor co-ordination and to loss of soft tissue padding over the hips. High protein diets have been associated with adverse effects on calcium metabolism, including hypercalcuria (*Younghee and Linkswiler, 1979; Arden, 1997*). High intakes of caffeine-containing drinks are also associated with an increased urinary calcium excretion (*Arden, 1997*). Other dietary constituents may be important and are currently under investigation. These include fibre, vitamin K, vitamin C, magnesium and various trace elements.

4.3. Ageing

Ageing is associated with progressive osteoblast incompetence, hypogonadism, a negative calcium balance and secondary hyperparathyroidism as well as an increased propensity to falling.

4.4. Diseases and drugs associated with osteoporosis

There are a large number of underlying conditions known to cause osteoporosis. Secondary causes of osteoporosis may be found in up to 30% of women and 54% of men with symptomatic vertebral crush fractures (*Anderson and Francis, 1997*). The most frequently encountered secondary causes of osteoporosis are

steroid therapy, myeloma, skeletal metastases and endocrine disorders like hypogonadism and hyperthyroidism (Table 1).

Table 1: Causes of Secondary Osteoporosis

Causes of Secondary Osteoporosis	
<u>Endocrine</u> Male hypogonadism Hyperthyroidism Hyperparathyroidism Hypercortisolism Diabetes (Type 1)	<u>Amenorrhoea</u> Amenorrhoeic athletes Eating disorders (Anorexia Nervosa) Hyperprolactinemia
<u>Drugs</u> Corticosteroids Excessive thyroid replacement therapy Anticonvulsants Chemotherapy Chronic phosphate binding antacids Aluminium	Immunosuppressive therapy Heparin Gonadotropin-releasing hormone agonists/antagonists Tamoxifen (premenopausal use) Long-term lithium therapy Prolonged parenteral nutrition
Neoplastic disease Multiple myeloma Skeletal metastases	
<u>Other conditions</u> Transplantation Gastric surgery Celiac disease Inflammatory Bone Disease Alcoholism Pregnancy	Rheumatoid arthritis Immobilization Osteogenesis imperfecta Homocystinuria Systemic mastocytosis



5. Diagnosis of osteoporosis

5.1. Definitions of osteoporosis

Osteoporosis is a systemic skeletal disease characterised by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture (*Hiller and Cooper, 1997; Kanis et al, 1997*). Given the fact that a low bone mass (bone mineral density, BMD) constitutes the most important risk factor for fracture, the World Health Organisation (WHO, 1994) has recently defined osteoporosis as follows:

Table 2: World Health Organization classification of osteoporosis.

World Health Organization Classification of Osteoporosis	
Definition	Criteria
Normal	BMC or BMD value within 1 SD of 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 (WHO) Study Group, 1994

5.1.1 Limitations of current definitions of Osteoporosis

While the WHO classification of osteoporosis has provided a practical basis to identify postmenopausal Caucasian women at risk of sustaining a fracture, it has limitations. The WHO criteria are exclusively based on data obtained for

Caucasian, postmenopausal women, employing dual energy X-ray absorptiometry (DEXA) of the axial (hip, spine) skeleton. Extrapolation of these criteria to other populations (ethnic groups, young individuals, males) assessed with different techniques, at different sites, is not acceptable. For this reason, most studies (*Carmichael and Carmichael, 1995; Grinspoon et al, 1996a; Ward et al, 1997; Gordon et al, 1999; Soyka et al, 1999; Treasure and Serpell, 1999*) assessing osteopenia/osteoporosis in young eating disorder subjects, many of whom have not reached a peak BMD, have employed age-matched, control BMD values (so called Z-scores).

5.2. Bone Mass Measurement

A number of techniques, able to measure BMD accurately and precisely, are available to diagnose osteoporosis.

Dual-Energy X-ray Absorptiometry (DEXA) is presently regarded as the gold standard for assessing bone mineral density. This method determines areal bone density (g/cm^2) of the spine, hip, wrist and total body. Bone mineral density measurements can thus be used to confirm a diagnosis of osteoporosis, to assess the risk of fracture, to guide the choice of treatment and to follow the response to specific therapy.

Other bone density techniques include *single photon absorptiometry* (SPA, *quantitative computed tomography* (QCT) and bone ultrasound. SPA, measures bone mass of the wrist and forearm. This is useful to predict fracture risk of the specific site measured, but does not always provide accurate information about bone density at other skeletal sites. QCT, accurately measures spinal bone mass. This technique is expensive, the radiation dose is higher and measurements are less reproducible compared to DEXA. Calcaneal Ultra Sound measures appendicular bone mass and possible bone quality. The technique provide useful information of fracture risk, but there is concern with regard to precision and accuracy and its role in the routine evaluation of osteopenic patients remains unsure.

Conventional radiography (X-rays) cannot be used to assess fracture risk, since bone loss is only apparent when the BMD has decreased by about 30-50%. X-rays are however essential to confirm the diagnosis of a fracture.

5.3. Bone turnover

5.3.1. Biochemical assessment

Biochemical evaluation of bone metabolism plays an important role, both in the prevention and treatment of osteoporosis. An increase in bone turnover significantly contributes to fracture risk independent of the BMD.

Specific biochemical markers have been developed to assess both bone formation and resorption. The most commonly used markers of bone formation are bone alkaline phosphatase, osteocalcin and carboxy-terminal propeptide of type I procollagen (*Kanis et al, 1997; Swaminathan, 1997*). The sensitivity and specificity of alkaline phosphatase are limited because the bone isoforms comprise only about 40% of the total activity (*Swanimathan, 1997*). The sensitive and specific collagen crosslink molecules and telopeptides of collagen I (the pyridinolines) measured in urine, and recently also in plasma, are used to assess bone resorption (*Kanis et al, 1997; Swaminathan, 1997*).

These biochemical indices provide a non-invasive and sensitive method to determine bone turnover and to further define an individual's fracture risk although they cannot be employed to confirm a diagnosis of osteoporosis.

5.3.2. Histological assessment

Static and dynamic parameters of bone turnover can be obtained via histological evaluation of time-spaced tetracycline labelled iliac crest bone biopsies (*Compston, 1997*). This is however, an invasive procedure and not routinely used to assess patients with osteoporosis. It remains the only method to diagnose mineralization defects (osteomalacia) in patients with osteopenia.

6. Management of Osteoporosis

Specific medical therapies are currently available to prevent and treat osteoporosis. Apart from specific pharmacologic therapy, it is also important to minimize modifiable risk factors by establishing a healthy lifestyle.

6.1. Life style modification

Life style adaptations to be recommended include:

- Balanced diet, rich in calcium
- Regular exercise, preferably weight-bearing
- Stop smoking
- Decrease alcohol intake

In the elderly with an increased tendency to fall, measures to prevent falling are also very important. External protection of the hip employing hip pads has been shown to significantly reduce hip fracture risk in the elderly (Nevitt and Cummings, 1993)

6.2. Pharmacologic Treatment

Drugs used to treat osteoporosis can be broadly grouped into those that decrease bone resorption and those that increase bone formation.

Anti-resorptive drugs act by decreasing the imbalance between bone resorption and formation, largely decreasing the overall rate of bone turnover. Anti-resorptive drugs include: calcium and vitamin D supplements, hormone replacement therapy, bisphosphonates and calcitonin (*Riggs and Melton, 1992; Kanis et al, 1997*).

Bone formation agents increase both the rate at which new bone-remodelling units are activated and the activity of individual osteoblasts. These agents have a greater potential to increase bone mass above the fracture threshold and are theoretically of greater importance in patients with severe bone loss. Formation-

stimulating drugs presently in use include sodium fluoride and anabolic steroids
(*Riggs and Melton, 1992*).

B. EATING DISORDERS

1. Introduction

The eating behaviour of individuals and even populations varies enormously. If an individual's eating pattern results in self-starvation or includes bingeing and vomiting, thereby compromising their physical and mental health as well as their quality of life, it may be indicative of an eating disorder. Another essential feature of all eating disorders is the relentless pursuit of thinness accompanied by intense, pathological fear of gaining weight. It is important to recognise that these disorders are associated with considerable morbidity, affecting almost every system in the body and that they may prove to be fatal. The death rate, apart from suicide, has been reported as 9% (*Fonseca, 1993; Becker et al, 1999*) and these disorders are therefore of great public health concern.

2. Epidemiology

The prevalence of eating disorders varies greatly among different population groups. In South Africa these disorders occur primarily in the white middle class population. It is rare in the coloured population and extremely rare in the black population, most likely due to different socio-cultural forces (*Ziervogel, 1990*). This seems to be changing due to influences of westernisation (*Gard and Freeman, 1996*). The demographic features of anorexia and bulimia suggest that the cultural value placed on thinness in the Western society plays a central role in the development of these disorders (*Herzog and Copeland, 1985*). It occurs 10 to 20 times more often in females than in males (*Hoek, 1995*).

3. Etiology

The etiology of eating disorders is considered to be multifactorial. It is generally acknowledged that a combination of biological, psychological and social factors contribute to the development of eating disorders (similar to many psychiatric disorders).

Biological factors:

Endogenous opioids may contribute to the denial of hunger in patients with AN. Starvation causes biochemical changes, (such as hypercortisolemia not suppressed by dexamethasone), which are also present in *depression* (Sharp and Freeman, 1993). Thyroid function is also suppressed (Støving et al, 1998a). Starvation produces amenorrhoea, which reflects decreased sex hormone levels. Some investigators have attempted to associate cycles of bingeing and purging with abnormalities in neurotransmitter secretion and function (Newman and Halmi, 1988). Because plasma endorphin levels are elevated in some BN patients who vomit, the feeling of wellbeing after vomiting that some of these patients experience may be mediated by raised endorphin levels. Abnormalities in serotonergic function have also been implicated in eating disorders (Kaye, 1995; Pirke, 1995).

Social factors:

Patients with eating disorders (AN and BN) often tend to be high achievers and respond to social pressures to be slender. As with AN patients, many patients with BN are depressed and have an increased incidence of familial depression, although the families of patients with bulimia nervosa are generally more conflictual than the families of AN patients. Patients with BN may describe their parents as neglectful and rejecting with low levels of nurturing and empathy (Gard and Freeman, 1996).

Psychological factors:

Anorexia nervosa appears to be a reaction to the demands requiring adolescents to behave more independently and to increase their social and sexual functioning. These patients may lack a sense of autonomy and selfhood. Many experience their bodies as being under the control of their parents, so that self-starvation may be an effort to gain validation as a unique and special person. Patients with BN, like those with AN, have difficulties with adolescent demands, but BN patients are generally more outgoing, angry and impulsive (Fahy and Eisler, 1993). Alcohol abuse, shoplifting and emotional instability are associated with BN. Patients with BN may lack the control and ego strength of their counterparts with AN. Their difficulties in controlling their impulses are often

manifested by substance abuse and self-destructive sexual relationships, in addition to the binge eating and purging that are the hallmarks of the disorder. Many BN patients have histories of difficulties in separating from caretakers. The struggle for separation from a maternal figure is thought to be played out in the ambivalence towards food: eating may represent a wish to fuse with the caretaker, and regurgitating may unconsciously express a wish for separation (Vandereycken, 1995).

4. Classification

Based on the criteria of the American Psychiatry Association's Diagnostic and Statistical Manual (*DSM IV*, 1994), eating disorders are classified into three groups, each with its own subdivisions: anorexia nervosa (AN), bulimia nervosa (BN) and eating disorder not otherwise specified (EDNOS).

4.1. Anorexia nervosa (AN)

Anorexia nervosa is a psychiatric syndrome characterised by severe restriction of food intake due to a pathological fear of weight gain. This results in excessive weight loss and refusal to maintain a normal body weight. The diagnostic criteria for AN include a deficit in body mass of at least 15% below expected weight, the presence of amenorrhoea of at least 3-months duration and body image distortion (*DSM IV*, 1994). The term anorexia ("lack of appetite") to describe this condition is misleading, because there is no decrease in appetite until a very late stage of the illness (Garfinkel, 1995). The pursuits of a decreased weight are due to reasons other than loss of appetite. Patients with AN often exercise excessively (e.g. cycling, jogging and running) in another attempt to reduce weight.

Anorexia nervosa can be subdivided into two types, the restricting type and the binge-purging type. In the restricting type, affected individuals restrict intake, but do not regularly engage in binge eating or purging by self-induced vomiting or using laxatives or diuretics. In the binge-purging type, affected individuals

regularly engage in binge eating and purging. Unlike subjects with BN both types of AN patients fail to maintain a normal body weight.

Anorexia nervosa usually starts in the midteens, but 5% of patients present in their early 20s. The majority (90%) of patients with this eating disorder are of the female gender (*Støving et al, 1998a*). It is estimated that AN affects about 0.28 to 1% of adolescent girls worldwide (*Hoek, 1995*). It occurs most frequently in developed countries and is seen most commonly amongst females pursuing a career that requires thinness such as modelling and ballet (*Gard and Freeman, 1996*).

4.2. Bulimia nervosa (BN)

The name 'bulimia' comes from the Greek words 'bous' (ox) and 'limos' (hunger). i.e. ox appetite. Essential features of bulimia nervosa are recurrent episodes of binge eating, a sense of lack of control over eating during the eating binges, self-induced vomiting, the misuse of laxatives or diuretics, fasting, or excessive exercise to prevent weight gain and persistent self-evaluation in terms of body shape and weight (*DSM IV, 1994*).

Bulimia nervosa can be subdivided into two types, the purging and non-purging type. The purging type shows recurrent compensatory behaviour such as self-induced vomiting or repeated laxative or diuretic abuse. The non-purging type uses methods like fasting or excessive exercise to prevent any weight gain. These patients maintain a normal body weight. A diagnosis of BN requires the presence of both binge and compensatory behaviour, at a frequency of at least twice a week for 3 months (*DSM IV, 1994*).

Bulimia nervosa is more prevalent than anorexia nervosa and occurs in 1 to 3 percent of young women. Like anorexia nervosa, bulimia nervosa is more common in women than in men. It often starts later in adolescence than anorexia nervosa. This disorder appears to reflect social influences rather than a genetic predisposition (*Fahy and Eisler, 1993*).

4.3. Eating disorder not otherwise specified (EDNOS)

Eating disorder not otherwise specified is a category used to describe eating disorders that do not meet the criteria necessary to diagnose a specific eating disorder (*DSM IV, 1994*).

Examples include recurrent episodes of binge eating without the compensatory behaviour typical of BN; females meeting all the criteria for AN, except amenorrhoea; those who meet all the criteria for AN except that their current weight is in the normal range (*DSM IV, 1994*).

5. Medical complications of eating disorders

5.1. Acute

Eating disorders can result in acute medical complications e.g. fluid and electrolyte disturbances most commonly resulting from vomiting and substance abuse, and acute renal failure.

5.2. Chronic

The longterm effects of eating disorders include:

5.2.1. Endocrine and metabolic abnormalities

Endocrine

Hypothalamic hypogonadism, presenting as amenorrhoea, is the most commonly encountered endocrine disturbance in patients with eating disorders. In some patients, amenorrhoea precedes weight loss and in many patients, return of menstruation is delayed after regaining body weight. Hypothalamic hypogonadism is present in all patients with AN. Although not a diagnostic feature, many patients with bulimia nervosa also have menstrual disturbances.

Hypothalamic dysfunction presenting as amenorrhoea is related to a loss of more than 15% of ideal body weight, or occurs when body fat content drops below a critical level (*Sharp and Freeman, 1993*). Hypothalamic hypogonadism is characterised by low basal levels of plasma luteinizing hormone (LH) and follicle stimulating hormone (FSH), attenuation of pulsatile gonadotrophin release, as well as an impaired response to stimulation with gonadotrophin releasing hormone. This results in reduced ovarian estrogen output. Estrogen deficiency may have a profound psychological impact and deleterious effects on the skeleton and cardiovascular systems of affected individuals (*Støving et al, 1998a*).

Other endocrine abnormalities seen in eating disorder patients appear to be of limited clinical relevance. Elevated growth hormone values have been documented in patients with AN and have been ascribed to a reduced production of insulin-like growth factor (IGF). A 'euthyroid sick syndrome', characterised by abnormal thyroid functions (low serum T3, normal or low T4 and normal TSH) in the absence of thyroid disease, occurs in some patients with AN and probably represents an adaptation to starvation (*Newman & Halmi, 1988*). Substance abuse sometimes includes the abuse of thyroid hormones in an attempt to enhance weight loss and may present as hyperthyroidism

Metabolic

A low basal metabolic rate is a known feature of starvation and AN. Impaired temperature regulation has been noted in anorectics, particularly the automatic changes required to respond to changes in environmental temperature. On exposure to cold, they do not increase their core temperature, stabilise temperature or shiver. On exposure to heat there is absent vasodilation and an abnormal elevation in core temperature (*Sharp and Freeman, 1993*).

Glucose metabolism is altered and hypoglycemia may occur in patients with marked malnutrition. Depletion of glycogen and fat stores prolongs recovery following a hypoglycemic event.

Lipid abnormalities have been described in eating disorder patients, but the findings of different studies are conflicting (*Sanchez-Munix and Marcus, 1991; Affenito et al, 1997*). Weight loss appears to be an important cause of changes in serum lipids. In the overweight individual, it usually results in a prompt decline in triglycerides and a later rise in HDL-cholesterol as ideal weight is approached. Serum cholesterol has been shown, however, to rise in humans subjected to short periods of total starvation.

Hypercholesterolemia is a complex issue. The genetic background of a study population must always be considered when interpreting study findings. It is important to remember to distinguish between the different eating disorder groups when evaluating serum lipid levels.

Significantly higher plasma total cholesterol concentrations are more common in AN than in the other eating disorder groups (*Sullivan et al, 1998; Mehler et al, 1998*). About 40% of patients with AN have elevated levels of total serum cholesterol and LDL cholesterol (*Stone, 1994*). The hyperlipidemia observed is probably a result of decreased faecal excretion of bile acids and cholesterol. Given the tendency for eating disorders, like AN, to have a chronic course, such elevated cholesterol concentrations could potentially increase the risk of coronary heart disease and stroke in these women.

Data have been published which suggest that the hyperlipidemia is strictly an acute phase finding and tends to normalise in the chronic period of AN (*Sanchez-Munix and Marcus, 1991*). If the latter is true, hyperlipidemia in eating disorder patients should be managed conservatively. Should LDL-Cholesterol levels be very high or multiple risk factors for coronary heart disease be present, active intervention should be undertaken.

5.2.2. Gastrointestinal complications

The gastrointestinal tract is commonly involved, particularly in patients with bulimia. Dental erosions with poor gum hygiene are common. Malnutrition-induced parotid enlargement is present in 25% of patients with bulimia and is

also seen in AN (*Sharp and Freeman, 1993*). Vomiting may result in oesophageal tears. The stomach is dilated in binge eaters and occasionally, gastric rupture occurs. Chronic laxative abuse leads to severe constipation and eventually to a huge, dilated colon (*Fonseca, 1993*).

5.2.3. Renal complications

Electrolyte and fluid disturbances (e.g. hypokalaemia, hyponatraemia, hypochloraemia, hypochloraemic metabolic alkalosis and hyperphosphataemia) (*Sharp and Freeman, 1993*) occur frequently in patients with eating disorders, especially in those with a purging type disorder. This may rarely result in renal failure (*Fonseca, 1993*).

5.2.4. Cardiac complications

Cardiac abnormalities may occur at some stage of anorexia in up to 87% of patients (*Sharp and Freeman, 1993*). The cardiac complications of anorexia and bulimia vary from minor electrocardiographic abnormalities to a decrease in cardiac size with thinning of the left ventricular wall, cardiac failure and life-threatening arrhythmias. Arrhythmias are caused by electrolyte disturbances especially hypokalaemia, hypocalcaemia and hypomagnesaemia. These electrolyte abnormalities are mainly seen in the purging type of eating disorder characterized by substance abuse.

5.2.5. Neurological complications

Neurological manifestations, similar to the cardiac complications, are secondary to electrolyte disturbances (e.g. hypokalaemia) and usually comprise muscle wasting and weakness. Hypocalcaemia and hyponatraemia may lead to a variety of acute neuropsychiatric problems, including epileptic convulsions (*Fonseca, 1993*).

5.2.6. Dermatological complications

Gupta et al divided the dermatological signs of eating disorders into three groups. Those resulting from 1. Malnutrition (dry skin, lanugo, carotenoderma) 2. Self-induced vomiting (purpura, bruising, calluses on the dorsum of hands) and 3. Abuse of laxatives and diuretics (*Sharp and Freeman, 1993*).

5.2.7. Skeletal complications

Osteopenia is a well known complication of eating disorders like AN. The pathogenesis, clinical relevance and appropriate therapy remain largely unknown and are discussed in the next section.

C. OSTEOPOROSIS IN EATING DISORDER PATIENTS

1. Introduction

Osteopenia is a common problem in patients with eating disorders and is known to be present in more than 50% of patients with anorexia nervosa (*Rigotti et al, 1984; Biller et al, 1989; Bachrach et al, 1990; Grinspoon et al, 1997*). Data regarding the impact of other eating disorders on bone health is, however, very limited. Bone loss often occurs at a young age and may persist even after recovery of the underlying eating disorder, thereby predisposing patients to fractures. Symptomatic compression fractures have, in fact, been reported in these patients. The mechanism(s) of bone loss in eating disorders, however, remain controversial. It cannot be assumed that the secondary osteoporosis documented in young eating disorder patients represents a disease process similar to the more common osteoporosis encountered in postmenopausal females. An improved understanding of the pathophysiology of the osteoporosis that occurs in eating disorders is necessary if more cost- and outcome effective therapeutic strategies are to be developed.

2. Prevalence of Osteoporosis

Rigotti et al (1984) published the first report of reduced BMD in subjects with AN. Similar observations have been reported in several studies (*Ayers et al, 1984; Biller et al, 1989; Bachrach et al, 1990; Davies et al, 1990a; Grinspoon et al, 1997; Soyka et al, 1999*), but BMD status remains poorly defined in the other eating disorder subgroups.

The majority of women with AN show evidence of bone loss and approximately 50 percent have bone density measurements greater than 1 standard deviation (SD) below age and sex-matched controls (*Rigotti et al, 1984; Biller et al, 1989; Bachrach et al, 1990; Grinspoon et al, 1997*). Both hip and spinal bone density appear to be reduced to a significant degree in subjects with AN, although data addressing this issue are limited to a single report (*Salisbury and Mitchell, 1991*). Significant osteopenia has been documented in young women who had AN for

only one year (*Bachrach et al, 1991*). The long-term natural history of bone loss in AN is not known, but data suggest that a significant degree of osteopenia is often a permanent consequence of anorexia despite disease recovery (*Rigotti et al, 1991; Herzog et al, 1993; Klibanski et al, 1995; Ward et al, 1997*). However, some studies have shown that BMD increases (*Bachrach et al, 1991*) with recovery of the illness or weight gain.

The prevalence of significant bone loss in BN and EDNOS are uncertain and the results are conflicting. Joyce et al. (1990) reported a decreased BMD in BN as well as EDNOS subgroups, while other studies found that bone mineral values for bulimics were similar to those of controls (*Howat et al, 1989; Newman & Halmi, 1989; Davies et al, 1990a; Carmichael and Carmichael, 1995; Sundgot-Borgen et al, 1998*).

3. Fractures

3.1. Fracture risk

Studies have shown that a significant number of AN patients have spinal bone densities at or below the fracture threshold (*Riggs and Melton, 1986; Newman and Halmi, 1988; Salisbury and Mitchell, 1991*). Rigotti et al (1991) estimated that the incidence of fractures among their AN patients was seven times higher than normal. Several longitudinal studies have revealed different recovery patterns of low BMD in the clinical course of anorexia nervosa patients with osteoporosis. Some studies suggest restoration of normal bone mass, with recovery from AN (*Treasure et al, 1987; Klibanski et al, 1995*). Others suggest that the improvement in bone density may only be partial (*Bachrach et al, 1990; Herzog et al, 1993*) or that bone mass remains low despite recovery (*Rigotti et al, 1991; Ward et al, 1997*). This is a cause for concern, even for the majority of anorectic women who recover, and suggests that a history of an eating disorder may adversely effect skeletal integrity throughout life and constitute a risk factor for the premature development of osteoporotic fractures. Ward et al (1997) measured bone density of the hip and lumbar spine in 18 eating disorder women

who had recovered from their disease, and documented osteopenia in 14 of the 18 women.

3.2. Prevalence of fractures

The prevalence of fractures in eating disorder patients is largely unknown. Several studies have reported fractures in patients (Table 3) at the time of the eating disorder, but data regarding long term fracture risk remain controversial. Recently, the presence of one or more non traumatic vertebral fractures has been shown to increase the risk of subsequent spine fractures 3-5 fold. In any patient, the presence of a previous fragility fracture should, therefore, be regarded as a risk factor for future fracture independent of the prevailing BMD. The earlier the age of fracture and the greater the number of previous fractures, the greater the subsequent risk (*Kanis et al, 1997*).

Table 3: Reported fractures in eating disorder patients

Studies: Authors (Date)	Eating disorder	Site of fractures
Ayers et al, 1984	AN	Vertebral compression
Rigotti et al, 1984	AN	Vertebral compression
Crosby et al, 1985	AN	Non specified
Brotman and Stern, 1985	AN	Vertebral compression
Szmukler et al, 1985	AN	Vertebral compression
Kaplan et al, 1986	AN	Hip
Treasure et al, 1986	AN	Vertebral, hip
Baum et al, 1987	AN	Femoral neck
Treasure et al, 1987	AN	Not specified
Biller et al, 1989	NS	Vertebral compression
Joyce et al, 1989	AN, BN	Clavicle, wrist, ankle
Hay et al, 1989	AN	Vertebral compression
Olmos et al, 1990	AN	Sternal
Rigotti et al, 1991	AN	Vertebral, hip, metatarsal
Verbruggen et al, 1993	AN	Clavicle
Klibanski et al, 1995	AN	Vertebral compression
Rose et al, 1999	AN	Femoral neck
Hartman et al, 2000	AN	Not specified

4. Bone loss: Cortical versus trabecular

The skeleton is composed of 80% cortical and 20% trabecular bone, the latter representing the metabolically more active component. Trabecular bone loss therefore often precedes cortical loss regardless of the underlying etiology. In women with anorexia nervosa, both cortical and trabecular bone loss have been documented, although the extent to which this occurs remains unclear. In the study of Grinspoon et al (1999) spinal and hip bone density measurements were comparable, suggesting similar involvement of cortical and trabecular bone. In the study of Carmichael and Carmichael (1995), however, greater involvement of trabecular bone was shown with spinal bone mineral density measurements significantly lower than those of hip and total body.

5. Bone turnover

Bone turnover status in eating disorder patients is poorly defined. Data derived from biochemical testing (Table 4) and histomorphometric analysis reveal conflicting results with both high and low bone turnover states reported in the literature (*Rigotti et al, 1984; Kaplan et al, 1986; Joyce et al, 1993*).

Total serum alkaline phosphatase (ALP) as a marker of bone formation was reported as normal in 5 of 6 studies (Table 4). Total ALP is however, too insensitive a marker to really be able to demonstrate the subtle effects of eating disorders on bone turnover and data must thus be interpreted with caution. In the three studies using the more sensitive biochemical indices of bone turnover (i.e. osteocalcin as a marker of bone formation and urinary deoxypyridinoline as a marker of bone resorption) an uncoupling phenomenon was noted with an increase in bone resorption accompanied by reduced bone formation – similar to that seen in some patients with steroid-induced osteoporosis (*Fonesca, 1993; Grinspoon et al, 1997; Hotta et al, 2000*). These observations differ from those reported in other populations of estrogen-deficient women in whom the increase in bone resorption is accompanied by a coupled increase in bone formation (Compston, 1997).

Table 4: Bone formation (Osteocalcin, ALP) and bone resorption (Deoxypyridinoline) parameters.

Biochemical Data			
Author (Date)	Osteocalcin (bone formation)	Total ALP (bone formation)	Deoxypyridinoline (bone Resorption)
Ayers et al, 1984		Normal	
Treasure et al, 1987		Normal	
Fonesca, 1993	Low	Normal	High
Carmichael & Carmichael 1995		Normal	Normal
Crosby et al, 1995		Normal	
Grinspoon et al, 1996a	Low		High
Grinspoon et al, 1997	Low		High
Hotta et al, 2000	Low		High

Histological data are very limited, based on only a few observational studies and case reports, and reveal both high and low turnover states (*Rigotti et al, 1984; Kaplan et al, 1986; Joyce et al, 1990*).

6. Proposed etiopathogenesis of osteoporosis in eating disorders

The pathogenesis of osteopenia in eating disorder patients is multifactorial and appears to be complex. A variety of nutritional factors, exercise abuse, estrogen deficiency and hypercortisolemia have all been proposed as potential contributing factors.

6.1. Nutritional factors

Undernutrition and nutritionally dependent factors (malnutrition) may play a significant role in the bone loss associated with eating disorders. In healthy normal subjects, short-term fasting over a period of 4 days results in a 50% reduction in the rate of bone formation (*Grinspoon et al, 1996a*). The influence of nutritional status on bone metabolism is also demonstrated by the findings that

bone density correlates with sensitive nutritional parameters such as body mass index (BMI), caloric intake, fat mass and leptin levels in women with AN (*Bachrach et al, 1990; Grinspoon et al, 1996b*). Nutritional factors including a low calcium and vitamin D intake; high protein, phosphate, caffeine or sodium diet; high intake of alcohol and low intake of trace elements/vitamins (e.g. fluoride, vitamin K, vitamin B6, B12, zinc and boron), may significantly contribute to bone loss in eating disorder patients.

Leptin

The protein leptin is encoded by the obese gene and synthesized by adipocytes (*Clement et al, 1998*). The receptor for leptin is expressed in the hypothalamus, in which it is proposed to act on the control of feeding (*Considine et al, 1996*).

Leptin regulates body weight by influencing energy intake and energy expenditure. Single meals do not significantly alter leptin levels, whereas restriction of food intake or short-term fasting and overfeeding have a rapid effect on leptin synthesis (*Nakai et al, 1999*). Plasma levels of leptin are well correlated with body fat content and body mass index (BMI, kg/m^2) in human subjects (*Grinspoon et al, 1996b; Støving et al, 1998b*).

It has been shown that BMI is a reliable measure of body fat in normal and obese subjects, but this may not be the case in severely emaciated or AN subjects. Therefore Støving et al (1998b) suggest that percentage body fat determined by DEXA scanning is more predictive than BMI in the relationship between emaciation and leptin levels. A poor correlation was observed between plasma leptin levels and body mass index (*Støving et al, 1998b*) whereas the correlation between serum leptin and body fat determined by DEXA scanning was statistically significant (*Støving et al, 1998b; Mathiak et al, 1999*). Contrary to this, Grinspoon et al (1996b) found a highly significant correlation between plasma leptin and BMI, and Ferron et al (1997) also reported that serum leptin levels in patients with AN, BN and EDNOS correlated with the individual BMI. Leptin secretion is not determined solely by the body fat mass. In humans, one day of overfeeding increased serum leptin and 72h fasting decreased serum leptin. This clearly demonstrates that the actual feeding status influences the leptin secretion disproportional to the body fat store.

It has been reported that AN patients show a severe reduction in plasma leptin (*Grinspoon et al, 1996b; Støving et al, 1997; Ballingand et al, 1998; Nakai et al, 1999*) compared to normal controls and bulimic patients (*Nakai et al, 1999*). Low body weight is associated with decreased leptin and this association is maintained even at an extreme degree of low weight (*Grinspoon et al, 1996b*). Ballingand et al (1998) showed that acute responsiveness of leptin to short-term refeeding is abolished in AN. This is in contrast with the acute rise of leptin produced by refeeding in healthy subjects.

Leptin has also been linked to the control of reproduction (*Chehab et al, 1997*). Low leptin levels are associated with past or present episodes of amenorrhoea in eating disorder females. However, in anorectics the amenorrhoea often precedes the weight loss and may persist after weight recovery. This suggests that a critical leptin level, rather than weight recovery or critical body weight is needed to maintain menstruation (*Clement et al, 1998*). Leptin is required not only for the regulation of body weight but also for sexual maturation and is therefore a critical link between energy stores and hypothalamic pituitary functions in humans.

Insulin-like-growth factor -1

One mechanism by which nutritional deprivation may alter bone metabolism, involves its effect on serum insulin-like-growth factor 1 (IGF-1) concentrations. Insulin-growth factor 1 (IGF-1) is a nutritionally regulated bone trophic hormone produced in the liver. Serum levels decrease acutely with caloric deprivation and are decreased in patients with AN. This hormone has potent effects on bone growth and is known to stimulate osteoblast function and collagen synthesis in vivo and in vitro (*Rigotti et al, 1991; Grinspoon et al, 1996a*). Patients with AN are markedly IGF-1 deficient and serum levels of IGF-1 decrease with weight loss, increase with weight recovery and predict bone loss (*Klibanski et al, 1995; Grinspoon et al, 1996a*). Altered IGF-1 may, therefore, constitute a critical element in the pathogenesis of decreased bone formation and osteopenia in eating disorder patients.

Macronutrients

Patients with AN have a daily total energy and macronutrient (protein, fat, carbohydrate) intake which is significantly lower than *controls* (Gwirtsman *et al*, 1989). The percentage intake of protein, fat and carbohydrate, however, appears to be similar to that of normal controls.

Calcium

Calcium homeostasis is essential for the maintenance of a healthy skeleton and calcium malnutrition may therefore contribute towards the decreased BMD observed in patients with eating disorders. A poor calcium intake is known to result in secondary hyperparathyroidism and to increase biochemical markers of resorption, reflecting the increase in bone remodelling activity (Kiriike *et al*, 1992). Data on calcium metabolism in patients with eating disorders are however conflicting. Dietary intake of calcium has been reported to be *low* (Crosby *et al*, 1995) or normal (Howatt *et al*, 1989) while urinary calcium excretion has been shown to be either increased (Abrams *et al*, 1993) or comparable to controls (Kaplan *et al*, 1986; Olmos *et al*, 1991). Carmichael and Carmichael (1995) found that calcium excretion was lower in patients with bulimia compared to those with AN, but provided no explanation for this observation.

As expected, serum calcium levels have generally been within normal limits, and calcium intakes have not been shown to correlate with BMD in AN (Bachrach *et al*, 1990; Rigotti *et al*, 1991; Carmichael & Carmichael, 1995). Moreover, calcium supplementation has not been shown to increase BMD in this disease (Rigotti *et al*, 1991; Kilbanski *et al*, 1995).

Phosphorus

Serum phosphorus levels were found to be slightly lower in women with AN and BN compared to population norms (Brotman & Stern 1985; Crosby *et al*, 1985). Normal urinary excretion of phosphorus, and no correlation between phosphorus levels and BMD have been reported in studies of AN (Crosby *et al*, 1985; Kaplan *et al*, 1986; Carmichael & Carmichael 1995).

Vitamin D

Vitamin D metabolism is highly variable in eating disorders since it can be affected by reduced dietary *intake* (Crosby *et al*, 1985), diminished binding capacity of vitamin D-binding protein (Olmos *et al*, 1992) or a decrease in vitamin D receptors in patients with estrogen deficiency (Liel *et al*, 1992).

The majority of studies have demonstrated normal levels of 25(OH) vitamin D (Rigotti *et al*, 1984; Kaplan *et al*, 1986; Olmos *et al*, 1991), while some reported elevated (Carmichael & Carmicheal, 1995) and yet others low or undetectable levels (Fonesca *et al*, 1988; Verbruggen, 1993). Concentrations of 1,25(OH)₂ vitamin D were lower in patients with AN, compared with controls, in various studies (Rigotti *et al*, 1984; Kaplan *et al*, 1986; Fonesca *et al*, 1988; Olmos *et al*, 1991; Kiriike *et al*, 1992). No correlation between BMD and plasma vitamin D metabolite levels could be demonstrated. (Rigotti *et al*, 1984; Bacharach *et al*, 1990; Kiriiki *et al*, 1992; Carmichael & Carmichael, 1995). The role, if any, of vitamin D abnormalities in the osteopenia of eating disorder patients, is not clear at present.

6.2. Mechanical factors

Weight

Low body weight per se would be expected to reduce the strain applied to the skeleton during normal activities, and may result in a loss of bone mineral. Therefore body weight is an important factor in the attainment and maintenance of BMD at all ages. Studies in patients with eating disorders show a consistent positive correlation between weight expressed as BMI and bone mineral density (Treasure *et al*, 1986; Bachrach *et al*, 1990; Carmichael & Carmichael 1995; Hotta *et al*, 2000), implying a potentially negative impact of weight loss on bone mass.

Exercise

Exercise is known to improve bone mass via enhanced mechanical stresses on bone, and results in improved muscle strength and co-ordination, thereby

reducing an individual's risk to fall and fracture (*Drinkwater et al, 1984*). On the other hand, excessive exercise, especially in females, may result in suppressed gonadal function and hypo-estrogenemia. This may result in increased bone resorption and bone mineral loss.

Physical activity varies greatly amongst eating disorder patients, from sedentary lifestyles to excessive exercise programmes. Results of the effect of exercise on bone mass in eating disorder patients are conflicting. Some studies report moderate exercise to be protective (*Rigotti et al, 1984; Joyce et al, 1990*), and strenuous exercise to be detrimental (*Joyce et al, 1990*), whereas others could not demonstrate any relationship between BMD and exercise (*Bachrach et al, 1990; Joyce et al, 1990*).

6.3. Hypercortisolism

The mechanisms of glucocorticoid-induced bone loss are complex. A direct effect of steroids on bone, whereby bone formation and collagen production are reduced, appears to be the most important mechanism. Other factors include the negative calcium balance and reduction in sex hormone levels observed in individuals with hypercortisolism. Although it has been suggested that elevated cortisol levels may predispose to bone loss in eating disorder patients (*Biller et al, 1989; Newman and Halmi, 1989; Carmichael and Carmichael, 1995; Grinspoon et al, 1996b*), scientific data are scant.

Elevated serum and urinary cortisol levels have been described in women with AN (*Newman and Halmi, 1988; Biller et al, 1989; Newman and Halmi, 1989*) as well as in patients of normal weight who have BN (*Mortola et al, 1989*). The elevated cortisol levels were ascribed to enhanced activity of the hypothalamic pituitary adrenal axis (*Newman and Halmi, 1989*). In a recent study of anorexic patients, 22% of women with severe osteopenia had mildly elevated urinary-free cortisol levels (*Grinspoon et al 1996b*). These data suggest that hypercortisolemia only contributes to the low bone density in a minority of patients with AN, but requires further study.

6.4. Hypogonadism

Any form of estrogen deficiency may potentially result in excessive bone loss, osteoporosis and ultimately in an increased risk of osteoporotic fractures. It is therefore not surprising that patients with AN, a disorder in which amenorrhoea is a principle diagnostic feature, were found to have diminished bone mineral density in numerous studies (*Ayers et al, 1984; Herzog et al, 1985; Fonesca et al, 1988; Davies et al, 1990; Kirikke et al, 1992*). Fifty percent (50%) of patients with BN have menstrual irregularities despite being of normal weight, and this raises the question whether these bulimia patients are also at risk of developing osteoporosis.

The relationship between estrogen deficiency, osteopenia and increased fracture risk in the general population has been well established in the literature (*Ayers et al, 1984*). Amenorrhoea, whether secondary to exercise (*Drinkwater et al, 1984*), hypothalamic disfunction, or oophorectomy in young women or to menopause in older women, is a risk factor for the development of osteoporosis. The amenorrhoea in patients with AN is most often the result of a decrease in the pulsatility of gonadotropin-releasing hormone, resulting in hypogonadotropic hypogonadism and low or undetectable levels of serum estradiol. A threshold level of weight or body fat is thought to be necessary for normal pulsatility of gonadotropin-releasing hormone. Attainment of normal weight in AN patients, however, does not necessarily imply recurrence of normal menses (*Hotta et al, 1998*).

Early onset of amenorrhoea and longer duration of the hypogonadal state are strong risk factors for a decrease in BMD (*Kanis et al, 1997*), and spinal BMD has been shown to correlate negatively with the duration of amenorrhoea in AN (*Biller et al, 1989; Rigotti et al, 1991; Baker et al, 1999*). Other authors, however, could not demonstrate a correlation between BMD and either duration of amenorrhoea (*Joyce et al, 1990; Bacharach et al, 1991*) or the plasma levels of estradiol (*Joyce et al, 1990; Rigotti et al, 1991*).

Since eating disorders often affect young girls, it may result not only in secondary loss of menses but also in delayed puberty. This may additionally lead to the arrest of linear growth and contribute to the bone loss experienced by these individuals. Hypogonadism with resultant hypoestrogenemia must be regarded as one of the key factors in the pathogenesis of osteopenia in the eating disorder patient.

7. Management of osteoporosis in eating disorders patients.

Effective prevention and treatment of osteoporosis in eating disorder patients have not been established, largely because its pathogenesis remains poorly understood. Clearly further studies are required. Maintenance of normal weight (*Bachrach et al, 1990; Rigotti et al, 1991*) and a good nutritional state is a necessary first step. Risk factors pertaining to osteoporosis should be addressed similar to osteoporosis in the general population. Dietary supplementation, specifically with regard to calcium and vitamin D should be provided if indicated.

Estrogen is often proposed as a therapeutic option in eating disorder patients with osteopenia. It cannot be universally recommended, because study data confirming the efficacy of estrogen in improving bone mass in these patients is limited (*Klibanski et al, 1986*). The decision on estrogen as a treatment modality, must be made individually for each patient. The role of other bone specific agents i.e. bisphosphonates and fluoride in the management of osteoporosis in eating disorders has not been established. Preliminary studies have shown a significant effect of short-term recombinant-human IGF-1 administration on bone metabolism in AN. Administration of recombinant-human IGF-1 has a dose-dependent effect on markers of bone formation and no obvious stimulative effect on bone resorption at low doses (*Grinspoon et al, 1996a*).

CHAPTER 3

METHODOLOGY

1. Subjects

1.1. Patient recruitment

This study was limited to female Caucasian eating disorder patients, aged 15 –45 years. Patients were recruited from the eating disorder clinic at Tygerberg Hospital and Kenilworth Mediclinic, as well as referrals from private practitioners.

1.2. Exclusion criteria

Subjects were screened to exclude factors known to independently affect bone metabolism. Those patients with a history of diseases or medication (e.g. corticosteroids, anticonvulsants) known to adversely influence bone health were excluded from the study.

1.3. Diagnosis of Eating Disorder

A total of 59 patients were studied. These patients were classified by a single specialist psychiatrist and were included in the study if they met the American Psychiatric Association Diagnostic and Statistical Manual criteria (*DSM IV, 1994*) for eating disorders. Three clinical categories emerged: (1) Anorexia Nervosa (AN), (2) Bulimia Nervosa (BN) and (3) Eating disorders not otherwise specified (EDNOS).

2. Methods

A bone mineral density measurement, anthropometric data, dietary assessment, venesection for biochemical evaluation and questionnaires concerning eating habits and conventional risk factors for osteoporosis were obtained during a

single visit to the Department of Endocrinology and Metabolism, at Tygerberg Hospital.

2.1. Clinical assessment

2.1.1. Risk factor analysis

The presence of conventional risk factors for osteoporosis was assessed by employing an adapted questionnaire. The original questionnaire is used in the Department of Endocrinology and Metabolism for the screening of possible osteoporosis patients. The questions were asked and responses noted by the researcher.

The following risk factors were addressed: Family history of osteoporosis, alcohol and calcium intake, smoking habits, history of previous fractures, activity level and menstrual history. (Addendum I & II)

The alcohol intake of the subjects was also obtained from the risk factor analysis as well as the dietary history of current eating habits, which were analysed to provide a more detailed picture of the alcohol intake of the subjects.

Exercise was scored by the following criteria, < 1 h/week (low activity), between 1 and 6h/week (moderate activity) and > 6h/week (high activity).

Menstrual history was assessed as follows: (1) age of menarche, (2) time since last menstrual period, (3) duration of amenorrhoea, defined as the total number of months since menarche with absent menses. Patients were further categorised into 3 categories: normal monthly menstrual cycles, amenorrhoea (no menses for three months or longer) and oligomenorrhoea (irregular/scant menses).

2.1.2. Diet history

The diet history was obtained by a qualified dietician. The method used was dietary recall (history of eating habits for a week before admission) obtained during a personal interview (Addendum III and IV). The Foodfinder program (Dietary Analysis Software - Medical Technology, MRC) was used to analyse the diet histories.

2.1.3. Anthropometric assessments

Subjects were weighed on a balance beam scale wearing light clothing without shoes. They were asked to remove their shoes to record height. Height was measured with the subject's back to the vertical rod of the scale. Weight and height measurements were used to calculate body mass index (BMI)*.

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

Normal reference values (Bray, 1978)

Normal range	20 - 25
Underweight	< 20
Overweight	25 - 30
Obese	> 30

Further sub-classification of these categories was not attempted, given the relatively small numbers of the study population.

2.2. Bone mineral density assessment

Bone mineral density of the lumbar spine (L1-L4) and various areas of the hip (femoral neck, trochanter, intertrochanter, total hip, and Ward's triangle) was quantitated employing Dual Energy X-ray Absorptiometry (Hologic QDR-1000). The researcher, a trained DEXA technician performed all the scans.

Bone mineral density measurements are conventionally expressed as either an absolute value (e.g. g/cm²) or a deviation from a specific norm defined as a so-

called T - or Z - score. A T-score refers to the BMD of a subject compared to 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 previously (p10), the WHO's classification of osteopenia/osteoporosis was designed to provide a practical basis for the identification of specifically postmenopausal Caucasian women at risk to sustain fragility fractures. This classification is applicable to children or young individuals who have not necessarily reached their peak BMD. Furthermore, the comparison of absolute BMD values in a heterogeneous study population, aged 15-45 years, is not practical.

In this present study we therefore employed the Z-score (BMD of subjects compared to age and sex matched controls), similar to previous studies examining bone mass in patients with eating disorders. Normative data (Z-scores) for Caucasians have previously been established in our unit (Rene Blaaw). The S-score of the lumbar spine and total hip were used to define the bone mass and to divide subjects into two groups which formed the basis of this study.

Group (1): Those with a normal lumbar BMD (Z- Score within 1 standard deviation of normal age and sex matched controls).

Group (2): Those with a low lumbar BMD (Z-Score decreased by more than 1 standard deviation below that of age and sex matched controls).

Group (2) was further sub-divided into those with a Z-Score between 1 and 2 standard deviations below the norm (arbitrarily referred to as mild osteopenia for the purpose of this study) and those with a Z-Score more than 2 standard deviations below the norm (referred to as more severe osteopenia for the purpose of this study) of the lumbar spine.

2.3. Biochemical assessment

A fasting venous blood sample was drawn between 10h00 -12h00 in all subjects.

Fifty millilitres was used for immediate analyses and 20 ml was stored at -70 °C. A spot urine sample was also obtained, between 10h00 -12h00 on the day of assessment.

2.3.1. Serum minerals

The following serum mineral and biochemical parameters were analysed using a multi channel analyzer (Technicon DAX 48): serum-calcium, magnesium and phosphate.

Enzymatic, timed end-point colorimetric methods were used for calcium (reaction with o-cresolphthalein), magnesium (xylidyl 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]

Normal laboratory reference values

S-Calcium (albumin corrected)	2.10 – 2.6 mmol/l
S-Magnesium	0.75 – 1.00 mmol/l
S-Phosphate	0.8 - 1.40 mmol/l

2.3.2. Bone turnover

Bone Turnover was assessed by measuring osteocalcin in serum (RIA kits, CIS Bio International, France) and deoxypyridinoline (Bayer Immuno 1™) in urine. Results obtained using the Bayer Immuno 1 system are generally expressed as a ratio of deoxypyridinoline to creatinine (nMDPD/mM Cr).

Normal laboratory reference values

Osteocalcin	2.7 – 6.9 ng/ml
U-Free DPD/Cr Ratio	1.4 – 13.6 nmol/mmol

2.3.3. Nutritional parameters and vitamin D

Serum albumin was measured with a multi-channel analyser (Technicon DAX 48). Vitamin D determination, described by Shephard et al, 1987, involves a competitive protein-binding technique, utilising tritiated 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 approx. 6%.

Normal laboratory reference values

S-Albumin	35 –50 g/l
25 (OH) Vitamin D	> 18 ng/l

2.3.4. Hormonal studies

2.3.4.1. Sex hormones and prolactin

Luteinizing hormone (LH), follicle stimulating hormone (FSH) and prolactin were quantitated by a manual method using the IRMA (immunoradiometric assay) principle with magnetic separation (Serono diagnostics, Switzerland).

Biochemical evaluation of estradiol was quantitated by RIA kits (in house) and sex hormone binding globulin (SHBG) by an inhouse radiometric method. Total testosterone quantitation was performed using a coated tube RIA method (Diagnostic Products Corporation, Los Angeles, USA).

Normal laboratory reference values

S-LH	1.7 - 13.9 U/l (Follicular phase)
	17.5 - 49.0 U/l (Midcycle phase)
	1.0 - 15.8 U/l (Luteal phase)
	17.9 - 74.3 U/l (Post Menopausal)

Normal laboratory reference values

S-FSH	1.1 - 7.6 U/l (Follicular phase)
	3.7 - 24.9 U/l (Midcycle phase)
	0.9 - 5.3 U/l (Luteal phase)
	41.0 - 88.3 U/l (Post Menopausal)
S-Estradiol	95 – 580 pmol/l (Follicular phase)
	253 - 1336 pmol/l (Midcycle phase)
	0.10 187 - 804 pmol/l (Luteal phase)
	< 172 pmol/l (Post Menopausal)
S-SHBG	50 – 90 nmol/l
Total S-Testosterone	0.4 - 2.9nmol/L
S-Prolactin	3.0 - 16.0 µg/l

2.3.4.2. Cortisol

The quantitation of serum-cortisol and 24-hour urine free cortisol were performed using a coated tube Ria method (Incstar Corporation, Stillwater, USA).

Normal laboratory reference values

S-Cortisol	pm: 171.1 - 800.4nmol/l
	am: 82.8 - 477.5nmol/l
DU-Free Cortisol	55 – 248 nmol/24h

2.3.4.3. Thyroid function tests

Thyroid stimulating hormone (TSH) was quantitated by manual methods using the IRMA principle with magnetic separation (Serono Diagnostics, Switzerland).

The determination of serum free thyroxine (T₄) was carried out using the Amerelex-MAB kit (Kodak Clinical Diagnostics).

Normal laboratory reference values

TSH	0.47- 6.9 mU/l
T ₄	9.7 - 25.2 pmol/l

2.3.4.4. Growth hormone

Growth hormone (GH) was quantitated by manual methods using the IRMA principle with magnetic separation (Pharmacia Diagnostics, Sweden).

Normal laboratory reference values

GH 1 -13.5 mU/L

2.3.5. Lipid profile

Serum-Cholesterol and Triglycerides were quantitated by automated methods using the Beckman Synchron CX4CE. HDL-Cholesterol was measured after precipitating LDL and VLDL with dextranulphate and magnesium. The LDL and VLDL fractions were removed by centrifugation and HDL-Cholesterol concentrations were then measured. LDL-Cholesterol was calculated employing the following formula:

$$\text{LDL-Cholesterol} = \text{S-Cholesterol} - (\text{Triglycerides}/21.18 + \text{HDL-Cholesterol})$$

Normal laboratory reference values

S-Cholesterol	3.8 – 5.7 mmol/l
S-Triglycerides	0.9 – 1.97 mmol/l
S-HDL Cholesterol	> 0.9 mmol/l
HDL:Cholesterol Ratio	> 0.2
HDL:LDL Ratio	> 0.24
S-LDL Cholesterol	0 – 4.0

3. Statistical analysis

All analysis were performed in consultation with a statistician (Dr H Nell). Statistical analysis was performed by analysing the group as a whole and dividing the group into the three eating disorder subgroups, as well as into those with normal lumbar BMD (Z-Score > -1) and those with a low lumbar BMD (Z-Score < -1).

Differences between the subgroups of eating disorders were assessed using Analysis of variance (ANOVA - TURKEY Multiple Comparison Test). To identify the group that differs significantly ($p < 0.05$), a post hoc test was performed. The clinical variables and biochemical parameters of the normal versus low BMD groups were compared by Students t test for parametric data. Correlations were calculated by a Pearson correlation coefficient. Results were regarded as significant at $p < 0.05$. Unless otherwise indicated, all data are expressed as the mean \pm SD.

CHAPTER 4

RESULTS

1. Demographic data of the study population

This study included 59 female Caucasian patients (age 15- 45 years) who met the criteria for eating disorders outlined in the Diagnostic and Statistical Manual IV (DSM IV) of the American Psychiatric Association. Twenty five of the patients met the criteria for Anorexia nervosa (AN), 17 for Bulimia nervosa (BN) and 17 for Eating Disorders not Otherwise Specified (EDNOS).

Patients in the different eating disorder groups were all of similar age, but the AN subjects had a significantly lower body mass index ($p = 0.0001$) compared to those with BN or EDNOS.

Table 1: Demographic data of the eating disorder subgroups

Diagnosis	AN	BN	EDNOS
N	25	17	17
Age (yr.)	21.8 ± 9.2	22.5 ± 5.8	23.6 ± 7.8
Weight (kg)	44.2 ± 7.2	56.8 ± 11.1	53.5 ± 8.9
Height (cm)	166.1 ± 5.9	166.4 ± 8.5	164 ± 8.1
BMI (kg/cm ²)	15.9 ± 2.2 *	20.34 ± 2.6	19.85 ± 2.6

Data presented as mean ± SD

*indicates statistical significance ($p < 0.0001$) compared to BN and EDNOS

2. Bone mineral density (BMD)

Normal bone development does not occur in a linear fashion, but follows a N-shaped curve with a rapid increase in bone density at the time of puberty and a corresponding decrease (in women) at the menopause. This means that it is important to compare bone density in any clinical group with an appropriately matched control group. This can be done using age-matched norms (expressed as standardized z-scores).

2.1. Lumbar spine

The Z-Score (BMD compared to age and sex matched controls) values were used to define the bone mass and to divide the subjects into two groups which formed the basis of this comparative study. (1) Those with a normal BMD (Z-Score within 1 SD of the norm) and (2) those with a low BMD (Z-Score decreased by more than 1 SD below that of age and sex matched controls). The BMD results of the different subgroups as well as the total patient population are summarised in Table 2.

Forty six percent of the total eating disorder group had a BMD more than 1 SD below that of age and sex-matched controls. Sixty four percent of AN patients had a low BMD. Of particular interest is the fact that 29.4% of BN and 35.3% of EDNOS patients also had a low BMD. Moreover, severe osteopenia (Z-Score < -2SD) occurred in 15% of the total patient population or in a third of those with a low BMD (Table2).

Table 2: Percentage of the total patient population with normal and low lumbar (L1 - L4) BMD (mild and severe osteopenia)

Diagnosis	AN	BN	EDNOS	Total
n (%)	25	17	17	59
Absolute BMD (g/cm ²)	0.689 ± 0.12 *	0.975 ± 0.16	0.936 ± 0.1	0.918 ± 0.14
(1) Normal BMD Z-Score > -1	9 (36)	12 (71)	11 (65)	32 (54)
(2) Low BMD Z-Score < -1	16 (64)	5 (29)	6 (35)	27 (46)
(2.1) Mild osteopenia Z-Score <-1>-2	10 (40)	3 (18)	5 (29)	18 (31)
(2.2) Severe osteopenia Z-Score < -2	6 (24)	2 (12)	1 (6)	9 (15)

Data presented as n (%)
Total Lumbar spine (L1-L4)
Z-Score (BMD compared to age and sex matched controls)
BMD (bone mineral density)
*indicates statistical significance (p = 0.03) ANOVA (post hoc)

2.2. Hip

Due to the lack of normative hip data (Hologic software incomplete) for patients < 20 years, the left hip BMD assessment of only 32 patients of the total patient population (59) could be analysed. These results are summarised in Table 3.

Of these patients 56% had a BMD (Z-Score) more than 1 SD below that of age and sex matched controls. Thirty six percent of BN and 30% of EDNOS patients had a low hip BMD, whereas 100% of AN patients presented with a low hip bone mass.

Table 3: Percentage of subjects (n=32) with a normal and low BMD (Left hip)

Diagnosis	AN	BN	EDNOS	Total
n (%)	11	11	10	32
1.Normal BMD				
Z-Score > -1	0 (0)	7 (63)	7 (70)	14 (44)
2.Low BMD				
Z-Score < -1	11 (100)	4 (36)	3 (30)	18 (56)

Data presented as n (%)

Left Hip (Total)

Z-Score (BMD compared to age and sex matched controls)

BMD (bone mineral density)

3. Clinical risk factor analysis for osteoporosis

3.1. In total eating disorder group and subgroups

It is noteworthy that 24% of the total patient population had a history of previous fragility fractures (Table 4). A history of amenorrhoea, with mean duration of \pm 30.8 months, occurred frequently in the total patient population. All the AN patients were necessarily amenorrhoeic as this is included in the diagnostic criteria for AN. Sixty four percent of the bulimic patients and 82.3% of EDNOS patients presented with a history of amenorrhoea at some stage during their illness. Amenorrhoea tended to be of longer duration in the AN subjects,

compared to the other eating disorder groups, and this approached statistical significance ($p = 0.07$). Compared to the BN and EDNOS groups, alcohol intake and smoking occurred less frequently in AN patients. Exercise programs exceeding 6 hrs/week occurred more commonly in the AN patients. Previous fragility fractures were reported more commonly amongst the AN (28%) and EDNOS patients (29.4%). An acceptable calcium intake was reported by most patients.

Table 4: Risk factors for osteoporosis in eating disorder subgroups

	AN	BN	EDNOS	Total
n	25	17	17	59
Previous fractures n (%)	7 (28)	2 (11.7)	5 (29.4)	14 (23.7)
Family History of OP n (%)	5 (20)	1 (5.8)	4 (23.5)	10 (16.9)
History of Amenorrhoea n (%)	25 (100)	11 (64)	14 (82.3)	50 (84.7)
Duration of Amenorrhoea (mth)	49.4 ± 75.3	23.2 ± 35.0	12.1 ± 13.6	30.8 ± 54.3
Nicotine usage n (%)	6 (24)	10 (58)	9 (53)	25 (42.3)
Alcohol intake n (%)	8 (32)	13 (76)	11 (65)	32 (54.2)
Exercise n (%)				
• < 1 hr/wk	6 (24)	1 (5.8)	1 (5.8)	8 (13.6)
• 1 – 6 hr/wk	8 (32)	13 (76.4)	13 (76.4)	34 (57.6)
• > 6 hr/wk	11 (44)	3 (17.6)	3 (17.6)	17 (28.8)
Low Ca intake n (%)	8 (32)	4 (23.5)	4 (23.9)	16 (27.1)

Data presented as n (%)

Data presented as mean ±SD

3.2. In those with a normal and low BMD

In the normal versus low bone mass groups (Figure1), no significant difference in age, weight, height or BMI could be demonstrated. Except for the duration of amenorrhoea ($p = 0.0048$), conventional risk factors for osteoporosis were similar in patients with normal and low bone mass. A significant correlation, between BMI and lumbar BMD ($r = 0.4$; $p = 0.0015$), as well as hip BMD ($r = 0.5$; $p = 0.001$), could be demonstrated in the total eating disorder patient population. We demonstrated a significant negative correlation between duration of amenorrhoea and BMD ($r = -0.4$; $p = 0.001$) in these patients.

Risk factor analysis for osteoporosis in normal and low BMD groups

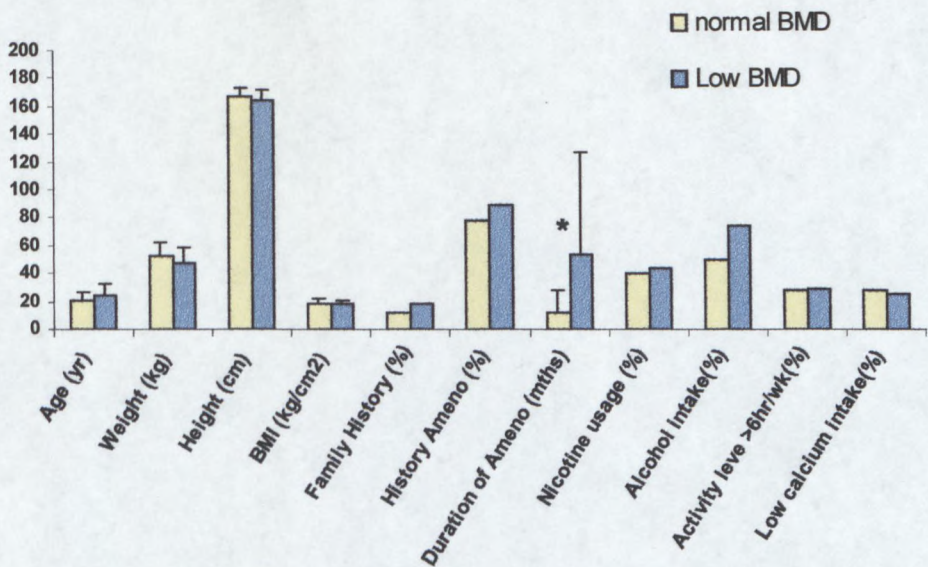


Figure1: Risk factor analysis for osteoporosis in subjects with normal and low lumbar (L1 - L4) BMD. * Indicates statistical significance at $p = 0.0048$

4. Nutrition parameters

Patients with eating disorders are known to be less than candid about their eating behaviour. It is also recognised that the “flat slope syndrome” namely the tendency for subjects to over-estimate what they have eaten when intake is low and to under-estimate when intake is high, may affect results. The dietary history of eating disorder patient’s must therefore be interpreted with caution. This is especially noted in the reported total daily energy intakes of the three eating disorder subgroups, where AN subjects reported the highest and BN patients the lowest intakes (Table 5).

The nutritional parameters, (Table 5) were similar in the three subgroups, except for a significantly lower body mass index (BMI) in the AN group ($p = 0.0018$) (Table 1). The percentage protein intake of the 3 eating disorder groups was normal. It is known that AN is not usually associated with inadequate protein intake, unlike other types of starvation. Our results were in agreement with these findings. Serum albumin, 25 (OH) Vitamin D and total serum-cholesterol were

normal in all the eating disorder patients and did not differ between the subgroups. Total serum-cholesterol levels were normal in all the eating disorder patients and it tended to be in the high normal range in patients with AN. Except for significantly higher S-HDL levels in the AN patients ($p=0.03$), the lipid profiles of the three subgroups were comparable. Low triglyceride levels were documented in all the eating disorder patients.

Table 5: Nutritional parameters for eating disorder subgroups

	Normal laboratory reference values	AN	BN	EDNOS
n		25	17	17
Dietary History (Daily intake)				
Energy (kJ)		6163 ± 4870	5083 ± 2849	5490 ± 3400
Macro nutrients				
Energy protein (%)	10 – 20	13.9	14.2	15.5
Energy fat (%)	<30	23.8	27.2	21.4
Cholesterol (mg)	<300	94.1 ± 75.7	93.8 ± 73.3	124.1 ± 159.1
Energy carbohydrates(%)	50 - 65	59.7	55.9	59.2
Alcohol (g)		8.5± 37.5	7.8 ± 17.2	10.6 ± 43.7
Minerals				
Calcium (mg) (%RDA)	1200-1500 (>67%)	733 ± 602 (61)	552 ± 244 (44)	690± 309 (57)
Phosphate (mg) (%RDA)	>1200 (>67%)	1080± 1042 (90)	909± 515 (76)	1063.± 639 (89)
Plasma Values				
Plasma albumin (g/l)	35 – 50	45.54 ± 4.5	45.5 ± 3.8	45.2 ± 2.1
25 (OH) Vit D (ng/ml)	>18	27.7 ± 7.6	31.3 ± 13.5	28.8 ± 7.5
Total Cholesterol (mmol/l)	3.8 – 5.7	5.3 ± 1.3	4.7 ± 1.3	4.9 ± 0.8
S-Triglyceride (mmol/l)	0.9-1.97	0.63 ± 0.19	0.82 ± 0.34	0.74 ± 0.33
S-HDL Cholesterol (mmol/l)	>0.9	1.57 ± 0.53 *	1.19± 0.31	1.43 ± 0.34
HDL:Cholesterol	>0.2	0.30 ± 0.07	0.26 ± 0.06	0.29 ± 0.06
HDL:LDL	>0.24	0.48 ± 0.17	0.42 ± 0.14	0.47 ± 0.14
S-LDL Cholesterol (mmol/l)	0-4.0	3.40 ± 0.93	3.10 ± 1.18	3.16 ± 0.65

Data presented as mean ± SD

* indicates statistical significance ($p = 0.03$) compared to BN and EDNOS

No evidence of malnutrition could be documented in osteopenic subjects. Mean body mass index (BMI), total energy intake, macro nutrients, minerals like phosphate, Vitamin D (μg) intake as well as plasma albumin and 25 (OH) Vitamin D levels were identical in osteopenic and non-osteopenic patients groups. Calcium intake in both groups tended to be low and was in fact significantly lower in those with a normal BMD. Total serum cholesterol was higher in those with a low bone mass. Patients with a low BMD consumed significantly more alcohol than those with a normal BMD (Table 6).

Table 6: Nutritional parameters of normal versus low BMD groups

	Normal BMD	Normal laboratory reference values	Low BMD
N	32		27
Dietary History (Daily intake)			
Energy (kJ)	4792 \pm 3288		6561 \pm 4672
Macro nutrients			
Total protein (%)	15.9	10 – 20	13.3
Total fat (%)	25.5	<30	22.8
Cholesterol (mg)	110.7 \pm 124.2	<300	95 \pm 84.8
Total carbohydrates(%)	59.8	50 - 65	57.8
Alcohol (g)	1.3 \pm 4.1		17.1 \pm 48.9*
Minerals			
Calcium (mg) (%RDA)	528 \pm 244 (44)	1200-1500 (>67)	819 \pm 545* (68)
Phosphate (mg) (%RDA)	881.2 \pm 567(73)	>1200 (>67)	1186 \pm 967 (98)
Plasma Values			
Plasma albumin (g/l)	45.41 \pm 3.39	35 - 50	45.45 \pm 4.1
25 (OH) Vit D (ng/ml)	29.86 \pm 10.8	>18	28.07 \pm 8.08
Total Cholesterol (nmol/l)	4.7 \pm 1.0	3.8 – 5.7	5.3 \pm 1.2 *
S-Triglyceride	0.67 \pm 0.24	0.9-1.97	0.77 \pm 0.37
S-HDL Cholesterol	1.36 \pm 0.34	>0.9	1.5 \pm 0.53
HDL:Cholesterol	0.29 \pm 0.05	>0.2	0.29 \pm 0.07
HDL:LDL	0.47 \pm 0.13	>0.24	0.46 \pm 0.18
S-LDL Cholesterol	3.05 \pm 0.91	0-4.0	3.47 \pm 0.91*
BMI	16.6 \pm 3.21		17.7 \pm 3.01

Data presented as mean \pm SD

* indicates statistical significance of $p < 0.05$ compared low BMD versus normal BMD

5. Biochemical Assessment

5.1. Serum Minerals

Serum minerals were similar in the different eating disorder subgroups.

Serum minerals were comparable amongst subjects with a normal and low bone mass, except for a slightly, albeit significantly higher ($p = 0.018$) phosphate in the osteopenic subjects. Mean phosphate levels documented for both groups were still within normal reference values.

Table 7: Serum minerals in subjects with a normal and low BMD

	Normal BMD	Normal laboratory reference values	Low BMD
Total Ca (mmol/l)	2.37 ± 0.09	2.1 – 2.6	2.4 ± 0.09
Ca (cor Alb) (mmol/l)	2.24 ± 0.07	2.1 – 2.6	2.26 ± 0.06
Mg (mmol/l)	0.87 ± 0.07	0.75 – 1.0	0.89 ± 0.09
PO ₄ (mmol/l)	1.27 ± 0.17	0.8 – 1.4	1.35 ± 0.15 *

Data presented as mean ± SD

* indicates statistical significance of $p = 0.018$ compared low BMD versus normal BMD

5.2. Bone Turnover parameters

Bone turnover in these eating disorder patients was assessed by analysis of serum osteocalcin and urinary deoxypyridinoline. Due to the known diurnal variation of these bone markers, all samples were collected between 10h00 and 12h00. The results of markers of bone formation (osteocalcin) and bone resorption (deoxypyridinoline) are seen in Table 8.

Mean urinary deoxypyridinoline (U-DPD/Cr ratio) was normal and comparable in those with a low and normal BMD.

Table 8: Bone turnover parameters in subjects with a normal and low BMD

	Normal BMD	Normal laboratory reference values	Low BMD
S- osteocalcin	8.1 ± 3.8	2.7 – 6.9 ng/ml	8.5 ± 4.1
U-DPD/Cr Ratio	8.3 ± 2.3	1.4 – 13.6nmol/mmol	8.9 ± 2.7
dU –Ca/dUCr Ratio	0.38 ± 0.23	2.8 - 3.7	0.51 ± 0.21 *
TRP%	87.6 ± 5.2	85 - 95	84.6 ± 6.4

Data presented as mean ±SD ; TRP% = % Tubular resorption of phosphate

*indicates statistical significance (p=0.05) compared to low BMD versus normal BMD

steocalcin levels were elevated (>6.9) in 60% of the total patient population, but the levels were similar in those with and without a low BMD (Table 8). In the total patient population no correlation between body mass index (BMI) and osteocalcin or between BMD and osteocalcin could be demonstrated. However, we did find a correlation between osteocalcin and age ($r = -0.33$; $p = 0.013$) in these patient population. The osteocalcin levels of patients who exercised more than 6hours/week were significantly ($p<0.05$) higher than those who exercised less than 6 hours (Figure2).

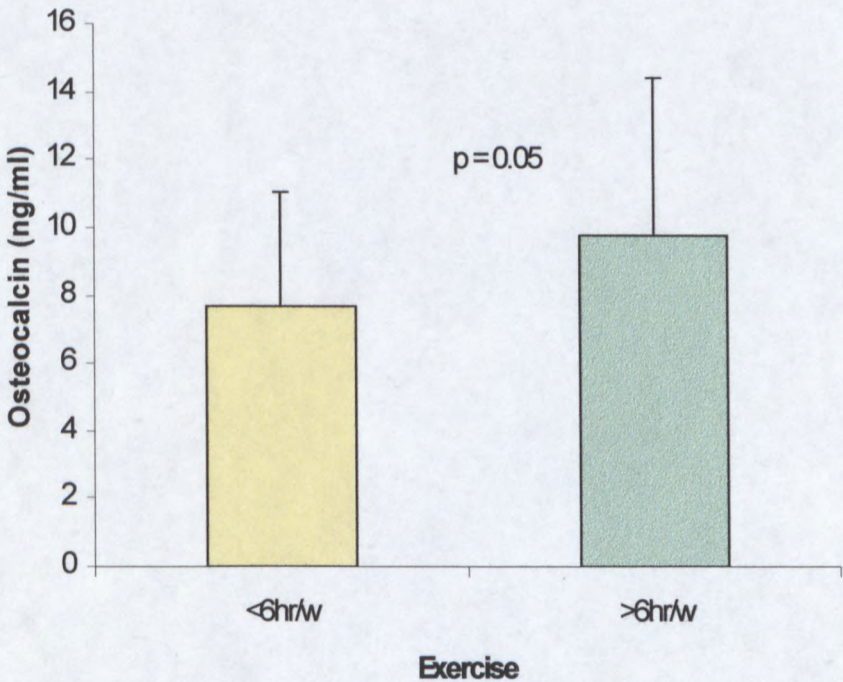


Figure 2: Relationship between osteocalcin and exercise

5.3. Hormonal levels

5.3.1. Sex hormone and prolactin levels

Mean plasma estrogen in patients with eating disorders were low and consistent with early follicular phase levels (Table 9). Serum gonadotropin, prolactin and testosterone levels were normal. No correlation could be demonstrated between BMD and any of the sex hormone levels.

Sex hormone binding globulin (SHBG) was also measured, as a surrogate marker of estrogen status. SHBG levels tended ($p = 0.06$) to be lower in patients with a low BMD. In the AN group, SHBG levels were in fact significantly lower ($p = 0.03$) in the osteopenic patients, compared to those with a normal BMD. No correlation between SHBG and BMI or BMD could be demonstrated in these patients.

A negative correlation could be demonstrated between serum cortisol and LH ($r = -0.3$; $p = 0.03$), FSH ($r = -0.5$; $p = 0.0001$) and E2 ($r = -0.3$; $p = 0.049$).

Table 9: Sex hormone and prolactin levels of subjects with normal and low BMD

	Normal BMD	Normal laboratory reference values	Low BMD
E2 (pmol/l)	193.7 ± 196	95 – 580	170.7 ± 118.2
LH (U/l)	4.5 ± 5.3	1.7 – 49.0	5.5 ± 7
FSH (U/l)	4.9 ± 3.2	1.1 – 24.9	7.1 ± 10.6
Testosterone (nmol/L)	1.31 ± 1.06	0.4 – 3.1	1.25 ± 0.81
SHBG (nmol/l)	69.7 ± 18.1	50 – 90	62.3 ± 17.9
Prolactin (µg/l)	9.3 ± 8.9	3.0 – 19.0	5.8 ± 4.2
Data presented as mean ±SD			

5.3.2. Cortisol, growth hormone and thyroid hormones (TSH, T4)

Timed serum and urinary free cortisol levels (expressed per unit creatinine) were within the normal range in all patients. These values were also similar in subjects with normal versus low bone mass, as well as in the different eating disorder patients. Cortisol values (measured in serum and urine) did not correlate with BMD, but a significant negative correlation between cortisol and osteocalcin ($r = -0.3$; $p = 0.038$) was noted in the total patient population.

Growth hormone (GH), thyroid stimulating hormone (TSH) and serum free thyroxine (T4) levels were similar in subjects with and without a low BMD.

Table 10: Serum and urine free cortisol levels, growth hormone and thyroid hormones (TSH, T₄) in subjects with a normal and low BMD

	Normal BMD	Normal laboratory reference values	Low BMD
S-Cortisol (nmol/l)	388.7 ± 243.5	171.1 – 800.4nmol/l VM	426.2 ± 202.2
U-Cortisol/u Cr (nmol/l)	11.1 ± 7.4	7.7 - 15.6 nmol/l	10.5 ± 8.9
Growth Hormone	9.5 ± 10.7	13.5 mU/L	9.47 ± 8.1
TSH	1.24 ± 0.78	0.47 – 6.9	1.35 ± 0.62
T ₄	14.2 ± 2.9	9.7 – 25.7 pmol/l	13.6 ± 4.9

Data presented as mean ±SD

6. Menstrual Characteristics

Age of menarche was comparable in the three eating disorder groups. Of the 59 patients, only one patient presented with primary amenorrhoea. In the total patient population, 83% of the patients had a history of amenorrhoea at some stage during their illness. At the time of evaluation amenorrhoea was documented in 61% of the subjects. The duration of amenorrhoea tended to be longer in the AN patients ($p = 0.07$). As per definition, 100% of the AN patients were amenorrhoeic, whereas 29% and 35% of the BN and EDNOS respectively were also amenorrhoeic.

Table 11: Menstrual characteristics of the eating disorder subgroups

	AN	BN	EDNOS	Total
n	25	17	17	59
Age at menarche (yr)	12.6 ± 0.9	12.5 ± 1.0	12.9 ± 1.2	12.7 ± 1.0
History of amenorrhoea n(%)	25 (100)	11 (64)	13 (76)	49 (83)
Presence of amenorrhoea n(%)	25 (100)	50 (29)	6 (35)	36 (61)
Duration of amenorrhoea (mth)	49.4 ± 75.3	23.2 ± 35.0	12.1 ± 13.6	30.8 ± 54.3

Data presented as mean ±SD

Data presented as n (%)

The age at menarche and a positive history of amenorrhoea were similar in subjects with a normal and low BMD. At the time of evaluation amenorrhoea occurred more commonly in patients with a low BMD (78% versus 47%). Of particular interest was the observation that the duration of amenorrhoea differed significantly ($p = 0.0048$) between these two groups. We could in fact demonstrate a significant negative correlation between the duration of amenorrhoea and lumbar BMD (Z-Score) in the total patient population ($r = -0.4$; $p = 0.007$), as well as in the different subgroups (AN $r = -0.4$, $p = 0.03$; BN $r = -0.6$, $p = 0.008$; EDNOS $r = -0.6$, $p = 0.005$).

Table 12: Menstrual characteristics of subjects with normal and low BMD

	Normal BMD	Low BMD
n	32	27
Age of menarche (yr)	12.7 ± 0.8	12.6 ± 1.2
History of amenorrhoea n(%)	25 (78)	23 (85)
Presence of amenorrhoea n(%)	15 (47)	21 (78)
Duration of amenorrhoea (mth)	12.4 ± 16	53.5 ± 74*

Data presented as mean ±SD

Data presented as n (%)

* indicates statistical significance ($p = 0.009$)

Amenorrhoea was of longer duration in the osteopenic patients compared to the patients with a normal bone mass in the AN and BN groups as seen in Figure 3.

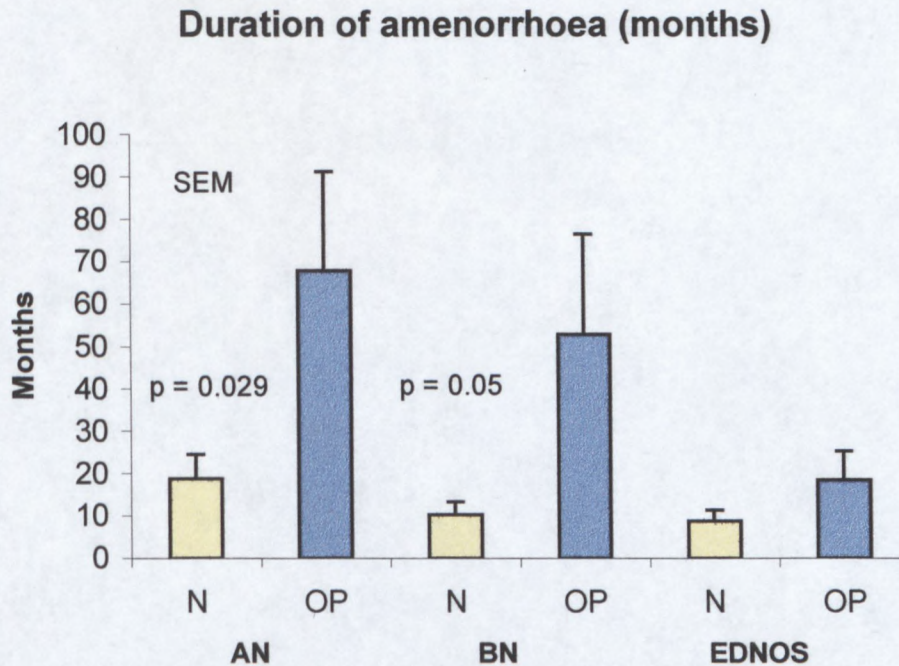


Figure 3: Duration of amenorrhoea in the subgroups with normal and low lumbar (L1 - L4) BMD.

Figure 4 compares body weight, mean serum estradiol and average lumbar BMD in patients with normal menses (Group 1), those with oligomenorrhoea i.e. scant or absent menses, but not for periods of 3 months or longer (Group 2), and those with secondary amenorrhoea i.e. absent menses for a period of 3 months or longer (Group 3).

Compared to subjects with a normal menstrual cycle, those with oligomenorrhoea and especially those with amenorrhoea had significantly lower weight ($p=0.006$), body mass index (BMI) ($p = 0.0008$), estradiol levels ($p = 0.017$), and lumbar BMD (L1-L4, Z-Score) ($p = 0.008$) (Figure 4).

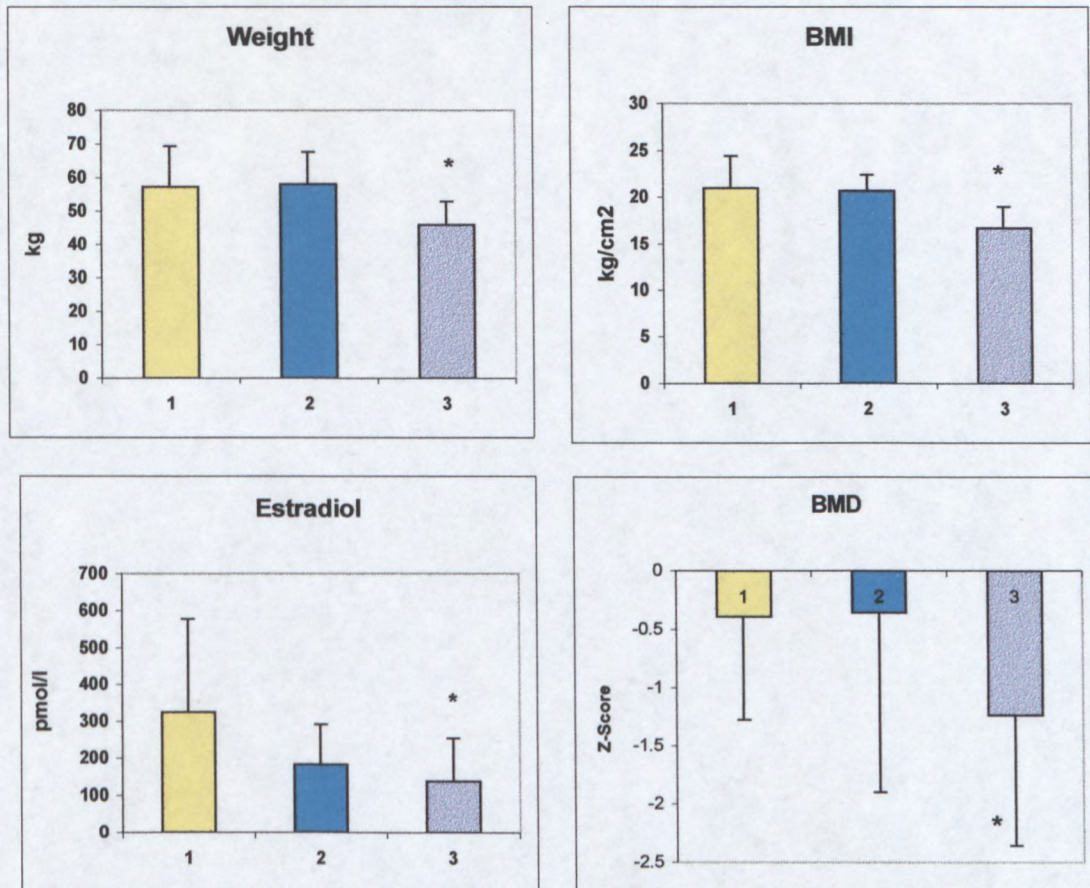


Figure 4: Comparison between weight, BMI, Estradiol and BMD in patients with normal menses (Group1), oligomenorrhoea (Group 2) and amenorrhoea (Group 3). The p value is for comparison of Group 1 and Group 3. * Indicates statistical significant at $p < 0.05$

CHAPTER 5

DISCUSSION

One of the difficulties in assessing the pathophysiology of eating disorder-induced osteoporosis involves the diverse way in which these subjects may manifest clinically. Patients with eating disorders may present for treatment after 6 months or 26 years of illness. Severity can range from those with a normal body mass index (BMI) with little overt disability to severe emaciation, a BMI of less than 12 and failure of major organ systems. Onset of disease can occur at any time from childhood to maturity, although it classically occurs within a few years of menarche. The impact on the skeleton is likely to vary considerably depending on these factors. For example, a period of anorexia nervosa (AN) during childhood is likely to result in stunted growth, whereas onset of the illness during the late teens and early twenties is likely to result in a failure to attain peak bone mass and increased risk of developing osteoporosis.

Understanding the pathogenesis of osteoporosis in these patients is further confounded by the fact that many studies have made no effort to differentiate between the different categories of eating disorders and have often employed a heterogeneous study population. In the present study we have paid particular attention to the correct classification of specific eating disorders - a diagnosis of anorexia nervosa (AN), bulimia nervosa (BN), or eating disorder not otherwise specified (EDNOS) was made by a single qualified psychiatrist employing the DSM IV diagnostic criteria (*DSM IV, 1994*).

In previous studies, the majority of women with AN show evidence of bone loss and approximately 50% have **bone mineral density (BMD)** values more than 1 SD below age and sex-matched controls (*Rigotti et al, 1984; Biller et al, 1989; Bachrach et al, 1990; Davies et al, 1990*). Our study is in agreement with these previous reports of low bone mass in patients with AN. There is little information

available on changes in BMD in the different eating disorder subgroups. The effect of bulimia nervosa (BN) on bone mass is largely unknown and both decreased (*Howat et al, 1989*) and normal (*Sundgot-Borgen et al, 1998*) BMD values have been reported. In the present study, low BMD (Z-Score 1 - 2 SD below the norm) occurred in 64% of AN patients as well as in 30% of BN and 35% EDNOS patients. More severe osteopenia (Z-Score < -2 SD) was not exceptional and occurred in approximately one third of those subjects with a low BMD.

The bone mass deficit documented in these patients has been shown to manifest as an increase in skeletal fragility **fractures**, usually involving the spine, hip or long bones (*Ayers et al, 1984; Brotman et al, 1985; Kaplan et al, 1986; Treasure et al, 1987; Biller et al, 1989; Rigotti et al, 1991; Klibanski et al, 1995; Rose et al, 1999; Hartman et al, 2000*). It has been suggested that patients with AN have a 7X higher incidence of fractures compared with healthy young women (*Kaplan et al, 1986; Verbruggen et al, 1993; Rigotti et al, 1991*). It is also known that patients who have sustained one or more fragility fracture are at increased risk of subsequent fracture, for any given BMD value (*Kanis et al, 1997*). In our study a history of previous fractures was obtained in 24% of the total patient population (AN=28%, BN=11.7%, EDNOS=29.4%). The average hip BMD of subjects with a history of fracture (Z-Score = -1.5) tended to be lower than that of individuals with no fracture history (Z-Score = -0.9), but this did not reach statistical significance ($p = 0.09$). This is most likely a function of the small number of fracture subjects, but may also reflect the temporal relationship between a BMD value obtained at one point in time and a previous history of fracture, not infrequently sustained many years previously.

Nature of the osteoporosis

Clinical (**lumbar versus hip bone loss**) and biochemical (**low versus high bone turnover**) parameters to determine the nature of eating disorder-induced osteoporosis revealed interesting results. Contrary to some previous reports, our study showed that osteopenia was not confined to the lumbar spine, but also involved total hip. A low total hip BMD was present in 56% of subjects in whom

the hip BMD was assessed. Moreover, the degree of hip (Z-Score = -1.66) and spinal (Z-Score = -1.89) bone loss was comparable in our study, supporting previous reports (*Grinspoon et al, 1999*) that trabecular and cortical bone are involved to the same extent.

Bone turnover data based on previous studies of patients with eating disorders suggest an uncoupling phenomenon, with an increase in bone resorption and a decrease in bone formation (*Fonesca et al, 1993; Grinspoon et al, 1997; Hotta et al, 2000*). Reasons for these observations remain unclear, although it is conceptually feasible that severe malnutrition and hypercortisolemia may be primarily responsible for the decreased bone formation/osteocalcin levels, whereas increased bone resorption/deoxypyridinoline excretion may largely reflect the hypo-estrogenemia known to occur in these patients. Our study could not confirm this uncoupling in bone turnover and, instead, revealed a modest increase in serum levels of the bone formation marker osteocalcin, and normal urinary excretion of deoxypyridinoline, an index of osteoclastic bone resorption.

The young age of this study population may be one of the reasons why the osteocalcin levels were not decreased as expected. Despite small patient numbers a negative correlation between serum osteocalcin and age ($r = -0.33$; $p = 0.013$) could in fact be demonstrated in our study. Exercise, is another factor that may have contributed to the slightly raised osteocalcin levels observed. All our patients were physically active and 30% exercised more than 6 hours per week. Osteocalcin levels of patients who exercised more than 6 hours per week were significantly higher ($p < 0.05$) than those who exercised less. The decrease bone formation and increased bone resorption previously documented in patients with eating disorders have been ascribed, at least in part, to hypercortisolemia. Our patients, however, had normal serum and urinary free cortisol levels. Finally, it would appear as if the severity of the malnutrition and emaciation is an important determinant of bone-turnover in these patients. Hotta et al. (2000) claimed that deoxypyridinoline levels were significantly increased, but normalised in patients when body mass index (BMI) values reached 16.5 to 18.5 kg/m². Given the fact that the average BMI of our study population was 18.1 kg/m², it is not surprising that their turnover markers were largely within normal limits. The

markers of both resorption (deoxypyridinoline) and bone formation (osteocalcin) tended to be higher in the osteopenic patients group, compared to those with a normal bone mass. Although this did not reach statistical significance, the trend towards an increase in bone markers observed in the osteopenic group, favour a high turnover pathogenesis and not bone loss due to a reduced formation rate.

Clinical (historic) risk factors

Osteoporosis is a multifactorial disease, largely determined by genetic, life-style and ageing factors, not infrequently precipitated by bone toxic drugs and /or medical diseases. In the present study, patients with a history of any medical diseases or drugs known to adversely influence bone health were excluded. We, therefore, largely evaluated life-style factors to determine whether they contributed towards the low BMD observed in 46% of our patient population.

Body weight is an essential factor in the development and maintenance of bone mass at all ages (*Holbrook et al, 1993*). A number of studies in patients with AN have reported a correlation between BMD and BMI (*Treasure et al, 1986; Bachrach et al, 1990*) or total body weight (*Kiriike et al, 1992*). In the present study BMD correlated significantly ($r = 0.4$; $p = 0.0015$) with BMI. A low BMI therefore proved to be a major predictor of osteopenia in these eating disorder patients.

Exercise has a dual effect on bone and both a sedentary life style and excessive exercise may have a negative influence on bone health, and predict a low BMD (*Joyce et al, 1990; Kanis, 1994b*). All the patients in this study were physically active, without clear evidence of exercise abuse. No correlation between BMD and the extent of exercise could be documented.

Alcohol is known to have a direct inhibitory effect on osteoblastic bone formation and may also adversely influence skeletal integrity via effects on sex hormone levels, vitamin D metabolism, renal calcium handling and glucocorticoid homeostasis (*Arden, 1997*). Severe alcohol intake was documented in only one

AN and three BN patients in our study. However, patients with a low BMD consumed significantly more alcohol than those with a normal BMD.

A **history of amenorrhoea** was more prevalent among the AN patients. This is not surprising given the fact that amenorrhoea is a diagnostic criterion for AN. Menstrual irregularities were, however, described in approximately 50% of women with BN (*Sungot-Borgen et al, 1998*). In the present study a history of amenorrhoea also occurred frequently in the BN (64%) and EDNOS (82%) groups. There was a significant difference in the duration of amenorrhoea in the osteopenic subjects compared to those with a normal bone mass. In fact, the duration of amenorrhoea correlated significantly ($r = -0.4$; $p = 0.001$) with BMD in the total patient population.

The failure of life-style factors such as exercise, dietary calcium intake or smoking to predict bone density in these patients is not surprising and merely underscores the fact that these risk factors influence bone mass over many years and often lack the necessary sensitivity in cross-sectional analyses. The study did, however, show that a low BMI, alcohol consumption and especially the presence and duration of amenorrhoea were useful clinical predictors of a low BMD.

Etiopathogenesis of osteoporosis

The reasons for bone loss in eating disorder patients are multifactorial, complex and may involve nutritional factors (inadequate calcium intake, low vitamin D, frank malnutrition), mechanical factors, hypercortisolemia and hypogonadism (hypo-estrogenemia).

Nutritional factors

It is well known that undernutrition can markedly decrease osteoblastic bone formation (*Grinspoon et al, 1996a*) and the role of leptin, IGF-I and macro-and micronutrients in this process has been discussed (see p 27).

The nutritional assessment of our patients yielded somewhat paradoxical information. On the one hand, the anthropometric data (BMI) suggested a state of undernutrition. At the same time, the biochemical data revealed normal serum albumin, cholesterol and mineral levels. Furthermore, total energy intakes appeared to be within the normal range. These findings were not consistent with significant protein calorie malnutrition. The undernutrition of eating disorders is, however, complex and not strictly comparable to that of classical protein-energy malnutrition.

It is also known that starvation causes growth retardation, and a decrease in growth hormone (GH) and osteocalcin levels. Adults who experienced growth retardation in childhood often have a decreased bone mass even when the BMD is corrected for their smaller size. Patients included in this study had normal GH and osteocalcin levels and reached their expected height.

A poor **calcium intake** has been associated with lower bone mass in population studies (*Cumming, 1990*), and may theoretically contribute towards the pathogenesis of eating disorder-induced osteoporosis. A recent NIH consensus conference (1994) has proposed a 1200 - to 1500 mg calcium intake as optimal in adolescents and young adults. On average, our patients consumed 658 mg calcium per day – i.e. 55% of the RDA. It is known that patients with AN may adapt to their low dietary calcium, and maintain calcium balance on extremely low intakes (*Callagher and Riggs, 1978*). Moreover, we found no significant relationship between self-reported calcium intake and measured bone mineral density in these patients. These results were similar to findings in other studies (*Rigotti et al, 1984; Biller et al, 1989; Bachrach et al, 1990*)

Vitamin D metabolism is highly variable in eating disorder. The majority of studies have demonstrated normal plasma levels of 25(OH) vitamin D (*Rigotti et al, 1984, Kaplan et al, 1986; Olmos et al, 1991*), while some reported elevated (*Carmicheal and Carnichael, 1995*) and yet others low or undetectable levels (*Fonseca et al, 1988; Verbruggen et al, 1993*). Vitamin D deficiency may cause secondary hyperparathyroidism and mineralization defects. In the present study,

mean plasma 25(OH) vitamin D levels were, however, well within the normal range.

In conclusion:

Although it is conceivable that nutritional factors may have contributed initially to the low bone mass observed in patients with eating disorders, our study provided no data to suggest that nutritional factors played a significant on-going role in the development of eating disorder-induced osteoporosis.

Mechanical factors

The role of **body weight** and physical exercise in the attainment and maintenance of BMD has been discussed (see p 31). Suffice to point out that in the present study, body weight expressed as BMI correlated significantly with lumbar BMD ($r = 0.4$; $p = 0.0015$) as well as hip BMD ($r = 0.55$; $p = 0.001$), and that a low BMI was a useful clinical predictor of a low BMD.

Excessive physical **exercise** is known to be associated with a low BMD in female as well as male, endurance athletes (*Drinkwater et al, 1984*). In the patients presented here, activity scores were quantitated and excessive exercise was found to be uncommon. Forty-four percent of the AN patients did exercise more than 6h/week, whereas only 18% of the BN and EDNOS patients exercised more than 6h/week. However, data demonstrated that the osteopenic subjects did not exercise more than those with a normal bone mass. We could also not demonstrate a correlation between exercise and BMD. These observations are in accordance with previous reports which generally failed to show a correlation between exercise and BMD (*Biller et al, 1989; Hay et al, 1989; Bachrach et al, 1991*). Rigotti et al (1984) in fact suggested that exercise may protect against bone loss. Our own data, while failing to show a correlation between exercise and BMD, did document higher osteocalcin values in those patients who exercised more than 6h/week.

In conclusion:

While a low body weight may predispose eating disorder patients to osteoporotic fractures, our study did not incriminate exercise abuse as an important etiologic factor. If anything, exercise appeared to protect against bone loss.

Hypercortisolism

Glucocorticoids directly inhibit osteoblastic bone formation and indirectly cause a PTH-mediated increase in bone resorption via effects on intestinal and renal handling of calcium and a decrease in plasma estrogen levels. Elevated serum and urinary cortisol levels have been reported in women with AN (*Newman and Halmi, 1988; Biller et al, 1989, Carmichael and Carmichael, 1995*) and BN (*Mortola et al, 1989*).

Due to the single measurement of cortisol, it was difficult to investigate the contribution of hypercortisolism to bone loss in our eating disorder patients. The significant negative correlation between serum cortisol and osteocalcin, as well as a relationship between cortisol and the plasma sex hormones, however, suggested that our data were indeed valid. None the less, a number of factors argued against an important role for hypercortisolism in the development of osteoporosis in these patients. Firstly, neither serum nor urinary free cortisol levels were found to be elevated in either the total patient population or in those with a low bone mass. Secondly, neither serum nor urinary cortisol levels correlated with BMD. Thirdly, biochemical parameters of bone formation and resorption revealed no evidence of the typical steroid-induced uncoupling phenomenon.

In conclusion:

A significant negative correlation between serum cortisol and osteocalcin and between cortisol and plasma sex hormone levels could be demonstrated in our eating disorder patients and underscores the potential deleterious effects of hypercortisolemia on bone health. Our data do not, however, suggest a primary etiologic role for hypercortisolism in the development of eating disorder osteoporosis.

Hypogonadism

Estrogen deficiency, regardless of its cause, is a major determinant of BMD, and has been suggested as one of the key factors in the pathogenesis of osteopenia in the eating disorder patient. Studies have, however, failed to show a correlation between serum estradiol concentrations and BMD (*Rigotti et al, 1984; Bachrach et al, 1991; Joyce et al, 1990*).

In this present study we observed low serum estradiol levels in our eating disorder population as a whole, but could not demonstrate a correlation between BMD and estrogen levels. This is not surprising given the fact that a single estrogen measurement is not sufficient to assess gonadal status. We therefore also determined sex hormone binding globulin (SHBG) levels and obtained a detailed history of menstrual abnormalities and their duration.

Plasma SHBG is increased by estrogen (*Goldfien and Monroe, 1997*). This surrogate marker of estrogen status was significantly lower in the AN patients with a decreased BMD, compared to those with a normal bone mass. Moreover, we could show that BMD correlated negatively with the duration of amenorrhoea in our total patient population. This observation is in accordance with the findings of *Biller et al, (1989)*, although a number of previous studies have failed to document this relationship (*Joyce et al, 1990; Bachrach et al, 1991*). Of particular interest was the observation that all our bulimic patients with a low BMD, experienced amenorrhoea at some stage during their illness. This is in agreement with the findings of *Howat et al, (1989)* who published the first work on osteoporosis in BN.

In conclusion:

The presence of amenorrhoea, regardless of the type of eating disorder, was associated with a significantly lower body weight, BMI, estrogen level and BMD, compared to subjects with oligomenorrhoea and especially those with normal menses. SHBG levels were lower in subjects with a low BMD. Estrogen deficiency is known to cause high turnover osteoporosis – this subset of the syndrome would not be incompatible with the biomarker data observed in our patients.

These observations allowed us to conclude that although nutritional and mechanical factors as well as hypercortisolism may play a permissive role in the development of eating disorder osteoporosis, this condition largely results from chronic hypogonadism.

CHAPTER 6

1. Study limitations

The present study assessed eating disorder patients in a cross-sectional fashion employing a single out-patient visit. Moreover, only patients with eating disorders were included and compared in this study. More detailed evaluation, including the assessment of appropriate control groups, would have made comparison between normal and eating disorder patients possible, thereby adding to findings observed in this study.

We are confident that interpretation of our BMD data is sound. Precise definition of the term "osteoporosis" in young, premenopausal subjects remain controversial. This term has therefore been avoided throughout the text and a "low bone mass" or "osteopenia" is used instead. We furthermore accept that our definition of a "low bone mass" and "more severe osteopenia" is an arbitrary one. Classification of biological variables in terms of 1 and 2 standard deviations below /above the norm is, however, conventional. None the less, we agree that the use of Z-scores to assess the risk of future fractures will need to be verified by prospective studies.

In the present study, we concluded that nutritional and mechanical factors as well as hypercortisolemia did not contribute significantly to bone loss observed in this study population of eating disorder patients. Hypogonadism, on the other hand, appeared to be the main cause of bone loss. We accept that these conclusions would have been substantiated by the inclusion of a control group. Moreover, more detailed assessment of nutritional status (e.g. inclusion of serum leptin, IGF-1 and resistin levels) and glucocorticoid metabolism (e.g. diurnal variations, dexamethasone suppression tests) would have added credence to our conclusions.

Finally, we need to take cognisance of the fact that a low BMD is but a risk factor for development of fracture. The present study did not assess the prevalence of fractures. The true clinical significance of the alterations in bone and mineral metabolism observed in these patients with eating disorders therefore remain unknown.

Directions for future research

The present study documented a high prevalence of osteopenia in patients with eating disorders. Longitudinal follow-up of BMD in this population and especially in those subjects with documented osteopenia, will be of interest. The influence of an improvement in the eating disorder on BMD will be of particular interest. The assessment of more sophisticated biochemical parameters of nutrition (e.g. leptin, IGF-1), as well as the impact of improved nutrition, may yield interesting information. Moreover, the influence of hormone replacement therapy, especially in those individuals with documented hypogonadism, on bone health should be evaluated. Finally, the incidence of skeletal fracture, and the impact of various nutritional, mechanical and hormonal interventions, in patients with defined eating disorders should be studied, in order to assess the clinical importance of this syndrome as a risk factor for the development of osteoporotic fractures.

CHAPTER 7

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ADDENDUM I

Risikofaktor Vraelys

RAS:

OUDERDOM:

FAMILIEGESKIEDENIS van OSTEOPOROSE:

LIGGAAMSBOU:

Lengte:

Gewig:

LMI:

ALKOHOL:

Aantal sopies per dag:

Geen (0) / Matig - < 4 sopies/dag (1) / Straf - ≥ 4 sopies/dag (2)

ROOK:

Aantal per dag:

KALSIUMINNAME:

Geen (0) / Onvoldoende (1) / Voldoende (2)

SISTEEMSIEKTES:

BEENTOKSIESE MIDDELS:

FRAKTUURGESKIEDENIS:

Aantal Frakture:

Tipe Fraktuur:

AKTIWITEITSVLAK:

Tipe oefening:

< 1 h/wk:

1 - 6h/wk:

> 6 h/wk:

MENSTRUELE GESKIEDENIS:

Ouderdom van menarg:

Siklus:

Absoluut normal (0):

Oligonormaal (1):

Amenoree - afwesigheid van stondes 3mnde of meer (2):

Ouderdom wanneer Amenoree begin:

Duurte van Amenoree:

Kontrasepsie:

Ja / Nee

ADDENDUM II

Risk Factor Analysis

GENDER:

RACE:

FAMILY HISTORY OF OSTEOPOROSIS:

ANTROPOMETRIE:

Length:

Weight:

BMI:

ALCOHOL:

Toads per day:

None (0) / Mild - <4 units/day (1) / Severe - ≥ 4 units/day (2)

SMOKING:

Cigarettes per day:

CALCIUM INTAKE:

Supplements: yes / no

Diet: none (0) / inadequate (1) / adequate (2)

DISEASES INFLUENCING BONE:

BONE TOXIC DRUGS:

FRACTURE HISTORY:

Number of fractures:

Type of fracture:

ACTIVITY LEVEL:

Type of exercise:

< 1h/wk:

1 - 6 h/wk:

> 6h/wk:

MENSTRUAL HISTORY:

Age of menage:

Cycle:

Normal (0):

Oligomenorrhoea (1):

Amenorrhoea - no menses for the last 3 months (2):

Age of Amenorrhoea:

Duration of Amenorrhoea:

Contraception:

Yes/No

ADDENDUM III

DIEET INLIGTING

Naam:

Diagnose:

Geboortedatum:

Ouderdom:

Gewig:

Lengte:

[illegible]

Adapted from: Department of Nutrition, Tygerberg Hospital

'n VEREENVOUDIGE FREKWENSIE VRAELYS

[illegible]

Adapted from: Department of Nutrition, Tygerberg Hospital

ADDENDUM IV

DIET INFORMATION

Name:

Weight:

Diagnosis:

Length:

Date of birth:

Age:

[illegible]

Adapted from: Department of Nutrition, Tygerberg Hospital

SIMPHIZE FREQUENCY QUESTIONNAIRE

[illegible]

Adapted from: Department of Nutrition, Tygerberg Hospital



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