Osteoporosis around the menopause : occurrence, determinants and preventive drug treatment

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Osteoporosis around the menopause

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Het schilderij afgebeeld op de voorkant van dit proefschrift, heeft als titel “Sigaretje roken” en is geschilderd in 1917 door Joseph Seckel. Dit prachtige kunstwerk is in 1919 tentoongesteld op de Tentoonstelling van Nederlandse Beeldende Kunst in Zwitserland. Joseph Abraham Seckel is geboren in Rotterdam 23 december 1881, woonde en werkte in Rotterdam, Amsterdam en Parijs, overleed 3 maart 1945 in Den Haag. Hij signeerde meestal met Jos. Seckel. Hij schilderde, tekende, aquarelleerde, etste en lithografeerde stillevens, figuren, portretten en landschappen. [Dit kunstwerk is particulier eigendom]

Osteoporosis around the menopause

occurrence, determinants
and preventive drug treatment

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit Maastricht,
op gezag van de Rector Magnificus,
Prof. Dr. A.C. Nieuwenhuijzen Kruseman,
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
op vrijdag 18 mei 2001 om 16.00 uur

door

Gerrina Lenette Leusink

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*Als ik oud word neem ik blonde krullen
ik neem geen spataders, geen onderkin,
en als ik rimpels krijg omdat ik vijftig ben
dan neem ik vrolijke, niet van die lange om mijn mond
alleen wat kraaiepootjes om mijn ogen.*

JUDITH HERZBERG

Uit het gedicht 'Een kinderspiegel'

Contents

Chapter 1	General introduction	9
Chapter 2	Osteoporosis: Epidemiological and clinical aspects	13
	2.1 Definition of osteoporosis	14
	2.2 Pathophysiology of osteoporotic fractures	15
	2.3 Risk factors	17
	2.4 Measurement of bone density	20
	2.5 Identification of patients at risk	23
	2.6 Prevention of osteoporosis	25
	2.7 Treatment of osteoporosis	28
	2.8 Compliance	36
Chapter 3	General design of the Eindhoven Perimenopausal Osteoporosis Study (EPOS)	47
	3.1 Introduction	48
	3.2 Background	48
	3.3 Design of the Study	49
Chapter 4	The prevalence of low bone mineral density in Dutch perimenopausal women: The Eindhoven Perimenopausal Osteoporosis Study	53
Chapter 5	Is depressed mood a risk factor for low bone mineral density in perimenopausal women?	65
Chapter 6	Prevention of early postmenopausal bone loss: A randomised trial of calcium, HRT and pamidronate in women with low bone mass selected from a population-based cohort and one-year follow-up	77
Chapter 7	Compliance to an oral bisphosphonate therapy in women with early postmenopausal bone loss	93
Chapter 8	General discussion	105
Chapter 9	Summary	119

Chapter 10	Samenvatting	123
	Publications	127
	Appendix	129
	Dankwoord	149
	Curriculum vitae	153

CHAPTER 1

General introduction

Over the past twenty years, osteoporosis has been the subject of intensive research, and the results have been encouraging. Therefore, it is generally accepted that, today, osteoporosis can be diagnosed, and to a large extent prevented and treated. Already in 1941, Albright *et al.*¹ defined osteoporosis pathologically and reviewed the clinical history of 42 patients. In their study, they described several etiological factors, including postmenopausal status. Subsequently, in 1947, they reported that osteoporosis was attributed to the decrease in oestrogen production following the menopause.²

In many countries, osteoporosis is the most common metabolic bone disease. In view of increasing life expectancy and changes in lifestyle, osteoporosis is now recognised as being one of the most common and serious problems faced by postmenopausal women and aging persons of both sexes, and is seen as an important health problem in the Western world and Asia. In the USA, approximately 1.5 million fractures a year are attributable to osteoporosis: these include 700,000 vertebral fractures, 250,000 distal forearm (Colles') fractures, 250,000 hip fractures, and 300,000 fractures at other limb sites. The lifetime risk of fractures of the spine (symptomatic), hip, and distal radius is 40% for white women and 13% for white men aged 50 years or older. Following a hip fracture, there is 10-20% mortality over the subsequent six months, 50% of patients will be unable to walk without assistance, and 25% will require long-term home care.³ The annual cost of osteoporosis to the US health system is at least US\$ 5-10 billion.³ In 1999 in the Netherlands, there were 18,475 registered hospital admissions for hip fractures in a population of 15 million, a quarter of which occurred in men.⁴ The one-year incidence of hip fractures (per 100,000 persons) increased from around 40 at the age of 55-59 years to about 3150 over the age of 95 years in men, and from around 40 to about 4450 in women of the same ages.⁴ The annual costs of treating patients with hip and spinal fractures amount to NLG 330 million and NLG 35 million, respectively, and account for around 0.6% of the national health care budget.⁵ These already high costs will increase further with the continued aging of the population, and will lead to at least a doubling of the number of patients with fractures over the coming 40 to 50 years. Seventy-five percent of all hip fractures occur in women. Women have a lower peak bone mass than men at many skeletal sites. In addition to this lower peak bone mass, women have a greater age-related loss, which is accelerated by the menopause. The average rate of bone loss in both men and women is approximately 1% per year starting from middle age, whereas, in women, higher rates of bone loss (2-4% per year) occur in the first five to ten year following the menopause, due to oestrogen deficiency.⁶ Women also have a longer life expectancy than men and so they are exposed to lower bone mass and a higher cumulative risk for falls for a longer period during their lives. Although differences in bone mass are important, there are other factors that account for the differences between the sexes. For example, elderly women fall more often than men, and the differences in bone mass may not entirely explain the different patterns of risk that are found between cultures and races.

Assuming that the literature on risk factors for developing osteoporosis and fractures related to osteoporosis is correct, the incidence, age of the elderly, and care and costs of osteoporotic fractures, will increase world-wide as the ageing population expands. Although we are still uncertain as to the best time for, and best methods of, intervention to prevent this increase,⁷⁻⁹ we do have effective methods for the diagnosis, prevention, and treatment of this disorder.

Background and overview of the thesis

In 1991, the Health Council of the Netherlands (Gezondheidsraad) advised the Secretary of State for Welfare, Public Health and Culture (WVC) on the prevention of osteoporosis: osteoporosis is an important cause of disease, especially in elderly women, and preventive measures of a general nature are strongly recommended. The plea for prevention was that bone mineral density measurements should be carried out in women of menopausal age, in order to gain insight into their bone mineral density and risk of developing osteoporosis and vertebral and hip fractures. In order to evaluate the possibility of prevention of osteoporosis using the measurement of bone mineral density, the Committee recommended that an exploratory study should be carried out in women around the menopause.

Based on the above recommendations, the Prevention Fund approved a research proposal, which resulted in this thesis. The aims of this thesis are:

- to determine the efficacy of two treatment regimens compared to calcium in preventing postmenopausal bone loss in women around the menopause, who are at risk for developing osteoporosis;
- to evaluate compliance to the respective treatment regimens, and to assess the rate of change in bone mineral density after treatment is withdrawn.

Contents of the thesis

Chapter 1 is the general introduction of this thesis.

Chapter 2 provides a general overview of the epidemiology, prevention, and treatment of osteoporosis. Moreover, it considers the effect of medications used in the prevention and treatment of osteoporosis, as well as the different measuring instruments used in this thesis, such as dual X-ray absorptiometry (DXA) and electronic lids for measuring compliance.

Chapter 3 describes the general design of the study, which is divided into a population-based cohort study and a randomised clinical trial, the intervention study.

Chapter 4 presents the baseline characteristics of all women of menopausal age living in the city of Eindhoven: the Eindhoven Perimenopausal Osteoporosis Study

(EPOS), as well as the relationship of these characteristics to osteopenia and osteoporosis.

Chapter 5 describes the relationship between depressive mood and low bone mineral density in this population-based cohort. A validated questionnaire, the Edinburgh Depression Scale (EDS), to assess the suggested association of depressed mood and low bone mineral density (BMD) was used.

Chapter 6 reports the outcome of the two-year intervention study and the follow-up of 392 perimenopausal women who were all treated with 400 mg calcium. The first group (129 women) received calcium only, while in addition the second group (133 women) received hormone replacement therapy (HRT) and the third group (130 women) pamidronate treatment. This chapter also describes the changes in bone loss during the year following cessation of treatment.

Chapter 7 describes the compliance of patients receiving pamidronate during the two years of treatment, measured by electronic microcircuitry, which monitored the opening and closing of the medication package.

Finally, **Chapter 8**, the general discussion, reflects on how this study was designed and carried out. It evaluates the relevance of population-based screening for BMD with DXA in women around the menopause. Further, it discussed the recommendations of the second Health Council Committee (Gezondheidsraad) on the prevention and treatment of osteoporosis from 1998. This advice is compared with the first Dutch Association of General Practitioners (Nederlands Huisartsen Genootschap, NHG) standard on osteoporosis, published in 1999. Recommendations for practice are made, and suggestions for further research are given, with regard to the prevention and treatment of low BMD in women.

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CHAPTER 2

Osteoporosis: Epidemiological and clinical aspects

2.1 Definition of osteoporosis

Osteoporosis is defined as a condition of skeletal fragility, characterised by reduced bone mass and microarchitectural deterioration of bone tissue. Consequently, there is an increase in bone fragility and susceptibility to fracture.¹ Put more simply, osteoporosis is a reduction of both the quantity and quality of bone.

Implicit in the definition of osteoporosis by bone mass alone is the insight into the relationship between low bone mass and risk of fracture. Low bone mass is comparable to high blood pressure or an elevated concentration of serum cholesterol. The risk of fracture rises when bone mass declines, just as the risk of stroke rises together with blood pressure, and as hypercholesterolemia leads to an increased risk of myocardial infarction. Clinically, osteoporosis is recognised by the occurrence of fractures, such as those of the hip and wrist, or by spinal impressions.

According to the World Health Organisation (WHO) criteria, the term osteoporosis is defined as a bone mass value of over 2.5 standard deviations (SD) below the mean value in young adults (T-score)² Low bone mass of osteopenia is defined by a bone density level of between -1 and -2.5 SD below the young normal mean. Established osteoporosis: a bone mineral density (BMD) value of more than -2.5 SD below the young adult mean value ($T \leq -2.5$) and the presence of one or more fragility fractures.

BMD can also be compared with the mean value in normal subjects of the same age and sex (Z-score). A Z-score of less than -1 at either the lumbar spine or the proximal femur would indicate a value in the lowest 25% of the reference range. At this value, the risk of fracture is approximately doubled. A Z-score of less than -2 would indicate a value in the lowest 2.5% of the reference range, a level associated with a considerably increased risk of fracture.

There are two categories of osteoporosis: primary and secondary. Primary osteoporosis is related to postmenopausal conditions, the loss of ovarian function with, thereby, the loss of oestrogen leading to exponential bone loss³ and also to age-related osteoporosis.⁴

In addition to these primary aetiologies, there are many secondary causes, including a large number of illnesses, medications, habits, and lifestyle factors. These secondary causes contribute significantly to bone loss and to the risk of fracture (Table 1). These factors may be solely or partially (together with a primary aetiology) responsible for the individual risk of osteoporosis and fractures. About 20% of women with postmenopausal osteoporosis also have a secondary cause contributing to bone loss. The reported presence of secondary aetiologies for osteoporosis in women with postmenopausal osteoporosis is as high as 64%.⁵

Table 1. Causes of osteoporosis**Endocrine causes**

- hypogonadism (primary and secondary)
- glucocorticoid excess (endogenous and exogenous)
- hyperparathyroidism
- hyperthyroidism

Haematological diseases

- multiple myeloma
- systemic mastocytosis
- lymphoma, leukaemia
- pernicious anaemia

Gastrointestinal diseases

- malabsorption syndromes (e.g., Crohn's disease, coeliac disease)
- chronic liver disease

Connective tissue diseases

- rheumatoid arthritis
- ankylosing spondylitis
- osteoporosis imperfecta

Drugs

- glucocorticoids
- antiepileptic drugs
- anticoagulant drugs

Genetic factors

- positive family history

Lifestyle factors

- nutritional factors
 - low calcium intake
 - excessive alcohol consumption
 - excessive caffeine intake
- low exposure to sunlight
- smoking

Exercise

2.2 Pathophysiology of osteoporotic fractures

As the population ages, the number of people at risk for developing fractures increases. The risk of fracture is correlated with bone mass and to age and menopausal state^{6, 7} The pathophysiology of osteoporosis involves more than just bone mass. Other skeletal components, such as fragility and extraskeletal factors, can lead to fracture. In later life, BMD depends upon the peak bone mass achieved in adolescence^{8, 9} After about 20-25 years of age, no further increase in bone mass is observed, however, peak bone mass is one of the major determinants of BMD¹⁰ The bone mass at skeletal maturity differs between the sexes, and is about 30% higher in men than in women^{8, 11} The interplay between the factors associated with low bone

Figure 1. Factors associated with the development of bone mass, leading to osteoporotic fractures.

mass, leading to osteoporotic fractures, is illustrated in Figure 1. These factors will be discussed later in this chapter.

Bone mass can be used as a predictor of the risk of fracture. Cummings *et al.*³¹ studied hip fractures in 8134 subjects aged 65 years or older, who were enrolled in the study of osteoporotic fractures. Each 1 SD decline in BMD was associated with a 2.4-3.0-fold increase in the age-adjusted risk of hip fracture, depending on the exact site measured. Although bone mass is frequently considered to be the most important determinant of fragility, this is not correct. Ross *et al.*¹³ found that a pre-existent fracture is a stronger predictor of future fractures than low bone mass. Each pre-existing fracture increases the risk of additional fractures two- or three-fold.

A number of other studies^{19,20} have demonstrated that a past history of fracture is an important independent risk factor for further fractures. Thus, the presence of two of more vertebral fractures was associated with a twelve-fold increase in fracture risk for any given BMD,¹⁹ and women with a past history of non-vertebral fractures were found to have a three-fold increased risk of subsequent spine fractures.²⁰

According to Hui *et al.*¹⁴ and De Laet *et al.*¹⁵, age is also an important factor regarding the risk of fracture. They have described the relationship between age and bone mass as being a predictor of the risk of fracture. Particularly in elderly persons, the age effect is greater than the bone mass effect, because age is correlated with a multitude of factors, such as medication, dizziness, loss of vision, and alcohol abuse.^{16,17} Ageing also includes: the tendency to fall more often; slow postural reflexes, causing a person to fall to the side; loss of soft tissue; and a decrease in the quality of the bone. Kanis¹⁸ describes the quality of bone as: architectural abnormal-

ities of bone, fatigue damage due to self-repair from repeated stress and the number of microfractures.

Most osteoporotic fractures result from injury. Such injuries usually occur during a fall. The three fracture sites most closely associated with osteoporosis are the hip, spine, and forearm. The likelihood of falling increases with age, and is greater in elderly women than in elderly men. Among postmenopausal women in the USA, the likelihood of experiencing at least one fall annually increases from about one in five women aged 60-64 years to one in three women aged between 80 and 84 years.¹² Both the frequency and the mechanics of falling change with age. These changes can be the result of altered tread and postural stability, decreased muscle strength, malnutrition, co-morbidity, and medication. Medication associated with hypotension, as well as psychotropic drugs have been implicated.^{16,17} Even more important than falling is the way in which the elderly fall. They more often fall to the side, directly onto the hip²¹ and, because of less soft tissue padding, there is no protection. Lauritzen²² studied the positive effects of external hip protectors on hip fractures. This randomised study was undertaken in a nursing home where half the patients were allocated to wearing a padded polypropylene external hip protector. The other halves were untreated, and hip fractures were significantly more frequently observed in this group. Of all osteoporotic fractures, those of the hip have the highest impact on morbidity and mortality. The mortality rate in the first year is as high as 25%, and the morbidity 40%.²³ In the USA, women who are currently 50 years old have a 15% risk of a Colles' fracture, a 16% risk of hip fracture, and a 32% risk of a vertebral fracture occurring in the future.²⁴ The lifetime risk of sustaining a hip, wrist, or clinically diagnosed spinal fracture is at least 40% for Caucasian women and 13% for men.^{25,26}

2.3 Risk factors

Risk factors are present before fractures occur and often provide insight into the aetiology of bone fragility and fracture. For osteoporotic fractures, there are at least two etiological factors

1. Low bone density.
2. Falls (This has been discussed in section 2.2).

In many cases, it is difficult to determine whether a risk factor is related to peak bone mass or bone loss. The regulation of peak bone mass is not fully understood, but a number of factors have been identified. Of these, the most important are genetic influences; other determinants which are potentially modifiable, include physical activity, nutritional factors, and hormonal status. Risk factors can be used to identify those persons who are at greater risk and who would benefit from preventive intervention before fractures occur. This section discusses the risk factors for low BMD.

Genetic factors

Genetic factors have important effects on peak bone mass. In dizygotic twins, much greater differences in bone mass are observed than in monozygotic twins,^{27, 28} which shows that between 60 and 80% of peak bone mass is genetically determined. There is also evidence that some aspects of bone architecture and geometry relevant to bone strength are inherited. The physiological mechanism by which genetic factors influence bone mass has not been clarified; effects on body size are likely to be important in this respect, and there may also be genetic effects on bone modelling and remodelling.

It has been observed that daughters of women with osteoporosis have reduced bone mass in the lumbar spine and femoral neck. Compared to daughters of non-osteoporotic women, the bone mineral content was about 5-7% lower.²⁹ In addition, a prospective trial in 1857 premenopausal women showed that daughters of women with osteoporosis had a risk ratio (RR) of 3.7 (1.6-8.9) for fractures.³⁰

Weight

Tallness and low weight are risk factors for hip fractures. The high incidence of hip fractures in Norway and Sweden and the low incidence in Japan are related to greater or lesser stature.¹⁵⁴ Large epidemiological trials have shown that height is a risk factor in hip fractures, with an RR of 1.3 per 6 cm height.³¹ Moreover, in the Longitudinal Ageing Study, an increased risk of fracture with a RR of 1.6 per 10 cm height was reported.³² A low body mass index is an important risk factor for osteoporosis. Many studies have shown a relationship between body weight and bone mass in osteoporosis and the risk of hip fractures.^{12,32,33} Those persons with a greater body weight or higher body mass index have a lower risk of fracture, although this relationship is not linear and the increase of risk is most pronounced in thin women. Thinness may affect rates of bone loss because plasma oestrone and oestradiol are proportional to body weight in postmenopausal women, possibly related to the efficacy of conversion of androstenedione to oestrone by the adipose tissue. However, individuals who weigh more have higher repetitive skeletal loads, and the rate of bone loss could be lower for this reason. In addition, extra weight in the form of more soft tissue padding helps to protect the hip in a fall to the side.

Hormonal factors

Although the most common cause of osteoporosis is related to oestrogen deficiency from ovarian failure associated with the menopause, many other causes of hypogonadism contribute to bone loss and fractures. Bone loss may also occur in relation to diseases and conditions associated with primary or secondary amenorr-

hea.³⁴⁻³⁶ Even women without amenorrhea, but with subclinical oestrogen levels, have lower femoral bone densities compared to age-matched controls.³⁷ In men, hypogonadism is also an important cause of osteoporosis and gives rise to fractures, for example, in Klinefelter's syndrome and hypopituitarism.

Nutrition

Adequate intake of calcium, 800-1000 mg/day, and vitamin D, 400 IU/day, is necessary for achieving optimal peak bone mass. Maintaining a sufficient intake of calcium and vitamin D also helps in reducing the rate of bone loss and in preventing fractures in later life.^{12,38-40} In the elderly, poor nutrition and low exposure to sunlight may contribute to calcium and vitamin D deficiency.⁴¹

Lifestyle

In most studies, smoking appears to be associated with increased bone loss and the risk of fractures. Accelerated bone loss may be related to the direct effects of smoking or, indirectly, to a sedentary lifestyle or other factors.^{38,41,42} The consumption of caffeine may contribute to a decline in BMD, and has been associated with an increased risk of hip fracture due to increasing calcium in the urine.^{12,43} Alcohol abuse is associated with low bone mass and the increased risk of fractures in both men and women. Possible mechanisms are impaired calcium metabolism secondary to liver disease, and an increase in falls related to poor balance and other physical regression.^{42,44,45}

Exercise

Physical activity helps to maintain BMD and to reduce the risk of fractures at overloaded skeletal sites.^{12,38,46-48} Some studies have demonstrated increases in bone density as a result of increased exercise. Increasing the strength of loading seems to provide more benefit to BMD than the frequency or duration of exercise.⁴⁹ Although both children and adults obtain skeletal benefit from exercise, the potential for increasing bone mass is probably greater in children. Immobilisation and bed rest often results in rapid bone loss, which increases the risk of fractures.¹⁸

Chronic health problems can increase the risk of fracture due to loss of physical function, leading to an increased risk of falling, and to impaired bone strength. Some diseases, such as hypogonadism, contribute to low bone mass. Other diseases, such as osteomalacia and Paget's disease, can cause defects in the structure and quality of the bone. Other factors that can contribute to fractures, e.g., pre-existing fractures and age, are described in section 2.2. Table 2 provides an overview of the risk factors for fractures, bone loss, and falls.

Table 2. Common risk factors for fractures, bone loss, and falls

Factor	Risk factor for fractures	Risk factor for bone loss	Risk factor for falls
Low bone density	▲▲	NA	—
History of fragility fractures	▲▲	?	?
History of frequent falls	▲	—	▲▲
Hypogonadism (including menopause)	▲	▲▲	?
Female gender	▲	▲	▲
Underweight	▲	▲	—
Caucasian race	▲	—	▲
Immobility/inactivity	▲	▲▲	▲
Bone geometry (longer hip axis length)	▲	—	—
Alcohol abuse	▲	▲	▲▲
Cigarette smoking	▲	▲	?
Caffeine excess	▲	▲	—
Calcium deficiency	▲	▲	—
Chronic health problems	▲	▲	▲
Genetics (family history)	▲	▲	?
Drugs:			
Corticosteroid use	▲	▲▲	?
Anticonvulsants	▲	?	?
Long-acting benzodiazepines	▲	—	▲
Hormone Replacement Therapy (HRT)	▼	▼▼	?
Thiazide use	?	▼	?

Note: Modified from Ross, ref. 50

▲ risk increases as the factor increases; ▲▲ risk increases strongly as the factor increases;

▼ risk decreases as the factor increases; ▼▼ risk decreases strongly as the factor increases

NA not applicable; ? association possible; — no association

2.4 Measurement of bone density

With regard to the interest in osteoporosis over the last decades, the technique for measuring BMD has been the subject of intensive research for the last 30 years. A large variety of non-invasive techniques are available for the assessment of bone mass. These techniques vary widely in precision and complexity. In Table 3, several aspects of the various non-invasive bone mass measurement methods are presented.

Table 3. Features of the various non-invasive methods of measuring bone mass

Technique	Precision (%)	Site	Costs	Comments
SPA				
Single-energy X-ray Absorptiometry	1-2	forearm calcaneus	inexpensive	low doses of radiation measures sites unresponsive to therapy (ref: 52-54)
DXA				
Dual-energy X-ray Absorptiometry	1-3	lumbar spine	fairly expensive	low doses of radiation measures sites responsive to therapy artifacts (spondylosis)
	2-4	proximal femur	fairly expensive	low doses of radiation measures sites responsive to therapy measures best sites for fracture predication
	1-2	total body	expensive	low doses of radiation allows assessments of body composition (ref: 55-58)
QCT				
Quantitative Computer tomography	2-5	spine	expensive	measures sites responsive to therapy allows assessment of trabecular bone alone
	2-5	forearm	inexpensive	uses low doses of radiation measures sites unresponsive to therapy (ref:59,60)
Ultrasound	1-2	calcaneus fingers tibia patella	inexpensive	uses no radiation measures sites unresponsive to therapy fairly portable (ref:61-64)

For the study described in this thesis, DXA (dual X-ray absorptiometry) was used to measure BMD in women, because it is a non-invasive method, it is precise, uses low doses of radiation, and the measurement sites are responsive to therapy.

In this section, the important aspects of this technique are described. The principle behind DXA is the measurement of transmission through the body of X-rays, using two different photon techniques. The absorption of photons depends on three vari-

ables: the photon technique, the kind of absorption material, and the thickness of the absorber. With the measurement of bone mineral mass, the absorber consists of soft tissue and bone mineral in bone tissue. To eliminate the effect of the soft tissue on the results of bone mass measurement, two different measurements (one with low energy, the other with high) are performed. The underlying principle is that the mass attenuation coefficients of two different measurements (soft tissue and bone) differ as a function of photon energy. By using two photon energies, it is possible to calculate the attenuation in the bone (hydroxyapatite) independently of the attenuation by the soft tissue. The result is expressed as grams (g) hydroxyapatite (ha) per cm, BMD means bone as the weight per unit area of bone scanned g/cm^2 . Multiplying mean BMD by projected area yields bone mineral content (BMC).

$$\text{BMC} = \text{BMD} \times \text{area}$$

DXA scans of the lumbar spine and hip are the most commonly performed bone densitometry studies. This is because of the clinical significance of the spine and the hip as sites of osteoporotic fractures. Although osteoporosis is a systemic disease, the correlation coefficients between BMD values at different sites are typically approximately 0.7,⁵¹ and therefore, a BMD measurement at one site is far from being a predictor of the BMD at any other site. The significance of a hip scan alongside a spinal scan is essential in elderly patients in whom spinal BMD is likely to be elevated due to degenerative disease (osteoarthritis), fracture, or arteriosclerosis of the abdominal aorta. In such patients, a scan of the spine should be disregarded, and skeletal status should be determined from the hip.

BMD measurements of the spine are of interest because the rapid turnover of the metabolically active trabecular bone in the vertebrae makes changes in the spine particularly responsive to the effects of ageing or other diseases.

Several measurement sites are used in the evaluation of the femur: the femoral neck, Ward's triangle, and the trochanteric region. The femoral neck represents an area of predominantly cortical bone, while Ward's triangle represents an area of predominantly cancellous (trabecular) bone. Total hip BMD is the area weighed mean BMD for the femoral neck, trochanter, and intertrochanteric sites.

To be of any use clinically, BMD results for individual patients must be related to values obtained from a healthy reference population. The reference population is described in terms of the mean BMD and the population SD correlated for age, sex, and race.

The *T-score* result is a parameter widely used to assist in the interpretation of BMD results. It measures patients' BMD values from the mean BMD of a young adult population in units of the population SD. The young adult mean and SD are derived from a group of healthy subjects aged 20-35 years and correlated for sex and race. In this group, subjects are expected to attain the maximum BMD possible. The WHO working group has published an interpretation of BMD measurements, based on a

classification of patients into normal, osteopenia, osteoporosis, and established osteoporosis (2.2).

Working definition for diagnosing osteoporosis by the World Health Organisation

Normal	BMD not more than 1 SD below the value of young adults
Osteopenia	BMD of 1 SD lower than the average value of young adults, but not more than -2.5 SD
Osteoporosis	BMD more than 2.5 SD lower than the average value of young adults
Established osteoporosis (Severe osteoporosis)	BMD more than 2.5 SD lower than the average value of young adults and the presence of one or more fragility fractures

However, caution should be exercised in interpreting the T-scores of elderly patients because of the normal age-related bone loss, and even the BMD values may be below T-scores of -2.5. To identify the need for treatment in patients aged 65 years and over, who are most at risk for fragility fractures, the use of Z-scores rather than T-scores may be more appropriate.

The Z-score is similar to the T-score, except that the mean BMD and SD of a healthy age-matched population are used as reference group, instead of the mean BMD and SD of a young normal group.

Apart from the measurements of bone mineral mass in the various regions of the skeleton, it is also possible to measure total body bone mass and to determine soft tissue composition. For the Eindhoven Perimenopausal Osteoporosis Study (EPOS), we used DXA measurements of the lumbar spine and hip regions. The response to treatment in this study was shown as a proportional (%) increase of BMD, and the interval between measurements was one year.

2.5 Identification of patients at risk (risk factors used in clinical practice)

The bone mass of an individual is a function of peak bone mass and subsequent losses. Since osteoporosis may arise from abnormalities at all stages of skeletal life, it is difficult to provide an accurate classification of osteoporosis, or to provide a classification for patients who are at risk for osteoporosis. Rather, it may be more useful to consider osteoporosis as being predominantly multifactorial, and to describe the factors and their relative importance. For example, as described in Table 2, factors such as age, sex, and disease, are important determinants of bone mass, fractures, and falls, as are lifestyle influences including diet, exercise, and smoking.

Although many risk factors have been identified for osteoporosis and fractures, we have not yet been able to determine why some persons show a marked reduction of

bone mass and are prone to multiple fractures, while other persons with similar risk factors do not have these characteristics. In a longitudinal study, Cummings *et al.*¹² described 9516 women aged over 65 years, with different numbers of risk factors for hip fractures. These women were followed for a mean period of 4.1 years, and 15% had BMD in the lowest tertile and five or more risk factors for a hip fracture. It was calculated that, under these conditions, the risk of a hip fracture in this population was 27/1000 women per year. When there were only two or less risk factors, the risk of a hip fracture was 1.6/1000 women per year.

Different kinds of gynaecological parameters, such as premature menopause, age of menarche, hysterectomy, pregnancy rates, and breastfeeding, are described as being risk factors for low bone mass. However, the literature cannot agree as to the extent to which these factors lead to the development of fractures.^{12,65-67}

When considering the European Community, it is interesting to see how doctors are dealing with osteoporosis in the different European countries. In the Netherlands⁶⁸ and the United Kingdom⁶⁹ (UK), guidelines for identifying and treating patients with osteoporosis have been published. Although the Dutch guidelines are aimed at general practitioners and the UK clinical guidelines at all workers in the field of osteoporosis, it is remarkable that these guidelines for the prevention and treatment of osteoporosis are rather conflicting, as can be seen from Table 4.

The definition of osteoporosis is different in both guidelines. The Dutch guidelines describe osteoporosis as a state, while the UK clinical guidelines describe it as a disease. The most remarkable difference between these guidelines is the rejection of case-finding in the Dutch ones. Case-finding is focused on those subjects at highest risk. The policy behind this rejection is the lack of evidence for risk factors which, in the long term, contribute to low bone mass, and the lack of evidence regarding the medical prevention and treatment for osteoporosis. The consequences of this rejection of case-finding will be considered in the general discussion together with the results of our study.

Osteoporosis should be considered in all patients presenting with the following clinical features: back pain, kyphosis, loss of height, and fractures⁷⁰; and patients at risk. Explicit indications are: early menopause, oophorectomized women, use of corticosteroids, multiple traumatic fractures, osteoporosis in primary relatives and anorexia nervosa. Serious indications are: history of late menarche, secondary amenorrhea, history of prolonged bedrest.¹⁸ Possible indications are: heavy smokers and women concerned about osteoporosis. When a patient is recognised and is being considered for treatment, bone densitometry is justified in those individuals in whom the result obtained will be used in treatment decisions. In patients with crush fractures of the lumbar spine, there is already satisfactory evidence of osteoporosis, and DXA is not reliable in these cases.

Table 4. Guidelines for the prevention and treatment of osteoporosis

	The Netherlands ⁶⁸	United Kingdom ⁶⁹
Definition	osteoporosis is a state of low BMD and increased risk of fracture	osteoporosis is a disease characterised by low BMD and increased risk of fracture
Patients at risk	patients using corticosteroids >7.5 mg/day for longer than 6 months patients with previous fracture due to minimal trauma	patients using corticosteroids > 7.5 mg/day, long-term patients with previous fracture due to minimal trauma early oophorectomy or hysterectomy < 45 years premature menopause prolonged amenorrhea > 6 months
Treatment	Alendronate	HRT Etidronate Alendronate Calcium Vitamin D Calcitonin Calcitriol
Best method of tackling osteoporosis	no active plan	individually: as part of counselling when seeing women with other complaints identify risk groups by computer and patient records

2.6 Prevention of osteoporosis

Introduction

The primary aim of any anti-osteoporotic intervention is the prevention of fractures in patients who have not yet experienced fractures, or the prevention of the disease in patients who have already sustained a fragility fracture.⁷¹

Prevention can be considered according to the stage in the natural history of the disease at which intervention is implemented:

Primary prevention is aimed at subjects without the disease, by reducing the risk factors for and/or causes of the disease.

Secondary prevention is aimed at those in whom the disease is potentially reversible and in whom intervention may reduce progression at an early, often asymptomatic stage.

Table 5. Prevention and treatment of osteoporosis: current and potential pharmacological intervention

Inhibitors of bone turnover
Bisphosphonates
Calcitonin
Calcium
Oestrogen's (including oestrogen derivatives and selective oestrogen receptor modulators)
Stimulators of bone formation
Fluoride salts
Parathyroid hormone
Uncertain modes of action
Anabolic steroids
Ipriflavone
Vitamin D and metabolites

Tertiary prevention is aimed at those with established disease in whom intervention may limit associated disability or progression. In practice, tertiary prevention is synonymous with treatment of the disease.

The management of patients can include both non-pharmacological and pharmacological interventions. The ultimate goal of the different prevention and treatment strategies is to decrease the incidence of new osteoporosis-related fractures.

Non-pharmacological and pharmacological interventions

Non-pharmacological intervention

Several non-pharmacological interventions may reduce the risk of fracture by increasing bone mass, reducing age-related bone loss, decreasing the risk of falling, improving the protective neuromuscular responses associated with falling, or reducing the impact of falls with the use of, for example, hip protectors (see 2.2). Nutritional factors as vitamin D and calcium, as well as physical exercise, have multiple effects, influencing peak bone mass, age-related bone loss and muscle strength.

Pharmacological intervention

Current pharmacological interventions for the prevention and treatment of fractures in patients with osteoporosis are intended to reduce bone resorption and bone turnover or to stimulate bone formation. An overview of current pharmacological interventions is provided in Table 5, and the pharmacology is described in section 2.7.

Primary prevention

The goal of primary prevention is to obtain a maximum bone mass (peak bone mass) during the growing period. The general group for primary prevention are children and adolescents. The high-risk group includes children or adolescents in whom inferior bone development can be expected due to, for example, chronic illness or medication. Primary prevention consists of information regarding the importance of calcium, vitamin D intake, and of undertaking physical exercise and weight bearing exercise, for example, during childhood and adolescence.

Secondary prevention

The goal of secondary prevention is the early detection of those who are at risk for developing osteoporosis. The group for secondary prevention is all women around the menopause and women with an early menopause or a history of osteoporosis in relatives, patients with gastrointestinal infections (Crohn's colitis), hyperthyroidism, and other chronic illnesses (2.2).

In general, a healthy lifestyle is important. A good vitamin-D status (exposure to sunlight) and good general health from taking part in sports, should be the rule. Calcium must be part of the diet; women around the menopause need 800-1000 mg calcium daily. In case of a calcium-deficient diet, calcium should be taken as tablets. Some authors^{72,73} emphasise increased bone resorption rates during the night, and recommend the use of calcium supplements at bedtime, although Dawson-Hughes⁷⁴ prefers small doses of calcium to be taken with each meal (calcium carbonate) and at bedtime, or only at bedtime (calcium lactate-gluconate). The effects of exercise on postmenopausal bone loss are described in a meta-analysis by Bérard *et al.*⁷⁵ A significant effect due to moderately intense physical activity was detected on lumbar spine BMD, but no consistent effect was seen on femoral neck or forearm bone mass. Exercise programmes in these studies consisted of running, walking, physical condition training, and aerobics.

Increases of between 2.5 and 5% in spinal BMD have been reported in postmenopausal women after seven to nine months on an exercise programme,^{76,77} although there was no additional benefit between 9 and 22 months and all gain was lost in those who left the programme. As in young adults, there is some evidence that calcium and exercise have additive effects on bone mass in postmenopausal women.⁷⁸ Overall, the gains from vigorous exercise compared to everyday activities are probably small, and must be maintained to retain any effect.

Preventive intervention such as oestrogen's or alendronate should be prescribed on an individual basis, taking into account bone density, hormone status, and family factors (e.g., breast cancer, if hormonal substitution therapy is an issue). The success of treatment is largely due to compliance to therapy.

An overview of double-blind, placebo-controlled randomised clinical trials assessing BMD in peri- and early postmenopausal women shows the treatment with regard to secondary prevention.

Tertiary prevention

Tertiary prevention is aimed at patients with established disease. This group consists of those people with a low bone density compared to persons of the same age (Z-score) or to the peak bone mass (T-score), and patients who have already had a fracture. Intervention consists of information about calcium-rich nutrition or calcium supplements, and supplementation of vitamin D also therapy such as oestrogen's or alendronate should be prescribed on an individual basis.

In the elderly, and people in retirement and assisted homes, exercise programmes based on balance, strength training and low impact aerobics, may be beneficial. From randomised controlled studies, there is evidence that such regimens reduce the risk of falls.⁷⁹ Walking and climbing stairs can be beneficial, and daily activities, social dancing, and group exercise should be encouraged, although motivation for long-term compliance is essential for the success of such programmes. The social aspects of exercising in groups can be an effective way to encourage elderly people to participate. A meta-analysis of trials in exercise prevention in community-based subjects suggested that it is possible to increase BMD, particularly if the exercise is of moderate intensity and enjoyable, and to reduce falls by 10%.⁸⁰

2.7 Treatment of osteoporosis

The treatment of osteoporosis still constitutes a problem. The ultimate goal of treatment is to obtain a reduction in (further) fractures. Nevertheless, it is important to remember that an increase of bone mass does not directly indicate a reduction of fractures. The skeleton in postmenopausal osteoporosis is reduced in mass (quantity), but the loss of tissue in cancellous bone also causes important architectural changes, with thinning and elimination of the trabecular structures.¹⁸ As stated above, mass and fragility of the bone are important determinants of fractures.

Bone is remodelled throughout life, and the rate of remodelling is increased in older adults.⁸⁷ The rate of resorption exceeds that of formation in older adults, resulting in osteoporosis. Bone remodelling occurs at all sites within the skeleton and proceeds in a well-ordered way, with bone resumption always being followed by bone formation. This process is similar in the cortical and trabecular bone.⁸⁸

The process of resorption of bone, followed by synthesis of the bone matrix and mineralization, takes up to several months.¹⁸ If the processes of bone resorption and bone formation are not well-matched, there is remodelling imbalance. In addition to the effect on remodelling activation, it is assumed that there must also be a defect

Table 6. Effect of preventive intervention on bone mineral density of the lumbar spine in early menopausal women. Double blind, placebo-controlled randomised trials

Author	Publication (year)	Patients (n)	Age (mean)	Treatment	% Change in BMD lumbar spine
Pepi Trial ⁸¹	1996	174	55.9	placebo	-1.8 [†]
		175	56.2	CEE*	3.5 [†]
		174	55.9	CEE/MPA [‡] , cyc	3.8 [†]
		174	56.4	CEE/MPA, con	5.0 [†]
		178	56.1	CEE/MP, cyc	3.8 [†]
Herd ⁸²	1997	77	55.1	placebo	-0.7 [‡]
		75	54.5	etidronate [§]	2.1 [‡]
Meunier ⁸³	1997	27	52.7	placebo	-2.3 [‡]
		27	52.7	etidronate [§]	0.6 [‡]
Pouilles ⁸⁴	1997	55	53.9	placebo	-2.4 [‡]
		54	53.6	etidronate [§]	0.1 [‡]
Hoskin ⁸⁵	1998	461	53	placebo	-1.8 [‡]
		452	53	alendronate, 2.5 mg	2.3 [‡]
		445	54	alendronate, 5 mg	3.5 [‡]
		102	53	estrogen/progestin, US	4.0 [†]
McClung ⁸⁶	1998			estrogen/progestin, EU	5.1 [†]
		90	51.3	placebo	-3.5 [†]
		92	51.7	alendronate, 1 mg	-1.2 [†]
		88	52	alendronate, 5 mg	2.9 [†]
		84	52.1	alendronate, 10 mg	3.9 [†]
		78	52.1	alendronate, 20 mg	4.4 [†]

[†] duration of treatment 36 months; [‡] duration of treatment 24 months; *CEE indicates conjugated equine oestrogen; [‡]MPA medroxyprogesteron acetate; MP micronized progesteron; cyc, cyclic administration, con, continuous administration; [§] indicates oral etidronate 400 mg/day 14 days, calcium 500 mg 76 days, 90 day treatment cycle; US indicates conj. oestrogen 0.625 mg daily, medroxyprogesterone acetate 5 mg daily; EU 2 mg micronized estradiol 22 day, 1 mg norethindrone acetate, day 13-22 and 1 mg of estradiol day 23-28.

within each remodelling cycle, such that the amount of new bone synthesised is less than the amount removed by the osteoclasts. Whether this results from excessive action of the osteoclasts or from inefficient osteoblast activity, remains a matter of speculation, although the general opinion is that the osteoclasts are responsible. Medications used to treat osteoporosis can be grouped into those that decrease bone resorption and those that stimulate bone formation, as summarised in Table 5. Most of the drugs used act by decreasing bone resorption⁸⁸, and are referred to as antiresorptive drugs. This group includes oestrogen, bisphosphonates, calcitonin, anabolic steroids, and the more recently developed SERM. Because the processes of

bone resorption and bone formation are related, these drugs decrease the effect of both processes. When an antiresorptive drug is given, the rate of bone resorption decreases within weeks, and that of bone formation within months. This difference in timing is a result of the coupling mechanism.

Antiresorptive therapy decreases the rate of new remodelling sites, resulting in fewer remodelling spaces and a decrease in remodelling spaces. The filling in of the remodelling spaces accounts for the 5-10% increase in BMD occurring in post-menopausal women receiving antiresorptive therapy. This process usually takes two to three years. After this filling in of the remodelling spaces, the bone density changes very little.

Some of the drugs used to treat osteoporosis act by increasing bone formation. This group includes fluoride and parathyroid hormone. The newly formed bone either overflows resorption capacities or overfills the surfaces that have not been resorbed previously.¹⁸ Drugs that stimulate bone formation result in annual rates of increase of BMD similar to those resulting from antiresorptive therapy, but this increase continues for more than two years, although, in studies using fluoride, there was no effect on fractures.^{89,99}

A brief description of the results of the treatment of osteoporosis is given below.

Oestrogen replacement therapy

The mechanism by which oestrogen affects skeletal remodelling is not fully understood. Although oestrogen receptors have been identified in bone cells in culture, there is no evidence that these cells represent the target cells *in vivo*.⁹¹ *In vivo*, the effect of oestrogen's is thought to involve the inhibition of osteoclasts,⁹² thus slowing bone turnover and improving the balance between bone formation and bone resorption. Oestrogen also improves calcium retention through increased calcium and renal reabsorption.⁹³ There is also evidence that oestrogen influences other factors related to the risk of fractures, e.g., extraskelatal effects, such as improved balance.^{94,95}

Information on the effects of oestrogen replacement therapy on the rates of vertebral fractures is limited. In a one-year study of transdermal oestrogen therapy in 75 women with osteoporosis, the relative risk of vertebral fractures was 0.39 (95% CI 0.16-0.95) in the treatment group compared to the placebo group,⁹⁶ although these numbers were expressed by means of 100 persons/years at risk.

Additional evidence that oestrogen therapy prevents fractures has been derived from prospective cohort studies.⁹⁷⁻¹⁰⁰ A meta-analysis described 11 studies in which oestrogen therapy was used to prevent fractures; ten of these studies showed a relative risk of 0.75. More than ten years' use of oestrogen showed a relative risk of 0.50.¹⁰¹ Moreover, a case control study from the Swedish Hip Fracture Study group showed that, for hip fractures, current HRT users had an odds ratio of 0.35 (95% CI 0.24-0.53) compared to non-users in the reference category; while former users had

Table 7. The benefits and risks of oestrogen therapy in postmenopausal women

Benefits	Risks
Relief of climacteric symptoms	Menstrual bleeding
Prevention of bone loss and fractures	Endometrial carcinoma ¹⁰⁶
Prevention of ischemic heart disease	Breast carcinoma ^{107,108}
	Deep venous thrombosis and pulmonary embolism ¹⁰⁹
The risks and benefits of HRT use are included in the General Discussion	

an odds ratio of 0.76 (95% CI 0.57-1.01). The protective effect increases with duration of use and higher doses of oestrogen's, and the oestrogen sparing effect is higher when progestins are included in the regimen.¹⁰²

There are conflicting data regarding the time to start treatment. Significant protection from hip fractures among women who started HRT within five years after the menopause was noted in a study of osteoporotic fractures, but not among women who started HRT later.¹⁰⁰ However, in the Swedish Hip Fracture Study¹⁰² and the study of Sneider¹⁰³, similar bone conservation was seen after oestrogen therapy started either before or after the age of 60 years. The daily doses of oestrogen needed to obtain a reduction in hip fractures are 2 mg estradiol and 0.625 mg conjugated oestrogen's, or equivalent.^{102,104} Treatment with skin patches produces similar results as oral regimens.

Bone mass declines after HRT is stopped, and therefore, for optimal protection, this should be continued for a long period, with five to ten years usually being recommended.^{102,105} Other beneficial effects and side-effects of oestrogen are listed in Table 7.

Bisphosphonates

Bisphosphonates are synthetic, stable analogues of natural pyrophosphate. They are poorly absorbed from the intestine (absorption of less than 1-5%¹¹⁰ of the administered dose, but absorption is nearly zero in the presence of calcium-containing foods). Bisphosphonates are potent inhibitors of bone resorption, acting via a mechanism not yet fully understood, but there are three possible mechanisms by which bisphosphonates may affect osteoclast bone resorption. Firstly, they may interfere with the function of mature osteoclasts. Secondly, they may maintain a concentration gradient at the bone surface of sufficient magnitude directly to affect the cellular processes involved in the initiation of osteoclast activation. Thirdly, they may alter the properties of the bone matrix responsible for the final formation and activation of osteoclasts.¹¹¹ Their net effect on osteoclasts or their precursors is an increase in cell

death, and therefore, a decrease in bone resorption. Bisphosphonates are deposited in the bone at sites of mineralization and in the resorption lacunae, and are eliminated by the kidneys.

Bisphosphonate therapy results in increased BMD and a decrease in fracture rate. Several compounds from this family have been evaluated for the prevention of bone loss (alendronate, clodronate, pamidronate, tiludronate, risidronate, and ibandronate). Data on fractures are available for etidronate, alendronate and risidronate, and are discussed below.

Two studies (RCTs) of similar design examined the effect of cyclical *etidronate* on fracture frequency in postmenopausal women with prevalent fractures; both found a decrease in vertebral fracture frequency with intermittent use.^{112,113} In neither study were vertebral fractures a specified endpoint, both were difficult to interpret, and both used questionable criteria for vertebral fractures. The follow-ups of both studies have been extended.^{114,115} Five years after starting his study, Storm¹¹⁵ showed a significant increase (5.5%) in spine BMD compared with a 2.7% decrease in the placebo group. There was also a significant reduction in the vertebral fracture rate in patients treated with etidronate.

Etidronate given continuously at high doses can result in impaired mineralization, which can be avoided by low doses of intermittent therapy.¹¹⁶ Therefore, this drug is usually given at a dose of 400 mg per day for two weeks, followed by 500 mg per day of supplementary calcium for 11-13 weeks. This regimen resulted in an increase of BMD,⁸⁴ and also in a decrease of non-vertebral fractures.¹¹⁷

Alendronate is given at a dose of 10 mg for the treatment of osteoporosis in postmenopausal women. This results in an increase in BMD and a decrease in fractures.^{85,86,117-120} Karf *et al.*¹²¹ described the overall effectiveness of alendronate in the prevention of non-vertebral fractures in a meta-analysis of five RCTs. The efficacy of alendronate in decreasing fractures has also been demonstrated in the Fracture Intervention Trial.¹¹⁸ In 2027 women (mean age, 71 years) with at least one vertebral fracture and femoral neck BMD of less than 2 SD of peak bone mass were randomised to receive 5 mg alendronate daily or placebo. After two years, the dose was increased to 10 mg per day for the final nine months of the study, as in parallel trials, this dose has been shown to induce optimal effects on the bone mass. New vertebral fractures (including clinical ones) occurred in 15% of the placebo group and in 8% of the alendronate group. Active treatment also significantly reduced the risk of multiple vertebral and wrist fractures. Alendronate has been associated with esophagitis, including the erosive type.¹⁶³ To minimize the risk of esophagitis and to increase drug absorption, the patient should take alendronate with a glass of water, not when lying down, at least 30 minutes before breakfast.

Pamidronate is also used in studies of the treatment of osteoporosis, both orally¹²²⁻¹²⁴ and intravenously.¹²⁵ These studies showed a significant increase in spinal BMD. The most widely used regimen is pamidronate 150 mg daily.

Risidronate was recently evaluated in the treatment of women with established osteoporosis.¹⁶² Compared to placebo, BMD increased significantly at the lumbar spine (5.4% versus 1.1%), femoral neck (1.6% versus -1.2%), trochanter (3.3% versus -0.7%), and midshaft of the radius (0.2% versus -1.4%).

The optimal duration of bisphosphonate therapy is still not known.

Calcium and vitamin D

Ninety-nine percent of total body calcium is found in the bones. If the supply of calcium is inadequate, mineralization can become sub-optimal. Calcium deficiency can also affect the bone mass by causing secondary hyperparathyroidism, which leads to increased bone resorption. Some patients in whom clinical osteoporosis develops may have a low calcium intake, but may also be vitamin-D-deficient, due to low exposure to sunlight or gastrointestinal disease, and may have some degree of secondary hyperparathyroidism resulting from these problems. Therefore, adjustment of calcium intake may improve a given physiological situation, but is unlikely to reverse other problems affecting the bone metabolism. Vitamin D increases intestinal calcium absorption and the active metabolite of vitamin D, calcitriol and related alfacalcidol, increases calcium absorption, and may have a direct effect on the bone cells.

In a study of 3270 institutionalised women in France, who were treated with calcium 1200 mg per day and vitamin D 800 IE per day for three years, the risk of hip fractures was 30% lower than in the placebo group. This therapy also resulted in a reversal of secondary hyperparathyroidism and in an increase of BMD in the femoral neck.¹²⁶ Care must be taken not to generalise the results of this study. In the Netherlands, in approximately 3000 women of similar age, studied by Lips *et al.*¹²⁷ who were treated with vitamin D (400 IE per day) or placebo for three and a half years, but not with supplemental calcium, the rate of hip fractures was similar between the groups. The probable explanation for the differences between these two studies is the differences between the women studied. The French women had lower dietary calcium intake, were frailer, and had lower serum 25-hydroxy vitamin D concentrations. Dawson-Hughes *et al.*¹²⁸ reported on approximately 400 older men and women in the USA who were treated with 500 mg calcium and 700 IU vitamin D per day, or placebo. Over the three years of the study, the rate of nonvertebral fractures decreased. This was surprising because the increase in BMD was small (lumbar spine 0.9%, femoral neck 1.2%, total body 1.2%). The major differences between this study and the Dutch one were the lower baseline dietary intake of calcium and the higher serum 25-hydroxy vitamin D concentrations in the US patients.

In general, a proportionate effect on BMD from calcium supplementation can be expected in cases in which the calcium intake is below 500 mg a day. In the Netherlands, the mean calcium intake is relatively high, 800 mg or more daily.

Calcitonin

Calcitonin is a 32-amino-acid peptide normally produced by the thyroid C cells, and results in decreased bone resorption. Osteoclasts have calcitonin receptors, and calcitonin rapidly inhibits the action of osteoclasts. Salmon or human calcitonin is given by subcutaneous or intramuscular injection at doses of up to 100 IU daily. Calcitonin therapy results in an increase in BMD, although the numbers of convincing trials are relatively small. Calcitonin is expensive and can have side-effects, such as nausea, flushing, and diarrhoea. The development of intranasal salmon calcitonin may make this therapy more acceptable, but at least 200 IU must be given to have an effect on BMD. The largest double-blind, placebo-controlled trial, with a two-year follow-up, consisted of 208 postmenopausal women with low BMD. BMD increased as the doses increased. The total number of fractures in this study was too small for an effect to be proved.¹²⁹

Four placebo-controlled trials have been performed to determine the analgesic effect of calcitonin in patients with bone pain related to osteoporosis. In the largest trial,¹³⁰ 60 women who had experienced a vertebral fracture due to low trauma were given subcutaneous injections of human calcitonin three times each week compared with placebo. There was a significant analgesic response in the treated group over a four-month period, but no change was observed in forearm BMD over the study period. These observations are supported by other short-term placebo-controlled studies.^{131,132}

Fluoride

Sodium fluoride stimulates bone by unknown mechanisms. In one study of 202 women with osteoporosis, who were treated with sodium fluoride, lumbar BMD increased by 8% per year in all four years of the trial.¹³³ There was substantial bone loss in the forearm, indicating a redistribution of bone mineral from the cortical to cancellous bone. Biochemical markers of bone formation increase in fluoride-treated women, but markers of bone formation do not. The large increase in BMD should be associated with a decrease in fracture rate, although, in most studies, the effect was limited.¹³³⁻¹³⁵ In one study, there was a significant reduction in the rate of vertebral fractures, the relative risk being 0.3.¹³⁶ In this case, the dose of fluoride was smaller than in earlier studies, and it was given intermittently as slow-release sodium fluoride. Fluoride can cause gastric irritation, but this can be reduced if the drug is taken together with a calcium supplement. It can also cause lower-extremity pain syndrome.¹³³ In the Dutch literature, fluoride is characterised as being controversial and experimental.^{137,138}

Raloxifene

Raloxifene has mixed oestrogen-agonist and oestrogen-antagonist activity and is referred to as a selective oestrogen-receptor modulator.¹³⁹ In a two-year study, raloxifene therapy resulted in a decrease of bone resorption.¹⁴⁰ Ettinger *et al.*¹⁴¹ published data from a large trial of raloxifene to the effect that it prevents bone mass and reduces the rate of vertebral fractures in postmenopausal women. The acute effect is less marked than that of oestrogen's because a smaller increase in bone mass is seen.¹⁴² Raloxifene also appears to decrease the risk of breast cancer,¹⁴³ but long follow-up trials are necessary to prove this effect. It decreases serum low-density lipoprotein cholesterol concentrations, but not does stimulate endometrial growth. Raloxifene increases the risk of venous thromboembolic events, as do oestrogen's.¹⁴⁴ Other selective oestrogen-receptor modulators are under development (droxifene, idroxifene, and Ivormeloxifene) and may provide an alternative to oestrogen therapy.

Tibolone

Tibolone is a synthetic steroid with an affinity for oestrogenic, progestogenic and androgenic receptors. The *parent* is structurally related to norethnodrel and appears preferentially to bind to oestrogenreceptors, whereas its metabolites have a greater affinity for progesterone and androgenreceptors.¹⁴⁵ Tibolone shows tissue-specific oestrogenic activity in controlling hot flushes and sweats. It does not stimulate endometrial proliferation (2.5 mg) and eliminates the need for progesterone administration. Androgenic effects have been observed with tibolone, and can improve mood and libido.¹⁴⁶ Clinical studies have shown oestrogenic activity on the bone in preventing postmenopausal bone loss.^{147,148} In elderly postmenopausal women with vertebral fractures, treatment with tibolone significantly increased bone mass.¹⁴⁹ Open, non-randomised studies suggest effects at all skeletal sites.¹⁵⁰ The long term-effects of tibolone on cardiovascular morbidity have not yet been evaluated, but it decreases both lipoprotein-(a) and low-density lipoprotein (LDL). Tibolone should only be used in women who are at least one year postmenopausal.

Parathyroid hormone

Daily injections of parathyroid hormone stimulate bone formation. It may be given as intact hormone or as a synthetic fragment. Treatment for up to two years results in an increase in bone density of the spine but in no change of that of the femoral neck, and an increase in the biochemical markers of bone formation and bone resorption.¹⁵¹ The effect of parathyroid hormone on fractures is not yet known.

Nandrolone

Nandrolone is an anabolic steroid and is given as an intramuscular injection. It appears to increase BMD, but only a few studies are available and these are all of short duration.^{152,153} The effect of nandrolone on fractures is not yet known.

Other therapies

A number of cytokines and growth factors have potent effects on bone cells. These factors also affect other organs. For example, cytokines modulate the immune system. The challenge will be to target such factors to the bone alone. Other therapies that have been developed for the treatment of osteoporosis include vitamin D analogues, strontium salts, and ipriflavone.

Women most at risk for fractures are the ones who should be treated, among whom those who have already sustained a fracture with minimal or no trauma, and those who have low BMD or other risk factors for fracture (section 2.4). It is important to select the appropriate treatment. Oestrogen or bisphosphonates are the treatments of first choice, depending on the age and risk profile of the patient. HRT should be given for at least five years, or preferably longer, because the benefits may not persist after treatment. Detailed discussions with the patient to consider the risks and benefits of oestrogen therapy can enhance compliance (Table 6). Bisphosphonates are particularly useful in women who are concerned about the side-effects of oestrogen therapy, or who are at risk of developing breast carcinoma. Elderly women with osteoporosis are also candidates for treatment with bisphosphonates.

2.8 Compliance

Measuring compliance

Patient compliance can be defined as "the extent to which the actual dosing history conforms to the prescribed dosing history".¹⁵⁵ In many areas of medicine, but most notably in non-symptomatic diseases such as hypertension, patient compliance to a drug regimen has been shown to be less than optimal.^{156,157} Unlike patients with symptomatic diseases, those with non-symptomatic diseases such as hypertension or osteoporosis should have a strong motivation to conform to drug prescription orders for up to ten or even twenty years. Compliance measurements can vary enormously. Patients can administer more or less than, or exactly the amount of, the medicine prescribed. Patients may take their medicine erratically (sometimes taking more and sometimes less than prescribed). Finally, patients may neglect the recom-

mended method or time to administer the medicine. Therefore, compliance is both a term for a behaviour and a measure of it.

In general, clinical trials rely on returned tablet counts as a measure of compliance. Each participant is given a package with a known number of doses, enough for the interval between scheduled visits, plus a few extras. At the following visit, a new package is dispensed, and the number of doses remaining in the old package counted. Of course, patients may discard untaken doses and return an empty or almost empty package, with the suggestion of good compliance. A series of trials in which oral dosage forms contained small quantities of a slow turnover chemical marker, subsequently assayed in plasma as a direct measure of compliance, showed that returned tablet counts overestimate compliance.¹⁵⁷ Another trial found that most patients returned an empty or near-empty container, irrespective of the number of tablets dispensed, although more tablets were given than necessary.¹⁵⁷

Patient compliance to a drug regimen can be accurately measured by the use of electronic monitoring. A time-keeping microcircuit integrated into the drug package records the time and date of opening of the medication package. Although this is only an indirect measurement (no proof of ingestion of the drug is acquired), the method has sufficient advantages over other compliance measurement instruments to make it the current gold standard.¹⁵⁸ Moreover, many studies using electronic monitoring have also included returned tablet counts, and have also found that many poorly compliant patients returned few or no tablets.¹⁵⁹

Drug holidays

The majority of patients take their medication almost as prescribed. When they do not, electronic monitoring has shown that the most common error is a lapse in dosing, creating longer intervals between doses than prescribed, often of hours, sometimes of days, occasionally of weeks. These longer intervals (especially three days or more) are known as drug holidays.¹⁶⁰ The major consequence is that the action of the drug diminishes and disappears. The clinical relevance of these drug holidays is the 'forgiveness' of the drug. (For example, oral contraceptives are very unforgiving, since if even one dose is missed, the contraceptive coverage can be lost.) Therefore, a longer-acting agent, can 'forgive' occasional or intermittent errors in compliance.

When prescribed drug therapy fails to produce the expected results, non-compliance is often the underlying reason. Drug information aimed at patients and prescribers can be improved by careful assessment of the degree to which drug efficacy and safety depends on compliance. Therefore, in clinical practice and when conducting research, accurate knowledge of patient compliance is important for both optimising pharmacotherapy and correctly evaluating the outcome of such drugs.¹⁶¹

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CHAPTER 3

General design of the Eindhoven Perimenopausal Osteoporosis Study (EPOS)

- 3.1 Introduction
- 3.2 Background
- 3.3 Design of the study
 - 3.3.1 Screening study (full report chapter 4)
 - 3.3.2 Intervention study (full report chapter 6)

3.1 Introduction

In July 1987, the Secretary of State for Welfare, Public Health and Culture (WVC) asked the Health Council of the Netherlands (Gezondheidsraad) for advice on the prevention of osteoporosis in the Netherlands. The Health Council appointed a Committee on Osteoporosis that reported to the Secretary in 1991 with the following advice: osteoporosis is an important cause of disease, especially in elderly women, and preventative measures of a general nature are strongly recommended.¹

The recommendation for prevention formed the main part of the Committee's advice, especially with respect to those women with an increased risk of osteoporosis. Furthermore, the Committee advised that bone mineral density (BMD) measurements should be carried out in women of menopausal age, in order to check their BMD and gain insight into their risk of developing osteoporosis and vertebral and hip fractures. Women at higher risk could be informed of this, and, in addition to primary prevention, could use this information in their choice of further intervention, *e.g.*, hormone replacement therapy, for the prevention of osteoporosis. In order to establish interest in the Netherlands for the prevention of osteoporosis and the measurement of BMD, the Committee recommended that an exploratory study should be carried out in women of menopausal age.¹

3.2 Background

The advice regarding oestrogen substitution in women of menopausal age for the prevention of osteoporosis, as recommended by the Health Council Committee to the Minister of WVC in 1991, considered two options:

1. All women should be advised to start using oestrogen when they reach menopausal age (without first having measurements of BMD); or
2. All women of menopausal age should be screened for BMD using dual X-ray absorptiometry (DXA), and women with low BMD should be advised to use oestrogen.

Due to the fact that few women were motivated to use oestrogen for the prevention of osteoporosis, without first being aware of their DXA results, the Committee chose the second of these two options. They recommended that a study be set up to gain insight into the attitude of women with regard to BMD measurements as the basis for oestrogen use, as well as into the costs of the procedure. Women with low BMD should be made aware of this fact and its consequences, and, if there were no contraindications, be advised to use oestrogen.

Although there are other therapies that can be used against osteoporosis, such as calcitonin, bisphosphonates, and anabolic steroids, the Committee did not regard the large-scale use of these medications to be warranted, since their effectiveness and safety had not yet been established in longitudinal research (1991).

After publication of this report in 1991, Prof. Dr. V.J.M. Pop, a general practitioner from Riethoven, North Brabant, in close cooperation with Dr. J.J. Keyzer, a clinical chemist and director of the Diagnostic Center of Eindhoven (DCE), took the initiative to carry out research on the basis of the above recommendation. Since this would be a general health care project, the expertise of Prof. J.A. Knottnerus (Department of General Practice, University of Maastricht) was solicited, as well as that of Prof. Dr. H.A.P. Pols (Department of Internal Medicine III, Dijkzigt Hospital, Rotterdam) and Prof. Dr. S.A. Papapoulos (Department of Endocrinology LUMC, Leiden), internists/endocrinologists in the field of osteoporosis. In January 1993, this team applied for a grant from the Prevention Fund, centred on the following aspect of research:

"A comparative study of the (secondary) preventive effects of a number of potentially relevant medication strategies in women around menopausal age with decreased bone mineral density, who are at risk for developing osteoporosis."

The Prevention Fund approved the research proposal on 8th October, 1993 (Grant No. 28-2401), so that, on 1 January, 1994, the Eindhoven Perimenopausal Osteoporosis Study (EPOS) could get under way.

3.3 Design of the study

The study consisted of two parts:

1. A screening study
2. A drug intervention study, designed as a randomised clinical trial

3.3.1 Screening study

Study population

In the period between September 1994 and September 1995, all women in the city of Eindhoven, born between 1941 and 1947 (aged between 46 and 54 years), were invited by the Diagnostic Centre Eindhoven (DCE), a diagnostic centre for general practitioners, and the Department of Municipal Public Health Services, Eindhoven, to participate in the study.

The aim of the study was to assess the prevalence of low bone mass and its determinants, with special emphasis on gynaecological variables in a large cohort of perimenopausal women, using the World Health Organisation (WHO) criteria for osteopenia and osteoporosis. A questionnaire was completed by all the women (Appendix 1), a clinical examination was performed, and BMD was measured at the lumbar spine (L1-L4) using DXA (S.A. Hologic, Brussels). At the screening visit, the

participants were asked if they could be contacted for a follow-up study. The results of this study are presented in Chapter 4.

3.3.2 Intervention study

The intervention study was designed as a randomised clinical trial (RCT), the objectives of which were as follows:

1. To determine and compare, in a randomised study, the efficacy of two treatment regimens compared to calcium for preventing postmenopausal bone loss in women in the lowest tertile of the DXA measurements after screening. The following regimens were compared:
 - a. calcium 400 mg/day
 - b. calcium 400 mg/day + oestradiol 2 mg continuously, combined with dydrogesteron 10 mg in the second half of the cycle
 - c. calcium 400 mg/day + APD (= pamidronate), 100 mg/day
2. To determine the rate of change in BMD one year after cessation of treatment
3. To determine the compliance for each treatment regimen

The results of the above issues are presented in Chapters 6 and 7, respectively.

Design of the drug intervention study

The study was designed as a single open-label, controlled, randomised study. It had to be an open study because blinding was not possible in the oestrogen/progestogen group. In this group, the women received cyclically oestrogen/progestogen and would therefore have had monthly withdrawal bleedings. The relatively low dose of calcium was selected to ensure that the women would not in fact have calcium deficiency. The participants were allocated to one of the treatment protocols for a period of two years, followed by a washout period of one year. No reallocation was offered to a different treatment group, based on individual preferences. The women were seen every three months during their participation in the study, and DXA measurements of the lumbar spine and hip were performed on four occasions during the study.

In all groups, compliance was measured based on counting by hand, and, in addition, in the group of women receiving pamidronate, it was also measured using the Medication Event Monitoring System (MEMS, Aardex Ltd., Switzerland). This system consists of a normal pill container with a special cap that contains electronic micro-circuitry to record the time and date of each opening of the container. Throughout the analysis, we assumed that one tablet was actually ingested each time the container was opened.

Study population

The study population consisted of healthy perimenopausal women who met the selection criteria and who were willing to participate in the study. The inclusion criteria were:

- women born between 1941 and 1947 and living in the city of Eindhoven
- a period of amenorrhea of a maximum of three years
- a changed menstrual pattern, with less than five bleedings in the past twelve months
- BMD in the lower tertile ($<0.998 \text{ g/cm}^2$)

The following cases were excluded:

- women who had undergone hysterectomy and/or ovariectomy
- women with a history and/or presence of a metabolic bone disease other than osteoporosis
- women with rheumatoid arthritis, or a history of serious cardiovascular disease
- women with uncontrolled hypertension
- women with diabetes mellitus or other endocrine diseases, such as pituitary, thyroid or parathyroid dysfunction
- women with a history and/or presence of malignancies
- women who had used bisphosphonates, fluoride, calcitonin, anabolic steroids, glucocorticoids, or other medications that might interfere with calcium and bone metabolism, in the twelve months prior to the intervention study
- no use of systemic oestrogen's/progestogens was permitted in the three months prior to the trial

Randomisation

Women who were eligible were randomised over one of the treatment groups. When a woman announced her willingness to participate, a central registration office was contacted, which had a list of the random treatment assignments.² The treatment assignment could be read off the randomisation list and was supplied to the investigator by telephone. No reallocation to a different treatment group was offered. Women who decided not to participate in the study after randomisation, because they had not received the medication they had requested, were regarded as dropouts immediately after randomisation.

BMD of the lumbar spine (L1-L4) and hip was measured at baseline and after one and two years of treatment with DXA model QDR-1000 (S.A. Hologic Europe, Brussels).

Study size

The aim was to detect a difference of 5% in BMD between the calcium group and the other intervention groups. Using Pocock's formula (1993)², it could be calculated

that, each group should consist of 150 participants ($= 0.05$, $= 0.90$, SD 0.1 g/cm^2). An estimated 300 participants were required as a minimum. Women discontinuing the study after having been included would be regarded as dropouts. Early discontinuation of the study could take place at the request of either the participant or the investigator. A participant could discontinue the study at any time, without explanation. Exclusion of participants from the study by the investigator was due to either exclusion criteria developing during the course of the study, serious adverse events, or emergence of a severe concurrent disease.

Data handling and statistical analysis

All the data from the study, both those collected during visits as well as the results of the laboratory analysis, were transferred to the Case Records Form (CRF) of the investigator. Statistical analysis was performed using the Statistical Products and Service Solution (SPSS).

The primary outcome, the percentage of change in lumbar spine BMD, was compared between the two treatment groups and the calcium-only group using the *t*-test for independent observations, adjusted for multiple comparisons with a Scheffe correction. Statistical significance was defined as $p < 0.05$, two-sided. The secondary outcome, the percentage of change in BMD at the different measurement sites in the proximal femur, was analysed accordingly. Analyses were made by intention to treat, including those women in whom lumbar spine BMD was measured at baseline and at least once during treatment.

The individual prognostic value of each variable was estimated using multiple linear regression analysis, with the percentage of change in lumbar spine BMD as dependent variable with adjustment for relevant covariables, such as BMI, age, duration of amenorrhoea, and smoking status (baseline data).

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CHAPTER 4

The prevalence of low bone mineral density in Dutch perimenopausal women: The Eindhoven Perimenopausal Osteoporosis Study

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Abstract

The aim of this study was to estimate the prevalence of osteopenia and osteoporosis in perimenopausal women, and to assess determinants of low bone mineral density (BMD). All women born between 1941 and 1947 (aged between 46 and 54 years) living in the city of Eindhoven were invited to participate in the study; 5896 white Dutch women, representing 73% of the total number of Dutch women in this age group, were studied. Of these, 24% were using oestrogen preparations and 19% had undergone hysterectomy, with or without oophorectomy. All women were interviewed and bone mineral density (BMD) of the lumbar spine was measured by dual energy X-ray absorptiometry (DXA). Osteopenia and osteoporosis were defined according to the criteria proposed by a WHO working group. In the population studied the prevalence of osteopenia and osteoporosis was 27.3% and 4.1%, respectively. With progression from premenopause to menopause, the prevalence of osteoporosis increased from 0.4% to 12.7%, and that of osteopenia from 14.5% to 42.8%. An increased risk for low BMD (osteopenia and osteoporosis) was associated with age, menopausal status, and smoking while alcohol consumption, high body mass index (BMI) and use of oestrogen's had a protective effect. This study of a large population-based cohort of perimenopausal women revealed a high prevalence of low bone mass and, therefore, a higher risk for osteoporotic fractures.

The data further suggest that, when issues on the long-term efficacy and safety of preventive treatments are resolved, it may be possible to identify women at higher risk who are most likely to benefit from screening strategies.

Key Words: Bone mineral density; Oestrogen's; Hysterectomy; Menopause; Osteopenia; Osteoporosis; Prevalence; Risk factors; Screening

Introduction

Osteoporosis, currently defined as a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase of bone fragility and susceptibility to fracture,¹ is recognised as a major health problem. Bone mass in later life is determined by the peak mass attained during growth and early adulthood and the rate of subsequent bone loss. In women, the period of accelerated bone loss following the loss of ovarian function is theoretically the best time for treatments aimed at preserving bone mass, provided that effective, safe and generally acceptable means are available. Therefore it is important to identify those women around the menopause who are at risk of developing osteoporosis and are most likely to benefit from such treatments. Screening of all women for low bone mineral density (BMD) around the menopause, as proposed by some authors,^{2,3} is debatable and certainly not justified by the available data.⁴ Alternative approaches are therefore needed. However, for the design of optimal strategies to prevent osteoporotic fractures, adequate knowledge of the problem around the menopause is essential. Prospective studies have shown bone mass measurements to be strong predictors of fractures,^{5,6} and a WHO working party has proposed an operational definition for osteoporosis and diagnostic criteria based on BMD measurements.⁷ In the present study we used these criteria to assess the prevalence of low bone mass and its determinants with special emphasis on gynaecologic variables in a large cohort of perimenopausal women.

Subjects and methods

Study Design

Between September 1994 and September 1995, all women born between 1941 and 1947 ($n=8503$) who were living in the city of Eindhoven, The Netherlands, were invited to participate in the study by the Diagnostic Centre Eindhoven (DCE), a diagnostic centre for general practitioners, and the Department of Municipal Public Health Services, Eindhoven. Of the 8503 women, 8098 of whom were Dutch, 6846 (81%) responded to the invitation and 6648 (78%) agreed to participate in the study. In order to obtain homogeneous data comparable with other studies, the present analysis includes only white Dutch women, 6262 (77%) of whom agreed to participate in the study. Of these, 31 women who failed to provide relevant information and 3 in whom (BMD) could not be measured, were excluded from the analysis. Three hundred and thirty-two women were evaluated in a pilot, feasibility study and these results are not included either. Their mean BMD was $1.015 \pm 0.138 \text{ g/cm}^2$, while that of the remainder of the cohort ($n=5896$) was $1.013 \pm 0.145 \text{ g/cm}^2$. A questionnaire was completed by all women, medical history was taken, clinical exami-

Table 1. Characteristics of white Dutch women in the Eindhoven Perimenopausal Osteoporosis Study ($n = 5896$)

Characteristics	Mean $\pm$ SD	No. (% of 5896)
Age (years)	50.0 $\pm$ 2.1	
Height (m)	1.65 $\pm$ 0.06	
Weight (kg)	69.02 $\pm$ 12.49	
BMI (kg/m ²)	25.46 $\pm$ 4.47	
Age at menarche (years)	13.3 $\pm$ 1.7	
Number of pregnancies	2.20 $\pm$ 1.31	
Current use of estrogen		1433 (24.3)
Hysterectomy		777 (13.2)
Hysterectomy and oophorectomy		340 (5.8)
Oophorectomy		141 (2.4)

nation was performed and lumbar spine BMD was measured. Evaluation and measurements were performed at two centres: the DCE and St. Joseph Hospital, Veldhoven, a suburb of Eindhoven. All responders gave their written informed consent and the study was approved by two medical ethics committees. The characteristics of all women studied are shown in Table 1.

Menstrual status

The following definitions were used:

1. *Premenopausal*: Women with regular menstrual periods, or those who had stopped using hormone replacement therapy (HRT) or oral contraceptives in the 3 months prior to screening, followed by a regular menstruation pattern.
2. *Perimenopausal*: (a) Women with irregular menses (at least one menstrual period in the preceding year). (b) Women who had stopped using HRT or oral contraceptives 3 months to 1 year prior to screening, followed by irregular menses. (c) Women who had stopped using HRT or oral contraceptives during the year before screening, followed by amenorrhoea.
3. *Menopausal*: Women with amenorrhoea for 1 year or longer before screening.

Bone Mineral Density

BMD was measured at the lumbar spine (L1-4) by dual energy X-ray absorptiometry (DXA; S.A. Hologic Europe, Brussels). At the DCE, DXA model QDR-1000 S/N 291 was used, at St. Joseph Hospital, model QDR-2000 S/N 2260. Cross-calibration of the two densitometers was performed in nine volunteers. The Pearson correlation coefficient of these measurements was 0.9862, $p < 0.0001$. For quality control, two

Figure 1. Bone mineral density of the lumbar spine (LS-BMD) in 5896 white Dutch women aged between 46 and 54 years (means and SDs).

calibrations were performed daily using a spine phantom. The coefficient of variation for the DCE densitometer for the duration of the study was 0.54%, calculated using a spine phantom with a value of 1.0354 g/cm². For the St. Joseph Hospital densitometer this was 0.41%, calculated using a different spine phantom with a value of 1.0409 g/cm². Vertebrae that could not be evaluated (due to calcification, operations, etc.), were not included in the calculation of BMD.

According to the diagnostic criteria proposed by a WHO working party⁶ osteopenia is defined as a BMD between 1 and 2.5 standard deviations (SD) below the young adult mean (the *T*-score). *T*-score values below 2.5 are defined as osteoporosis. According to the reference data obtained by Hologic, the mean ($\pm$ SD) BMD of the spines (L1-4) of 650 healthy women studied at the University of San Diego, California, was 1.047 $\pm$ 0.110 g/cm². Osteopenia is therefore defined as a value between 0.937 and 0.772 g/cm², and osteoporosis as a value below 0.772 g/cm². The mean BMD value of the premenopausal women in the present study was 1.069 $\pm$ 0.129 g/cm² (mean $\pm$ SD). The BMD equivalent to -1 and -2.5 SD was therefore 0.940 and 0.747 g/cm², respectively. Both thresholds were used for the calculation of the prevalence of osteopenia and osteoporosis in the whole cohort. The Hologic thresholds were used in the further analysis of the data.

Statistics

The statistics were performed with the use of the Statistical Products and Service Solutions (SPSS). To correct for confounding factors the relationship (odds ratio (OR)) between low bone mass (osteopenia and osteoporosis) and potential determinants of BMD was examined by multivariate logistic regression analysis. The variables were hormonal use (use of HRT or oral contraceptives), age at screening and body mass index (BMI), gynaecological operations (hysterectomy, unilateral and bilateral oophorectomy), gynaecological parameters (menopausal status, age at menarche and previous pregnancies, smoking (current or past smokers), drinking (current alcohol consumption), and milk consumption before and after the age of 25 years.

Results

The mean ($\pm$ SD) BMD of the 5896 women studied was 1.013 ± 0.145 g/cm² and, of these, 4.1% had osteoporosis and 27.3% osteopenia, according to the BMD thresholds provided by Hologic. When the BMD threshold obtained in our premenopausal women was used, the prevalence of osteoporosis and osteopenia was 2.7% and 29.5%, respectively; similar thus to that estimated with the use of the Hologic thresholds. As expected, there was a progressive decline in lumbar spine BMD with increasing age (Figure 1), due to the increasing presence of menopausal women in the higher age groups.

Separate analysis of perimenopausal women according to age showed that the prevalence of osteoporosis was 1.4% at 48 years and 1.3% at 53 years. The corresponding values for menopausal women of the same ages were 13.4% and 14.1%, respectively. The prevalence of low bone mass (osteopenia and osteoporosis) in the postmenopausal women was related to the number of years since menopause (per year OR=1.12, $p<0.001$).

The BMD values and the prevalence of osteoporosis and osteopenia in the 3681 women in whom menstrual status could be determined are shown in Table 2.

In 2215 women, the menopausal status could not be determined due to hysterectomy, oophorectomy, use of HRT or oral contraceptives. Of these, 782 women did not use oestrogen (580 had undergone hysterectomy, 195 hysterectomy and oophorectomy, and 7 bilateral oophorectomy). Their mean BMD was 1.008 ± 0.149 g/cm² and 5.0% had osteoporosis, while 27.9% had osteopenia (Table 2). The prevalence of osteoporosis in women who had had a hysterectomy was 4.3%, and this rose to 11.1% in those who had had hysterectomy and bilateral oophorectomy and to 28.6% in those who had had bilateral oophorectomy only. However, the number

Table 2. Bone mineral density in Dutch women aged between 46 and 54 years

Menstrual status	No.	Mean age (years)	Mean BMD (g/cm ²)	Osteoporosis (%)	Osteopenia (%)
Premenopausal	760	48.8	1.069	3 (0.4)	110 (14.5)
Perimenopausal	1842	49.6	1.032	28 (1.5)	450 (24.4)
Menopausal	1079	51.3	0.930	137 (12.7)	462 (42.8)
Hysterectomy and/or oophorectomy	782	50.2	1.008	39 (5.0)	218 (27.9)
Estrogen use	1433	49.9	1.022	35 (2.4)	371 (25.9)

With progression from premenopause to menopause, there was an increase in the prevalence of osteoporosis from 0.4% to 12.7% within a narrow age range; the corresponding prevalence of osteopenia was 14.5% and 42.8%, respectively

Table 3. Bone mineral density of women using oestrogen (n=1433)

Status	No.	Mean age (years)	Mean BMD (g/cm ²)	Osteoporosis (%)	Osteopenia (%)
No hysterectomy and/or oophorectomy	1049	49.8	1.020	26 (2.5)	267 (25.5)
Hysterectomy alone	197	50.3	1.045	2 (1.0)	47 (23.9)
Hysterectomy with:					
unilateral oophorectomy	83	50.5	1.015	3 (3.6)	23 (27.7)
bilateral oophorectomy	62	50.1	0.994	2 (3.2)	23 (37.1)
Oophorectomy					
unilateral	38	49.8	1.007	2 (5.3)	9 (23.7)
bilateral	4	48.8	1.060	0	2 (50.0)

of women in the last group was too small to allow any definite conclusions. The mean BMD and prevalence of osteoporosis and osteopenia in the remaining 1433 women who used HRT or oral contraceptives are shown in Table 2, and the respective values in subgroups of these hormone users in Table 3.

In these women, the prevalence of osteoporosis and osteopenia was also highest in those with bilateral oophorectomies with or without hysterectomies.

The results of the multivariate analysis of the risk factors for low bone mass (osteopenia and osteoporosis) are shown in Table 4.

An increased risk for low BMD was associated with age, peri- and postmenopausal status, bilateral oophorectomy and smoking, while alcohol consumption, high BMI and use of oestrogen's had a protective effect. To obtain more insight into the rela-

Table 4. Determinants of low bone mineral density (T-score ≤ 1 SD) in perimenopausal women

Variable	OR	95% CI
Estrogen use	0.81	0.60-1.11
Age	1.12	1.09-1.17
BMI	0.90	0.89-0.92
Hysterectomy	0.93	0.68-1.27
Unilateral oophorectomy	1.21	0.92-1.58
Bilateral oophorectomy	2.25	1.44-3.52
Premenopause (indicator)	1.00	
Perimenopause	1.72	1.34-2.19
Menopause	4.91	3.77-6.40
Undetermined menstrual status	2.28	1.53-3.40
Age at menarche	1.03	0.99-1.07
Previous pregnancies (n)	0.95	0.91-1.00
Smoking ¹	1.25	1.08-1.44
Alcohol consumption ²	0.71	0.61-0.83
Milk consumption:		
Before 25 years	0.86	0.56-1.34
After 25 years	0.92	0.58-1.45

BMI, body mass index. ¹never smoked, past or current smoker. ²no use and current use

Table 5. Risk for low bone mass in relation to gynaecological variables

	HYST (-)		HYST (+)	
	OVX (-)	OVX (+)	OVX (-)	OVX (+)
ESTR (-)	Pre: 1.0			
	Peri: 1.72 (1.34-2.19)	5.14 (3.44-7.67)	2.12 (1.42-3.16)	4.77 (3.19-7.13)
	Post: 4.91 (3.77-6.40)			
ESTR (+)	1.85 (1.24-2.77)	4.17 (2.79-6.24)	1.72 (1.15-2.57)	3.88 (2.60-5.79)

Odds ratios and confidence intervals are shown. HYST, hysterectomy; OVX, oophorectomy; ESTR, oestrogen's; Pre, premenopausal; Peri, perimenopausal; Post, postmenopausal

tion between gynaecological parameters and bone mass we further estimated the risks of the various subgroups (Table 5).

In general, gynaecological operations (hysterectomy, oophorectomy) increased the risk for low BMD, relative to premenopausal women, and the risk was always reduced by the concurrent use of oestrogen's. It should be noted, however, that the prevalence of low bone mass corrected for age, was related to the number of years since the operation (hysterectomy, OR 1.04 per year, $p=0.001$, bilateral oophorectomy, OR 1.05 per year, $p=0.07$).

Discussion

The present study of a large population-based cohort of perimenopausal women, revealed the presence of osteoporosis and osteopenia of the axial skeleton in 4.1% and 27.3% of the women, respectively. For this classification, the definitions for osteoporosis and osteopenia proposed by a WHO study group were used, together with threshold values of BMD provided by the manufacturer of the bone densitometer. These values were obtained in young healthy American women and are comparable to those reported in the UK⁹ and Germany¹⁰, as well as to those obtained in the premenopausal women in our study (mean BMD 1.047 ± 0.110 g/cm² and 1.069 ± 0.129 g/cm², respectively). However, although the mean BMD of our premenopausal group is slightly higher than that of the American population, the SD is larger, accounting for a lower BMD threshold for defining osteoporosis: 0.747 g/cm² compared with 0.772 g/cm² using the manufacturer's data. Using this threshold, we diagnosed osteoporosis and osteopenia in 2.7% and 29.5% of the women, respectively. It should be mentioned that these reference values were obtained in an unselected group of premenopausal women who were, however, older than 45 years. Bone mass in such women may not be representative of the peak bone mass, as some bone loss may occur even before the menopause.¹¹ Furthermore, the present estimates of osteoporosis and osteopenia are based on BMD measurements at a single skeletal site, the lumbar spine, which may be an underestimation of the general risk for osteoporotic fractures. We chose to measure this site because trabecular bone is more sensitive to changes in oestrogen status which are likely to occur in this narrow age-range group of women.

Our findings, therefore, while emphasising the need for obtaining well-defined normal ranges for BMD, underline the high risk for osteoporotic fractures in relatively young women, even using the most conservative criteria for diagnosis. Our data, which were obtained in an unselected population cohort, cannot be compared directly with those obtained in other studies, mainly due to different study designs and subject selection characteristics. They are, however, generally in agreement with the results of studies of women of similar ages in the UK¹² and France¹³ evaluated in menopause clinics and of a select Finnish population cohort of 1600 women.¹⁴

Even within the narrow age-range of the women in our study, there was a clear age-related decrease in BMD of the lumbar spine. This was due more to the increased representation of menopausal women in the higher age groups than to an effect of chronological age per se. Separate analysis of perimenopausal women according to age showed that the prevalence of osteoporosis was 1.4% at 48 years and 1.3% at 53 years. The corresponding values for menopausal women were 13.4% and 14.1%, respectively. Indeed, menopause was found to be a very strong risk factor for low BMD which was also related to years since menopause. On the other hand, a high BMI and use of oestrogen had a protective effect on the skeleton,

as commonly reported.¹⁵ From our data it appeared initially that hysterectomy was associated with an increased risk of low bone mass when this group was compared with premenopausal women. Caution is needed however, in interpreting this result, as the prevalence for low bone mass adjusted for age was also related to the years since the operation in these women, which might have accounted for a higher representation of menopausal women. Nevertheless, the use of oestrogen's decreased this risk. The number of hysterectomies varies greatly in different countries^{16,17} reflecting local gynaecological practices rather than absolute indications for performing the operation.¹⁸ Our findings, though not definite, suggest that an increased risk of osteoporosis may be considered a potential complication of this operation in young women, which can be, however, reduced by oestrogen use. Of the other commonly assessed risk factors for osteoporosis, smoking had a negative effect on BMD, while alcohol consumption had a protective one.

The question arising from the present study is whether the results of this large unselected cohort of perimenopausal women can help in the design of preventive strategies, a subject that is currently under debate¹⁹⁻²². Twenty-four percent of the women studied were using oestrogen preparations and, in these cases, BMD measurements are not indicated.²² Premenopausal women, representing 13% of our population, can also be excluded from screening due to the lack of an effective treatment in this group. This leaves 63% as potential candidates for BMD screening. As shown here, however, the greatest differences in BMD occur between the perimenopause and the menopause and more than half of the total number of the menopausal women of this age group, not using oestrogen, had either osteoporosis or osteopenia. Thus, screening of these women (18.3% of the total population) is likely to reveal low bone mass in 55%. The chances of detecting a low bone mass are highest in this group of women. When it can be shown prospectively that safe and effective treatments that preserve or increase bone mass at the menopause, protect against fractures later in life, screening of these women might be realistic. However, until the above-mentioned requirements are fulfilled, we do not feel that screening is indicated around the menopause, and BMD measurements should only be performed in this age group according to specific indications.²

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CHAPTER 5

Is depressed mood a risk factor for low bone mineral density in perimenopausal women?

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Abstract

Previous studies showed an association between depression and decreased bone mineral density (BMD) suggesting that hormone levels could play an important role. We examined the relationship between depression and BMD in a large population-based cohort of healthy women around menopausal age. The study population consisted of 4944 healthy women, aged between 47 and 53 years. These women completed a questionnaire about their lifestyle habits, such as smoking, alcohol intake, medication intake, and physical activity, and completed a depression self-rating scale. Moreover, BMD of the lumbar spine was measured with dual energy X-ray absorptiometry (DXA)

One thousand and fourteen (20.5%) of the women were depressed, according to a cut off score of ≥ 12 on the Edinburgh Depression Scale (EDS). Excluding lifestyle habits, the characteristics of the depressed and non-depressed women were rather similar. The women with depressed mood had a significantly lower BMD compared to the non-depressed women

This study confirmed the relationship between depressed mood and decreased BMD at a univariate level. However, after adjustment for several important determinants of bone mass related to lifestyle habits, depressed mood showed no relation to decreased BMD. These findings suggest that the relationship between depressed mood and low BMD is influenced by lifestyle habits

Keywords: depression, osteoporosis, bone mineral density, women, perimenopausal, Edinburgh Depression Scale (EDS)

Introduction

Depression is a common and often chronic disease. A recent report by the WHO estimates that, within 30 years, over 300 million people throughout the world will be suffering from depression¹ Apart from its negative impact on quality of life in general - depression being the major cause of suicide^{2,3} - depression has also been associated with an increased risk of chronic diseases⁴ The association between depression and the subsequent development of cardiovascular diseases is well known.^{5,6} Depression has been shown to increase the risk of auto-immune syndromes,^{7,8} and an association between chronic depression and an increased risk of cancer has been suggested^{9,10} Recently, several studies have shown an association between depression and decreased bone mineral density (BMD) or osteoporosis^{11-14,15} However, the number of subjects involved in these studies was rather small, which might explain why only tentative theories were formulated to explain this finding. Another study in a large cohort of older women with established osteoporosis found no differences between depressed and non-depressed women.¹⁶

In order to achieve appropriate epidemiological power, the assessment of depressed mood (or high depressive symptomatology) in large samples, by means of depression self-rating scales, is a good approach, a high score on this self-rating scale being the strongest predictor of the presence of a depressive syndrome.¹⁷

The present study investigates the relationship between depressed mood and BMD in a large (5000) population-based cohort of healthy women around menopausal age¹⁸ Although no established osteoporosis would be expected within this population, a substantial variation - because of the declining oestrogen production in menopausal women - of BMD was found. Moreover, previous research within this sample has shown that up to 23% of these women suffer from high depressive symptomatology.¹⁹

Methods

Subjects

The initial study population consisted of 8503 women, aged 47-54 years, living in the city of Eindhoven, the Netherlands. Between December 1994 and November 1995, these women were invited to take part in a BMD assessment. A total of 6846 women responded (response rate, 81%), of whom 6648 (78%) actually had their BMD measured. Moreover, they completed a questionnaire in connection with their lifestyle (smoking habits, alcohol intake, medication intake, physical activity) and underwent a physical examination (blood pressure, pulse, weight, height). Poor physical activity was defined by less than two hours a week of physical exercise

(during daily life, such as walking and sports). Data regarding these baseline measurements have been published in detail elsewhere.¹⁸

Subsequently, the women were asked to complete a depression self-rating scale at home and to return it within one week of screening. Because of possible language problems, only Dutch Caucasian women (5896 in total) were included, of whom 5655 (95.6%) completed the depression self-rating scale correctly. Of these women, 711 failed to complete questions concerning lifestyle habits accurately. Therefore, the analysis refers to the remaining 4944 (83.8%) women. This group did not differ in baseline characteristics from the original study population. All women provided informed written consent, and the study was approved by an Independent Medical Ethical Committee.

Assessments

Bone mineral density

BMD of the lumbar spine (L1-L4) was measured with dual energy X-ray absorptiometry (DXA, model QDR-1000, S.A.Hologic Europe, Brussels). Calibration of the densitometer, scan quality control and scan performance were carried out by one qualified operator. The daily spine phantom quality controls were within 1.5% of the reference value. The coefficient of variation for the anatomical phantom (1.0354 g/cm²) for the duration of the study was 0.54%. All scans were performed in the supine position. Vertebrae that could not be evaluated (due to calcification, operation, etc.) were not included in the calculation of BMD.

Edinburgh Depression Scale

Depressive symptoms were assessed using the Edinburgh Depression Scale (EDS), a ten-item self-rating scale originally designed for use in postpartum women, and recently validated in non-childbearing women.^{20,21} The EDS has already been validated in the Netherlands in the postpartum period²², and recently in women of menopausal age.³¹ Scores vary between 0 and 30 (with higher scores indicating more depressive symptomatology), with a commonly used cut-off score of ≥ 12 .^{20,21} According to their EDS scores, the women were divided into five categories: those with hardly any depressive symptomatology (EDS < 7); those with moderate depressive symptomatology ($7 \leq \text{EDS} < 12$); those with clear depressive symptomatology ($12 \leq \text{EDS} < 16$); those with high depressive symptomatology ($16 \leq \text{EDS} < 21$); and finally those with EDS ≥ 22 , a score generally referring to severe depression.²¹

Statistics

Statistics tests were performed with the use of Statistical Products and Service Solutions (SPSS). Mean scores of BMD between the depressed (EDS ≥ 12) and non-depressed women were compared with Student's *t*-test. Differences between

proportional were assessed using the chi-square test for independent proportions. The effect of the severity of depressed mood on BMD was investigated by means of multiple logistic regression analysis, with low BMD ($\text{BMD} < 0.869$, osteopenia and osteoporosis) as the dependent variable and depressive mood, age, smoking, body mass index (BMI , kg/m^2), and physical activity as independent variables. A two-tailed significance level of 0.05 was used.

Results

The mean BMD was 1.008 g/cm^2 ($\text{SD} \pm 1.440$). One thousand and fourteen (20.5%) of all women were depressed according to a cut off score of ≥ 12 on the EDS. The characteristics of the depressed and non-depressed women are presented in Table 1. Except for their lifestyle habits, the two groups were rather similar. However, depressed women had poorer lifestyle habits, as far as smoking and physical activity were concerned. Also, depressed women used antidepressant drugs and tranquillisers significantly more often. The number of women in this study who used other medications that could contribute to a decline in bone mass, such as corticosteroids, anticonvulsant, or heparin, was small, and did not differ between the two groups (data not shown).

The women with depressed mood ($\text{EDS} \geq 12$) had a significantly lower BMD of the lumbar spine (mean: 0.998 g/cm^2 ; $\text{SD} \pm 0.143$), compared to the non-depressed women (mean: 1.018 g/cm^2 ; $\text{SD} \pm 0.144$; t -test, $p < 0.00$). This relationship was seen in the group as a whole, in those using oestrogen's, and in those not using oestrogen's.

In order to investigate the effect of an increasing EDS score on BMD, Table 2 shows the mean BMD scores in the five different EDS groups: the higher the EDS score, the lower the mean BMD. Subsequently, the severity of depressed mood was related to BMD, adjusted for age, BMI, smoking habits and physical activity, all of which are determinants of BMD (Table 3). In multiple logistic regression analysis, these independent factors substantially still affected BMD, while the influence of depressed mood disappeared. When menopausal state was included in the model instead of age, similar results were found. In women with an EDS score of ≥ 12 ($n=1014$), the mean BMD in those using antidepressant drugs ($n=69$) was compared to those with an EDS score of ≥ 12 not undergoing antidepressant therapy: the values were rather similar, 0.988 and 0.989 g/cm^2 , respectively.

Table 1. Baseline characteristics of the 4944 menopausal women aged (47- 53 years)

	Not depressed EDS <12		Depressed EDS ≥12	
Number (n)	3930		1014	
Age (years)	50	± 2	50	± 2
BMI (kg/m ²)	25.4	± 4.4	25.8	± 4.6
Menopausal state	n	%	n	%
Premenopausal	546	13.9	94	9.3
Perimenopausal	1273	32.4	293	28.9
Postmenopausal	696	17.7	201	19.8
Oestrogen users	928	23.6	272	26.8
Hysterectomy	452	11.5	141	13.9
Oophorectomy	35	0.9	13	1.3
Life style habits				
<i>Smoking</i>				
Never smoked	1254	31.9	280	27.6
Past smokers	1352	34.4	269	26.5
Current smokers	1324	33.7	465	45.9*
Alcohol intake				
Never	731	18.6	258	25.4
Incidentally	1804	45.9	431	42.5
Regularly	389	9.9	89	8.8
Daily	1006	25.5	236	23.3
Physical activity	1816	46.2	371	36.6*
Medication intake				
Painkillers	900	22.9	268	26.4
Antidepressants	55	1.4	69	6.8*
Benzodiazepines	102	2.6	136	13.4*

*significantly different on chi-square ($p < 0.05$)

Table 2. EDS scores compared to mean BMD

EDS score	N	BMD (mean) (g/cm ²)
< 7	2679	1.0194
≥ 7 and < 12	1159	1.0176
≥ 12 and < 16	574	1.0036
≥ 16 and < 22	410	0.9982
≥ 22	122	0.9924

Table 3. Determinants of bone mineral density of the lumbar spine in perimenopausal women. Logistic regression analysis. Dependent variable: low BMD (defined as osteopenia and osteoporosis)

Variable	OR	95% CI
Age	1.25	1.20 - 1.30
BMI	0.90	0.88 - 0.91
Smoking	1.15	1.09 - 1.22
Physical activity	0.70	0.62 - 0.86
Depressive symptomatology	1.10	0.98 - 1.22

Discussion

While this study investigated the occurrence of high depressive symptomatology rather than syndromal depression, the relationship between depression and decreased BMD, as shown in several other studies^{11,12,13,15} was confirmed at an uni-variate level. It is the first study in which such a relationship has been demonstrated in a large healthy community-based population consisting of 5000 perimenopausal women. Contrary to other studies, hospitalised patients were excluded from this study. Moreover, it showed a linear association: the higher the score on a depression self-rating scale, the lower the bone mass. However, after adjustment for several important determinants of bone mass (mostly related to life style habits), depressed mood showed no relation to decreased BMD.

The first study to question whether subjects with depression are at risk for low BMD investigated a rather small sample of 80 severely depressed inpatients (both men and women)¹¹ Each patient was matched with five controls for several other determinants of bone mass (age, sex, BMI, and menopausal state).

Hypercorticism was suggested as an explanation for this finding.¹¹ In the study by Halbreich *et al.*¹², the effect of several psychiatric disorders (mania, depression, schizophrenia, adjustment disorder) on bone mass in hospitalised medicated male patients was mainly explained by hypogonadism, which questions the possible role

of neuroleptics. Michelson et al.¹³ found lower BMD in 24 women with past or current depression. A decrease in bone turnover (as reflected by a decrease in osteocalcine and urinary deoxypyridinoline) and higher cortisol levels, in depressed women versus controls, was hypothesised to explain the lower bone mass. Another population-based study in 7414 older women, in whom decreased bone mass had already been established, could not find a difference in BMD between depressed and non-depressed women.¹⁶ Finally, a small community sample study of 102 older women, with a rather similar design as the present study, also found a higher prevalence of osteoporosis in women with high scores on a depression self-rating scale.¹⁵

From a conceptual point of view, the finding in the present study that higher scores for depressive symptoms in 'healthy' women (no psychiatric inpatients, and a high response rate, 81%, of all women of menopausal age from the city of Eindhoven) are related to decreased BMD, is rather intriguing. Contrary to what has been suggested so far, it might be hypothesised that – at least in a 'healthy' (non-hospitalised) population – a possible explanation for this finding is more likely to be found in the differences in lifestyle habits between depressed and non-depressed subjects (which are strongly related to BMD), rather than in primarily endocrinological factors directly related to depressed mood and bone mass (such as differences in cortisol levels). Previous studies have shown that depression – particularly major depression – is significantly associated with poorer lifestyle habits: high alcohol intake,^{23,24} high tobacco consumption,^{25,26} and decreased physical activity.^{27,28}

The latter two have also been shown to be related to decreased BMD.^{29,30} The almost linear association between scores on the depression scale (EDS) and bone mass (the higher the score, the lower the BMD) can also be explained by the association with these lifestyle habits. It has been shown that very high scores (≥ 17) on the EDS are commonly associated with the occurrence of severe (major) depression.³¹ Clinical studies have shown that severely depressed patients do indeed present with low physical activity,³² the latter being a major determinant of low bone mass. The suggestion that the use of antidepressant drugs might influence BMD was not supported by the present study: depressed women with and without the use of antidepressants showed similar bone mass. Although the odds ratio in this study is rather low, from a conceptual point of view, it is important to realise that the possible relationship between depressed mood and low BMD might be influenced by other factors.

As shown in the EDS validation study, scores above 16 are highly suspicious of the existence of major depression (positive predictive value, 75%).³¹

A limitation of the study was the assessment of depressive mood by self-rating scales, rather than by making a syndromal diagnosis of depression in a semi-structured interview. However, as pointed out earlier, the assessment of depressed mood (or high depressive symptomatology) in large samples by means of depression self-rating scales is a good alternative, a high score on this self-rating scale being the

strongest predictor of the presence of a depressive syndrome.¹⁷ Another limitation is the fact that this study used a cross-sectional rather than a prospective design, which made it impossible to evaluate the effect of the duration of depression on BMD. However, repeated assessments of depressed mood in large samples have shown that markedly elevated scores on the self-rating scale are highly suspicious of the occurrence of chronic depression.

The finding that depressed mood (indirectly rather than directly) negatively affects bone mass, might be regarded as another argument for treating depression. Major problems of depression are its high incidence,¹ the small proportion of subjects who seek professional help,³² the high number of depressed patients seeking help in whom the diagnosis is missed by the physician,³³ the high number of depressed patients who - once they receive pharmaceutical intervention - are treated with inadequately low levels of antidepressants,³⁴ and, finally the poor compliance to drug therapy.³⁵ All these factors are thought to contribute to the chronicity of depression and the high rate of recurrence. In turn, this chronicity may increase the risk of concomitant chronic diseases, such as cardiovascular and auto-immune syndromes, cancer and osteopenia or osteoporosis.

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CHAPTER 6

Prevention of early postmenopausal bone loss: A randomised trial of calcium, HRT and pamidronate in women with low bone mass selected from a population-based cohort and one-year follow-up

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Abstract

Objectives: The objective of this study was to compare the effect of calcium supplementation ($\pm$ 400 mg/d) alone, calcium with HRT (oestradiol 2 mg/dydrogesterone 10 mg), and calcium with pamidronate (100 mg/d) on early postmenopausal bone loss in women with low bone mass and to evaluate the rate of change in (BMD) one year after medication withdrawal.

Design: A randomised clinical trial.

Setting: A collaborative primary care centre in Eindhoven, the Netherlands.

Subjects: From a population-based cohort of 8503 women aged 47-54 years, 649 fulfilled the study criteria, and of these, 392 were randomised to receive calcium ($n=129$), calcium and HRT ($n=133$), or calcium and pamidronate ($n=130$), for two years and were followed one year after the completion of treatment.

Outcome measurements: BMD of the lumbar spine and the hip were assessed at baseline and after one, two and three years.

Results: Three hundred and four women (77.6%) completed the two-year study. At one and two years, the mean increases in lumbar spine BMD were significantly higher in the HRT group (4.5% and 5.2%, respectively) and the pamidronate group (1.4% and 0.5%, respectively) compared to the calcium-only group (-1.1% and -2.3%, respectively; $p < 0.001$ for all comparisons). During treatment, no bone loss was observed at the proximal femur or femoral neck in any of the treatment groups. In the 302 women (77%) who were studied in the third year, but who were no longer undergoing treatment, spinal BMD decreased by -4.5% in the HRT group, by -2.6% in the pamidronate group, and by -1.6% in the calcium group. There was also a decrease of BMD in the proximal femur (HRT -3.3%, pamidronate -2.6%, and calcium -2.0%), and a decrease was observed at the femoral neck in all three groups (HRT -2.9%, pamidronate -2.0%, and calcium -1.2%).

Conclusions: In early postmenopausal women with a low bone mass, bone loss can be prevented by HRT and pamidronate. One year after the completion of treatment, lumbar and femoral BMD was still increased in the HRT group compared to baseline measurements, while BMD in the pamidronate group was slightly decreased. The highest decrease in spinal BMD was observed in the calcium group.

Key words: osteoporosis, prevention, perimenopause, Hormone Replacement Therapy (HRT), calcium, bisphosphonates

Introduction

The loss of ovarian hormones in the menopause is a major risk factor for osteoporosis.^{1,2} The rate of bone loss is accelerated for approximately five to ten years after the menopause. It has been estimated that the risk of a women developing fractures later in life is as great as that of cardiovascular diseases and six times higher than that of breast cancer.³ Prevention of bone loss with hormonal replacement therapy (HRT) is associated with a reduced incidence of vertebral and hip fractures, and is considered to be the primary intervention for prevention of the disease.⁴⁻⁶ However, long-term compliance with HRT is low,⁷ necessitating the development of effective alternative interventions. Bisphosphonates, which suppress bone resorption and reduce bone turnover, have been shown to decrease postmenopausal bone loss⁸⁻¹¹ and, when given to women with osteoporosis, to decrease the risk of new osteoporotic fractures.^{12,13,14} Hosking *et al.*¹⁵ reported that oral alendronate was as effective as HRT in preventing bone loss in postmenopausal women younger than 60 years. However, studies assessing the efficacy and safety profiles of HRT and bisphosphonates in a population-based cohort of women, particularly those at higher risk for osteoporosis, have not yet been undertaken. Moreover, the effect of the discontinuation of these interventions in this group has not yet been studied in a randomised clinical trial.

In the present study we reported the results of a randomised clinical trial comparing the effects of HRT, the bisphosphonate, pamidronate (APD), and calcium, in early postmenopausal bone loss in women with low BMD selected from a population-based cohort and to evaluate the rate of change in (BMD) one year after medication withdrawal.

Material and methods

The initial study population consisted of 8503 women, aged from 47-54 years, living in the city of Eindhoven, the Netherlands. Between December 1994 and November 1995, a total of 6846 women responded to a postal questionnaire (response rate 81%); 6648 women (78%) consented to having their BMD measured, completed a questionnaire, and had a physical examination. Details of the characteristics of this population have been reported previously.¹⁶

Six hundred and forty-nine women (7.6%) fulfilled the inclusion criteria for the study, as follows: amenorrhoea for up to three years, altered menstrual pattern with less than five bleedings in the past 12 months, and a BMD of the lumbar spine in the lowest tertile of premenopausal women ($< 0.998 \text{ g/cm}^2$). Of those eligible, 56 women did not wish to participate in the study, and 201 were excluded. Exclusion criteria included: hysterectomy and/or ovariectomy, history and/or presence of a metabolic bone disease, rheumatoid arthritis, history of serious cardiovascular

diseases, endocrine diseases such as pituitary, thyroid or parathyroid dysfunction, history and/or presence of malignancies, and use of bisphosphonates or medications that could interfere with calcium and bone metabolism in the 12 months prior to the intervention study. The use of systemic oestrogens/progestagens was not permitted in the three months prior to the trial.

The final study population consisting of 392 women, who were randomly assigned to the three different treatment modalities (see below). All women provided informed written consent, and the study was approved by two medical ethical committees.

Treatment

All the women were given a calcium carbonate tablet (1000 mg Davitamon®), providing 400 mg elementary calcium. One group received no additional treatment; the second received continuous 2 mg oestradiol tablets, combined with 10 mg dydrogesterone in the second half of the cycle (Femoston®, Solvay Pharmaceuticals, the Netherlands); the third group received pamidronate (gelatin capsule) 100 mg/day, (Aminomux®, Gador, Argentina). The women were instructed to take the pamidronate on an empty stomach, half an hour to one hour before breakfast or dinner, with two glasses of water. The calcium was to be taken at bedtime. The women were randomly assigned to one of the treatment groups by computer, and no reallocation to another treatment group was offered. The total duration of the intervention was two years. The follow-up was an one year open study, women who had completed the two-year study received no medication and no calcium supplementation.

Bone mineral density measurements

BMD of the lumbar spine (L1-L4) and hip was measured at baseline during the subsequent three years with dual energy X-ray absorptiometry (DXA, model QDR-1000 S.A. Hologic Europe, Brussels). Calibration of the densitometer, scan quality control, and scan performance were carried out by one qualified operator. The daily spine phantom quality controls were within 1.5% of the reference value. The coefficient of variation for the anatomical phantom (1.0354 g/cm²) for the duration of the study was 0.54%. All the scans were performed in the supine position. The following sites were measured at the left proximal femur: total hip, femoral neck, and trochanter.

Assessment of safety of the treatment

The participants were seen every three months during the first two years, and every six months during the third year of treatment.

The following items were evaluated at each visit: any symptoms reported, occurrence of vaginal bleeding, medication used, adverse events, pill counting, blood pressure, weight, and pulse rate. Laboratory analyses, namely haematology, renal function and liver function tests, were performed every six months, for safety reasons. Mammograms were performed at the start and after two years of intervention. Women with abnormalities (suspected lesions)¹⁷ on mammography were carefully followed throughout the trial, and mammography was performed yearly.

Statistical analysis

The primary outcome, the percentage change in lumbar spine BMD, was compared between the two treatment groups and the calcium-only group using the *t*-test for independent observations, adjusted for multiple comparisons with a Scheffe correction. Statistical significance was defined as $p < 0.05$, two-sided. The secondary outcome, the percentage change in BMD at the different measurement sites at the proximal femur, was analysed accordingly. Analyses were by intention to treat, including those women in whom lumbar spine BMD was measured at baseline and at least once during treatment. The statistical analysis was performed with the use of the Statistical Products and Service Solutions (SPSS).

Using multiple linear regression analysis with the percentage change in lumbar spine BMD as the dependent variable, the effect of each treatment was compared, adjusted for relevant covariables such as BMI, age, duration of amenorrhoea, and smoking status (baseline data).

Results

The baseline characteristics of the 392 women randomised to the three treatment groups are shown in Table 1. The mean age of the participants in the study was 51.6 years, and there were no significant differences in any of the baseline characteristics between the three groups. Twenty women (5.1%) declined further participation in the study immediately after randomisation, and 42 women (17.3%) did not complete the study. The reasons for discontinuation are shown in Figure 1 for each treatment group. Eighteen percent of the women in the HRT group withdrew from the study because of menstrual disturbances (withdrawal bleedings, menorrhagia) and mastopathy; 11% of the women in the pamidronate group discontinued treatment because of gastrointestinal complaints, namely nausea and vomiting. The other main reason in the calcium and pamidronate groups for discontinuation of the study was the occurrence of climacteric complaints. After two years, 304 women had completed the study (77.6%): there were no significant differences in any of the baseline characteristics between those women who did or did not drop out. Compli-

Table 1. Baseline characteristics of the 392 women

Characteristics	Calcium	Calcium/ Oestradiol/dydrogesterone	Calcium/ Pamidronate
No. randomised	129	133	130
Age (yr)	mean $\pm$ SD 51.8 $\pm$ 2.4	mean $\pm$ SD 51.7 $\pm$ 2.7	mean $\pm$ SD 51.4 $\pm$ 2.5
Race (%)			
Caucasian	94	98	95
Negroid	2	1	1
Oriental	4	1	4
Smoking			
Current (%)	40	42	40
Cigarettes (n)	13 $\pm$ 7	16 $\pm$ 8	16 $\pm$ 10
Body mass index	24 $\pm$ 3	25 $\pm$ 4	25 $\pm$ 4
Time since menopause Months	18 $\pm$ 11	17 $\pm$ 11	17 $\pm$ 11
Bone mineral density			
Lumbar spine	0.871 $\pm$ 0.09	0.881 $\pm$ 0.07	0.883 $\pm$ 0.08
Trochanter (hip)	0.631 $\pm$ 0.08	0.646 $\pm$ 0.07	0.640 $\pm$ 0.07
Neck (hip)	0.749 $\pm$ 0.11	0.745 $\pm$ 0.13	0.755 $\pm$ 0.12
Total hip	0.860 $\pm$ 0.10	0.867 $\pm$ 0.11	0.867 $\pm$ 0.10

ance to treatment, assessed by pill counts, was high throughout the trial: the mean compliance in all the treatment groups was 86.3%.

Three hundred and two women entered the follow-up study; two subjects withdrew because they chose to stay on hormone therapy due to the possible recurrence of hot flushes. Three hundred women completed the study, while two withdrew (one in the pamidronate group because of a pancreas carcinoma, and one woman in the calcium group was lost to follow-up).

Lumbar spine bone mineral density

Two years of treatment

Lumbar spine BMD steadily decreased in the calcium-treated women, while it clearly increased in both the pamidronate and HRT treated women Table 2, Figure 2. This increase in BMD was most prominent in the HRT group (after one year, 4.5%;

Figure 1. Study profile and patient disposition

after two years, 5.2%). Compared to the calcium group, both HRT and pamidronate significantly prevented bone loss. However, the BMD response to HRT was significantly higher than that to pamidronate ($p < 0.001$).

Follow up year

After withdrawal of treatment, there was a significant decrease of BMD in all groups (HRT -4.5%, pamidronate -2.6%, calcium -1.6%), Table 2, Figure 2. The mean

Table 2. Percentage change of BMD during treatment and one year follow-up

in/decrease	Year 1		Year 2		Year 3		Total	
	%	SEM	%	SEM	%	SEM	%	SEM
<i>Calcium</i>								
Lumbar spine	-1.1	± 0.3	-2.3	± 0.3	-1.6	± 0.3	-4.0	± 0.3
Femoral neck	1.0	± 0.4	0.4	± 0.4	-1.2	± 0.3	-1.0	± 0.5
Total hip	1.5	± 0.2	0.2	± 0.2	-1.8	± 0.3	-1.8	± 0.3
<i>Calcium/Oestradiol-dydrogesterone</i>								
Lumbar spine	4.5	± 0.3**	5.2	± 0.4**	-4.5	± 0.4	1.3	± 0.4
Femoral neck	3.9	± 0.5**	5.0	± 0.5**	-2.9	± 0.3	2.8	± 0.7
Total hip	3.5	± 0.2**	4.0	± 0.3**	-3.3	± 0.3	1.4	± 0.3
<i>Calcium/Pamidronate</i>								
Lumbar spine	1.4	± 0.3	0.5	± 0.4*	-2.6	± 0.3	-2.0	± 0.3
Femoral neck	1.5	± 0.4	1.1	± 0.4	-2.0	± 0.4	-1.0	± 0.3
Total hip	1.2	± 0.2	0.7	± 0.3	-2.6	± 0.2	-1.8	± 0.4

* p < 0.001 treatment versus calcium. † p < 0.001 Oestradiol-dydrogesterone versus pamidronate.
SEM = standard error of the mean.

percentage change in BMD versus baseline was significantly increased in the HRT group (1.3%), and significantly decreased in both the pamidronate and calcium groups (-2.0% and -4.0%, respectively).

Bone mineral density of the femur

Two years of treatment

There was no significant decrease in mean BMD, as measured at the different sites of the proximal femur in any of the treatment groups, Table 2, Figure 3. There was a significant increase in BMD in the HRT-treated women, compared to both the calcium- and pamidronate-treated women. The major increase in BMD occurred after one year.

Follow up year

After the withdrawal of treatment, there was a significant decrease of BMD in all groups (HRT -3.3% and pamidronate -2.6%, calcium -1.8%), Table 2, Figure 3. The mean percentage change in BMD from baseline was significantly increased in the HRT group (2.8%) and significantly decreased in both the pamidronate and calcium groups (-1.0% and -1.0%, respectively).

Figure 2. BMD of the lumbar spine during two years of intervention and 1 year follow up.

Figure 3. BMD of the total hip during two years of intervention and 1 year follow up.

Subgroup analysis

This analysis was limited to those women who adhered to treatment regimen for the entire study period of two years (Table 2). Age and smoking were not significantly related to changes in lumbar spine BMD over the two years, in all the treatment groups combined. Women with a longer duration of amenorrhoea gained slightly, but significantly, more bone: calcium group, 7.1%; HRT group, 12.9%; and pamidronate group, 0.2%. In the HRT group, women with a higher body mass index gained less bone (-3.7%), and those who smoked more than ten cigarettes a day gained significantly less bone (-7.8%) at the lumbar spine than smokers in the pamidronate (-1.4%) and calcium (-0.8%) groups. It should be emphasized that the effects of the covariables examined contributed very little to the overall effect of the intervention.

Adverse events

Overall safety was comparable between the three treatment groups. A high percentage of participants reported adverse events: calcium-only group, 90%; HRT group, 97%; and pamidronate group, 89%. Gastrointestinal complaints were equally frequent in all three groups (calcium, 22%; pamidronate, 25%; and HRT, 21%).

As expected, the typical HRT-related adverse events were significantly more frequent in this group, including breast tenderness (15%) and dysmenorrhoea (12%). Interestingly, musculoskeletal complaints, such as arthralgia, myalgia and tenosynovitis, were significantly less frequent in the HRT group (33%) compared to the calcium and pamidronate groups (48% and 50%, respectively; $p < 0.05$). During the third year, 50% of the woman on HRT treatment reported the recurrence of hot flushes. Serious adverse events occurred in all three groups. In the calcium group, one woman developed an endometrial carcinoma, while, in the pamidronate group, one case of severe endocarditis and one of vaginal postmenopausal blood loss requiring a hysterectomy, occurred. In the HRT group, three women with breast cancer were detected during follow-up: one tumour appeared after one year and two carcinomas after two years of treatment. During the third year, one woman developed a pancreas carcinoma, (pamidronate group), and at the last visit, a woman was diagnosed with an inoperable brain tumour (calcium group).

Discussion

Bone loss occurring after the menopause is accelerated in the early postmenopausal period, making this a popular period for administering interventions aimed at reducing bone loss and preserving bone mass. This is particularly important in

women who already have a low BMD. We focused on a group of peri- or early postmenopausal women who already had a low BMD. Consistent with the anti-resorptive action of HRT and pamidronate, our results demonstrated that both treatments given together with calcium prevented bone loss.

Usually, women included in osteoporosis prevention studies are selected from postmenopausal clinics, advertisements or personal invitation and, therefore, may not be representative of the population as a whole. In the present study, we selected a group of peri- and early postmenopausal women with BMD at the lowest tertile of premenopausal women, from a population-based cohort of women aged between 47 and 54 years. In this way, we did not only study those women at greatest risk for osteoporosis in the community. Individual preferences, which might indicate selection bias, were also noted in the present study: 5.1% declined participation immediately after randomization, due to preference for another intervention than the one assigned. The majority of these women had been allocated to the HRT group. Reallocation to another treatment group, as had occurred in the only published study of similar design¹⁵ was not offered.

Consistent with the anti-resorptive action of HRT and pamidronate, our results demonstrated that both treatments given together with calcium prevented bone loss. The response to HRT was significantly better than that induced by pamidronate. At first sight, the effects of pamidronate on postmenopausal bone loss appeared to be less favourable than those recently observed by Hosking *et al.*,¹⁵ using another aminobisphosphonate, alendronate. In contrast to this study, we focused on a younger group of peri- or early postmenopausal women with an already low BMD, and used the lowest effective dose of pamidronate, since our aim was to prevent bone loss rather than to increase bone mass. In the treatment of patients with established osteoporosis, pamidronate 150 mg/d has been shown to induce changes in BMD similar to those ascribed to alendronate in a similar patient population.^{8,18} As already observed in other studies,¹⁹ smoking interacted with the gain in BMD in HRT-treated women. Furthermore, the most prominent effect of HRT appeared to occur in women with a relatively low BMI and in those with a longer duration of amenorrhoea. Nevertheless, we wish to emphasize that the overall effect of these factors was limited, and did not essentially influence the final responses to intervention.

During our study of women using pamidronate and HRT, BMD gain was observed to slow up in the second year of treatment, and a significant loss of BMD following the withdrawal of treatment was noted. These data are consistent with the anti-resorptive action of these drugs, leading to filling in the remodelling space rather than to permanently resetting the balance between formation and resorption. The response of BMD induced by HRT, observed after two years and one year after withdrawal, was significantly better than that induced by pamidronate. BMD showed a significant increase from baseline in the spine and the hip, while pamidronate produced a decrease in BMD at both sites compared to baseline

measurements. However, we used the lowest effective dose of pamidronate, since our aim was to prevent bone loss rather than to increase bone mass. This dose does not seem to be sufficient to reach a similar effect as HRT.

HRT and pamidronate were well tolerated in the present study, and any reported adverse events were very mild or irrelevant. The proportion of women who discontinued the study due to an adverse event was higher in the HRT group than in the pamidronate group, but the incidence of gastrointestinal complaints did not differ between the three groups. The occurrence of three cases of breast cancer in the HRT-treated women, compared to none in the other two groups, is worrying. However, the period of exposure to oestrogen's was too short to account for this, and perhaps it was a chance finding³⁰ rather than a drug-related event.

Oestrogens

The mechanisms of the anti-resorptive action underlying the effect of oestrogen treatment on the bone is not clearly understood. It is thought to involve the inhibition of osteoclasts,^{20,21} which reduces bone turnover and improves the balance between bone formation and resorption.^{21,22} In addition, oestrogen improves calcium retention through increased testinal calcium absorption and renal calcium reabsorption.²³ The bone loss 'catch up' effect following the termination of treatment has a negative effect on the efficacy of short-term and early-applied treatment. Therefore, the bone loss catch up effect favours long-term treatment, or treating women at the age when fractures occur (*i.e.*, around the age of 75 years for hip fractures, and around the age of 65 years for vertebral and wrist fractures).

Recently, Le Pen *et al.*²⁴ described a computer-based stimulation model which compared the long-term effectiveness of different preventive strategies. In this model, strategies combining both early (starting at menopausal age) and later treatment (at the age that fractures occur) are shown to be the most effective.

The Framingham study found a relative risk of 0.34 (95% confidence interval 0.11-1.09 after multivariate adjustment) among current or recent users of oestrogen and of 0.70 (0.45-1.08) in former users for the protection of fractures.²⁵ Also, significant protection from hip fractures in women who began HRT within five years of the menopause was seen in a study of osteoporotic fractures, but not in woman who started treatment later.²⁶ However, in a cross-sectional study of bone density, a nearly equal bone conserving benefit was seen for oestrogen therapy, starting before or after the age of 60 years, if the treatment was continued.²⁷ Several studies have suggested that oestrogen therapy only taken at the time of the menopause preserves bone during use, but may not preserve bone density later in life^{28,39} or protect against osteoporotic fractures.^{26, 29-31} The above-mentioned studies show that the timing of starting HRT and its optimal duration are still matters for discussion. From a skeletal perspective, very long-term HRT treatment appears to carry the greatest chance of preventing clinical osteoporosis, although this will be influenced by the

weight given to non-skeletal issues, including other benefits and the risk of side-effects.

Pamidronate

The findings in our study are consistent with those of Meunier *et al.*,³² using the bisphosphonate etidronate in the prevention of early postmenopausal bone loss: a marginal increase in BMD of the lumbar spine after two years of treatment, and a significant decrease in the following year without treatment.

Orr-Walker *et al.*³³ observed in women with a mean age of 66 years and established osteoporosis, an increase in BMD during three years of treatment, but also a decline in BMD after discontinuation of pamidronate (150 mg/day). Consistent with the concept of the mechanism of action of an anti-resorptive agent, the increase in lumbar spine BMD occurred wholly during the first year of treatment. Pamidronate inhibits bone resorption with a consistent increase in bone mass until a new steady state is reached. At steady state, the decrease in bone resorption is matched by a decrease in bone formation and bone mass is maintained, and therefore, withdrawal of treatment induces a rapid decrease of BMD.

Landman *et al.*³⁴ described a cohort of 30 patients with established osteoporosis who had been treated with pamidronate (150 mg/day) for an average of 6.5 years. BMD of the lumbar spine and femoral neck did not change during two years of follow-up, despite biochemical evidence of the reversal of the suppression of bone turnover within six months of the discontinuation of treatment. In this study, a quarter of the patients was male, and one-third was taking vitamin D supplements or thiazides for the duration of the study. However, the effect of the longer duration of treatment with the greater skeletal accumulation of bisphosphonates may explain the apparently more persistent of treatment.

Our findings imply that pamidronate treatment for the prevention of osteoporosis in a dose of 100 mg/day may be insufficient to result in a substantial increase in bone mass, and will not affect bone loss after the cessation of treatment.

Calcium

An interesting observation was the lack of any significant bone loss at the proximal femur in the calcium-treated women for two years, and a decrease in BMD during the third year, following the withdrawal of calcium supplementation. This increase apparently contrasts with findings from other studies.^{15,35} An explanation for this might be that the calcium supplement added to the already high calcium intake of Dutch women (1000-1200 mg/day) provided a total, pharmacological amount of calcium³⁶ sufficient to decrease bone turnover at cortical sites, while this treatment is insufficient to decrease bone turnover at sites containing more trabecular bone, where the bone turnover is higher. Therefore, the subsequent bone losses at all sites measured, after the cessation of calcium supplementation, might be explained by a higher bone turnover, resulting in a loss at both the hip and lumbar spine.

Conclusions

This randomised clinical trial indicates that HRT is preferable for the prevention of BMD in women with early postmenopausal osteoporosis, but must be continued for a long period of time, taking other non-skeletal benefits and the risk of side-effects into consideration. Secondly, calcium supplementation may play a role in the prevention of cortical bone loss in women with early postmenopausal osteoporosis.

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CHAPTER 7

Compliance to an oral bisphosphonate therapy in women with early postmenopausal bone loss

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Abstract

In order to achieve optimal benefit from the treatment of postmenopausal bone loss, strict compliance with bisphosphonate ingestion instructions is required. Low absorption (< 2%) and significant food-drug interaction make it necessary for the drug to be ingested at least 30 minutes before a meal. We examined the compliance of a cohort of early postmenopausal women to oral pamidronate (Aminomux®), prescribed for the prevention of bone loss. Patient compliance was measured using: MEMS (Medication Event Monitoring System, AARDEX Ltd., Switzerland). This consists of a special, microprocessor-equipped pill-phialcap that records the time and date of opening the cap. The women were instructed to take the pamidronate half an hour before breakfast or dinner. Eighty-six women were followed for a mean duration of 38,268 days (104 patient years).

Overall, compliance was high: 90 ± 13 % (range, 20-101) of all tablets were ingested. Seventy-eight percent of patients took the capsules within a 25% time window around the prescribed dosing intervals (timing compliance). There were 133 periods of three or more days without drug intake (drug holidays), with large inter-individual variation. Overall compliance for the time of day was consistent: 33.1 % of the women took the pamidronate capsule in the morning and 58.4 % took it in the evening. However, 50% of all patients showed a significant variation in the time of ingestion of capsules (standard deviation for time of ingestion > 2 hour), making it probable that food-drug interaction could have occurred. No relationship between the time of capsule ingestion and changes in lumbar spine bone mineral density (BMD) was observed.

Overall, taking and timing compliance was high. This was surprising because of the asymptomatic nature of low BMD. No difference was found in BMD response between women who took pamidronate in the mornings and those who took it in the evenings.

Key Words: compliance, osteoporosis, bisphosphonate, bone mineral density, pamidronate

Introduction

Osteoporosis is a common and important cause of morbidity and mortality among postmenopausal women. It arises as a consequence of progressive loss of bone, and results in an increased risk of fractures. Four in about ten white women currently at the age of 50 years will sustain one or more osteoporotic fractures in their remaining lifetime.¹⁻⁶ As the elderly population grows, the worldwide annual incidence of hip fractures is projected to increase from 1.7 million in 1990 to 6.3 million by 2050, obviously placing great economic strain on health care systems.⁷

There are several strategies to reduce the incidence of fractures in postmenopausal women. Among these, bisphosphonates which can reduce the incidence of osteoporotic fractures by about 50% are used in the prevention and treatment of osteoporosis.⁸⁻¹² Specific pharmacological properties of bisphosphonates include very low intestinal absorption and significant drug-food interactions, most notably with calcium.¹³ These properties necessitate specific instructions about the timing and conditions of the administration of these drugs. For example, for alendronate, the manufacturer recommends taking the bisphosphonates in the morning 30 to 60 minutes before breakfast with water only.¹⁴ If such instructions are not carefully followed, it is assumed that the full efficacy of treatment will not be achieved. In addition, such strict instructions may reduce patient compliance over longer periods.

Patient compliance to a prescribed drug regimen can be accurately measured using electronic monitoring of the opening of medication phials. Although an indirect measurement, as there is no proof of drug intake, this method has many advantages over other techniques for measuring compliance and is currently considered the gold standard.¹⁹ The advantages and disadvantages of other methods of measuring compliance have been described in detail elsewhere.^{17,18}

Surprisingly, data on patient compliance with bisphosphonates are not available. In the present study, we examined the compliance to once daily administration of the aminobisphosphonate pamidronate in asymptomatic early postmenopausal women with low bone mineral density (BMD), selected from a population-based cohort, who participated in a trial of the effects of various interventions for the prevention of bone loss. For this, electronic monitoring instruments capable of recording the time and date of removing tablets from a container were used.

The objectives of the study were, firstly, assessment of the overall compliance rate to treatment and to specific instructions about the timing of drug intake and, secondly, the relationship between compliance to these instructions and changes in BMD after two years.

Methods

In a population-based cohort of 8503 women aged from 47-54 years,¹⁵ 649 fulfilled the following criteria: menopause for up to three years and BMD of the lumbar spine in the lower tertile of premenopausal women $< 0.998 \text{ g/cm}^2$ (DXA Hologic). All patients were given calcium carbonate 1000 mg (Davitamon[®]), which consists of 400 mg elementary calcium. Of these, 392 women were randomised to the following groups: the first group ($n=129$) received no additional treatment; the second group ($n=133$) received oestradiol 2 mg continuously combined with dydrogesterone 10 mg in the second half of the cycle (Femoston[®]); and the third group ($n=130$) received oral pamidronate (APD) 100 mg/day, (Aminomux[®], Gador, Argentina). The duration of treatment was two years. BMD was assessed at baseline, and after one and two years.

In the group receiving pamidronate, compliance was measured using the Medication Event Monitoring System (MEMS, Aardex Ltd., Switzerland). This system consists of a normal pill container with a special cap that contains electronic micro-circuitry to record the time and date of every opening. Throughout the analysis, we assumed that with every opening a tablet was actually taken. The data from the monitors were downloaded to an IBM compatible personal computer, using a dedicated modem and CSS software version 2.1 (AARDEX Ltd, Switzerland), which was also used for the calculation of the compliance variables.

Patients were instructed to take the pamidronate capsule 30-60 minutes before breakfast or dinner, with two glasses of water, and not together with food or calcium tablets. All patients had given their written informed consent and were told that the cap was capable of 'counting pills'. We did not use electronic monitoring in the calcium and hormone replacement therapy (HRT) group, because the calcium tablets did not fit into the special boxes and HRT is accompanied by special dose-organizers with instructions to take the dydrogesterone in the second half of the cycle.

In addition to the electronic data in the pamidronate group, we counted the number of returned tablets in all three groups. Monitoring was applied for at least six months after the initiation of treatment, and patients were followed until two years after baseline.

Compliance was calculated as

Taking compliance = (total number of doses taken/number of days monitored) $\times$ 100%

Timing compliance = (number of doses taken at 24 ± 6 hourly intervals/number of days monitored) $\times$ 100%

The response to treatment was assessed by the changes of the BMD in the lumbar spine, measured by dual energy X-ray absorptiometry (DXA, model QDR-1000 S.A.

Hologic Europe, Brussels). Calibration of densitometers, scan quality control, and scan performance were carried out by one qualified densitometry operator. All daily spine phantom quality controls were within 1.5% of the reference value. The coefficient of variation for the anatomical phantom (1.0354 g/cm^2) for the duration of the study was 0.54%. All scans were performed in the supine position. BMD of the lumbar spine was measured at baseline, and at 12 and 24 months of follow-up. Treatment success was defined as an increase in BMD, expressed as the percentage change score between BMD at two years and baseline BMD. A positive change (increase in BMD or no change) was labelled 'responder', while a negative change (decrease in BMD) was labelled 'non-responder'.

Data are expressed as mean $\pm$ standard deviation. Correlation's are estimated using Pearson's correlation coefficient. The relationship between compliance and change in BMD was investigated with the χ^2 test and by linear regression analysis, and by when compliance was related to success of treatment. All calculations were performed in SPSS version 7.5 for Windows 95.

Results

The data from four caps could not be retrieved: two had been lost, and two were not readable. Nine women had almost finished the study by the time the electronic monitors became available and therefore did not participate in this arm of the study. Thirty-one women dropped out of the study for several reasons, for example, adverse events such as epigastric pain and nausea, protocol violation, and motivation problems. Therefore, compliance data were available for 86 women. Table 1 shows the patients' characteristics and demographic data.

A total of 38,268 days (105 patient-years) were monitored in 86 patients (average 450 ± 93 days of follow-up). Taking compliance was high: 90.4% of all tablets were taken, of which 86.3% were taken as prescribed (once daily), whereas on 11.7% of the days, no medication was taken, and on 1.9% of the days, extra medication was taken. Figure 1 shows a histogram of the distribution of taking compliance. Analysis of timing compliance showed that the majority of the prescribed doses (77.7%) were

Table 1. Baseline characteristics of the 86 women

Characteristics	Mean $\pm$ SD
Age (years)	51.5 ± 2.5
Body mass index	24 ± 3.5
Time since menopause (months)	17 ± 11
Bone Mineral Density Lumbar Spine (g/cm^2)	0.884 ± 0.09

Figure 1. Taking compliance of pamidronate

taken at 24 ± 6 hourly intervals. However, 4.4% were taken too early and 8.2% too late. Since timing compliance uses the prescribed number of doses as its denominator, which is higher than the number of recorded openings, these do not add up to 100%.

Distribution of the timing of drug intake revealed that 24.8% of all doses were taken in the morning (arbitrarily defined as between 6.00 and 10.00 a.m., average 7.45 a.m.), while 55.6% were taken in the evening (arbitrarily defined as between 15.00 p.m. and 19.00 p.m., average 16.45 p.m.). Figure 2 shows the distribution of the timing of drug intake.

Drug holidays, defined as three or more consecutive days without evidence of dosing,^{20,21} were not uncommon: 47 of 86 patients (55%) had at least one holiday, and overall there were 216 drug holidays (55% of all dose-free days), with an average duration of eight days. There were eight exceptionally long drug holidays (>30 days), the longest of which lasted for 89 days.

The correlation coefficient between the returned tablet count and taking compliance was low (0.52.). Figure 3 shows that returned tablet counts led to the overestimation of compliance in the majority of patients.

We specifically studied patients with correct timing of drug intake, defined as >30 minutes and <120 minutes before breakfast or dinner, in order to test whether there was a relationship between time of drug intake and change in lumbar spine BMD. Forty-nine women had an increase in BMD of the lumbar spine after two years, and 37 women had a decline in their lumbar spine BMD. Of the 49 responders, 24 took their medication within the predefined time window, while 25 did not. Of the 37 non-responders, 24 women took their the medication on time, while 13 did not ($\chi^2 = 2.16$, $p = 0.14$).

Figure 2. Time distribution of drug intake

Figure 3. Compliance of Returned Tablet Count versus Electronic Monitoring

Figure 4a. Chronology plot of a responder

Figure 4b. Chronology plot of a non responder

Linear regression analysis showed a positive but weak association between taking compliance and percentage change in BMD. However, this association was not statistically significant.

Discussion

In general, no drug can work if it is not taken, and it is reasonable to assume that large deviations from the prescribed dosing regimen result in sub-optimal results. A general property of all bisphosphonates is their low absorption (usually <2%) and significant food-drug interactions,¹³ necessitating attention to the timing of their intake. This is the first study in which an electronic instrument has recorded the time and date of the opening of medication phials. This manoeuvre allowed detailed investigation of patient compliance and of the relationship between the intake of pamidronate and the change in BMD of the lumbar spine.

Overall, the taking and timing compliance were high compared to studies with a variety of other drugs, such as antihypertensives, cholesterol lowering and non-steroid anti-inflammatory drugs, anti-epileptics, migraine and anti-AIDS drugs.^{16,22-27} This was surprising because of the asymptomatic nature of low BMD. Several factors may have contributed to the high compliance in this population, including the selection procedure utilised in the enrolment, the relatively high visit frequency, and the fact that patients were aware of the monitoring capacity of the caps.

Study enrolment comprised a three-step selection process. Participating women were selected from the lowest tertile for lumbar BMD of a population-based cohort of 8,000 women (step 1); they were invited by telephone to visit the doctor and were informed of their low BMD (step 2); and finally made a conscious decision, in a consultation with the physician lasting approximately one hour, to participate in the study (step 3). Since each of these steps requires the active co-operation of the patients, it is possible that these steps resulted in a relatively compliant population.

After inclusion in the study, the women were seen by the same physician every three months for two years. This is more frequent than the usual follow-up of patients who are at risk for osteoporosis, and a more frequent follow-up may result in better patient compliance.

Although all patients in the pamidronate group were informed that compliance was measured electronically, this seems an unlikely explanation for the good compliance rate observed, because compliance was also high in the other study groups, based on tablet counting (calcium, 82.1%; HRT, 90.5%). Furthermore, during the study, no feedback was given on compliance measurements. Finally, the monitoring technique used in this study has been used in many other fields, such as hypertension¹⁶ and epilepsy,²⁴ where compliance was much lower, making it unlikely that knowledge of electronic monitoring is commonplace.

Bisphosphonates such as pamidronate and alendronate are given with instructions regarding the time of ingestion, because of the above-mentioned low gastrointestinal absorption and drug-food interaction. Therefore, we evaluated the relationship between time of ingestion during the day (morning or evening) and time of meals (breakfast or dinner) to changes in BMD. Given the design of our study, it was possible to evaluate the relationship between the time of bisphosphonate intake and changes in lumbar spine BMD. Surprisingly, there was no difference in BMD response between women who took pamidronate correctly (more than 30 and less than 120 minutes before breakfast or dinner) and those who took it at other times intervals. In addition, there was no difference in BMD response between the women who took the bisphosphonate in the morning and those who took it in the evening. Of particular practical significance was the much higher preference for taking pamidronate in the evening, which underscores the inconvenience of currently recommended regimens. These results suggest that the instructions regarding medication ingestion, as given for the bisphosphonates, may perhaps be too stringent and need to be further evaluated.

The current study had a high rate of compliance, making it impossible to draw any conclusions on factors regarding non-compliance. Furthermore, the study was population-based and the results cannot be extrapolated to patient populations attending hospitals or those with secondary osteoporosis. Therefore, further research is needed to evaluate the validity of stringent instructions for the ingestion of bisphosphonates, as well as other determinants of compliance efficacy, and to study the relationship with drug exposure more closely.

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CHAPTER 8

General discussion

Introduction

The central theme of this thesis is the question of whether or not an intervention with anti-resorptive drugs (oestrogen or pamidronate) is useful in the prevention of further bone loss in early postmenopausal women with low bone mass. Other questions of major importance are: do women with low bone mineral density (BMD), and therefore at risk of developing osteoporosis, want to take medication to prevent osteoporosis, and what is the compliance rate regarding the medication taken. The results of the randomised clinical trial and the compliance study, which are presented in full in chapters 6 and 7, are discussed below. The relevance and implications for population-based screening of BMD in early menopausal women will be outlined. The results of the data obtained in the screening study and the intervention study will be estimated in a population of 100,000 women, in order to show how many women can be reached regarding the prevention of osteoporosis. Finally, the relevance for future research of the results presented in this thesis will be discussed.

Developments over time

After the Health Council of the Netherlands (Gezondheidsraad) published the report *Prevention of osteoporosis* in 1991,¹ a second report, *The prevention of osteoporosis-related fractures*, appeared in 1998.² This second report was written due to the rapidly increasing knowledge on osteoporosis, new epidemiological insights, and new ways of treatment. An important difference between the two reports is the approach to the screening of BMD in women around the menopause. In the first report, the committee advised the Minister of Health to study the need for screening, while in the second report, the committee made the following recommendation:

“Osteoporosis-related fractures make osteoporosis an important health problem. In its considerations, the committee has attached prime importance to the effects on the risk of fractures of various ways of prevention. The committee notes that the effect of many interventions on the fracture risk has not been established. This is one of the reasons why the committee rejects a screening study.”

In this report, osteoporosis is characterised as a public health problem. Apart from promotion of a healthy lifestyle, including exercise, and attention to a healthy diet, it is important to recognise those who are at increased risk for fractures, in other words, case finding is advocated. This advice contradicts the osteoporosis guidelines for general practitioners published by the Dutch College of General Practitioners in 1999,³ which rejects case finding on the basis that many risk factors for bone density have not yet been fully clarified.⁴

Implications of the findings

Screening study

The definition of osteoporosis implies that low bone mass is an important determinant of the risk of fracture, and that other factors such as falls are also important. The clinical significance of osteoporosis lies in the fractures that occur. BMD measurement by dual-energy X-ray absorptiometry (DXA) provides us with relevant information for clinical management. Many prospective studies have shown that the risk of fractures increases approximately two-to-three-fold for each standard deviation (SD) decrease in BMD.⁵ BMD measurement predicts fractures as well as blood pressure predicts strokes, and significantly better than serum cholesterol predicts myocardial infarction.⁶ By themselves, BMD measurements have a high specificity, but a lower sensitivity. This means that a negative test (the absence of osteoporosis) indicates a very low risk of future fractures. However, moderate sensitivity (approximately 50%) means that half of all osteoporotic fractures will occur in a population not defined as having osteoporosis.⁷ For this reason, it has been suggested that this test is more useful in the context of a case finding strategy than for screening at a population level.⁸ Case finding is focused on those subjects with the highest risk of fractures, and BMD measurements are indicated in those subjects. Risk factors that are an indication for BMD measurements are listed in Table 1.

Case finding for the prevention of osteoporosis is advised by the Health Council of the Netherlands³ and the Clinical Guidelines for the Prevention and Treatment (Royal College of Physicians, UK),⁷ but this is in contrast to the guidelines of the Dutch College of General Practitioners. These guidelines do not advise an active policy for a particular section of the population at possible risk for osteoporosis. The policy is based on a lack of evidence of risk factors which, in the long-term, contribute to low bone mass, and a lack of evidence regarding the medical prevention and treatment of osteoporosis in the long-term. Our population-based study showed that, according to the World Health Organisation (WHO) criteria, 4.1% of the nearly 6000 women studied in the age group from 46–54 years, had osteoporosis, and 27.3% osteopenia. An important subgroup ($n=1079$) of this population were menopausal women with a mean age of 51 years. The prevalence of osteopenia and osteoporosis was 42.8% and 12.7%, respectively, and none of these women used hormone replacement therapy (HRT). If we follow the Guidelines of the Dutch College of General Practitioners in this population, this would imply that a substantial portion of these women would not have their BMD measured, although they already have osteoporosis and are at risk for fractures.

When considering the Guidelines for General Practitioners, it might be possible to agree on whether factors that contribute to the risk of fractures can improve prediction and detection in patients in whom long-term treatment might be useful.⁹

Table 1. Risk factors for identifying patients in a case-finding strategy

- Early menopause
- Amenorrhoea for more than a year
- Primary hypogonadism
- Long-term use of corticosteroids, 7.5 mg or more daily
- Maternal family history of hip fracture
- Clinical increase of thoracic kyphosis
- Prior fragility fracture
- BMI lower than 19 kg/m²
- Anorexia, malabsorption syndrome, primary hyperparathyroidism, hyperthyroidism, renal – osteodystrophy, or Cushing's syndrome
- Status after organ transplantation, status after Billroth II resection
- Immobilisation for several months
- X-ray with an indication of low bone mass

Intervention study

The intervention study described in Chapter 6 compared the effect of calcium supplementation (± 400 mg/d) alone, or together with HRT (oestradiol 2 mg/dydrogesterone 10 mg) or pamidronate (100 mg/d), on early postmenopausal bone loss in women with low bone mass. The conclusion from this study was that women at around menopausal age with low bone mass have a substantial increase in BMD when taking HRT, and have a marginal increase of BMD when taking pamidronate. Women in the calcium group had a significant decrease in the lumbar spine (compared to HRT and pamidronate), but a marginal increase of BMD at the hip. During the third year, all groups showed significant bone loss, although in the HRT group, BMD remained above baseline levels.

Oestrogens

From other studies we know that if HRT is initiated at the start of the menopause it will prevent bone loss for the duration of therapy.¹⁰ In contrast, to our study, a significant increase in BMD from the baseline measurement was observed one year after withdrawal of medication. The extent to which the benefit of the BMD gain is sustained after the cessation of HRT is still a matter of debate. There is some evidence of this in observational studies that show fewer fractures in woman who have used HRT.¹¹⁻¹³ Also, the timing of starting HRT and the optimal duration of substitution are points of discussion and will be influenced by other factors, including other benefits and the risk of side-effects in women using HRT.

From a skeletal perspective, long-term HRT treatment appears to provide the greatest chance of preventing clinical osteoporosis. The possibility that long-term use of HRT

may increase the risk of breast cancer is a serious concern. There is various epidemiological literature on this topic, which has been reviewed in meta-analyses.¹⁴⁻¹⁸ The overall conclusion of these meta-analyses is that the short-term use of HRT does not increase the risk of breast cancer, but that long-term use (possibly after five years, but most probably after more than ten years) may be associated with an increased risk. This has been confirmed in a systemic reanalysis of the epidemiological literature, covering 160,000 women world-wide, by the Collaborative Group on Hormonal Factors in Cancer (CGHFC).¹⁹ In women using HRT for less than five years, no increase in the risk of breast cancer was observed, while the use of HRT for more than five years resulted in an increased risk of breast carcinoma (RR 1.35). This risk appears to decrease after termination of HRT, and there was no detectable risk five years after the cessation of treatment.

It should be mentioned that the above data refer to the incidence of breast cancer, not to mortality. This reanalysis of the CGHFC study¹⁹ stated that the effect of HRT on mortality from breast cancer remains unknown. Several other studies^{20,21} reported a reduction in the death rate due to breast cancer in HRT users. Two possible mechanisms have been reported:

1. La Croix²² reported that 81% of hormone users underwent at least one mammography, while this occurred in only 53% of non-users.
2. The use of HRT was associated with a reduced rate of axillary lymph node and metastatic spread.¹⁹

The possible association between the use of HRT and the risk of breast cancer hinders its use by some women and doctors. Therefore, more data on incidence and mortality are needed with regard to the type of HRT, dosages, and the definition of subgroups of women most at risk.

The occurrence of three cases of breast cancer in the HRT-treated women in our trial, compared to none in the other two groups, seems worrying. However, the period of exposure to oestrogen's was short, and supported by data from the meta-analysis, it may be a chance finding rather than a drug-related event.

A long-term effect of HRT use could be the prevention of cardiovascular disease,²³ although the mechanism of overall cardiovascular prevention is not exactly known. Another possible mechanism is that oestrogen's beneficially influence the lipid and lipoprotein profile (increase of high density lipoprotein and decrease of low density lipoprotein).²⁴ However, in the Heart Oestrogen Replacement Study (HERS),²⁵ the first placebo-controlled RCT in this field, the HRT group showed an increase in cardiovascular mortality in the first year, followed by a (non-significant) progressive fall in mortality over the next two to four years. This report may indicate that the use of HRT may have an initial adverse thrombogenic effect, but also in the long-term, a more beneficial effect. Further research is certainly needed to define the role of HRT in the prevention of cardiovascular disease in postmenopausal women.

Pamidronate

The most widely used regimen for pamidronate in the treatment of osteoporosis is 150 mg daily. Previous open and controlled studies with oral pamidronate 150 mg in patients with established osteoporosis showed significant increases of BMD in the lumbar spine and hip.^{27,28} The doses of pamidronate used in the study of Halminn *et al.*²⁹ were 150 mg/day, which was fully effective in the treatment of osteoporosis, and 75 mg/day, which caused significant suppression of bone resorption. The 100 mg/day of pamidronate used in our study falls between the doses used in the above-mentioned study, and was used on the assumption that it would be effective in the *prevention* of osteoporosis compared to 75 or 150 mg, which are both effective in the *treatment* of osteoporosis. The moderate increase during the two years of intervention and the significant decrease after withdrawal of treatment, both suggest that the dose of pamidronate (100 mg/day) was not enough to prevent further bone loss in menopausal women who already had a low bone mass.

The increase of BMD in the treatment of osteoporosis with pamidronate is the effect of a reduction in the remodelling space induced by the primary anti-resorptive action of the bisphosphonates. Therefore, inhibition of bone turnover by bisphosphonates is probably responsible for the early increase of BMD. In our study, it is a point of discussion as to whether, due to the low dose, during the one year of treatment, the reduction in remodelling space reached a plateau phase by the filling of this space. Landman *et al.*²⁷ described a cohort of 30 patients with established osteoporosis who had been treated with pamidronate (150 mg/day) for an average of 6.5 years, in which BMD of the lumbar spine and femoral neck did not change during two years of follow-up. However, more research is needed regarding the optimal dose and the duration of bisphosphonates.

Calcium

Women in the calcium group had a slight increase in BMD, but only in the cortical bone. After cessation of treatment, the BMD decreased significantly. At the lumbar spine (trabecular bone), a slight but significant decrease was observed during the two years of treatment and after withdrawal. It may be that the calcium supplement added to the already high calcium intake of Dutch women (1000-1200 mg/day) provided a total, pharmacological amount of calcium, sufficient to slow down bone loss in the femur, but clearly insufficient to have the same effect in the spine, where bone turnover is higher. This finding is consistent with other studies that indicate that supplements of calcium salts (generally exceeding 1 g daily) are capable of slowing down the rate of bone loss in women around the menopause with or without fractures at various skeletal sites.³⁰⁻³²

Long-term effectiveness of different preventive strategies

Recently, Pen *et al.*³⁵ described a computer-based stimulation model to compare the long-term effectiveness of different preventative strategies for osteoporotic fractures. These strategies were compared with the 'no treatment' strategy. The results showed that early intervention (ten years of HRT in 50-year-old women), followed by a five-year course of bisphosphonates starting from the age of 65 years, is the most effective strategy. Strategies applied later, and dealing exclusively with women at risk (*i.e.*, osteopenic and osteoporotic) are the least effective. Combined short-term intervention (*i.e.*, five years of HRT from the age of 50 years) with later intervention in women at risk only, is effective to a certain extent. There are several limitations to this study, for example, the model concentrated on the prevention of fractures and did not consider the other effects of hormone treatment, such as cardiovascular diseases and cancer, especially breast cancer.

The authors stated in their article that modelling is an appropriate way to assess the long-term benefits of various therapeutic or preventive strategies and to incorporate various hypotheses concerning the duration of treatment effect. Furthermore, there are no randomised trials of anti-osteoporotic drugs which are capable of assessing the 20-30-year impact of such treatment. Therefore, is it interesting to see what a computer-based model regarding the prevention of fractures can calculate. Although this model has several limitations, it presents us in a model long-term data on the prevention of fractures.

Compliance

In all groups, compliance was measured based on pill counts during the follow-up visits and, in addition, in the group of women receiving pamidronate compliance, using the Medication Event Monitoring System (MEMS, Aardex Ltd., Switzerland). This system consists of a normal pill container with a special cap that contains electronic microcircuitry for recording the time and date of each time the container is opened. Throughout the analysis, we assumed that one tablet was actually ingested each time the container was opened. This is the first study in the field of osteoporosis prevention in which an electronic instrument is used that records the time and date of opening of medication bottles. It enabled a detailed investigation of patient compliance and of the relationship between the intake of pamidronate and the change in BMD of the lumbar spine.

Overall, ingestion and timing compliance was high. This was surprising because of the asymptotic nature of low BMD. Bisphosphonates such as pamidronate and alendronate are given with instructions regarding the time of ingestion, because of the earlier mentioned low gastrointestinal absorption and drug-food interaction (paragraph 1.7). We evaluated the relationship between the time of ingestion during the day (morning or evening) and the time to the next meal (breakfast or dinner) to

changes in BMD. Surprisingly, there was no difference in BMD response between women who took pamidronate correctly (more than 30 and less than 120 minutes before breakfast or dinner) and those who took it at other times intervals. In addition, there was no difference in BMD response between the women who took pamidronate in the morning and those who took it in the evening. Of particular practical significance was the much higher preference for taking pamidronate in the evening, which underscores the inconvenience of currently recommended regimens. These results suggest that the instructions regarding the ingestion of bisphosphonates, may perhaps be too strict and need further evaluation.

Acceptance of screening

In the decision as to whether active screening around the menopause should be promoted, there are general considerations to be taken into account, such as:

- Are women willing to have their bone mass measured?
- How many women diagnosed with low bone mass wish to have information about the prevention of osteoporosis?
- How many women diagnosed with low bone mass will take medication for the prevention of further bone loss and the prevention of fractures?

When screening bone mass for the prevention of osteoporosis, 19% of our population did not respond to the invitation to participate in our study, and 3% did not agree to having their BMD measured by DXA. In total, 78% of women participated in our screening study for the prevention of osteoporosis.

We divided the bone mass into tertiles, and 649 women with their bone mass in the lowest tertile were invited to participate in the intervention study. Fifty-six of these women (8.6%) did not want any further information on osteoporosis, even though they had been informed of their low BMD and therefore that they were at risk for developing osteoporosis.

Of the 392 women who were included in the two-year intervention study, 22.4% (88 women) prematurely stopped taking medication. However, 77.6% of the women took the medication, with a compliance rate of almost 90%, wanted to continue after the two years of the intervention study, which suggests a high motivation for treatment.

Although the above numbers have been estimated from a population-based cohort in a specific region, they give a rough estimation of the population at large.

Table 2. Flow chart. Data from the screening and intervention study extra polated to a population of 100,000 women. With an indication how many women will be reached for the prevention of osteoporosis

Population-based screening: This flow chart indicates which women have osteoporosis (≤ 2.5 SD below the mean) in a Dutch population-based cohort and how many of these women will take medication for the prevention of fractures

100,000 women in the study population: 19% of this population did not respond to the invitation to measure BMD, 3% did not agree to having their BMD measured by DXA. In total, 22% women will not participate in a population-based screening for the prevention of osteoporosis

78,000 women will have a measurement of BMD. Of these, 19,000 women (24.3%) are already users of HRT or oral contraceptives (OC) and will be excluded.

59,000 women

7,500 women will have osteoporosis (≥ -2.5 SD below the mean); 645 (8.6%) do not want medication for the prevention of fractures, although they have been diagnosed with osteoporosis

6,855 women will take medication for the prevention of fractures; 1508 (22%) of these will take the medication for less than two years, because of unwanted side-effects

5,347 women 5.3% of the original 100,000 who are diagnosed with osteoporosis will be motivated to take their medication for longer than two years, means $\pm 80\%$ of the women diagnosed with osteoporosis

Methodological reflections and limitations

There are several methodological issues that should be considered when interpreting the results of the present study, which was designed as a single-centre open-label, controlled, randomised clinical trial. It had to be an open study because blinding was not possible in the oestrogen/progestagen group. In this group, women received oestrogen/progesterone cyclically, and had monthly withdrawal bleedings. In an open study, possible biases can occur because everyone involved in the trial is aware of the treatment each patient is receiving. In this respect, there are three main actors to consider: the patient, the doctor, and the DXA operator. The bias is minimal if the treatments being compared are rather similar to each other and the end points of the study are clear.³³ In our clinical trial, the treatment evaluation was clear and the BMD measurements were evaluated blindly. Moreover, the women were randomly assigned to one of the treatment groups by computer, and no reallocation to another treatment group was offered, so neither the patient nor investigators could choose a preferred treatment. This procedure optimised the quality of the trial and avoided any selection bias. The relatively low dose of 400 mg calcium was selected to ensure that the women would not, in fact, have calcium deficiency. However, the calcium dose used seems to prevent bone loss at the hip. The hypothesis was that calcium would be much less effective on BMD compared to HRT and pamidronate. HRT and pamidronate had to be more effective in order to demonstrate any significant increase in BMD. A study design including a fourth arm, women not undergoing any treatment, would have offered the possibility of adjusting for a placebo effect. However for such a fourth arm we did not expect enough women willing to be included.

Another limitation was that compliance in those women who remained on treatment during the study was very high, which made it difficult to evaluate the effect of non-compliance.

Finally, the effect of treatment measured as the percentage change of BMD has no clinical impact *per se* with regard to the long-term fracture rate. However, although no fractures were observed during three years of follow-up based on evidence from other sources, it may be assumed that women with low BMD are at high risk for developing fractures.³⁴

Recommendations and conclusions

Recommendations

Based on the results of our study, a number of conclusions and recommendations can be made:

- The prevalence of osteoporosis in the screenings study (total cohort) was 4.1%, and of osteopenia 27.3%. The prevalence of osteoporosis and osteopenia in a subgroup of this total cohort, postmenopausal women, was 12.7% and 42.8%, respectively.
- Population-based screening in early postmenopausal women seems to be of limited value. 5.3% of the women are diagnosed with osteoporosis.
- Case-finding for the prevention of osteoporosis is indicated because $\pm$ 80% of the women who are diagnosed with osteoporosis will take medication for the prevention of osteoporosis with a compliance rate of almost 90%.
- The most effective preventive treatment for perimenopausal and early postmenopausal women with low BMD, and therefore potentially at risk for future fractures, is HRT, bearing in mind the contraindications.
- If HRT treatment is to be continued for many years, starting in the early postmenopausal period, the patient could eventually switch to another treatment, e.g., bisphosphonates.
- With regard to the development of fractures in this cohort, it is important that these women are monitored for a longer period of time, e.g., at least 30 years. This might provide an insight into the risk factors and causes of fractures in this population.
- The compliance study suggests that, perhaps, the instructions regarding the ingestion the time of bisphosphonates are too strict and need to be further evaluated.

Conclusions

This thesis evaluates three different ways in which the prevention of perimenopausal and early postmenopausal osteoporosis can be managed: treatment with HRT, pamidronate, or calcium alone or in combination with the other treatments. The available evidence does not allow us to choose an optimal treatment plan, which will be adequate for the long-term prevention of osteoporotic fractures. However, based on our results, HRT seems to be the most effective treatment in women around the menopause. Not only does it prevent bone loss, but it also results in a significant gain of BMD. Moreover, calcium supplementation should be considered in women of menopausal age.

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CHAPTER 9

Summary

Osteoporosis has been the subject of intensive research over the past 20 years, and the results are encouraging. Therefore, it is generally accepted that, today, osteoporosis can be diagnosed, and to a large extent prevented and treated.

The objectives of the randomised controlled study presented in this thesis were as follows:

- to determine and compare the efficacy of two treatment regimens compared to calcium for preventing postmenopausal bone loss in women in the lowest tertile assessed by dual X-ray absorptiometry (DXA) measurements after screening;
- to assess the rate of change in bone mineral density (BMD) once treatment has been withdrawn and,
- to evaluate the compliance rate in the respective treatment regimens.

Chapter 2 provides a general overview of the epidemiology, prevention, and treatment of osteoporosis. Moreover, it considers the effect of medications used in the prevention and treatment of osteoporosis, as well as the different measuring instruments used in this thesis, such as DXA and electronic caps for measuring compliance.

Chapter 3 describes the background and rationale of the study on the prevention of low BMD in early postmenopausal women presented in this thesis. The study was conducted in two parts: a screening study and a drug intervention study designed as a randomised clinical trial. All women living in the city of Eindhoven and born between 1941 and 1947 (aged between 46 and 54 years), were invited by the Diagnostic Centre Eindhoven (DCE), a diagnostic centre for general practitioners, and the Department of Municipal Public Health Services, Eindhoven, to participate in the study. All the women were interviewed and BMD of the lumbar spine was measured by dual energy X-ray absorptiometry (DXA).

The study population in the intervention study consisted of healthy perimenopausal women who met the selection criteria and who were willing to participate in the study. The intervention study was designed as a randomised clinical trial (RCT). Women who were eligible were randomised to one of the treatment groups, and no reallocation to a different treatment group was offered.

Chapter 4 presents the baseline characteristics of the 5896 women born between 1941 and 1947 (aged between 46 and 54 years) and living in the city of Eindhoven, who participated in the study (the Eindhoven Perimenopausal Osteoporosis Study, EPOS), as well as the relationship between these characteristics and osteopenia and osteoporosis.

Osteopenia and osteoporosis were defined according to the criteria proposed by a World Health Organisation (WHO) working group. The prevalence of osteopenia and osteoporosis was 27.3% and 4.1%, respectively. With progression from premenopause to menopause, the prevalence of osteoporosis increased from 0.4% to 12.7%, and that of osteopenia from 14.5% to 42.8%. Of the women studied, 24%

were using oestrogen preparations and 19% had undergone hysterectomy, with or without oophorectomy.

An increased risk of low BMD (osteopenia and osteoporosis) was associated with age, menopausal status, and smoking, while alcohol consumption, high body mass index (BMI), and the use of oestrogen's, had a protective effect.

Previous studies have shown an association between depression and decreased BMD.

Chapter 5 describes the relationship between depressive mood and low BMD in a population-based cohort consisting of 4944 healthy women aged between 46 and 54 years. These women completed a questionnaire about their lifestyle habits, such as smoking, alcohol intake, medication intake, and physical activity, and completed a validated depression self-rating scale, the Edinburgh Depression Scale (EDS). BMD of the lumbar spine was measured. One thousand and fourteen (20.5%) of the women were depressed according to the EDS (cut-of score >11). The women with depressed mood had a significantly lower BMD compared to the non-depressed women. This study confirmed the relationship between depressed mood and decreased BMD at a univariate level. However, after adjustment for several important determinants of bone mass related to lifestyle habits, depressed mood showed no relationship to decreased BMD. These findings suggest that the relationship between depressed mood and low BMD is influenced by lifestyle habits.

Chapter 6 describes the outcome of the two-year intervention study designed as a randomised clinical trial, and the follow-up of 392 perimenopausal women, all of whom were treated with 400 mg calcium. The first group (129 women) received calcium only, while the second group (133 women) also received hormone replacement therapy (HRT) treatment, and the third group (130 women) received pamidronate in addition. After one and two years, the mean increases in lumbar spine BMD were significantly higher in the HRT group (4.5% and 5.2%, respectively) and the pamidronate group (1.4% and 0.5%, respectively) compared to the calcium-only group (-1.1% and -2.3%, respectively). No bone loss was observed at the proximal femur or femoral neck in any of the treatment groups. Moreover, in the group women treated with HRT, there was a highly significant rise in BMD. We can conclude that, in the early postmenopausal period, in women with low bone mass, bone loss can be prevented by HRT and pamidronate. In the HRT-treated group, a consistent increase in BMD was observed at all measurement sites.

This chapter also describes the change in bone loss during the year following cessation of treatment. Lumbar and femoral BMD remained increased in the HRT group, while in the pamidronate group, BMD decreased slightly. The highest decrease of spinal BMD was observed after three years in women in the calcium group.

Chapter 7 presents the compliance rate of patients receiving pamidronate during the two years of treatment, as measured by electronic microcircuitry, which monitored the opening and closing of the medication package. This is the first study on the prevention of osteoporosis in which an electronic instrument has recorded the time

and date of the opening of medication phials. The compliance rate was calculated, and data was available for 86 women. Overall, taking and timing compliance rates were high.

Instructions regarding the time of ingestion were given for pamidronate, because of the low gastrointestinal absorption and drug-food interaction. We evaluated the relationship between the time of bisphosphonate intake and changes in the lumbar spine. There was no difference in BMD response between women who took pamidronate correctly (more than 30 and less than 120 minutes before breakfast or dinner) and those who took it at other time intervals. There was no difference in BMD response between the women who took the bisphosphonates in the morning and those who took it in the evening. These results suggest that the instructions regarding bisphosphonates, may perhaps be too stringent and need to be further evaluated.

Chapter 8, the general discussion, reflects on how this study was designed and carried out. It evaluates the relevance of population-based screening for BMD with DXA in women around the menopause. Furthermore, it describes the revised recommendations on the prevention and treatment of osteoporosis by the Health Council of the Netherlands in 1998. This advice is compared with the first standard on osteoporosis of the Dutch College of General Practitioners, published in 1999. Finally, recommendations are made and suggestions given for further research on the prevention and treatment of low BMD in early postmenopausal women.

CHAPTER 10

Samenvatting

In de afgelopen 20 jaar is osteoporose veelvuldig het onderwerp van studie geweest. De resultaten van dit onderzoek zijn hoopgevend. Osteoporose kan tegenwoordig worden gediagnosticeerd en voor een belangrijk deel worden voorkomen en succesvol worden behandeld.

Het doel van de in dit proefschrift gepresenteerde studie was drieërlei:

1. het bepalen en vergelijken van de effectiviteit van twee behandelingen, hormoonsubstitutie en pamidronaat, afgezet tegen een behandeling met calcium. De medicaties hadden als doel het voorkomen van post-menopausale botontkalking bij vrouwen met een lage botdichtheid.
2. het bepalen van de compliance (therapietrouw) in de verschillende behandelregimes (hormoonsubstitutie, pamidronaat en calcium); en
3. het vaststellen van de mate van verandering in de botdichtheid nadat de behandeling is gestopt.

Hoofdstuk 2 geeft een algemeen overzicht van de epidemiologie, de preventie en de behandeling van osteoporose. Er wordt ingegaan op het effect van medicatie om osteoporose te voorkomen en te behandelen. Eveneens worden de in deze studie gebruikte meetinstrumenten zoals Dual X-ray absorptiometry (DXA) en de elektronische deksels die gebruikt werden bij de compliance meting besproken.

Hoofdstuk 3 beschrijft de achtergrond en de rationale van de studie naar lage botdichtheid bij vrouwen in de overgang zoals gepresenteerd in dit proefschrift. De studie bestond uit twee delen; een screenings studie en een medicijn interventie studie in de vorm van een gerandomiseerd onderzoek. Alle vrouwen woonachtig in de stad Eindhoven die geboren zijn tussen 1941 en 1947 werden uitgenodigd door het Diagnostisch Centrum Eindhoven (DCE) om deel te nemen aan de studie, het DCE is een centrum voor diagnostiek voor patiënten van huisartsen. Alle vrouwen werden geïnterviewd en de botdichtheid van de lumbale wervelkolom werd gemeten met behulp van een DXA.

Hoofdstuk 4 presenteert de basis gegevens van deze vrouwen (5896) geboren tussen 1941 en 1947 en die woonachtig zijn in Eindhoven.

De prevalentie van osteopenie en osteoporose in dit cohort was respectievelijk 27.3 en 4.1%. Met de overgang van pre-menopausaal naar menopausaal steeg de prevalentie van osteoporose van 0.4 naar 12.7% en die van osteopenie van 14.5 naar 42.8%. Van deze vrouwen slikten 24% oestrogenen en 19% onderging een hysterectomie met of zonder ovariectomie.

Een verhoogd risico voor een lage botdichtheid (osteopenie en osteoporose) werd geassocieerd met leeftijd, menopausale status en roken, terwijl alcoholgebruik een hoge body mass index (BMI) en het gebruik van oestrogenen een beschermend effect hadden.

Hoofdstuk 5 beschrijft de relatie tussen depressie en een lage botdichtheid in dit zelfde cohort van gezonde vrouwen (4944) tussen de 46 en 54 jaar. De vrouwen vulden een vragenlijst naar leefstijl gewoontes zoals roken, alcoholgebruik, medica-

tiegebruik en fysieke activiteit in. Zij vulden eveneens de gevalideerde depressie zelf-score, Edinburgh Depression Scale (EDS) in. De botdichtheid van de lumbale wervelkolom van deze vrouwen werd gemeten. Duizend viertien vrouwen (20.5%) waren depressief volgens de EDS score, met een afkappunt van ≥ 12 . De vrouwen met depressie hadden een significant lagere botdichtheid in vergelijking met niet depressieve vrouwen.

Deze studie bevestigt de relatie tussen depressie en een verlaagde botdichtheid op univariaat niveau. Depressie vertoonde echter geen relatie meer met een verlaagde botdichtheid na correctie voor een aantal belangrijke determinanten gerelateerd aan levensstijl.

Hoofdstuk 6 beschrijft de uitkomsten van de twee jaar durende interventie studie en het daaropvolgende vervoljaar van 392 vrouwen rondom de overgang die allen behandeld werden met 400 mg calcium. Een groep van 133 vrouwen kreeg aanvullend hormoonsubpletie en een groep van 130 vrouwen kreeg aanvullend pamidronaat. Na een en twee jaar was de gemiddelde toename in botdichtheid van de lumbale wervelkolom hoger in de hormoonsubstitutiegroep, respectievelijk 4.5 en 5.2%, en de pamidronaatgroep, respectievelijk 1.4 en 0.5%, vergeleken met de alleen-calcium groep, respectievelijk -1.1 en -2.3%. In geen van de groepen werd botverlies gezien van de heup. Er werd in de hormoonsubstitutie groep juist een significante toename te zien van de botdichtheid. We kunnen concluderen dat, vrouwen rondom de overgang met een lage botmassa, botverlies voorkomen kan worden door hormoonsubstitutie of door pamidronaat. Maar in de hormoonsubstitutiegroep was er consistente toename in botdichtheid van alle gemeten punten.

Dit hoofdstuk beschrijft ook de verandering in botdichtheid gedurende het vervoljaar zonder medicatie. De botdichtheid van de lumbale wervelkolom en de heup bleven gedurende dit jaar verhoogd in de hormoonsubstitutiegroep, terwijl in de pamidronaatgroep de botdichtheid daalde. De grootste afname in de botdichtheid van de lumbale wervelkolom werd gezien in de calciumgroep.

Hoofdstuk 7 presenteert de compliancegegevens van de patiënten die pamidronaat kregen gedurende de twee studie jaren. De compliance werd gemeten met behulp van een elektronisch microcircuit dat het openen en sluiten van het deksel registreert. Dit is de eerste studie naar de preventie van osteoporose waarbij een elektronisch instrument datum en tijd van openen van de medicatie inname registreert.

De compliance werd berekend als de inname compliance en compliance met betrekking tot tijd in totaal 86 vrouwen. Beide vormen van compliance waren hoog.

Pamidronaat werd gegeven met instructies ten aanzien van de tijd van inname, dit vanwege de lage gastro-intestinale absorptie en de interactie tussen het medicijn en voedsel. Daarom onderzochten wij de relatie tussen de tijd van pamidronaat-inname en de veranderingen in de lumbale wervelkolom. Er was geen verschil in botdichtheid response tussen vrouwen die pamidronaat volgens voorschrift namen, d.w.z. tussen 30 en 120 minuten voor het ontbijt of avondeten, en vrouwen die zich niet aan dit voorschrift hielden. Er was ook geen verschil in botdichtheid response tussen

vrouwen die pamidronaat 's-ochtends namen in vergelijking met die het 's-avonds namen. Deze resultaten suggereren dat de huidige inname instructie zoals voorgeschreven voor bisfosfonaten misschien te strikt zijn en verdere evaluatie verdienen.

Hoofdstuk 8 bediscussieert het studiedesign en de uitvoering van de studie. De relevantie van population-based screening van botdichtheid van vrouwen rond de menopauze met behulp van DXA wordt geëvalueerd. Het beschrijft ook de aanbevelingen van de Nationale Gezondheidsraad in 1998 over de preventie en behandeling van osteoporose. Dit wordt vergeleken met de eerste Huisartsen standaard gepubliceerd in 1999. Tenslotte worden aanbevelingen en suggesties gedaan voor verder onderzoek naar de preventie en behandeling van lage botdichtheid bij vrouwen.

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Appendix

Geachte mevrouw,

Wij weten dat u mogelijk een deel van de volgende vragen tijdens uw bezoek al heeft beantwoord. Zou u desondanks zo vriendelijk willen zijn alle vragen in te vullen?

Hierdoor krijgen wij een beter inzicht hoe vrouwen zich rondom de overgang voelen.

Het zal ons erg veel helpen om de vragen van vrouwen over hun gezondheid beter te kunnen beantwoorden.

Zoals beloofd in de brief worden de gegevens volledig vertrouwelijk verwerkt, zij vallen onder het medisch geheim.

A. Overgangsklachten.

Wij willen u graag enkele vragen stellen over typische overgangsklachten, zoals opvliegers en zweetaanvallen.

Een opvlieger is een plotseling abrupt gevoel van hitte, met of zonder zweten.

Een zweetaanval is je zweterig en warm voelen, geen plotseling abrupt gevoel van hitte.

1. Hoeveel nachten bent u afgelopen week zwetend wakker geworden?

☐ geen één nacht, ga naar vraag A3	☐ vier nachten
☐ één nacht	☐ vijf nachten
☐ twee nachten	☐ zes nachten
☐ drie nachten	☐ elke nacht van deze week

2. Werdt u de afgelopen week wel eens meerdere keren op één nacht zwetend wakker?

☐ nee
☐ ja nachten per week.

3. Hoeveel dagen heeft u overdag opvliegers gehad in de afgelopen week?

☐ helemaal geen opvliegers gehad	☐ vier dagen
overdag, ga naar vraag A6	☐ vijf dagen
☐ één dag	☐ zes dagen
☐ twee dagen	☐ elke dag van deze week
☐ drie dagen	

4. Hoeveel opvliegers had u gemiddeld overdag in de afgelopen week?

☐ ik heb helemaal geen opvliegers gehad overdag, ga naar vraag A6	☐ 5-6 opvliegers per dag
☐ soms geen, soms één per dag	☐ 7-8 opvliegers per dag
☐ 1-2 opvliegers per dag	☐ 9-10 opvliegers per dag
☐ 3-4 opvliegers per dag	☐ meer dan 10 opvliegers per dag

5. Wat was de afgelopen week het hoogste aantal opvliegers op één dag?

..... opvliegers op één dag.

6. Hieronder volgen een aantal voorbeelden van klachten die kunnen voorkomen rondom de overgang. Wilt u voor elk van de onderstaande klachten aangeven, in hoeverre u hiervan de afgelopen 4 weken last heeft gehad? S.v.p. een cirkel plaatsen rondom het antwoord dat het meeste van toepassing is.

	geen	weinig	matig	veel
- tintelingen	1	2	3	4
- duizeligheid	1	2	3	4
- 's nachts zweten	1	2	3	4
- zweten overdag	1	2	3	4
- obstipatie (moeilijke stoelgang)	1	2	3	4
- diarree	1	2	3	4
- pijn in spieren of gewrichten	1	2	3	4
- gebrek aan zelfvertrouwen.....	1	2	3	4
- hartkloppingen	1	2	3	4
- droge vagina.....	1	2	3	4
- jeuk aan de schaamlippen.....	1	2	3	4
- vaginale afscheiding.....	1	2	3	4
- branderig gevoel bij het plassen.....	1	2	3	4
- ongewild urine verlies.....	1	2	3	4
- pijn bij de gemeenschap.....	1	2	3	4
- warmte niet kunnen verdragen	1	2	3	4
- kou niet kunnen verdragen.....	1	2	3	4
- moeheid	1	2	3	4
- kortademigheid.....	1	2	3	4
- opvliegers.....	1	2	3	4
- gejaagdheid.....	1	2	3	4
- trillende handen	1	2	3	4
- droog haar.....	1	2	3	4
- haaruitval.....	1	2	3	4
- een droge huid.....	1	2	3	4
- moeite met concentreren	1	2	3	4
- hoofdpijn.....	1	2	3	4

Hieronder volgen nog een aantal voorbeelden van klachten die kunnen voorkomen rondom de overgang. Wilt u voor elk van de onderstaande klachten aangeven, in hoeverre u hiervan de afgelopen 4 weken last heeft gehad? S.v.p. een cirkel plaatsen rondom het antwoord dat het meeste van toepassing is.

	geen	weinig	matig	veel
- moe bij het opstaan.....	1	2	3	4
- prikkelbaarheid.....	1	2	3	4
- vergeetachtigheid	1	2	3	4
- moeite met inslapen.....	1	2	3	4
- gewichtsverlies	1	2	3	4
- het plotseling koud hebben.....	1	2	3	4
- neerslachtigheid.....	1	2	3	4
- migraine	1	2	3	4
- lusteloosheid	1	2	3	4
- 's nachts wakker worden	1	2	3	4
- rusteloos gevoel in de benen	1	2	3	4
- somber.....	1	2	3	4
- toegenomen gewicht.....	1	2	3	4
- opgeblazen gevoel.....	1	2	3	4
- verminderde eetlust	1	2	3	4
- minder zin in vrijen	1	2	3	4
- rugpijn.....	1	2	3	4
- angstig zijn, gespannen	1	2	3	4
- paniekaanvallen hebben	1	2	3	4
- minder interesse in dingen hebben	1	2	3	4
- snel bezorgd zijn	1	2	3	4
- een toegenomen eetlust hebben	1	2	3	4
- afgenomen zelfwaardering.....	1	2	3	4

B. Stemming en Gevoel.

De volgende vragen hebben betrekking op hoe u zich de afgelopen 7 dagen heeft gevoeld. Omcirkel dat antwoord dat het beste aangeeft hoe u zich voelde. Per vraag is slechts 1 antwoord mogelijk.

1. Ik heb kunnen lachen en de leuke kant van de dingen kunnen inzien:
 1. zoveel als ik altijd kon.
 2. niet zo veel nu als anders
 3. zeker niet zo veel nu als anders
 4. helemaal niet
2. Ik heb met plezier naar dingen uitgekeken:
 1. zoals altijd of meer
 2. wat minder dan ik gewend was
 3. absoluut minder dan ik gewend was
 4. nauwelijks.
3. Ik heb mijzelf onnodig verwijten gemaakt als er iets fout ging:
 1. ja, heel vaak
 2. ja, soms
 3. niet erg vaak
 4. nee, nooit
4. Ik ben bang of bezorgd geweest zonder dat er een aanleiding was:
 1. nee, helemaal niet
 2. nauwelijks
 3. ja, soms
 4. ja, zeer vaak
5. Ik reageerde schrikachtig of paniekerig zonder echt goede reden:
 1. ja, tamelijk vaak
 2. ja, soms
 3. nee, niet vaak
 4. nooit
6. De dingen groeiden mij boven het hoofd:
 1. ja, meestal was ik er niet tegen opgewassen
 2. ja, soms was ik minder goed tegen dingen opgewassen dan anders.
 3. nee, meestal kon ik de dingen erg goed aan
 4. nee, ik kon alles even goed aan als anders
7. Ik voelde mij zo ongelukkig dat ik er bijna niet van kon slapen:
 1. ja, meestal
 2. ja, soms
 3. niet vaak
 4. helemaal niet
8. Ik voelde mij somber en beroerd:
 1. ja, bijna steeds
 2. ja, tamelijk vaak
 3. niet erg vaak
 4. nee, helemaal niet
9. Ik was zo ongelukkig dat ik heb zitten huilen:
 1. ja, heel vaak
 2. ja, tamelijk vaak
 3. alleen af en toe
 4. nee, nooit
10. Ik heb er aan gedacht mijzelf iets aan te doen:
 1. ja, tamelijk vaak
 2. soms
 3. nauwelijks
 4. nooit

C. Bewegen en Sport.**1. Beoefent u momenteel een sport?**

Zo ja, welke sport beoefent u het meest frequent?

In welk jaar bent u met deze sport begonnen?

Hoeveel uur per week?

Hoeveel maanden per jaar?

Wel of niet bij een sportvereniging?

Op welk nivo?

☐ ja

☐ nee, ga naar vraag C3

.....

.....

..... uur per week

..... maanden per jaar

☐ sportvereniging

☐ ongeorganiseerd

☐ recreatief

☐ competitieverband

☐ (semi)top

2. Als u een tweede sport beoefent, welke sport is dat?

In welk jaar bent u met deze sport begonnen?

Hoeveel uur per week?

Hoeveel maanden per jaar?

Wel of niet bij een sportvereniging?

Op welk nivo?

.....

.....

..... uur per week

..... maanden per jaar

☐ wel bij een sportvereniging

☐ niet bij een sportvereniging

☐ recreatief

☐ competitieverband

☐ (semi)top

3. Heeft u vroeger gesport?

Zo ja, welke sport beoefende u het meest frequent?

In welk jaar bent u met deze sport begonnen?

In welk jaar bent u met deze sport opgehouden?

Hoeveel uur per week?

Hoeveel maanden per jaar?

Wel of niet bij een sportvereniging?

Op welk nivo?

☐ ja

☐ nee, ga naar vraag C6.

.....

.....

.....

..... uur per week

..... maanden per jaar

☐ wel bij een sportvereniging

☐ niet bij een sportvereniging

☐ recreatief

☐ competitieverband

☐ (semi)top

4. Als u meer sporten heeft beoefend, welke sport was dat?
 In welk jaar bent u met deze sport begonnen?
 In welk jaar bent u met deze sport opgehouden?
 Hoeveel uur per week? uur per week
 Hoeveel maanden per jaar? maanden per jaar
 Wel of niet bij een sportvereniging? ☐ wel bij een sportvereniging
☐ niet bij een sportvereniging
- Op welk nivo? ☐ recreatief
☐ competitieverband
☐ (semi)top
5. Als u meer dan twee sporten heeft beoefend, welke sport was dat?
 In welk jaar bent u met deze sport begonnen?
 In welk jaar bent u met deze sport opgehouden?
 Hoeveel uur per week? uur per week
 Hoeveel maanden per jaar? maanden per jaar
 Wel of niet bij een sportvereniging? ☐ wel bij een sportvereniging
☐ niet bij een sportvereniging
- Op welk nivo ☐ recreatief
☐ competitieverband
☐ (semi)top
6. Hoeveel uren loopt/liep u gemiddeld per week naar het werk en/of naar de winkel?
 Ongeveer uren per week voor uw 25^e jaar.
 Ongeveer uren per week na uw 25^e jaar.
7. Hoeveel uren van uw vrije tijd besteedt u per week in totaal aan bezigheden zoals, tuinieren, fietsen (niet wielrennen), wandelen, de hond uitlaten, klussen, huis opknappen, schoonmaken en reparaties?
 Ongeveer uren per week voor uw 25^e jaar.
 Ongeveer uren per week na uw 25^e jaar.

D. Leefgewoonten: Eet-, drink- en rookgewoonte.

Uit onderzoek is gebleken dat veel mensen min of meer geregeld zes of meer glazen alcoholhoudende drank per dag gebruiken.

1. Op hoeveel dagen per week gebruikt u gemiddeld genomen alcoholhoudende drank?

☐ 7 dagen per week	☐ 3 dagen per week
☐ 6 dagen per week	☐ 2 dagen per week
☐ 5 dagen per week	☐ 1 dag per week
☐ 4 dagen per week	☐ 0 dag per week, ga naar vraag D3

2. Als u op een dag alcohol drinkt, hoeveel glazen drinkt u dan gemiddeld?
N.B. halve glazen naar boven afronden.

☐ 11 glazen of meer	☐ 3 glazen
☐ 7 a 10 glazen	☐ 2 glazen
☐ 6 glazen	☐ 1 glas
☐ 4 a 5 glazen	

3. Rookt u nu sigaretten of een andere vorm van tabak (aankruisen wat voor u het meest van toepassing is)?

☐ nee	
☐ sigaretten	 sig. per week ga naar vraag D5
☐ sigaretten	 sig. per dag ga naar vraag D5
☐ shag/zelfgerolde sigaretten	 sig. per week ga naar vraag D5
☐ shag/zelfgerolde sigaretten	 sig. per dag ga naar vraag D5
☐ sigaren	 sig. per week ga naar vraag D5
☐ sigaren	 sig. per dag ga naar vraag D5

4. Heeft u vroeger sigaretten of een andere vorm van tabak gerookt (aankruisen wat voor u het meest van toepassing is)?

☐ nee, nooit ga naar vraag D8	
☐ sigaretten	 sig. per week ga naar vraag D5
☐ sigaretten	 sig. per dag ga naar vraag D5
☐ shag/zelfgerolde sigaretten	 sig. per week ga naar vraag D5
☐ shag/zelfgerolde sigaretten	 sig. per dag ga naar vraag D5
☐ sigaren	 sig. per week ga naar vraag D5
☐ sigaren	 sig. per dag ga naar vraag D5

5. Op welke leeftijd bent u begonnen met roken?
 Ik was toen jaar

6. Heeft u ooit bewust geprobeerd te stoppen met roken?

☐ ja
☐ nee, ga naar vraag D8

7. Bent u daarna weer gaan roken?

☐ ja
☐ nee

8. Rookt één van uw huisgenoten?

☐ ja
☐ nee

Welke aanduiding beschrijft het beste hoeveel melkprodukten u gebruikt heeft bij de verdere vernoemde periodes (denk hierbij ook aan o.a. pap en vla):

9. Hoeveel melkprodukten gebruikte u voor uw 25^e jaar?

☐ 3 of meer glazen per dag (haast bij elke maaltijd)
☐ 1-2 glazen per dag (haast elke dag doch niet bij elke maaltijd)
☐ elke week maar niet elke dag
☐ minder dan één keer per week
☐ geen

10. Hoeveel melkprodukten gebruikte u na uw 25^e jaar?

☐ 3 of meer glazen per dag (haast bij elke maaltijd)
☐ 1-2 glazen per dag (haast elke dag doch niet bij elke maaltijd)
☐ elke week maar niet elke dag
☐ minder dan één keer per week
☐ geen

11. Komen er bij u in uw familie (vader, moeder, broer, zus) veel botbreuken voor (denk bijvoorbeeld ook aan breuken van heupen en wervels)?

☐ nee
☐ ja, bij

E. Medicijngebruik.

Medicijnen tijdens ziekenhuisopname hoeft u niet mee te rekenen. Onder medicijnen verstaan we alle middelen die u voor een aandoening gebruikt. Dit zijn bijvoorbeeld ook poeders, zalf, druppeltjes en injecties. Wilt u ook de pil vermelden indien u deze gebruikt?

1. Heeft u de laatste 14 dagen medicijnen gebruikt die zonder recept waren gekocht?

☐ nee, ga naar vraag E3
☐ ja

2. Wat zijn de namen van die medicijnen? Wilt u de naam zo nauwkeurig mogelijk noteren?
Eventueel kunt u de verpakking raadplegen.

.....

.....

.....

3. Heeft u de afgelopen 14 dagen medicijnen op recept gebruikt?

☐ nee, ga naar vraag F1.

☐ ja

4. Wilt u deze medicijnen hieronder aankruisen?

☐ Pijn- en koortswerende middelen

☐ Medicijnen tegen hoest, verkoudheid, griep en keelpijn

☐ Middelen tegen bloedarmoede, zoals ijzertabletten

☐ Versterkende middelen zoals vitaminen, mineralen en tonicum

☐ Medicijnen voor het hart of de bloedvaten

☐ Medicijnen voor de bloeddruk

☐ Medicijnen voor een te hoog cholesterol

☐ bloedverdünnende middelen

☐ plaspillen

☐ laxemiddelen (voor de stoelgang)

☐ medicijnen voor maag- en darmklachten

☐ slaap- en kalmeeringsmiddelen, middelen tegen de zenuwen

☐ antibiotica, zoals penicilline en sulfapreparaten

☐ medicijnen voor de huid (bv jeugdpuistjes, eczeem, jeuk, roos, wonden)

☐ medicijnen voor reuma, gewrichtspijn enz.

☐ medicijnen tegen allergie

☐ medicijnen tegen astma

☐ hormonen

☐ medicijnen tegen suikerziekte

☐ medicijnen voor de ogen (zalf, druppels)

☐ de pil, namelijk

☐ andere medicijnen, namelijk

F. Opleiding en Beroep.

1. We zijn geïnteresseerd in de hoogste opleiding die u met een diploma heeft afgesloten. Kunt u aangeven in welke categorie deze opleiding thuishoort? (één antwoord aankruisen)
 - ☐ Lager onderwijs (basisonderwijs).
 - ☐ Lager beroepsonderwijs (LTS, LHNO, LEAO, huishoudschool, lagere land- en tuinbouwonderwijs enz.)
 - ☐ Middelbaar algemeen onderwijs (LAVO, ULO, MULO, MAVO, 3-jaar HBS enz.)
 - ☐ Middelbaar beroeps onderwijs (MTS, MEAO, praktijkdiploma boekhouden, kleuterkerkweekschool enz.)
 - ☐ Voortgezet algemeen onderwijs (HBS, MMS, gymnasium, HAVO, VWO enz.)
 - ☐ Hoger beroepsonderwijs (HTS, HEAO, HHNO, sociale academie, lerarenopl. enz.)
 - ☐ Wetenschappelijk onderwijs (doctoraal/ ingenieursexamen enz.)
 - ☐ Anders, namelijk
2. Volgt u op dit moment een dag- (of avond-)opleiding? Zo ja, welke?
 - ☐ nee
 - ☐ ja, namelijk
3. Welke omschrijving is op dit moment op u het meest van toepassing?
 - ☐ ik heb een betaalde werkkring
 - ☐ ik ben werkloos (geregistreerd bij het GAB)
 - ☐ ik ben arbeidsongeschikt (WAO, AWW, enz.)
 - ☐ ik ben rentenier
 - ☐ ik ben gepensioneerd/ vervroegd met pensioen (AOW, VUT, enz.)
 - ☐ ik ben huisvrouw
4. Wat is uw beroep of functie? Of, als u geen betaalde baan heeft, wat was dan uw laatste beroep of functie? **N.B. wilt u uw beroep zo nauwkeurig mogelijk omschrijven?** Bijvoorbeeld: directie-secretaresse, metaallasser, hoofd boekhouding (en niet ambtenaar, manager, arbeider enz.)

Tot Slot.

1. Als er naar aanleiding van deze vragenlijst nog onduidelijkheden zijn, mogen wij dan met u contact opnemen voor nadere informatie?
☐ nee
☐ ja, mijn telefoonnummer is
2. Hoe lang heeft u erover gedaan om de vragenlijst in te vullen en heeft u deze vragenlijst alleen ingevuld?
..... minuten.
☐ ja ik heb de vragenlijst alleen ingevuld.
☐ nee ik heb deze vragenlijst met mijn partner ingevuld.
☐ nee ik heb deze vragenlijst met een derde (bijvoorbeeld met een tolk) ingevuld.
3. Wat is de reden geweest van uw aanmelding voor dit onderzoek?
.....
.....
.....
.....
4. Hoe vond u het om deze vragen in te vullen.
.....
.....
.....
.....

Wilt u als u klaar bent controleren of u alles heeft ingevuld.

WIJ WILLEN U HEEL HARTELIJK BEDANKEN VOOR DE TIJD EN DE MOEITE DIE U HEEFT GENOMEN OM DE VRAGEN TE BEANTWOORDEN.

Mocht u nog op- of aanmerkingen hebben, dan zouden wij het zeer op prijs stellen als u dat zou willen opschrijven.

Met vriendelijke groeten,

Diagnostisch Centrum Eindhoven.

Patiënt Identificatie

Screeningsdatum

patiënt nummer _____

datum ____ ____ (dd/mm/jj)

A. Patiënten identificatie/administratie

1. Wat is uw geboortedatum?

2. Wat is uw postcode en huisnummer?

postcode _____

huisnummer _____

3. Wat is uw telefoonnummer waarop u overdag bereikbaar bent?

4. Wie is uw huisarts en in welke plaats heeft uw huisarts zijn praktijk?

.....

5. Bent u momenteel onder controle bij uw huisarts of bij een specialist?

☐ nee☐ ja, voor

6. Denkt u er over binnenkort te verhuizen?

☐ nee, ga naar vraag 8☐ ja

7. Indien uw nieuwe adres al bekend is wilt u dit dan hieronder opschrijven. Indien dit nog niet bekend is wilt u ons dan een adreswijziging toesturen?

naam:

adres:

woonplaats

telefoonnummer

B. Menstruatie anamnese

8. Heeft u ooit de (prik)pil gebruikt?

☐ nee, ga naar vraag 11.☐ ja, gebruik ik nog steeds, ga naar vraag 10.☐ ja, maar gebruik ik al > 3 jaar niet meer.☐ ja, maar gebruik ik al < 3 maanden niet meer.☐ ja, maar gebruik ik al 3 maanden tot 3 jaar niet meer.

9. Wanneer bent u gestopt met de pil (maand + jaar)?
19 maand
10. Deze vraag altijd stellen !
Waarom gebruikt(e) u de pil (nog) en hoe lang gebruikt(e) u de pil al?
.....
11. Heeft u ooit oestrogeenpleisters/andere vrouwelijke hormoonpreparaten (overgangspil) gebruikt?
☐ nee, ga naar vraag 14.
☐ ja, gebruik ik nog steeds, ga naar vraag 13.
☐ ja, maar gebruik ik al > 3 jaar niet meer, ga naar vraag 12.
☐ ja, maar gebruik ik al < 3 maanden niet meer, ga naar vraag 12.
☐ ja, maar gebruik ik al 3 maanden tot 3 jaar niet meer, ga naar vraag 12.
☐ weet ik niet
12. Wanneer bent u gestopt met het gebruik van oestrogeenpleisters of andere vrouwelijke hormoonpreparaten (overgangspil) (maand + jaar)?
19 maand
13. Waarom, gebruikt(e) u deze oestrogeenpleisters/ andere vrouwelijke hormoonpreparaten (overgangspil) en hoe lang?
.....
14. Hoe oud was u toen u voor het eerst menstueerde?
..... jaar
15. Menstueert u nog?
☐ nee
☐ ja
16. Hoe vaak bent u de laatste 12 maanden ongesteld geweest?

☐ niet	☐ vier keer
☐ één keer	☐ vijf keer
☐ twee keer	☐ zes keer of meer
☐ drie keer	
17. Deze vraag altijd stellen !!!
Hoe lang is het geleden dat u uw laatste natuurlijke menstruatie had? (niet meetellen als de menstruatie werd veroorzaakt door het innemen van vrouwelijke hormoonpreparaten, overgangspil, anticonceptiepil). Graag maand en jaar invullen.
maand: 19.....
☐ < 1 maand geleden
☐ 1 tot 3 maanden geleden
☐ 3 tot 6 maanden geleden
☐ 6 maanden tot 1 jaar geleden
☐ > 1 jaar geleden
☐ > 2 jaar geleden, ga naar vraag 23
☐ > 3 jaar geleden, ga naar vraag 23

Indien men nu de pil, oestrogeenpleisters of de overgangspil gebruikt, doorgaan naar vraag 21.

18. Is de regelmaat van uw menstruatie de laatste jaren veranderd (maand + jaar)?
 - ☐ nee
 - ☐ ja, sinds 19
 - ☐ is altijd al onregelmatig geweest
19. Om de hoeveel dagen wordt u ongesteld?

..... dagen
20. Hoeveel dagen verliest u bloed tijdens de menstruatie?

..... dagen
21. Hoe schat u de hoeveelheid bloedverlies in tijdens de menstruatie?
 - ☐ weinig
 - ☐ normaal
 - ☐ veel
22. Is uw hoeveelheid bloedverlies tijdens de laatste 12 maanden veranderd?
 - ☐ nee
 - ☐ ja, minder geworden
 - ☐ ja, meer geworden
 - ☐ ja, afwisselend
23. Is uw baarmoeder verwijderd, zo ja, wanneer is dit gebeurd (maand + jaar)?
 - ☐ nee
 - ☐ ja, 19
24. Is er ooit een eierstok bij u verwijderd?
 - ☐ nee, ga naar vraag 27.
 - ☐ ja, één
 - ☐ ja, beide
 - ☐ weet ik niet
25. Wanneer is uw eierstok verwijderd (maand en jaar invullen)?

De eerst: 19

De tweede: 19
26. Menstrueerde u nog steeds na deze operatie?
 - ☐ nee
 - ☐ ja
 - ☐ weet ik niet
27. Hoeveel eigen kinderen heeft u in totaal?

..... kinderen.

28. Hoe vaak bent u zwanger geweest? Hiermee bedoelen wij ook te vroeg afgebroken zwangerschappen.
..... zwangerschappen. Indien u nooit zwanger bent geweest door naar vraag 32.
29. In welk jaar werd uw eerste en laatste kind geboren?
19 geboorte eerste kind
19 geboorte laatste kind
30. Heeft u uw kinderen borstvoeding gegeven?
O nee, ga naar vraag 32
O ja, gemiddeld
31. Hoeveel kinderen gaf u borstvoeding?
..... kinderen
32. Heeft uw arts u ooit wel eens verteld dat u een afwijking aan de schildklier heeft (gehad) en bent u hiervoor nog steeds in behandeling?
O nee
O ja, te snel werkend
O ja, te traag werkend
O vergrote schildklier
O weet ik niet
33. Komen er in uw familie schildklierziekten voor?
O nee
O ja, bij uw
O weet ik niet
34. Heeft uw arts u ooit wel eens verteld dat u een kwaadaardige aandoening heeft (gehad), zo ja, wat?
O nee
O ja, namelijk
O weet ik niet

35. Heeft uw arts u ooit wel eens verteld dat u één van de onderstaande ziekten heeft (gehad)?
(Aankruisen wat voor iedere ziekte apart van toepassing is en op de stippellijn invullen welke ziekte men heeft gehad. Indien men een van onderstaande ziekten heeft (gehad) vragen of men hiervoor nog steeds in behandeling is).

ziekte/ maand + jaar	nee	ja	nog in behan- deling	weet ik niet
- Reuma (reumatoïde arthritis).....	☐	☐	☐	☐
- slijtage van de gewrichten (arthrose)	☐	☐	☐	☐
- andere ziekte waardoor u moeilijk kunt bewegen?	☐	☐	☐	☐
- Een trombosebeen?.....	☐	☐	☐	☐
- De ziekte van Cushing?.....	☐	☐	☐	☐
- Een longembolie?.....	☐	☐	☐	☐
- Een botziekte, bv de ziekte van Paget, osteoporose, Engelse ziekte?.....	☐	☐	☐	☐
- Een hartinfarct?.....	☐	☐	☐	☐
- Een beroerte/ attaque?.....	☐	☐	☐	☐
- Hoge bloeddruk?.....	☐	☐	☐	☐
- Een nieraandoening/ afwijking van de nieren?	☐	☐	☐	☐
- Een ziekte van de bijnieren?.....	☐	☐	☐	☐
- Een ziekte van de bijnier?.....	☐	☐	☐	☐
- Een leverziekte, (bv hepatitis, geelzucht of een leverontsteking).....	☐	☐	☐	☐
- Suikerziekte.....	☐	☐	☐	☐
- Een stofwisselingsziekte?.....	☐	☐	☐	☐
- Een aandoening van het spijsverteringskanaal: - Zweetjes in de stekdarm	☐	☐	☐	☐
- Een zweer van de twaalfvingerige darm.....	☐	☐	☐	☐
- Ziekte van Crohn.....	☐	☐	☐	☐
- Een maagzweer, ontstoken maagslijmvlies of een operatie.....	☐	☐	☐	☐
- Colitis ulcerosa.....	☐	☐	☐	☐
- Andere.....	☐	☐	☐	☐

36. Bent u ooit langer dan 1 maand bedlegerig geweest?
☐ nee
☐ ja
☐ weet ik niet

De volgende vragen gaan over drinkgewoonten.

37. Drinkt u wel eens alcohol?
☐ nee nooit, ga naar vraag 40
☐ ja, elke dag
☐ ja, 5-6 dagen per week
☐ ja, 3-4 dagen per week
☐ ja, 1-2 dagen per week
☐ ja, minder dan één maal per week
38. Als u dan drinkt hoeveel glazen alcohol drinkt u dan gemiddeld per dag?
 glazen per dag.

De volgende vragen gaan over medicijngebruik.

39. Heeft u het laatste jaar geneesmiddelen tegen botontkalking (osteoporose) gebruikt? Zo ja, welke?
☐ nee
☐ ja,
☐ weet ik niet
40. Heeft u het laatste jaar één van de volgende geneesmiddelen gebruikt?
	nee	ja	weet ik niet
- Fluoride (tabletjes).....
(bv. SAN (0,56 mg NaF, 0,25 mg per tabletje,
Zymafluor (0,56 mg NaF, 0,25 mg per tabletje)	☐	☐	☐
- calcitonine.....	☐	☐	☐
- hormonen.....	☐	☐	☐
- anabole steroïden.....	☐	☐	☐
- bijnierhormonen (glucocorticoïden)
(bv. prednison, dexametason)	☐	☐	☐
Heeft u <u>ook</u> bisfosfonaten gebruikt (bv Didrokit, APD)	☐	☐	☐
41. Indien u medicijnen gebruikt welke medicijnen zijn dit?

42. Vindt u het goed als uw huisarts de uitslag van de botmeting krijgt?
☐ nee
☐ ja

43. Vindt u het goed dat we indien nodig bij uw huisarts informeren naar medische gegevens, die mogelijk betrekking hebben op dit onderzoek?
☐ nee
☐ ja
44. Als blijkt dat er sprake is van enige afwijkingen of klachten, mogen we u dan benaderen om aan een vervolgonderzoek mee te doen.
☐ nee
☐ ja
45. Mogen wij u, ook als er nu geen afwijkingen gevonden zijn, in de toekomst nogmaals uitnodigen voor een vervolg onderzoek?
☐ nee
☐ ja
46. Als er naar aanleiding van deze vragenlijst nog onduidelijkheden zijn, mogen wij dan met u contact opnemen voor nadere informatie?
☐ nee
☐ ja, dit kan het beste onder telefoonnummer:

Medisch onderzoek

1.	bloeddruk sys.	____	____	____
2.	bloeddruk dia.	____	____	____
3.	pols	____	____	____
4.	gewicht	____	____	____
5.	lengte	____	____	____
6.	Quetelet-index (gewicht/lengte ²)	____	____	____
7.	spanwijdte van de armen	____	____	____

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Dit proefschrift is het verslag van een onderzoek dat alleen mogelijk werd gemaakt door de professionele, waardevolle en plezierige samenwerking met vele mensen. Graag wil ik, gekomen aan de eindstreep een aantal mensen speciaal bedanken.

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Curriculum vitae

- 1965 geboren te Nunspeet op 27 maart 1965
- 1983 eindexamen Havo Lodensteyn college te Amersfoort
- 1983-1987 HBO-Verpleegkunde Hogeschool de Vijverberg te Ede
- 1988-1994 Studie Geneeskunde aan de Universiteit van Maastricht
- 1994-1995 Alberta Children's Hospital, Calgary Canada. Arts op de kinderoncologieafdeling.
- 1995 Zuiderzeeziekenhuis, Lelystad, Assistent Geneeskundige niet in opleiding (AGNIO) op de eerste hulp
Catharina Ziekenhuis Eindhoven, AGNIO Interne Geneeskunde
- 1995-1999 Arts-onderzoeker, Eindhoven Perimenopausal Osteoporosis Study (EPOS) bij het Diagnostisch Centrum te Eindhoven
- 1998 opleiding epidemiologie VU Amsterdam, status als Epidemioloog-A
- 1999-2000 Medical Adviser Organon International, Oss
- 2000-2001 Medisch Coördinator van het Diagnostisch Centrum te Eindhoven