MEASUREMENT OF BONE MINERAL MASS IN CLINICAL PERSPECTIVE

(Botmassa metingen
in een klinisch perspectief)

Proefschrift

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Aan mijn ouders,

Voor Penny, Bas en Anne-Claire

List of abbreviations

ADFR	Activate-Depress-Free-Repeat
APD	3-Amino-1-hydroxyPropylidene-1,1-bisphosphonate
BMC	Bone Mineral Content
BMD	Bone Mineral Density
BUA	Broadband Ultrasonic Attenuation
Ca	Calcium
Cl	Chloride
CS	Compton Scattering
CV	Coefficient of Variation
DEQCT	Dual Energy Quantitative Computed Tomography
DPA	Dual Photon Absorptiometry
DEXA	Dual Energy X-ray Absorptiometry
ERT	Estrogen Replacement Therapy
FT	Fracture Treshold
Ha	Hydroxyapetite
HRT	Hormonal Replacement Therapy
iPTH	immunoreactive ParaThyroid Hormone
Gd	Gadolinium
KeV	Kilo electron Volt
L	Lumbar vertebral
MRI	Magnetic resonance Imaging
NA	Neutron Activation
OR	Odd's Ratio
ROI	Region Of Interest
P	Phosphorus
PTH	ParaThyroidHormone
SEQCT	Single Energy Quantitative Computed Tomography
SHBG	Sex Hormone Binding Globuline
SPA	Single Photon Absorptiometry
QDR	Quantitative Digital Radiography
QCT	Quantitative Computed Tomography
QMD	Quantitative Micro Densitometry
U	Unit or Units
μSv	micro-Sievert

TABLE OF CONTENT

1. CHAPTER 1

OSTEOPOROSIS 11

2. CHAPTER 2

NON-INVASIVE METHODS FOR THE ASSESSMENT OF BONE MINERAL MASS 23

3. CHAPTER 3

BIOLOGICAL AND CLINICAL ASPECTS OF BONE MINERAL MEASUREMENTS 37

4. CHAPTER 4

TREATMENT OF POSTMENOPAUSAL AND GLUCORTICOID OSTEOPOROSIS 51

5. CHAPTER 5

PERIPHERAL AND AXIAL BONE MASS IN DUTCH WOMEN. RELATIONSHIP TO AGE AND MENOPAUSAL STATE 79

6. CHAPTER 6

NON-INVASIVE AXIAL AND PERIPHERAL ASSESSMENT OF BONE MINERAL CONTENT: A COMPARISON BETWEEN OSTEOPOROTIC WOMEN AND NORMAL SUBJECTS 95

7. CHAPTER 7

ESTROGENS, ANDROSTENEDIONE, SEX HORMONE BINDING GLOBULINE AND BODY MASS INDEX AS DETERMINANTS OF BONE MINERAL MASS IN ELDERLY POSTMENOPAUSAL WOMEN 105

8. CHAPTER 8

BONE MASS IN WOMEN WITH PRIMARY BILIARY CIRRHOSIS: THE RELATION WITH HISTOLOGICAL STAGE AND USE OF GLUCOCORTICOIDS....119

9. CHAPTER 9

BONE LOSS IN PATIENTS WITH LOW MAINTENANCE GLUCOCORTICOID TREATMENT FOR CHRONIC OBSTRUCTIVE LUNG DISEASE. IS TREATMENT WITH 1α-HYDROXYVITAMIN D_3 INDICATED?....127

10. CHAPTER 10

PREDICTION OF FUTURE FRACTURES AND SCREENING FOR OSTEOPOROSIS....139

11. CHAPTER 11

SUMMARY....157

SAMENVATTING....162

APPENDIX....165

NAWOORD....175

CURRICULUM VITAE....177

CHAPTER 1

OSTEOPOROSIS

1.1 Osteoporosis: a major health problem

Osteoporosis is an important public health care problem in the Western world. More than 40% of the women will have experienced a fracture by the time they reach the age of 70. Moreover, the incidence of hip fracture appears to be increasing, and this is explained only in part by a longer life expectancy[1]. In the Netherlands, this trend has also been observed: Hoogendoorn described an increase in the number of fractures of the hip in men and women of over 50 years, which number gradually increased year by year[2]. In 1972 approximately 6000 subjects aged 65 years and over were admitted to the hospital for fractures of the hip, while 10 years later this number had increased by 65% to more than 10,000 patients[3]. Based on recent data it has been estimated that the total number of hip fractures in the year 2010 will be increased to 22,726[4].

The very high prevalence of this fracture, resulting in morbidity with the risk of invalidation and social isolation, has lead to an increasing interest of both (candidate) patients and medical practitioners in this disorder.

Osteoporosis is the most common metabolic bone disease, and is sometimes compared to hypertension: in both conditions irreversible damage may occur without significant prodromal symptoms or warnings, and in both conditions treatment should be started before symptoms occur.

1.2 Definition of osteoporosis and osteopenia

Difficulty in defining osteoporosis not only arises from the multiplicity of its etiologic and pathogenetic factors, but also from differences in points of view. From a clinical and radiological stand point osteoporosis is seen as a fracture syndrome, while an epidemiologist would describe osteoporosis as a major public health problem in the general aging population. Histologically, osteoporosis is characterized by diminishment of bone volume, caused by increased bone resorption by osteoclasts and/or decreased bone formation. From a densitometric point of view, Nordin suggested that osteoporosis should be defined as a bone mineral mass more than two standard deviations below that of young normal subjects as measured by photon absorptiometry[5]. For several reasons (see 3.8) there has been much criticism of such a densitometric definition of osteoporosis.

Clinically, osteoporosis is defined as a condition in which bone tissue is reduced in mass and quality, resulting in a diminished strength with an increased susceptibility to fractures. Typical osteoporotic fracture sites are the vertebral bodies, the proximal femur and distal radius. A fall, blow, or any other form of trauma that would not injure the average person can

easily cause one or more fractures in a person with osteoporosis. As a consequence of this clinical definition, the bone disorder manifests itself by fracture. During the last decades intensive research has been done to develop techniques to diagnose osteoporosis before fractures occur, in other words to determine the fracture risk. The assessment of bone mass and quality is as yet mainly restricted to measuring the bone mineral mass at certain regions of interest. The clinical definition of osteoporosis is now widely accepted, while it is also generally accepted to define a low state of bone mass as yet without fractures as osteopenia. However, osteopenia is still a poorly defined entity, and no agreement exists whether a bone mineral mass (2 standard deviations) below the normal average for sex and age-group indicates osteopenia.

1.3 Classification of osteoporosis

There are two recognized categories of osteoporosis: primary and secondary (Table I). Primary osteoporosis is a state of low bone mass with increased fracture risk which occurs in the absence of known disorders that may affect bone structure and quality. Four subtypes are recognized:

1) idiopathic osteoporosis, mainly occurring in young premenopausal women and in young and middle aged men,
2) juvenile osteoporosis, occurring before puberty,
3) postmenopausal osteoporosis (also called type I osteoporosis), occurring in postmenopausal women aged 50-70 years,
4) age-related osteoporosis (also called senile or type II osteoporosis).

The latter two conditions are by far the most common forms of osteoporosis. Differences in the rate of loss between the bone compartments may lead to these two distinct forms of osteoporosis. In 1947 Albright described these two types of osteoporosis[6], a clinical observation, which was supported by photonabsorptiometry several decennia later[7]. Type I osteoporosis occurs mainly in postmenopausal women between the age of 51 to 65 years and is characterized by vertebral (crush) fractures and distal forearm (Colles-)fractures, while fractures of the hip are relatively rare. This type of osteoporosis is the result of a disproportionally high trabecular bone loss in comparison with cortical bone loss[8]. Type II osteoporosis occurs predominantly in women and men above the age of 75 years. This type is characterized by the loss of cortical as well as trabecular mineral mass resulting in a high prevalence of hip fractures (but vertebral (wedge) fractures are common as well).

Secondary osteoporosis represents a fracture syndrome resulting from bone loss caused by conditions or diseases that are known to affect bone, such as immobilization, glucocorticoid excess, nutrient and vitamin deficiencies, alcoholism, endocrinopathies (thyreotoxicosis, hyperparathyroidism, oestrogen or androgen deficiency), multiple myeloma, rheumatoid arthritis and many other diseases. Recently Johnson et al reported on 300 consecutive persons who were presented to an osteoporosis clinic[9]. They found that 60% (180) had osteoporosis, of these 180 patients 83 (46%) showed one or more conditions or diseases contributing to the syndrome of osteoporosis.

Table I

Clinical classification of osteoporosis

PRIMARY OSTEOPOROSIS

1) Idiopathic osteoporosis

2) Juvenile osteoporosis

3) Postmenopausal osteoporosis (type I)

4) Age-related osteoporosis (type II)

SECONDARY OSTEOPOROSIS

Endocrinopathies

Hypogonadism

Hyperadrenocorticism

Thyreotoxicosis

Hyperparathyroidism

Acromegaly (?)

Gastrointestinal diseases*

Gastrectomy

Malabsorption syndromes

Chronic liver diseases

Miscellaneous causes

Glucocorticoid osteoporosis

Immobilization

Alcoholism

Anorexia nervosa

Osteogenesis imperfecta

Multiple myeloma

Rheumatoid arthritis and other connective tissue diseases

Pregnancy

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* Combinations with osteoporosis and osteomalacia

1.4 Diagnosis of osteoporosis

As a consequence of the clinical definition of osteoporosis the diagnosis should include the confirmation of a fracture. This is routinely done by X-ray investigation of the spine, and (as indicated on clinical grounds) of the hip, distal forearm or other skeletal sites (e.g. the ribs or the humerus). Standard radiographs of the spine can establish the diagnosis osteoporosis only in the absence of specific causes of fractures such as a significant trauma, a focal bone disorder (e.g. a metastasis) or other abnormalities. Furthermore, the kind of fracture and the location may be typical for osteoporosis. Although no clear definition exists of osteoporotic fractures, fractures of the hip, vertebrae or distal forearm should raise the suspicion of osteoporosis.

All patients presenting with one or more osteoporotic fractures should be evaluated comprehensively to exclude secondary osteoporosis, while assessment of the degree of bone loss may be helpful in monitoring the effectiveness of subsequent treatment.

The general medical evaluation should include:

1) Medical history; special attention is aimed at chronology, location, type and severity of back pain, location and kind of fractures, previous treatment (glucocorticoids, anti-epileptics, estrogens, diuretics, etc), age at menopause (natural or surgical), diet (calcium, protein (?), vitamin D intake, alcohol and tobacco).
2) Physical examination. Of course, clinical examination can not assess the amount of bone lost and in fact the most important information to be obtained by a physical examination concerns possible causes of secondary osteoporosis. Examination with regard to osteoporosis itself should include a measurement of height and of the arm span and a careful investigation of signs and symptoms of vertebral fractures: spinal angulation, upper abdominal transversal skin fold and leaning of the ribs on the pelvis should be noted. Although no general agreement exists, it might be useful to do a complete blood cell and differential count, routine blood chemistry plus (including measurements of calcium, alkaline phosphatase, creatinine, protein spectrum, thyroid function and erythrocyte sedimentation rate. To exclude osteomalacia a measurement of 25-(OH) vitamin D_3 may be helpful. Abnormalities in these studies might point to a form of secondary osteoporosis. A dexamethasone screening (suppression) test and a bone marrow examination should be reserved for special cases.

1.5 Radiography, osteoporosis and osteopenia

A routine radiograph is insensitive with respect to the estimation of bone mineral mass: the bone mineral density must have decreased by at least 30% before a reduction can be observed[10]. However, vertebral deformities such as ballooning of intervertebral discs and wedging or collapse of vertebral bodies may indicate osteoporosis.

Radiographic criteria for osteopenia of the spine are:

1) a pattern of vertical stratification (representing the remaining vertical plates and trabeculae in the vertebrae),
2) decreased radio-density, recognized by visibility of the iliac crest through L4 and L5 on the lateral spine film, and decreased contrast in radio-density between the interior of the vertebral body and the adjacent soft tissue,
3) the increased relative density of the vertebral endplates compared with the central part of the vertebral body.

For the hip, changes in cancellous pattern of the upper part of the femur, have been graded according to the Sing index[11]. A comparable index was developed for the calcaneus[12]. Correlations with the results of quantitative methods of bone mineral assessment are weak. Although it appears to be a simple method, it is rarely used in clinical practice, probably because it is time consuming and the standardization remains a difficult issue.

1.6 Osteoporotic fractures

As stated before, non-traumatic fractures may help to define osteoporosis. The diagnosis of vertebral fractures in clinical practice is usually biased by the personal view of the physician who interprets the lateral X-ray films of the spine. Several methods have been developed to quantify spinal deformity, Doyle used an index of biconcavity of the lumbar vertebrae[13] and Horsman's method is based on the number and severity of the vertebral deformities[14]. Recently arbitrary criteria have been developed to define spinal fractures and how to measure spinal deformity[15 16 17]. These criteria are used for monitoring osteoporosis and its treatment, although in daily clinical practice these methods are seldomly used.

Typical fractures in osteoporotic patients are:

1) wedge fracture of a vertebral body, sometimes called anterior wedging (ventral height of the vertebral body amounts to 80% of the dorsal height or less), the limit of 80% may however, vary per region of the vertebral column[15],
2) collapse fracture (both anterior and posterior compression); this regards especially the vertebrae Th12 through L4,
3) severe biconcavity can be seen as an osteoporotic fracture (central compression),
4) fractures of the hip,
5) Colles fractures.

1.7 Scope of the thesis

The first aim of this thesis was to investigate the clinical potentials of the most common non-invasive methods of bone mineral assessment.

First, the calculation routine of one of the measurement devices used in this thesis, the Dual Photon Absorptiometry (DPA) of the vertebrae L2 through L4, was modified. Our modification resulted in a faster performance. This is described in the Appendix.

Secondly, reference values were obtained by measuring 171 healthy dutch females, this was done by measuring the mineral density in the proximal and distal forearm by Single Photon Absorptiometry (SPA) and in the lumbar vertebrae 2-4 by Dual Photon Absorptiometry (DPA). Based on these results a transversal study was preformed of the rate of bone loss over the decades at the various measuring sites. This is described in detail in Chapter 5.

Thirdly, the diagnostic sensitivity of several non-invasive methods to detect osteoporosis (SPA, DPA and Single Energy Quantitative Computed Tomography (SEQCT or QCT) densitometry of the vertebrae L1 through L3) were studied by comparing a group of osteoporotic females with a group age-matched healthy women (Chapter 6).

The second aim was to study several potential determinants of the bone mineral mass applying the non-invasive techniques for bone mineral assessment.

In order to study the importance of endogenous estrogens and their binding protein and body mass index as determinants of the bone mineral mass in elderly postmenopausal women we selected two groups of women from the open population with high and low estrone levels,

respectively. Within these groups a subdivision was made based on body mass index and on the serum level of sex hormone binding globulin (SHBG). The results obtained with SPA, DPA and QCT are given in Chapter 7.

In order to investigate the effect of glucocorticoids on bone mineral density we performed two studies: 1) A cross-sectional study was done in patients with Primary Biliary Cirrhosis with and without glucocorticoid treatment (Chapter 8), 2) a longitudinal study was carried out to investigate the possible bone sparing effect of the vitamin D_3 metabolite, 1α-hydroxyvitamin D_3 on glucocorticoid-induced bone loss in patients with chronic obstructive lung disease. The results are described in Chapter 9.

Finally, a survey has been performed about the usefulness of several putative risk factors with regard to osteoporotic fractures (Chapter 10.). Based on data from the literature the usefulness of mass screening is discussed.

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CHAPTER 2

NON-INVASIVE METHODS FOR THE ASSESSMENT OF BONE MINERAL MASS

2.1 Introduction

The increasing interest in osteoporosis has lead to the development of several methods for measuring the bone mineral content and density in a non-invasive way. Beginning with the quantitative assessment of cortical thickness, the field has steadily grown throughout the years. Several quantitative methods for assessing bone mineral status are now operational. These techniques are whole body calcium measurements as well as regional measurements at various skeletal sites.

Assessment of human total body calcium is difficult to achieve in vivo. Neutron activation of the whole body followed by whole body counting of ^{49}Ca has been used for this purpose. The only other techniques which are able to estimate total body calcium, are dual photon absorptiometry or dual energy X-ray absorption (DEXA) of the whole skeleton, which method will be discussed later on. Clinically better applicable is the approach of the regional measurements of the bone mineral mass. These techniques provide information focused on fracture sites and they are nowadays common practice in the research of osteoporosis and other metabolic bone diseases.

In this chapter an overview of the various available methods of quantitative bone mineral assessment will be given.

2.2 Precision and accuracy

In evaluating the various methods of the assessment of the bone mineral content and density it is necessary to determine their precision and accuracy[1]. The precision or reproducibility of a measurement is usually given as the coefficient of variation (CV) of the results of repeated measurements of the same object or subject, this is calculated by dividing the standard deviation by the mean. Especially in longitudinal studies, a high precision or reproducibility is of the utmost importance in assessing changes over time of the bone mineral content and density and in deciding whether an observed difference constitutes a real biologic change or not. It was shown by LeBlanc et al. that two measurements with a scanner with a CV of 4% would have to differ more than 5.6% (the square root of (4^2+4^2)) to be confident (confidence level of 95%) that a real change had occurred[2].

In the evaluation of a reported precision of a measuring device several aspects are of importance:

1) short- and long-term precision (for real long-term precision assessment phantoms are necessary),
2) repeated measurements with and without repositioning,
3) CV's obtained with phantoms, normal subjects or osteoporotics,
4) intra- and inter-observer variations.

In general the short-term reproducibility is better than the long-term one. Both systemic and random errors contribute to this difference[3].

Repositioning of the object under investigation will introduce additional variance in the results of repeated measurements. Therefore it is of importance to know whether the CV is based on measurements with or without repositioning.

Repeated measurements of osteoporotics show a larger CV than those of normals or phantoms[4]. This is partly explained by a more difficult location of the region of interest (for spinal measurements), a low bone mineral mass in relation to the mostly normal soft tissue mass.

Intra- and inter-observer variations are nowadays a relatively small problem, because most devices operate (semi)-automatically.

Accuracy is a measure of the degree to which the bone mineral measurement agrees with the true (or an accepted "true") bone mineral mass[5]. These "true" values are generally obtained by measuring cadavers followed by chemical or physical analysis[6]. Accuracy is important in cross-sectional studies in which results between two or more populations or investigations are compared. In Table I the precision, accuracy and radiation doses are given.

Table I

Precision, accuracy and radiation dose of several non-invasive methods for measuring bone mineral mass.

	Precision	Accuracy	Radiation	References
Radiogrammetry	1-2%	-	50-100 μSv	8
QMD	1%	-	50-400 μSv	10
SPAprox	1.0%	2-5%	20-100 μSv	11,13,14,15
SPAdist	1.9%	2-5%	20-100 μSv	11,13,14,15
DPA	2.3-3.7%	3-5%	50 μSv	3,4,6,15,17
DEXA	1.5%	1.0%	10-30 μSv	15,19
QCT	2,7%	20%	1-10 mSv	1,15,22,23, 24,25,26

2.3 Radiogrammetry

Radiogrammetry is the measurement of the thickness of the cortex of metacarpal or phalangeal bones using standard antero-posterior radiographs. The outer and inner diameter of the metacarpal or phalangeal bones are measured. Advantages of this method are the relative simplicity, the low costs and negligible radiation dose. Disadvantages are the limitation to the peripheral skeleton: No information is obtained on the cancellous bone. Furthermore, this method does not take into account the possible existence of intracortical porosity.

The correlation of metacarpal bone density with bone density measured at other sites with other techniques is reasonable and is comparable with that of the results of single photon absorptiometry of the distal forearm. For epidemiological investigations with large numbers of participants and a long period of follow up metacarpal radiogrammetry appears to be a valuable tool[7]. The precision is improved by multiple measurements of the metacarpal bones and is than 1-2%[8].

2.4 Radiographic densitometry

Quantitative radio-microdensitometry (QMD) of a phalanx on standardized radiographs gives an indication of the BMD. The density of the bone on the radiograph is analyzed with an

optical microdensitometer together with a simultaneously radiographed aluminum reference wedge[9]. Because two standardized radiographs are made in planes perpendicular to each other an estimation of the bone mineral content per unit of volume can be achieved. The results are expressed in mm aluminum equivalent/mm^3. In normal people the coefficient of variation was found to be less than 1%[10].

2.5 Photon Absorptiometry

2.5.1 Single photon absorptiometry (SPA)

SPA was first described by Cameron and Sorenson in 1963[11]. They developed a method to measure bone mineral content and bone width. The technique uses a linear scan by a radiation beam across the region of interest. The beam consists of gamma photons emitted by ^{125}I and a detection system measures the attenuation. The source holder and detector-photomultiplier are mechanically coupled and move with a constant speed over the region of interest which is placed between source and detector. The collimated beam (^{125}I 27,5 KeV.) passes through the forearm, which is surrounded by a soft tissue-equivalent (mostly water) to constant thickness. The attenuated beam is detected by a NaI crystal-photomultiplier and transformed into a digital read out against the position of the scanning device. The result is expressed in arbitrary units (U) per unit of axial length of bone (the region of interest) or after calibration in grams hydroxyapatite (Ha) per cm. By division of this result by the bone width (measured at the individual scans) the data are expressed as U or g Ha/cm^2 and are thus normalized for inter-individual comparison. Most commercial available devices have some kind of fat correction, the raw value of BMC is corrected by an algorithm based on the various amount of fat in the surrounding soft tissue. This is of particular importance since treatment of osteoporosis may alter body composition, without a fat correction the results of bone mineral content measurements by SPA may be spuriously altered[12]. In our laboratory the coefficient of variation was determined by measuring (with repositioning) 50 normal subjects and proved to be 1.9% and 1.0% for the distal and proximal site, respectively[13]. The proximal measurements show a better CV than the distal ones, this is because small differences in the location of the forearm in the apparatus (repositioning) will result in a slightly different measurement site. The difference in bone mineral density along the forearm is smaller in the proximal site (tubular bone of relatively constant composition). The accuracy has been determined by measuring excised bones or phantoms containing known weights of bone mineral. This was done by Cameron[11], who found values about 3%, later higher values (6-8%) were found some of this difference may have been related to whether or not the calibration bone samples contained bone marrow[14]. The radiation dose is low (20 to 200 μSv) with a

negligible whole-body dose[15].

2.5.2 Dual photon absorptiometry (DPA)

DPA is developed to measure the bone mineral content of lumbar vertebrae (mostly L2 through L4), the femoral necks or the whole skeleton. As is the case with SPA, the measurement is an integral one, which means that cancellous bone and cortical bone can not be measured separately.

The dual photon source employed in DPA devices is mostly Gadolinium^{153}, but a combination of other radionuclides is also possible. The advantage of Gadolinium^{153} is the common decay of both photons (100 and 44 KeV), as this source is commonly used we restrict ourselves to the description of the use of this source.

The physical half-life of Gadolinium^{153} decaying to stable Europium^{153} is 242 days. The source strength used is 1-1.5 curie and a lifetime of about 18 months is common in clinical routine. A collimated beam of two gamma photons with energies of 100 KeV and 44 KeV is attenuated by the object. A detector is coupled to the source-holder, which is located at the other site of the object measures the non-absorbed photons.

The method is based on the following principle: absorption of photons is dependent of the photon energy, the kind of absorbing material and the thickness of the absorber. In this case the absorber consists of soft tissue and bone mineral in bone tissue. To eliminate the influence of the (variable) soft-tissue mass on the results of bone mineral measurement two separate measurements are done with two different energies. The principle is that the mass attenuation coefficients of bone and soft tissue differ as a function of photon energy. By using two photon energies it is possible to calculate the attenuation in soft tissue independent from the attenuation in bone. Subsequently, the computer calculates the BMC.

The algorithms used to calculate the BMC and BMD are discussed in the appendix.

Several manufacturers are developing new methods such as the replacement of the detector by a gamma scintillation camera. Gamma cameras are readily available at nuclear departments and can register two energies simultaneously. However, there are considerable difficulties such as scatter from the patient and scatter from the high energy after passage through the patient to the lower energy window. Improvements are the use of multiple detectors, which decrease the scan time. There is also interest in obtaining lateral measurements, because in the case of severe calcifications of the aorta in the lumbar region the frontal measurement will give a spuriously high BMC. In our laboratory the coefficient of variation was determined by measuring (with repositioning) 20 osteoporotic women and proved to be 3.7% and 2.3.% for BMC and BMD, respectively[13]. The accuracy based on multiple

measurements of excised vertebrae or spines of cadavers is between 5 and 10%[16 17].

However, future developments will probably be influenced by the break-through of the Dual Energy X-Ray Absorptiometry technique.

2.6 Dual Energy X-Ray Absorptiometry (DEXA or DXA)

An important new method for assessment of bone mineral mass is Dual Energy X-Ray Absorptiometry (DEXA or DXA) also known as Quantitative Digital Radiography (QDR). The concept of DEXA is quite similar to DPA, but differs from DPA in that the radioactive source is replaced by a special X-ray tube. Like the emission of two photons with different energy and absorption characteristics in DPA, DEXA uses dual energy X-rays. The advantage of this X-ray source is the much higher intensity compared to Gadolinium[153]. A tube with an average current of 1 mA produces 500 to 1000 times more photon flux than a new 1 Curie Gadolinium[153] source. DEXA is used in the same regions of interest as DPA.

In order to overcome technical problems such as instability of the x-ray source and beam hardening due to polychromaticity, an internal reference device is implemented. The apparatus measures the patient together with a calibration disk consisting of various x-ray absorbing reference materials (the calibration wheel). This is done on a pixel-by-pixel basis for both energies, so that when the x-ray beam is detected it contains information of both the unknown patient absorption characteristics and the known absorption characteristics of the calibration wheel.

Advantages of this method over DPA are a faster performance (5 min. versus 20 min. with DPA for a lumbar scan), a higher resolution and consequently a better precision. The very high correlation (r=0.94) found for the lumbar vertebrae between DEXA and DPA underlines once more that principally the BMC is assessed in a similar manner[18]. In normal people the coefficient of variation was found to be less than 1.5% for spinal measurements and 2.9% for measurements of the hip[19].

2.7 Quantitative Computed Tomography (QCT)

QCT is the only non-invasive technique for bone mineral assessment which is capable of measuring selectively the cancellous and cortical BMD. This capability is a great advantage over the other methods because cancellous bone has a higher metabolic turnover rate than cortical bone[20 21]. Another advantage of the method is the fact that QCT measurements can be performed with commercially available Computed Tomography (CT) scanners with minor

adaptations only. The method is described in chapter 6. The precision based on measurements of phantoms is 1-2%, but in vivo the precision is much poorer[1]. We found a precision of 2.5% and 2.7%, respectively, for L2-L3, in scanning (with repositioning) 10 osteoporotic women twice[22]. The radiation dose is higher than with photon or roentgen absorptiometry[23 24].

The accuracy of QCT is less than with the other non-invasive methods and is about 20%[25]. Intravertebral fat may lead to an underestimation of the BMD, due to the lesser attenuation by fat. Intravertebral fat increases with age and bone marrow mass falls, in order to overcome this problem Dual Energy QCT (DEQCT) has been utilized. To this end CT scanners have been programmed to make scans of the same slide with both high and low kilovolt tube potentials. The differences of the density values are used as a measure for the bone mineral density[26].

2.8 Other techniques:

Compton scattering (CS)

Photon absorptiometry and QCT have in common the attenuation of an energy beam by the tissue which is measured. Furthermore, the source of the beam, the object under investigation and the detector are placed in line. CS, however, employs a scatter-detector at different angles with the line source-object. The method is based on the scattering of X-rays or photons by the electrons of an atom, whereby part of their energy is transferred to the electrons. Consequently, the energy of the x-ray or photons falls and is dependent on the angle of the scatter. The method is rather complicated and the radiation dose is between 3 and 10.000 μSv[5]. Furthermore, a disadvantage is the inability to distinguish between bone tissue and bone marrow, Also no distinction can be made between the cortical and cancellous bone compartments. Precision and accuracy are between 3 and 5%. Up to date there have no important clinical applications been described of CS.

Neutron activation (NA)

In vivo Neutron Activation (NA) is a complex technique and only operational in a few research centres, because of the special equipment needed for the particle acceleration and the difficulties in detecting the very low levels of radiation activated from the elements. With this method neutrons from an accelerator (or reactor) are used which bombard the total natural (constant) fraction of ^{48}Ca in the body. By absorbing a neutron the calcium nucleus is excited. The ^{48}Ca changes to ^{49}Ca, a radioactive isotope with a half-life of only about 9 minutes. By counting the decay of ^{49}Ca externally an estimate of the total amount of calcium in the body is

made. As a consequence of the neutron bombardment other elements in the human body are also converted (^{24}Na, ^{38}Cl, ^{32}P and others). The gamma rays emitted are detected by a whole-body counter and subsequently analyzed by a spectrometer system. NA cannot distinguish between cancellous and cortical bone. However, the major disadvantage is the high radiation dose of 2000-30000 μSv[27 28].

Because it is an expensive and extremely complicated method and has a high radiation exposure NA is not suitable for routine practice and will be a research tool only.

Magnetic resonance imaging (MRI)

MRI is a non-invasive technique, that recently has become operational in clinical practice and that does not use ionizing radiation. In vivo recording of ^{31}P MR spectra of the bones of the fingers and wrist has been reported[29]. Signals from soft tissue and bone marrow ^{31}P may interfere with the precision and accuracy. No clinical experiences on bone analysis have been reported up till now.

Broadband ultrasonic attenuation (BUA)

BUA of the ankle or patella is used to assess bone mineral mass and structure. The great advantage is the absence of radiation which opens the possibility for large scale population investigations. The method is based on measuring the rate of change of attenuation with varying the frequency of the ultrasound. A moderate but significant correlation ($r=0.75$, $p<0.001$) between BUA and SPA of the forearm was found in patients with different disease conditions[30].

An important aspect of BUA is the possibility to study trabecular structure by ultrasonic parameters[31]. BUA is a rather new technique and little clinical experience is available.

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CHAPTER 3

BIOLOGICAL AND CLINICAL ASPECTS OF BONE MINERAL MEASUREMENTS

3.1 Introduction

In recent years much effort has been put into the development of non-invasive assessment of bone mineral mass and the possible prediction of the fracture risk in suspected osteopenia or in osteoporosis. Various techniques have been developed to quantify the bone mineral mass, each of which provided different information on cancellous and/or cortical bone mineral mass in the axial or peripheral skeleton. It has been demonstrated that the compressing or breaking strength of bone is linearly related to mineral content[1] [2].

Another indication for bone mineral measurement is the monitoring of the longitudinal course of the bone mineral mass. For instance to evaluate the effect of aging, disease or medication (e.g. glucocorticoids).

3.2 Bone mineral mass, content and density

The term bone mineral mass may be used to refer to the mass of hydroxyapatite (Ha) in the whole skeleton. However, the results of regional measurements may also be referred to as bone mineral mass. The term bone mineral content (BMC) is reserved for the absolute mass of bone mineral measured in the forearm (as in the case with SPA, expressed as units or grams Ha/cm), or measured in the lumbar spine along the region of interest L2-L4 (as with DPA, expressed as units or gram Ha per L2-L4). This expression is mostly used in longitudinal studies of the same individual. Evidently, exact reposition of the region of interest is mandatory in this type of study.

It is now widely accepted to use the term bone mineral density (BMD) for two types of measurements. Strictly speaking density means mass divided by volume (e.g. g of Ha/ml). This applies to the results of QCT. The results of the photon absorptiometric devices are expressed as arbitrary units and after calibration in g Ha. Dividing this entity by the projected surface of the measured bone region (which generally applies to the lumbar vertebrae measured by DPA) gives the dimension g HA/cm^2, which is also called BMD. This expression is especially used for inter-individual comparisons, because it corrects for the size of the bone measured and thereby for the total body mass[3].

3.3 Peak bone mineral mass

Research on osteoporosis has been focused on the rate of bone mineral loss, and only recently attention has been given to the peak bone (mineral) mass (also called peak adult bone mass). It is becoming increasingly clear that the (peak) bone mass from which the bone loss starts off is a major factor in the pathophysiology of fractures. Moreover, because it appears to be difficult to replace lost bone, more effort has to be aimed at preventing bone loss and at attaining a higher peak bone mass in growing individuals. Recently it has been demonstrated with QCT that vertebral cancellous BMD reaches its peak around the time of cessation of longitudinal growth at epiphyseal closure[4]. In contrast, with DPA it appears that bone (mineral) mass increases until the mid-thirties[5]. Because of the reluctance to expose the growing individual to gamma radiation, data are relative scare concerning peak bone (mineral) mass based on densitometric studies. Consequently, little is known about the factors which are thought to influence peak bone mineral mass, such as genetic factors, exercise (weight loading factors), nutrition (Calcium, proteins, calories, vitamin D) and environmental factors (sun exposure). In two cross-sectional studies on premenopausal women a significant positive correlation was observed between daily calcium intake and (peak) bone mass[6 7].
The (limited) information on peak bone mass and its determinants is based on cross-sectional and not on longitudinal studies, that would have been more conclusive. Nevertheless, increasing attention is directed towards the peak bone (mineral) mass of young women as an important risk factor of osteoporotic fractures of elderly women.

3.4 Bone mineral mass and bone loss

In order to determine rates of bone loss densitometric and biochemical methods are employed. Two bone mineral mass measurements with a certain interval of time will give the overall result of bone formation and bone resorption. The significance of differences between the results of repeated measurements is dependent on the precision of the method used (see 2.2) and the order of magnitude of the expected rate of loss of bone (mineral) mass. On the other hand, also biochemical parameters have been studied in order to estimate the rate of bone loss[8 9].

It has been estimated from cross-sectional and longitudinal studies with SPA and DPA that in women peak bone mass is reached at the age of 30-35 years. There is probably essentially no premenopausal bone loss from the age of 18 to 44[10]. In the last decennium before the menopause axial BMD diminishes by 7-8%, while loss of peripheral BMD (mainly corti-

cal) is minimal or absent[11]. After the menopause an acceleration of cancellous (and to a lesser extend cortical) bone loss occurs[12], followed by a lower rate of bone loss at higher age[13 14]. It has been documented that in the first ten years after menopause 50% of the total vertebral bone loss takes place[15]. By DPA measurements it was shown that about 20% of the lifetime femoral neck bone mineral loss and 30% of the trochanteric loss occurs in the early post-menopausal period[16]. The total loss of bone mineral content is 30-35%[17 18].

Although on male human beings less information is available, there is probably a different pattern of bone loss: after the age of 35 years a more or less constant rate of loss of bone mineral occurs leading to a total loss of 10%[19].

With QCT the number of studies of the normal population is lower than those with DPA. Bone loss assessed with QCT is comparable to the results obtained by DPA. It appeared that the first years after ovariectomy the rate of bone mineral loss was 5 to 7 times higher in the lumbar vertebrae (cancellous bone) than measured at the forearm with SPA (cortical bone)[20]. From these results it has been concluded that cancellous bone is more sensitive to estrogen deficiency than cortical bone. Consequently, it illustrates the importance to study selectively the cancellous bone compartment. With QCT a mean yearly cancellous vertebral bone loss of 1.0-1.2% is observed in women from 20 to 80 years. Also with this method an acceleration of the rate of loss is observed around the menopause[21].

3.5 Bone mineral mass and loss at different skeletal sites

During more than 20 years SPA measurements of the forearm have been performed in research and daily practice. The relatively cheap equipment and the good precision are responsible for the popularity of this method. The technique for ultra-distal measurements in the forearm has been developed in an attempt to measure a higher percentage of cancellous bone and to better predict the bone mineral mass at an axial site (more cancellous bone). The results of the measurements at the ultra-distal and more proximal sites in the forearm correlate very well with the bone mineral mass of the whole body[22], but only moderately with spinal BMD[23 24]. Furthermore, the correlation between peripheral and axial bone mass weakened with aging[23]. Moreover, there was no correlation between the rate of bone loss at the various sites[25]. Some investigators even claim that the peripheral bone mineral mass will predict vertebral fractures better than axial measurements[26]. These controversies are partly due to differences in method and patient selection.

While evidence is accumulating that bone mineral mass measurements at different skeletal sites yield different information, there is still uncertainty to what extent the results of peripheral and axial measurements can predict vertebral and other osteoporotic fractures. As

could be expected the results of measurements of the bone mineral density at the so-called fracture sites correlated better with the incidence of those fractures than those of measurements at other skeletal sites[27]. There appear to be different patterns of bone loss at the various sites not only during aging[14], but also in disease or in response to medical treatment[28] (e.g. fluoride[29]).

In general, the peripheral bone mineral mass provides at least in normals a reasonable impression of the total bone mineral content. In the individual however, information obtained at the forearm is insufficient to predict BMD of the lumbar vertebrae or the hip.

3.6 Bone mineral mass and seasonal variations

Because the occurrence of seasonal variations in 25-hydroxyvitamin D levels is well established[30 31], several investigators looked for evidence of seasonal variations in bone mineral mass. Krolner described a cyclic fluctuation of the lumbar bone mineral mass, which he explained by differences in mechanical loading of the vertebrae over the year[32]. This finding was confirmed by investigators from the Mayo clinic, who found an average higher BMD of the lumbar spine of 1.4% in the late summer[33]. Later other investigators reported a seasonal variation of the peripheral bone mass accompanied by cyclic fluctuations of alkaline phosphatase and whole body retention of ^{99}Tc-diphosphonate[34]. Using neutron activation Tothill et al, however, could not find evidence of a seasonal variation of bone mineral mass[35].

Although no agreement exists about the existence and, if so, the magnitude of seasonal differences in bone mineral mass, it is of importance to keep this phenomenon in mind when longitudinal studies are performed or when data on bone mineral mass obtained in different seasons are compared.

3.7 Bone mineral mass, bone strength and fractures

In clinical practice bone mineral measurements are performed to predict the risk of fractures or to monitor therapeutic interventions. However, several studies report a lack of discriminatory power of bone densitometric measurements in the separation of women with and without fractures (see also chapter 6). This relative insensitivity of densitometric measurements in "predicting" fractures (or better: diagnosing already existing fractures) might be explained by:

1) a wide biological variation in both the fracture and the non-fracture groups,

2) several forms of potential bias inherent to cross-sectional designs, such as postfracture bone loss due to immobilization or, on the contrary, spurious elevations of bone mineral density due to callus formation. Furthermore, healthy case-controls may not be as healthy as expected,

3) limited correlation between the results of cortical measurements and the occurrence of certain fractures or between the bone mineral mass at peripheral and axial sites respectively,

4) a poor correlation in vivo between bone mineral mass and bone strength in the regions where osteoporotic fractures occur.

Because most densitometric methods measure cortical and cancellous bone together, no distinction can be made between cortical or cancellous bone losses. In certain regions of the skeleton changes in cancellous bone mass might reduce bone strength to a higher extent than quantitatively comparable changes in cortical bone mass.

The inadequacy of this -of necessity- mass-based approach of osteoporosis has directed attention to causes of fragility other than reduced bone mineral mass, the so-called "quality versus quantity" concept. One of those qualitative (intrinsic) bone factors is fatigue damage, a well known phenomenon of solid materials. It is understandable that accumulated fatigue damage associated with a low turnover of bone tissue, may weaken bone quite apart from its mass[36]. This is illustrated by the increased incidence of fractures in osteopetrosis, where bone density is above normal, but bone turnover rate is low. Unfortunately, it is at the moment nearly impossible to quantify fatigue damage in an individual. The importance of this phenomenon is as yet not its application in daily clinical practice, but awareness of this concept will lead to a better understanding why fractures occur. Furthermore, fatigue damage fractures may be conditioned by the age of bone tissue (e.g. the proportion of dead bone), which means that a low bone turnover may favour the occurrence of this type of fracture. This may have consequences for therapeutic interventions.

Another factor contributing to fragility apart from bone mineral mass is connectivity or the degree with which bone plates and trabeculae are connected with each other. Kleerekoper et al. have investigated the three-dimensional architecture of vertebrae by high resolution CT scanning and found evidence for a lower connectivity in severely osteoporotic bone than in normal bone[37]. The decrease in bone mass and the loss of connectivity in the vertebral body cancellous bone will lead to an extreme loss of strength with age[38 39]. Besides fatigue damage and decreased connectivity of trabeculae, changes in chemical properties of the bone matrix and mineral depositions are of importance in determining the quality of bone. These three intrinsic factors of bone quality are also operating in other solid materials. However, bone differs from solid materials by a "built-in-repair" mechanism, namely the osteocytes. It has been postulated that these osteocytes (bone remodelling units) are stimulated by fatigue damages[40]. This hypothesis raises a number of fascinating questions: What is the nature of the signal that is produced by fatigue microdamage? How is this signal detected and processed?

In a recent paper Heaney postulated a three-dimensional fracture space: Low bone mass, fatigue damage and cancellous discontinuity are placed on three axes[41]. This scheme may help to understand why some people will have fractures and others will not, given the same amount of bone mineral mass and why they develop fractures of a specific type (Colles- and hip-fractures as examples of fatigue damage and vertebral crush fractures as an example of trabecular discontinuity). Another important aspect of this scheme is that it places bone mass in a larger context, as only one of the intra-osseous factors causing fragility. Furthermore the interaction between these factors is interesting: as bone mass declines more strain is put on the remaining bone elements thereby increasing the amount of fatigue damage, whereas less mass will also lead to less connectivity and thus to a higher fragility. Not taken into account in this scheme as intra-osseous factors are the relative quantity and the chemical quality of the mineral (Ha) and organic components (collagen and other) of the bone tissue.

Extra-osseous factors in the development of fractures are the neuromuscular condition (the tendency to fall) and the energy absorbing quality of the surrounding subcutaneous adipose tissue. In a postal survey of 2000 females and 2000 males it was shown that the higher incidence of distal forearm fractures in the perimenopausal period is correlated with a higher tendency to fall during that period[42]. Furthermore, in a longitudinal survey several risk factors for falling were identified and their adjusted odds ratio's were calculated varying from 28,3 for sedative use to 1,8 for foot problems[43].

It should be kept in mind, that although in vitro studies show a high correlation between bone strength and bone mineral mass[38 39], in vivo the above mentioned factors may lessen the correlation between fracture incidence and bone mineral mass.

The effects of age and bone mass were studied simultaneously on fracture risk by Hui et al[44]. They observed that both age and bone mass are important determinants of future

fractures. In addition, age appeared to be a stronger predictor of hip fractures, whereas midshaft radius bone mass was a strong predictor of fractures at the forearm. A difference in age of 10 years compared with a comparable difference in bone mass (0.1 g/cm, which is the average population decline in 10 years) showed a two and a half times greater fracture risk. In other words a bone mass of an older age is more fragile than an equivalent younger bone mass, which is completely compatible with the concept of fatigue damage and a less sufficient repair mechanism.

In conclusion, the risk of fractures is determined by several factors and not only by bone mass. Factors like bone architecture (trabecular connectivity), age and quality of the bone tissue (fatigue damage) and the tendency of elderly people to be increasingly involved in minor traumatic events may be equally important for the occurrence of osteoporotic fractures.

3.8 Bone mineral mass and the fracture threshold

The fracture threshold (FT) is a hypothetical level which should discriminate between individuals with a high or low risk of developing osteoporotic fractures. Knowledge of such an FT would be most helpful in determining which individual is at risk for osteoporosis and should be treated prophylactically. It will be clear that for defining an FT, quantitative techniques will be necessary. Based on a prospective study, Ross et al. defined it as the BMC at which the risk of fractures doubles as compared to the risk in premenopausal women[45]. Others chose their FT at the lower limit of BMC of young normals[46]: either below the 10th percentile or more than 2 standard deviations below the mean of young normals. This would imply that 50% of all the women aged 65 and over are classified as osteoporotics. If the highest BMD in the osteoporotic group is defined as FT, the bone mass of half of the women above 55 years and of almost all women above the age of 70 will be below this threshold. Therefore, the choice of such a cut-off level is highly arbitrary and as a consequence of these definitions an important percentage of normal women will be classified as high risk or (pre-?)osteoporotic.

Several studies have compared fracture with non-fracture cases and although the latter had higher average BMC's or BMD's the differences were small and the overlap was considerable (see Chapter 6). Because of these findings, the usefulness of densitometric measurements for detecting osteoporosis has been questioned, however several longitudinal studies have shown that bone mineral measurements may predict future fractures to some extent (this issue is discussed in detail in Chapter 10). Furthermore, there exists controversy about which measurement device at which skeletal site and in which bone compartment (cancellous or cortical) is the best method with regard to these issues[47 48].

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CHAPTER 4

TREATMENT OF POSTMENOPAUSAL AND GLUCOCORTICOID OSTEOPOROSIS

4.1 Introduction

The treatment of osteoporosis has two aims. Firstly, the treatment of spinal fractures consists of analgetics and in severe cases by short periods of immobilization. In order to reduce further bone losses the patient should be instructed to ambulate as soon as possible. Fractures of the long bones, especially of the femoral neck may require surgical intervention and this will not be discussed here. Particularly in these older patients immobilization carries a very high risk of morbidity and mortality.

The second goal in the treatment of osteoporosis is to prevent new fractures. This means preventing further reduction in bone mass and when possible increasing bone mass. Because the amount of bone (mineral) reflects the balance of bone formation and bone resorption, therapy (or rather secondary prophylaxis) is aimed at increasing osteoblast recruitment and activity while inhibiting osteoclast recruitment and activity.

Medical treatment of osteoporosis consists of drugs which can modify the processes of bone remodelling. Roughly, three groups of drugs are used:

1) inhibitors of bone resorption, such as calcium, estrogen, calcitonin and bisphosphonates,
2) stimulators of bone formation, such as fluoride and possible anabolic drugs,
3) drugs with a different or complex action, such as vitamin D derivatives, thiazide drugs, combinations of drugs (ADFR, see 4.3.8.).

4.2 Primary and secondary prevention

Once osteoporosis is established (and fractures have occurred), it appears to be very difficult to increase bone mass and prevent future fractures. Therefore, regardless of the type of osteoporosis, much attention has been given to
the prevention of early postmenopausal bone loss. Because almost 50% of the total loss of the cancellous bone mass is lost in the early postmenopausal years[1], prevention should be exerted especially in this period. This is called primary prevention. Therapeutic interventions when fractures already have occurred is called secondary prevention.

Of course the final criterium with regard to the effectiveness of preventive strategies is the reduction of the incidence of fractures.

4.3 Postmenopausal osteoporosis

4.3.1 Calcium

Calcium and calcium-regulating hormones have important effects on bone, but it is generally accepted that abnormalities in the secretion of calcium-regulating hormones are not the primary determinants in the pathogenesis of osteoporosis[2]. A distinction has to be made between studies investigating physiologic (low or high calcium intake) or supra-physiologic (pharmacologic) calcium supplementations. There are several epidemiologic studies investigating different amounts of dietary calcium intake. In his cross-sectional study Matkovic et al found a 60% to 75% reduction in hip fracture in Yugoslav women with calcium intakes in the range of 1,000 to 1,100 mg/day, compared to the incidence of hip fracture in women with intakes of about half that level[3]. The women with the higher calcium intake had also a higher intake of calories, while the average body weight was comparable between the two groups of women. This might lead to the conclusion that the women with the higher calcium intake had probably a higher level of physical activity, and thereby higher bone mineral mass and less fractures. Holbrook et al reported, in a prospective study, a 60% lower rate in hip fracture in individuals with high intakes (above 765 mg/day) versus those with low intakes (below 470 mg/day) of calcium[4]. These observations are compatible with those from a recent study in which it was shown that healthy older postmenopausal women with a daily calcium intake of less than 400 mg can reduce their bone loss by increasing their calcium intake to 800 mg per day[5]. This latter study is an example of the bone sparing effect of increasing calcium intake, although the intake of 800 mg of calcium a day is not supra-physiologic. The conclusion from this study is probably that correction of a deficient calcium intake to a normal intake reduces bone mineral loss.

In another (prospective) study, however, it was concluded that a reduced intake of dietary calcium does not seem to be a risk factor for hip fracture[6]. Moreover, no protective effect of a higher habitual calcium intake on the rate of cortical bone loss in the forearm could be demonstrated in a 8-years follow up study[7]. In an other study the same investigators could not find a correlation between habitual daily calcium intake (range 560-2580 mg/day) and either bone mineral content of the radius, the lumbar spine and the femoral neck[8]. Comparable results of dietary calcium and peripheral bone mineral loss in postmenopausal women are reported by Recker and Heaney[9].

It was estimated from a calcium balance study that dietary calcium in the post-menopause should be as much as 1500 mg daily[10]. On the other hand well controlled clinical trials could not demonstrate a beneficial effect of supra-physiological elementary calcium

suppletion after the menopause[11 12 13 14]. In combination with estrogens calcium supplementation may be beneficial[15], although this observation is not confirmed by others[16].

The positive effects of thiazides on calcium balance have been well documented[17 18]. It is interesting that thiazide users had significantly more bone mineral content than non-users did[19], but further work is required to investigate the effect of thiazides on fracture risk.

In conclusion, it is amazing that there still exists no consensus about the efficacy of a high dietary calcium intake during childhood and in the perimenopausal years, however a deficient calcium intake (less than approximately 500 mg/day) should be corrected to 800-1000 mg daily. Furthermore, the prescription of extra calcium as a therapeutic or preventive drug in the management of osteoporosis has to be investigated prospectively[20 21].

4.3.2 Estrogens

The usefulness of estrogens for the prevention of postmenopausal bone loss has been clearly demonstrated in cross-sectional[22] and longitudinal[23 24 25] studies as well as in retrospective ("case-control") studies[26 27]. Beneficial effects of estrogens have been observed both in the axial and in the appendicular skeleton[28 29]. A dose-related inhibiting effect of estrogen treatment on bone loss was demonstrated by Horsman et al[30]. Furthermore, they showed that the minimal effective daily dose was 25 microgram ethinyl estradiol. Christiansen et al. showed that already 1 mg 17ß-estradiol-valerate inhibits bone mineral loss, while 2-4 mg daily may even increase bone mineral mass[31]. For conjugated equine estrogens (Premarin) the minimal effective dose turned out to be 0.625 mg[32].

It must be pointed out that all of these prospective studies on postmenopausal bone loss have been carried out in non-osteoporotic postmenopausal and/or oophorectomized women. Additionally, also women with established postmenopausal osteoporosis will benefit from treatment with combined estrogens/progestagen therapy (2 mg estradiol + 1 mg norethisterone acetate)[33].

A new development is the transdermal administration of estrogens. Although few controlled studies on bone mass measurements and fractures are available, there is supportive evidence that transdermally administered estrogen will also reduce bone resorption[34 35 36].

There is general agreement about the bone preserving properties of estrogens, and in early postmenopausal osteoporosis estrogen replacement therapy (ERT) is regarded as the treatment of first choice.

Nowadays, in women with an intact uterus estrogen therapy is no longer given without a progestagen, because of the increased risk for endometrial hyperplasia or carcinoma[37 38 39]. The concomitant administration of an exogenous progestagen (this combination is called hormonal replacement therapy, HRT) has to be sufficient in dosage and duration to prevent

hyperplasia of the endometrium by the ERT. Moyer et al showed that a cyclic combination of estrogen and progestagen in postmenopausal women leads to partial maturation of the endometrium and significantly reduces the number of mitoses in both gland and stromal cells[40]. It is generally accepted that the risk of endometrial carcinoma can be abolished by giving an adequate dose of progestagen cyclically[41]. In one prospective study it was shown that the use of estrogens with cyclic progestagens either removed the increased risk of endometrial carcinoma or delays its onset[42]. No agreement exists as to the minimal frequency of the progestagen cycles necessary to prevent endometrial hyperproliferation (monthly?, 3-monthly?). Another possibility is the continuous substitution of both estrogens and progestagens, the latter in a low dosage[43 44]. No long-term prospective studies on this issue (with respect to fracture risks) have yet been published.

Apart from the protection against endometrial hyperproliferation, several other effects of progestagen addition during estrogen therapy are unwanted and of little benefit to the patient. These include recurrence of menses, mastodynia, fluid retention, lower abdominal cramps and cyclic changes in mood. Uncertainty exists about the relation between HRT and the risk of (increased) breast cancer[45 46]. While breast cancer is affecting one in 16 women, already a small enhancement of the relative risk due to HRT might induce a major increase in breast cancers. The association between exogenous estrogen use and cardiovascular mortality has been controversial. There exists evidence that estrogens will increase the risk of cardiovascular disease[47], and recently a negative association between estrogen use and cardiovascular disease mortality has been reported[48]. However, the favourable changes in serum lipids induced by estrogen therapy[49] may to some extent be counteracted by progestagens. There is evidence that little negative effects on serum lipoproteins occur with medroxyprogesterone acetate (Provera) and dydrogesterone (Duphaston)[45 50].

Although consensus is reached about the effectiveness of estrogens in secondary prevention[51], there still are many unanswered questions about the optimum age to start HRT and especially how long this therapy should be continued.

4.3.3 Anabolic steroids

Anabolic steroids (e.g. methandrostenolone) are believed to prevent the loss of bone in patients with established osteoporosis[52], although this was not confirmed by others[53]. A double-blind controlled study performed by Geusens and Dequeker showed a beneficial effect of another anabolic steroid (nandrolone, 19-nor-testosteron) on bone mineral mass at the radius[54]. In an open study a comparable result was found by Need et al[55 56]. Later the same authors reported an increase in vertebral density in osteoporotic postmenopausal women. The

study was designed as an open uncontrolled trial with a follow up of maximal one year[57]. Of importance with respect to BMC and BMD measurements is the observation of Johansen et al about the apparent positive influence of soft tissue body composition changes on bone mineral assessment during nandrolone therapy[58]. They reported an increase in lean body mass and a decrease in fat mass, and therefore a fat-corrected BMC of for example the forearm is indispensable. It was concluded that nandrolone may increase fat-corrected BMC of the radius by an increase in bone size with a constant BMD. No significant changes were observed at the spine.

Commonly reported side effects are changes of the voice and an increase in growth of facial hair. Orally administrable anabolic steroids (17-alkyl-derivatives) may induce liver damage. Nandrolone has to be administrated intramuscularly and it appears not to cause liver damage. The place of anabolic steroids in the treatment of osteoporosis remains to be elucidated and special attention should be given to their side effects.

4.3.4 Calcitonin

Since calcitonin is an inhibitor of osteoclastic activity, a deficiency of this hormone may theoretically be involved in the pathogenesis of osteoporosis and, consequently, substitution might prevent further bone loss. However, calcitonin levels and reserve have not found to be decreased in osteoporosis[59] and no low bone mass has been found in patients without thyroid glands[60]. On the other hand, Alevivazaki et al reported a case of a young male patient with osteoporosis and no detectable plasma concentrations of calcitonin. Genomic clones representing his calcitonin gene were analyzed and one single base alteration was detected[61].

Reginster et al demonstrated that intranasal calcitonin can counteract early postmenopausal bone loss[62]. Several investigators found a bone sparing effect of intranasally given calcitonin in the spine but not in the peripheral skeleton[63 64]. An additional finding is the analgesic effects of calcitonin on acute and chronic back pain in different forms of osteoporosis[65].

The major disadvantage of calcitonin is that it has to be injected or has to be administrated intranasally, furthermore the costs of this treatment are impressive compared with the other treatment regimens for osteoporosis.

4.3.5 Bisphosphonates

Like calcitonin bisphosphonates are potent inhibitors of bone resorption. In an uncontrolled study it was demonstrated that treatment of patients with osteoporosis with 3-amino-1-hydroxypropylidene-1,1-bisphosphonate (APD, pamidronate) resulted in an 3%

annual increase in lumbar spine bone mineral mass[66]. It has furthermore been shown that during treatment for 6 months with tulidronate, another bisphosphonate, bone mineral density at the lumbar spine did not significantly change, while the placebo group showed a significant decrease of 2,1%[67]. In two prospective double-blind placebo controlled studies of postmenopausal osteoporosis etidronate (Didronel) was given in a cyclical (intermittent) scheme: lumbar BMD increased, while the incidence of new vertebral fractures (deformations) was lowered[68 69].

APD appeared also to be effective in the treatment of juvenile osteoporosis[70].

The role of bisphosphonates in the treatment of osteoporosis has to be investigated further, but this type of agent appears to be interesting in future treatment regimes. It is advisable to restrict this kind of treatment only for severe cases of osteoporosis.

4.3.6 Fluoride

It is known that fluoride is able to increase bone formation in vitro and in vivo[71 72 73], although at higher doses osteomalacia changes of bone have been reported[74]. Despite the impressive bone formation stimulating effects of fluoride, there is controversy about the effect of fluoride on the incidence of fractures. There exists some epidemiological evidence that non-pharmacological doses fluoride may reduce the incidence of fractures[75 76], whereas the therapeutic use of fluoride may result in stress fractures of the lower extremities[77] and may lead to an increase in spinal crush fractures[78]. Recently it was demonstrated that treatment with 75 mg NaF daily resulted in a higher spinal bone mineral mass, but without a decrease of spinal fracture[79]. Moreover, in that study a significant increase of the incidence of non-vertebral fractures has been observed in the fluoride treated patients. In contrast with these findings, Manelle et al found a beneficial effect of fluoride on spinal fracture incidence[80].

It is concluded that (long-term) fluoride therapy with 75 mg daily will increase axial bone mineral mass, but the higher rate of non-vertebral fractures during the therapy appear to make fluoride a dangerous drug.

4.3.7 Vitamin D and its derivatives

Some investigators have suggested that patients with postmenopausal osteoporosis have impaired intestinal calcium absorption[81 82 83]. 1,25-$(OH)_2$ vitamin D_3 (calcitriol) is the most important hormone in the regulation of the intestinal calcium absorption[84] and several studies have demonstrated low 1,25-$(OH)_2$ D_3 serum levels in patients with osteoporosis[85 86 87]. There

is a decreased synthesis of 1,25-$(OH)_2$ D_3 in response to PTH infusion in women with postmenopausal osteoporosis[88]. Additionally, administration of 1,25-$(OH)_2$ D_3 to postmenopausal women (with or without osteoporosis) restores calcium absorption to premenopausal levels[89]. It is therefore not surprising that the effect of 1,25-$(OH)_2$ D_3 on bone mass has been investigated. The findings have been conflicting, with some reports suggesting that 1,25-$(OH)_2$ D_3 is without value in the treatment of postmenopausal osteoporosis[90 91], while others have found favourable results[92 93]. In these two latter studies the beneficial effect of 1,25-$(OH)_2$ D_3 was achieved by decreasing bone resorption, no increase in bone formation could be observed. It is not clear why the results of these 4 studies show a discrepancy, it might be due to differences in calcium intake, vitamin D status (or sun exposure) or differences in patient selections.

Higher doses of 1,25-$(OH)_2$ D_3 (2 μg/day) caused a marked stimulation of bone formation[94]. However, relatively small doses (0.5 μg/day) will normalize intestinal calcium absorption, whereas higher doses (>1.0 μg/day) with a normal or high calcium intake will inevitably result in hypercalcemia and/or hypercalciuria. This small therapeutic range and the potential toxicity are disadvantages of this therapy (e.g. in combination with thiazide diuretics or a higher calcium intake the risk at hypercalcemia, decreased renal function or formation of kidney stones is considerable).

Finally, most side effects are dose related and further studies of efficacy and safety of lower doses of 1,25-$(OH)_2$ D_3 (up to 0.5 μg/day) are necessary, a parenteral route (and higher doses) or other vitamin D metabolites might be of interest.

4.3.8 Combinations of drugs

Normally the activities of osteoblasts and osteoclasts are rather tightly coupled in order to fill in the resorption sites with newly formed bone. The theory behind the combination therapy is that by giving the appropriate drugs sequentially and intermittently, it may be possible to both stimulate bone formation and depress bone resorption. ADFR stands for Activate-Depress-Free-Repeat, which is the sequence of this kind of therapy. The treatment starts with an activating (A) agent to recruit, stimulate and thereby synchronize osteoclasts (e.g. oral phosphate, PTH or PTH-fragments, 1,25-$(OH)_2D_3$, thyroid hormone). The newly recruited and activated osteoclasts will stimulate by chemical signals adjacent osteoblasts and bone formation will take place. Before osteoclasts will have removed large amounts of bone they are "turned off" by a depressing agent (D). To depress resorption bisphosphonates (or calcitonin) are commonly used. Because osteoclasts will function for 2 to 3 weeks and generations of osteoblasts for 2 to 3 months it was thought to be possible to increase bone mass

in this way. During the free (F) period new bone might be formed. After this cycle the procedure is repeated (R).

Several ADFR studies have been published[95 96] or are under investigation. Although no general agreement exists about the efficacy of ADFR therapy, it is believed that the main effect is probably due to the antiresorptive action. This is illustrated by the results of the intermittent etidronate treatment trials mentioned above[67 68].

4.3.9 Exercise

Physical activity, as the counterpart of immobilization, is commonly accepted to have a beneficial role in preserving and probably restoring bone mass[97]. Despite this consensus there are still controversies about exercise. The controversy is probably due to the fact that too much exercise is harmful for the skeleton. For example, female marathon runners may become amenorrhoic and osteoporotic because of the induction of hypoestrogenism[98] and infantry recruits may easily develop stress fractures[99]. Also intensive exercise over the age of 50 years may be associated with low bone density[100]. However, most studies report a beneficial role of exercise in increasing bone mineral mass[101 102 103].

In a recent report by Kirk et al it was found that long-distance running enhances vertebral bone density in premenopausal women, while it does not appear to prevent age and/or gonadal hormone dependent bone loss in postmenopausal women[104].

The mechanism by which physical activity exerts its influence on bone remodelling is not clear, although it was thought that weight-loading activities were important. The observation that also swimming (a non-weight-loading activity) may enhance bone mass is interesting and deserves further investigation.

Exercise seems to be an attractive alternative for drug therapy in increasing bone mineral mass, although intensive exercise (overexercise) may be harmful to the bone mineral mass. It remains unclear for which group of patients and to which extent exercise is beneficial.

4.4 Glucocorticoid osteoporosis

4.4.1 Introduction

Supraphysiologic doses of glucocorticoids and endogenous hypercortisolism may induce bone loss and ultimately osteoporosis[105]. The first description of osteoporosis in the presence of an excess of endogenous glucocorticoids is of Mooser[106]. Later Cushing described the syndrome bearing his name as a clinical entity[107].

4.4.2 Pathophysiology

The mechanism whereby glucocorticoids induce bone loss is not entirely understood, although evidence is abundant that there is a reduction of bone formation as well as a stimulation of bone resorption[108 109 110]. The effect on the osteoblasts has generally been attributed as a direct inhibitory effect of glucocorticoids, while the increased osteoclastic activity has been regarded as a secondary phenomenon, probably due to an elevated parathyroid hormone (PTH) secretion or an enhanced PTH activity[111 112 113 114 115]. Secondary hyperparathyroidism in glucocorticoid excess has not been generally found[116]. Another mechanism whereby glucocorticoids may interfere with calcium homeostasis is the diminishment of the absorption of intestinal calcium[117 118]. This is assumed to be a direct effect of glucocorticoids on the gut that may be partly overcome by the administration of supraphysiologic amounts of vitamin D(-derivatives)[119].

In addition to an impaired intestinal absorption of calcium an increased urinary calcium excretion has been reported in patients treated with glucocorticoids[96], which appears as least in part to be due to a reduced tubular reabsorption of calcium in these subjects[120]. Impaired absorption of intestinal calcium and an increased calcium loss in the urine may both explain the sometimes reported secondary hyperparathyroidism in glucocorticoid-treated patients.

Furthermore, Feldman has demonstrated the presence of glucocorticoid receptors in bone cells[121] and negative effects of glucocorticoids on cell growth, RNA, protein and collagen synthesis have been demonstrated[122 123].

Other mechanisms whereby glucocorticoids may interfere with bone metabolism are currently under investigation. They include prostaglandins, growth hormone, insulin growth factor-I and other growth factors[124].

4.4.3 The clinical syndrome

It has been shown that (depending upon dosage) chronic glucocorticoid excess induces loss of especially trabecular bone, leading to a high incidence of vertebral compression fractures. Children and postmenopausal women are prone to the deleterious effects of glucocorticoids. The former because high bone turn-over makes bone more susceptible for glucocorticoid action (and because of inhibition of growth), the latter because an excess of glucocorticoids, in addition to the negative effects on bone resorption and formation, will suppress adrenocortical activity leading to a lower adrenal production of androgens and ultimately a lower production of estrogens in adipose and other tissues[125].

Only a few cases are reported about the reversibility of steroid-induced osteoporosis. Aloia et al published the cases of two patients (aged 14 and 21 years) showing an increase in total body calcium content after treatment of Cushing syndrome, although two older patients did not show such an improvement[126]. Recovery from steroid-induced osteoporosis was confirmed by densitometric and histomorphometric data of a case report by Pocock et al[127].

Although the clinical syndrome of glucocorticoid-induced osteoporosis is well known, a dose-response curve of steroids on bone mass is difficult to assess. Most studies differ considerably with respect to potencies of, dosages of and duration of treatment with glucocorticoids. Moreover, the patients are mostly not comparable with regard to the nature, severity or duration of the underlying disease, initial bone mass, menopausal state, mobility and sex. Despite these shortcomings, Dykman et al. found that fractures occurred when the cumulative dose of glucocorticoids exceeded 30 g equivalent of prednisone[128].

Earlier studies addressing this issue have been restricted to patients with rheumatoid arthritis, renal disease[82] and asthmatics[129]. We studied the possible effect of glucocorticoids in patients at different stages of primary biliary cirrhosis. This was of particular interest because it has been assumed that glucocorticoids would be rather strongly contraindicated in these patients because of the negative effects of the liver disease itself on bone mass. This study was cross-sectional and is reported in Chapter 8.

4.4.4 Prevention and treatment

The last decennium studies on therapeutic interventions have been reported. Several approaches are or have been investigated in an attempt to: 1) increase bone formation or 2) decrease bone resorption or 3) counteract negative interactions of excess glucocorticoid with vitamin D action.

4.4.4.1 Derivatives of vitamin D

Several experimental studies showed variable effects of pharmacological doses of vitamin D or its derivatives on calcium metabolism during glucocorticoid excess[130 131 132]. In glucocorticoid-treated patients, Hahn et al demonstrated a beneficial effect of 25-hydroxyvitamin D on calcium absorption, a reduction of iPTH and an increase in forearm bone mass[133]. Braun et al showed that placebo-controlled administration of 2 μg of 1α-hydroxyvitamin D_3 for 6 months to glucocorticoid-treated patients raised calcium absorption and reduced the serum iPTH level and the hydroxyprolinuria, while exerting a positive effect on the trabecular bone volume as determined with histomorphometry[116].

In a randomized placebo-controlled trial we studied prospectively for 2 years the effect of 1 μg 1α-hydroxyvitamin D_3 daily in asthmatic who had chronic treatment with at least 7.5 mg prednisone daily. The results of this study were presented in a paper read at the second International Symposium on Osteoporosis (1987) in Aalborg (Denmark) and the study is described in Chapter 9.

The final answer concerning the possible effectiveness of active vitamin D derivatives (e. g. 1α-hydroxy- or 1,25-dihydroxyvitamin D_3) in the treatment or prevention of corticosteroid osteoporosis has not yet been given.

4.4.4.2 Calcium supplementation

As stated above treatment with vitamin D or its active derivatives can improve the calcium absorption in steroid-treated patients. Therefore it seems likely that adequate calcium supplementation may be beneficial in these patients. A daily supplementation of 1 g of elementary calcium decreased the fasting urinary hydroxyproline-creatinine ratio, suggesting an inhibition of bone resorption in steroid-treated patients[134]. In a prospective trial using microcrystalline hydroxyapatite versus placebo only a slight reduction in the rate of bone loss was observed[135]. It is surprising that despite the advantages of safety and low cost of calcium supplementation in steroid-treated patients relatively little is know about its effects.

4.4.4.3 Stimulating bone formation

Because osteoblastic activity is directly suppressed by steroid treatment, stimulation of bone formation has been applied in glucocorticoid-treated patients. Fluoride in combination with calcium and vitamin D proved not to be effective in preventing steroid-induced bone loss in the forearm[136]. Using bone histomorphometry Meunier et al showed a beneficial effect of

fluoride on trabecular bone in glucocorticoid-treated patients[137]. Although the stimulation of osteoblasts by fluoride is widely accepted, much doubt has risen about the antifracture efficacy of this drug[79].

Other putative bone formation stimulating agents are the anabolic steroids. One of the synthetic anabolic substances is nandrolone decanoate of which it was shown that, whether or not, in combination with micro crystalline calcium hydroxyapatite, it may induce an increase in forearm bone mineral density in corticosteroid-treated patients[138] [139].

4.4.4.4 Inhibiting bone resorption

Steroid treatment will among other effects result in an increased bone resorption[108]. Several agents are known to be able to inhibit osteoclastic activity and are being investigated with regard to their effect in glucocorticoid-induced bone-disease. Ringe et al reported on 38 glucocorticoid-treated patients randomly allocated to two groups: one group receiving 100 IU of salmon calcitonin subcutaneously every other day and a control group[140]. The calcitonin-treated group showed a significant increase in forearm bone mineral density while the control group lost bone.

Recently, it was demonstrated that APD given for one year may prevent bone loss and even may increase (transiently?) bone mineral mass in glucocorticoid-treated patients[141].

4.4.4.5 A new glucocorticoid drug

Recently, a new synthetic steroid (Deflazacort) has been developed. It has been claimed to have on weight basis the same degree of anti-inflammatory activity as prednisolone, while on the same basis its negative effects on bone mineral mass would be less[142] [143]. It was also shown that statural growth proceeded normally in children treated with deflazacort[144]. Evidence was provided that deflazacort produced minimal or no changes in the levels of iPTH and nephrogenous cyclic adenosine 3',5'-monophosphate (cAMP), whereas equivalent amounts of prednisone did[145]. However, since the glucocorticoid receptor in bone appears to be the same as in other target organs it remains questionable whether it is possible to separate the anti-inflammatory effect from the catabolic effect of glucocorticoids[146].

4.4.4.6 Thiazide diuretics

Glucocorticoids not only reduce intestinal calcium absorption but will also enhance calcium excretion. Both mechanisms may lead to an increase of PTH secretion[147]. The hypocalciuric effect of thiazide diuretics in glucocorticoid-treated patients is well

documented[148], and with these agents an improvement of the calcium balance was observed[17,18]. However, no clinical trials assessing the effects of thiazide diuretics on bone mineral mass in glucocorticoid-treated patients have been published.

4.5 Conclusions

No general agreement exists how to prevent or treat glucocorticoid-osteoporosis. Because glucocorticoids interfere at multiple sites with calcium and bone metabolism, it seems unlikely that one single agent is able to counteract all deleterious effects of excess glucocorticoid on bone metabolism.

Several regimens have been investigated with contradictory results (e.g. vitamin D and its derivatives), or without sufficient evidence of a favourable effect to justify widespread clinical application (calcium and thiazide diuretics). Still other agents (bisphosphonates, calcitonin and anabolic steroids) appear to offer interesting possibilities but more clinical evidence of their effectiveness is needed.

4.5 References

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CHAPTER 5

PERIPHERAL AND AXIAL BONE MASS IN DUTCH WOMEN. RELATIONSHIP TO AGE AND MENOPAUSAL STATE

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Original Article

Peripheral and axial bone mass in Dutch women. Relationship to age and menopausal state

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Bone mineral density was measured in 171 healthy Dutch females using single photon absorptiometry at the forearm (distal and proximal sites) and dual photon absorptiometry of the second to fourth lumbar vertebrae. The cross-sectional data showed no peripheral bone loss before the menopause and an acceleration of bone loss at an average interval of 15 years after the menopause. Vertebral bone loss was characterized by a premenopausal loss starting in the fifth decade and from then onwards a fairly constant continuous loss of bone of approximately 7–8% per decade. The age-related bone loss for the population studied was 26.7% for the spinal column and 33.6 and 32.3%, respectively, for the distal and the proximal peripheral sites. Significant correlations were found between all measurement sites, but these relationships seemed too weak to allow the forearm measurements to be a predictor of spinal bone mass.

It is concluded that bone loss follows different patterns at the various skeletal sites. Neth J Med 1988;32:226–234.

Key words: Bone mineral density; Photon absorptiometry; Bone loss; Menopause; Normal female

Introduction

Osteoporosis is characterized by the occurrence of non-traumatic vertebral fractures and fractures of the appendicular skeleton due to a decrease of mineral bone mass and a loss of bone structure. During the last few decades, osteoporosis has been recognized as a major health-care problem, especially in elderly women [1]. In

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the Western world, postmenopausal osteoporosis with vertebral compression fractures occurs in 5–15% of all women between 51–60 years of age. In the U.S.A. osteoporosis has been estimated to occur in 25% of women of 65 years and older [2]. The risk of an osteoporotic fracture depends on the relationship between the severity of the trauma and the strength of the bone, which is determined by the bone mineral density and the bone structure [3].

Increasing interest in this common syndrome has led to the development of non-invasive techniques to measure mineral bone mass [4]. Methods such as single photon absorptiometry (SPA), dual photon absorptiometry (DPA) and quantitative computed tomography (QCT), have provided the opportunity for more detailed study of the patterns of bone loss. Nowadays, SPA and DPA are the most widely used techniques, while QCT, due to its costs and higher radiation exposure compared to photon absorptiometry, is less attractive for epidemiological studies. At the forearm, bone mineral content (BMC) and bone mineral density (BMD) are measured with SPA. Although DPA and QCT can be applied for measurements at various anatomical regions in the skeleton, the lumbar spine is the region of interest in most studies. There are several reports of cross-sectional studies of bone density measured in the forearm and in lumbar vertebrae [5–7]. However, there is no agreement on the question of the relative contribution of age and of menopause on bone loss in the axial and appendicular bone [8–10]. In other words: does one see an accelerated bone loss at the menopause at the various sites of measurement? The question whether the results of forearm measurements can predict vertebral bone density is another matter for debate [11,12].

The aim of the present study was to establish reference values at the various skeletal sites for the Dutch female population, information necessary to define whether bone density in an individual differs from normal. Furthermore, from these cross-sectional data, we estimated peripheral and axial bone loss in relation to age and menopausal state. Special emphasis was given to the correlations between the values obtained at the various measurement sites.

Methods

All participants were female volunteers and gave their informed consent. They were recruited by advertising in a local newspaper and from hospital employees. All women were white, in good health, ambulatory and not on medication thought to influence calcium metabolism. Excluded were those with a history of multiple fractures or with chronic back pain. No additional laboratory tests were performed. The ages ranged from 21 to 87 years. Women menstruating normally were regarded as premenopausal; those who had ceased menstruating for more than 6 months were classified as postmenopausal.

Peripheral bone measurements were carried out at the right forearm according to the method described by Nilas et al. [5] using a Nuclear Data 1100a bone density scanner. The forearm is placed in a water bath in order to obtain a constant soft tissue equivalent and is transversely scanned with a monochromatic iodine-125 source emitting photons at 27.5 keV. The scanning includes both radius and ulna

and is corrected for fat tissue. Measurements were performed both distal (SPA_{dist}) and proximal (SPA_{prox}) to the site where ulna and radius are separated by a distance of 8 mm. Using this technique, the bone measured distally consists of more trabecular bone than that measured proximally [13]. The results are expressed as BMD in g/cm^2. In our hands, the coefficient of variation based on 50 duplicate measurements in normal subjects is 1.9% for the distal site and 1.0% for the proximal site [14].

Axial bone mass was assessed at the lumbar spine (DPA_{spine}) with L_2–L_4 as the region of interest. Measurements were done with a Novo BMC-lab 22a scanning device as described by Krølner and Nielsen [15]. This instrument uses a dichromatic Gadolinium-153 radiation source with emissions at 44 and 100 keV. The technique is based on the difference in attenuation of the two photon energies through a medium consisting of different materials, in this case bone and soft tissue. After calibration, the BMC is expressed in grams hydroxyapatite (gHa). Dividing the BMC by the projected region of interest results in BMD (gHa/cm^2). In order to correct for the interindividual differences due to differences in skeletal size, the results are expressed in BMD. In contrast, in longitudinal studies, use is often made of the BMC. The coefficient of variation calculated on duplicate measurements of the lumbar BMD of 20 osteoporotic patients in our laboratory is 2.3% [14].

In order to differentiate the effects of aging and menopausal state on the bone mineral mass, we divided the women into four groups: 71 premenopausal women (group 1), 35 women less than 10 years postmenopausal (group 2), 39 women 10 to 19 years postmenopausal (group 3), and 24 women postmenopausal for 20 years or more (group 4). Two women could not be classified. The Student's *t*-test was used for unpaired data. A level below 0.05 was regarded as significant. Linear regressions and correlations were calculated using the method of least-squares. The number of data were too small for a meaningful analysis by segmented regressions.

Results

In Table 1, the distributions of height, weight and the results of the bone measurements are listed according to age. Females in the fourth decade had a significantly lower height than the women in the third decade. After the fifth decade there was a further, but not significant, decline in height when compared with the average height in the preceding decade. The peripheral sites showed no age-related bone loss before the fifth decade in contrast to the vertebral bone mass, which decreased significantly from the fourth decade onwards. After the average age of 45, there was loss of bone mass at all three measurement sites. An acceleration of peripheral bone loss was seen in the sixth decade, while axial bone loss was, once started, rather constant through all decades studied. In the last age-group studied, the peripheral bone mineral mass showed no significant decrease as compared with the preceding decade. Omitting the postmenopausal women from the fifth decade group and the premenopausal women from the sixth decade group did not essentially alter the respective percentages of bone loss (data not shown). The overall

TABLE 1

Weight, height and bone densities according to decade.

Decade	Weight (kg)	Height (cm)	SPA_{dist} (gHa/cm^2)	SPA_{prox} (gHa/cm^2)	DPA_{spine} (gHa/cm^2)
Decade 3					
age 25 ± 3.2 ($n = 9$)	67 ± 8.8	172 ± 5.4	1.19 ± 0.14	1.55 ± 0.14	1.01 ± 0.07
Decade 4					
age 35 ± 2.4 ($n = 14$)	62 ± 9.3	167 ± 5.5 [a]	1.13 ± 0.14 NS	1.47 ± 0.16 NS	1.02 ± 0.07 (7%) [a]
Decade 5					
age 45 ± 2.8 ($n = 32$)	66 ± 11.4	168 ± 6.3	1.16 ± 0.15 (9%) [b]	1.49 ± 0.15 (6%) [a]	0.95 ± 0.09 (7%) [a]
Decade 6					
age 54 ± 2.9 ($n = 54$)	66 ± 7.4	166 ± 5.5	1.05 ± 0.15 (17%) [b]	1.39 ± 0.18 (17%) [b]	0.89 ± 0.12 (8%) [a]
Decade 7					
age 64 ± 2.9 ($n = 41$)	64 ± 8.8	165 ± 4.6	0.85 ± 0.14 NS	1.13 ± 0.19 NS	0.81 ± 0.12 (7%) [a]
Decades 8 + 9					
age 75 ± 4.2 ($n = 21$)	65 ± 8.0	163 ± 5.1	0.79 ± 0.14	1.05 ± 0.18	0.74 ± 0.10

SPA_{dist} and SPA_{prox} = single photon absorptiometry of the distal and proximal forearm, respectively; DPA_{spine} = dual photon absorptiometry of the lumbar spine (L_2–L_4).

In parentheses: % bone loss compared with the preceding age-group. The data are expressed as mean ± SD. [a] $P < 0.05$; [b] $P < 0.002$.

bone loss comparing the age groups 20–30 years and 70–87 years was 26.7% for the vertebrae, 33.6% for the distal forearm site and 32.3% for the proximal forearm site.

Rearranging the data according to the number of years since menopause (Table 2) enabled us to rule out the influence of data from relatively young post-

TABLE 2

Weight, height and bone densities according to menopausal state.

Group	Weight	Height	SPA_{dist}	SPA_{prox}	DPA_{spine}
Group 1 ($n = 71$)	66 ± 9.6	167 ± 6.7	1.14 ± 0.15 (10%) [b]	1.49 ± 0.15 (6%) [a]	0.96 ± 0.10 (8%) [b]
Group 2 ($n = 35$)	67 ± 8.2	166 ± 6.0	1.03 ± 0.16 (17%) [b]	1.40 ± 0.17 (20%) [b]	0.88 ± 0.13 (7%) [a]
Group 3 ($n = 39$)	65 ± 8.6	165 ± 4.4	0.86 ± 0.15 NS	1.12 ± 0.20 NS	0.82 ± 0.12 (9%) [a]
Group 4 ($n = 24$)	65 ± 8.6	163 ± 5.0 [a]	0.80 ± 0.14	1.07 ± 0.17	0.75 ± 0.11

See legends to Table 1.

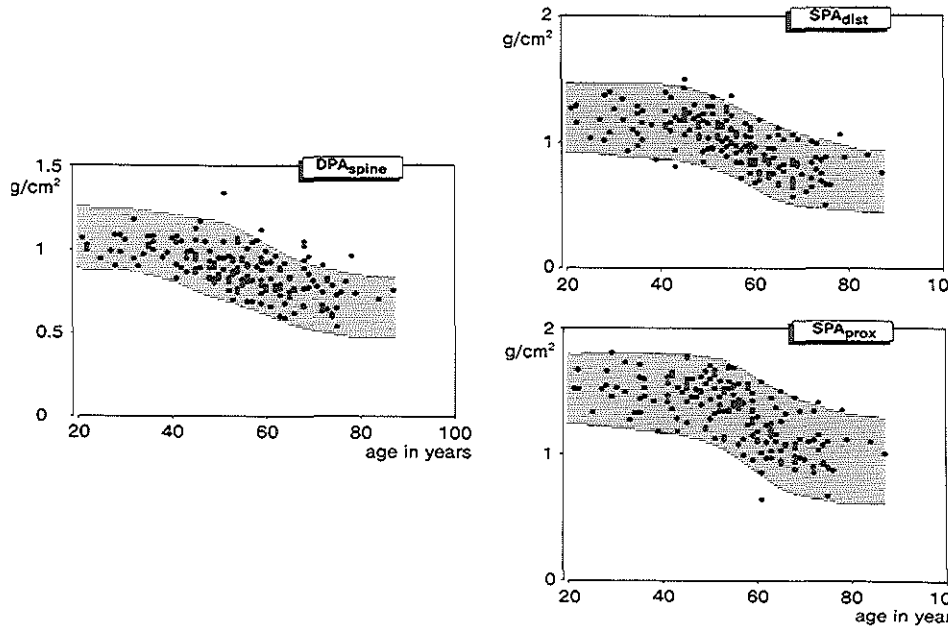

Fig. 1. The individual values ($n = 171$) for BMD at the three measurement sites plotted as a function of age; DPA_{spine} = dual photon absorptiometry of the lumbar spine (L_2–L_4); SPA_{dist} and SPA_{prox} = single photon absorptiometry of the distal and proximal forearm, respectively. The results are expressed in grams hydroxyapatite per cm^2. The shaded areas denote the 95% confidence limits.

menopausal women on the results of women under the age of 50. In this way the effect of menopause on bone mass can be studied in more detail. The subjects were classified in groups 1 to 4 (see Methods). Group 2 was compared with group 1 (all premenopausal women). Groups 3 and 4 were compared with the preceding groups. The differences between the groups were expressed in percentages. Appendicular bone loss was maximal in group 3. This is again in contrast to the vertebral bone

TABLE 3

Correlation matrix of bone densities between the various skeletal sites.

	DPA_{spine}	SPA_{dist}	SPA_{prox}	DPA_{spine}	SPA_{dist}	SPA_{prox}
	Group 1			*Group 2*		
DPA_{spine}	–	0.49	0.43	–	0.67	0.58
SPA_{dist}		–	0.86		–	0.87
	Group 3			*Group 4*		
DPA_{spine}	–	0.23 [a]	0.34 [a]		0.46	0.59
SPA_{dist}		–	0.87		–	0.88

Correlations between single photon absorptiometry of the distal and proximal forearm (SPA_{dist} and SPA_{prox}, respectively) and dual photon absorptiometry of the lumbar spine (DPA_{spine}). The subjects are divided into groups as defined in Methods. All correlations $P < 0.0001$, except: [a] $P < 0.05$.

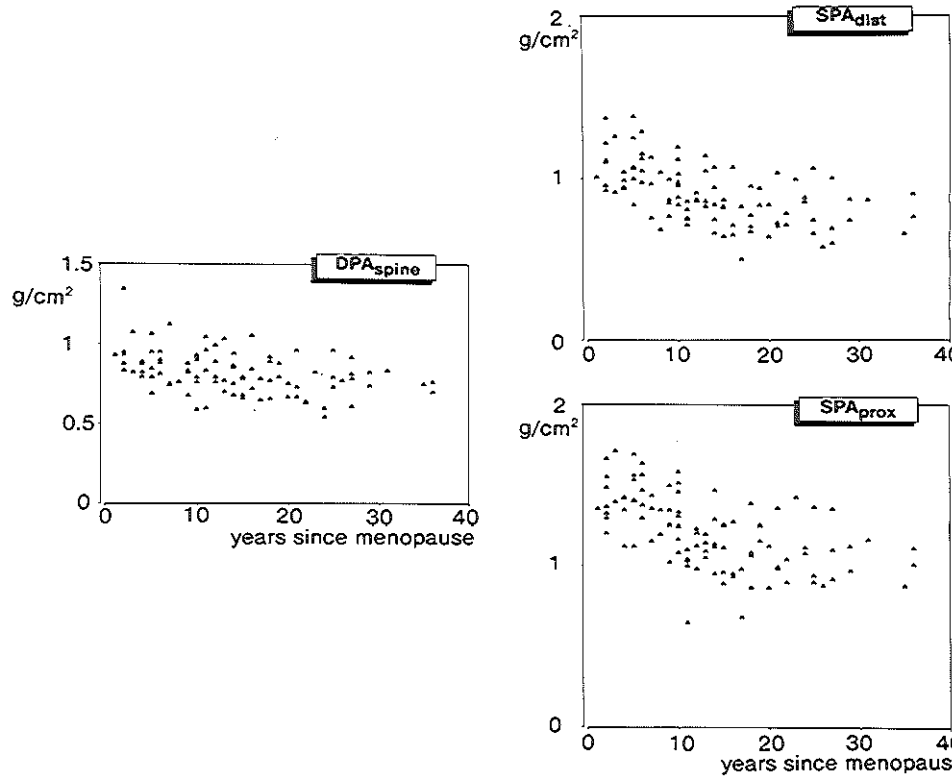

Fig. 2. The individual values ($n = 98$) for BMD at the three measurement sites plotted against years since menopause; DPA_{spine}: dual photon absorptiometry of the lumbar spine (L_2–L_4); SPA_{dist} and SPA_{prox}: single photon absorptiometry of the distal and proximal forearm, respectively. The results are expressed in grams hydroxyapatite per cm^2.

loss, which appeared to be constant between all groups. Therefore, comparison of Tables 1 and 2 only results in minor differences. The bone mineral densities are plotted against age in Fig. 1. The plot shows the individual measurements and the 95% confidence limits. The figure suggests a breakpoint around the age of 50. However, no significant difference in slope was detected. In Fig. 2, the results of bone mineral density are depicted against the number of years since menopause. Again there were no principal differences with the original plots.

The correlations found between BMDs measured at the different sites are given in Table 3. In this table, the population studied is divided into 4 groups defined as mentioned in the Methods section. In all groups vertebral bone mineral density was significantly correlated with the densities at the other measuring sites. This correlation was strongest for the women in group 2. As could be expected, the best correlations were found between the results of the two peripheral sites (SPA_{dist} and SPA_{prox}). There were no significant correlations between bone density parameters and Quetelet index (data not shown).

Discussion

This paper contains data on bone densities in 171 healthy Dutch women. The study was undertaken to obtain reference values for the normal Dutch female population. Reference values are not only influenced by geographic and racial factors [16], but also by differences in techniques. Several cross-sectional studies have provided evidence that premenopausal loss of bone in the appendicular skeleton is low or absent and that bone loss during the early postmenopausal years is accelerated [6,7,10]. Our results show that the acceleration of the peripheral bone loss did not occur shortly after the menopause, but was maximal about 15 years after the menopause. Both distal and proximal sites in the forearm showed this pattern of bone loss, which may indicate that during that period mainly cortical bone is lost. It has been assumed that the relatively moderate decline observed in the 5th decade could be influenced by the presence of premenopausal women [10]. However, this moderate peripheral bone loss is also seen when the data are rearranged according to the number of years since menopause. This is in contrast to our findings with respect to the rate of loss of bone in the axial skeleton. Here the loss is already seen before the menopause and is constant thereafter.

Some investigators found that axial bone mass follows a linear decrease with age [6,17], while others suggested a different pattern with a peak bone mass around 35 years [7] and a sharp perimenopausal decline [18]. However, a premenopausal axial bone loss has not been found in all studies [19]. These discrepancies in the literature concerning the bone loss in the vertebral column are not only due to technical differences but also to a lack of uniformity in defining menopausal state and differences in inclusion and exclusion criteria.

Mazess collected densitometric data from several laboratories in the U.S.A. and found a diminution in the spinal bone mass prior to the usual age of menopause, but not during young adulthood [8]. That study could not exclude the influence of the data of women having an early menopause on this premenopausal bone diminution. Our study confirmed this vertebral bone loss before the age of 50, even after the exclusion of women who were postmenopausal before the age of 50 years. Evidence in favour of this observation is obtained from longitudinal studies in pre- and postmenopausal women [20,21]. We found no acceleration of axial bone loss during the sixth decade. Once started, the rate of vertebral bone mineral loss remained fairly constant during life with a loss of approximately 7% per decade. However, in the later decades this rate of bone loss may be an underestimation (see below). An explanation for the spinal premenopausal bone loss may be found in a decreasing oestrogen production shortly before menses ceased [22].

The different patterns of bone loss at the various sites may depend on differences in bone composition but also on differences in skeletal function. The spinal column is weight-bearing and is affected by other mechanical forces than the forearm. A recent study revealed that trabecular bone accounts for approximately 25% of the bone mineral mass in whole female vertebrae [23]. The trabecular bone percentage in the forearm is estimated at the proximal and distal site at 7 and 25%, respectively [5,13], but these percentages are not firmly established. Photon absorptiometric

techniques cannot differentiate between cortical and trabecular bone at one site, nor between the bone itself and calcifications in the region of interest, which will be discussed below. Direct measurements of the bone compartments at the various skeletal sites can be done with QCT. Moreover, for definitive conclusions concerning patterns of bone loss in these compartments a longitudinal study will be necessary.

The correlations between peripheral and vertebral bone mineral density obtained in the normal population may be changed in various metabolic bone diseases [24]. It has, therefore, been suggested that peripheral measurements can only predict axial bone mass in normal individuals. Pocock showed that correlations between the results of forearm and axial measurements of about 0.66 are insufficient to predict axial bone on the basis of forearm mineral bone mass [12]. Our data show that the relationships between the peripheral and axial densities differ considerably between the groups studied. This could be explained by the already mentioned differences in patterns of bone loss at these measurement sites. In this respect, the possible interference by spondylosteoarthritis with the results obtained with DPA at the lumbar spine has also to be mentioned [7]. Inevitably, aortic calcifications and/or osteoarthritic lesions [25] within the region of interest will spuriously increase the results obtained by DPA. Unfortunately, both aortic calcification and osteoarthritic lesions increase with age, and because bone mass falls with age the relative influence will be greater in elderly women and in women with a low bone mass.

The percentage of axial bone loss found in our study is comparable to that observed by others [8,17], but is probably an underestimation of the actual (trabecular) bone loss, due to the above mentioned opposing effect of calcified lesions. Although these lesions will heavily influence reference values, exclusion of women with osteoarthritis of varying severity would result in variably biased reference values.

The consistent and rather high correlations between SPA_{dist} and SPA_{prox} found in all subgroups of the normal female population studied, raise the question whether these results may not provide us with essentially the same information. Previously, we found that it was impossible to differentiate a group of osteoporotic patients from normal females using the proximal measurement, while the distal measurement allowed such distinction [14]. The superiority of the distal over the proximal measurement can be explained by the higher content of trabecular bone in the distal forearm, which is generally considered to be affected earlier by postmenopausal osteoporosis than cortical bone.

In conclusion, this study provides evidence for different patterns of bone loss at the three skeletal sites, whereby the forearm measurements show an acceleration of postmenopausal bone loss. Finally, these data indicate that forearm densitometry is not suitable as a screening technique for detecting low vertebral bone mass.

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CHAPTER 6

NONINVASIVE AXIAL AND PERIPHERAL ASSESSMENT OF BONE MINERAL CONTENT: A COMPARISON BETWEEN OSTEOPOROTIC WOMEN AND NORMAL SUBJECTS

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Noninvasive Axial and Peripheral Assessment of Bone Mineral Content: A Comparison Between Osteoporotic Women and Normal Subjects

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ABSTRACT

We compared different methods of bone densitometry in women with spinal osteoporosis and normal subjects to assess their discriminatory capability. The methods used included: quantitative computed tomography of the spine (QCT) specified as to trabecular (QCT_{trab}) and cortical bone (QCT_{cort}), dual-photon absorptiometry of the spine (DPA_{spine}), single-photon absorptiometry of the distal and proximal forearm (SPA_{dist} and SPA_{prox}), and quantitative roentgen microdensitometry of the phalanx (QMD). A total of 25 postmenopausal osteoporotic women and 24 healthy comparison subjects matched for age and years since menopause were studied. In the osteoporotic group an average decrement of the axial bone mineral density of -50% ($p < 0.001$) and -20% ($p < 0.001$) were observed for QCT_{trab} and QCT_{cort}, respectively. For DPA_{spine}, SPA_{dist}, SPA_{prox}, and QMD the difference between normal and osteoporotic subjects was -20% ($p < 0.001$), -12% ($p < 0.05$), -7% (NS), and -6% (NS), respectively. With the peripheral measurements (SPA and QMD), alone or in combination, no adequate discrimination between women with or without vertebral compression fractures could be obtained. Although QCT_{trab} showd the highest diagnostic sensitivity (81%), it appears not to be superior to DPA_{spine}. Combinations of the various axial and peripheral measurements did not result in an essentially better sensitivity.

In normal women as well as in osteoporotic individuals the trabecular and cortical QCT measurements showed two opposite trends, suggesting an increase in cortical and a decrease in trabecular density from L1 to L3.

INTRODUCTION

THERE IS CURRENTLY DISCUSSION about the optimal site and method for determining the risk of osteoporotic fractures.[1,2] Moreover, because trabecular bone is thought to be more sensitive to hormonal deficiencies and metabolic bone disease than cortical bone,[3] it may be preferable to measure exclusively trabecular bone instead of a combination of trabecular and cortical bone.[4] Additionally, disagreement exists as to the best skeletal site and type of measurement for follow-up studies.[5-7]

In an attempt to identify the measurement of choice, we selected a group of women with spinal osteoporosis and compared the results of various methods of bone density

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assessment with the results in a group of normal subjects matched for age and years since menopause. The correlations between these various measurements were studied, and discriminant analysis on the data was performed.

MATERIALS AND METHODS

A total of 25 postmenopausal osteoporotic women and 24 healthy women were studied. The women were defined as having osteoporosis if they had radiographic evidence of at least one vertebral compression fracture without a history of significant trauma. A vertebral body deformity was considered a fracture when the anterior height or, in some cases for the lumbar vertebrae, the middle height was equal to or less than 80% of the posterior height of the vertebral body. History, physical examination, and routine laboratory tests were performed to exclude known causes of osteoporosis. The normal postmenopausal women were recruited by advertisement. They were included in the study if there was no radiographic evidence for vertebral fractures. The osteoporotic and normal subjects were prospectively matched according to age and years since menopause (for both parameters a difference up to 5 years was accepted). Characteristics of the participants are given in Table 1. All women gave informed consent.

Photon absorptiometry

All participants were measured with photon absorptiometry as described elsewhere.[8] Peripheral bone measurements were done at the right forearm according to the method described by Nilas et al.[9] using a Nuclear Data 1100a bone density scanner. Measurements were performed both distally (SPA_{dist}) and proximally (SPA_{prox}) in the right forearm. With this technique the bone measured distally consists of a higher proportion of trabecular bone than proximally.[10] The results are expressed as bone mineral density (BMD) in arbitrary units (U/cm^2). In our hands the coefficient of variation based on 50 duplicate measurements in normal subjects is 1.9% for the distal site and 1.0% for the proximal site.

TABLE 1. CHARACTERISTICS OF THE PARTICIPANTS[a]

Characteristic	*Normals (n = 24)*	*Osteoporotics (n = 25)*
Age (years)	60.5 ± 5.0	59.5 ± 5.0
Menopause (years)	50.0 ± 2.9	48.0 ± 5.7
Years since menopause	10.6 ± 5.6	11.5 ± 5.3
Height (cm)	164 ± 3.9	163 ± 7.9
Weight (kg)	66.3 ± 5.8	68.5 ± 13.7

[a]Mean values ± SD. None of the parameters showed a significant difference between the two groups of women (Mann-Whitney U test).

For the photon absorptiometric measurements of the lumbar spine (DPA_{spine}), L_2–L_4 was the region of interest (ROI). Measurements were done with a Novo BMC-lab 22a scanning device as described by Krølner and Nielsen.[11] Results were expressed as g hydroxyapatite (Ha) for L2–L4 (BMC) or as g Ha per cm^2 (BMD). The coefficient of variation calculated on the basis of duplicate measurements of the lumbar BMD of 20 osteoporotic patients in our laboratory is 2.3%.

QCT measurements

A Philips Tomoscan-350 (120 kVP, 200 MA) was used for the QCT measurements of the lumbar vertebrae. The midplane scans of L1–L3 were selected from the lateral scanogram using a modification of the method of Kalender et al.[12] Instead of semiautomatically, we selected each midplane scan manually. Subsequently, these scans, with a slice thickness of 6 mm, were used to select the cortical and trabecular region of interest (Fig. 1).[13] The cortical ROI was defined as follows. From the center of gravity of the vertebral body radial lines were drawn through the cortical area. The area comprising the basivertebral vessels and their surroundings was excluded. The highest CT value on the radial lines was considered to correspond to the center of the cortex. Along the radial line, the inner and outer border of the cortex was defined between two consecutive points with the largest difference in CT values. The cortical ROI consisted of all pixels measured between the determined outer and inner border, using all radial lines (approximately 120 in number).

The trabecular ROI consisted of an approximately circular area, excluding (1) the sector comprising the basivertebral vessels and their surroundings, and (2) a subcortical area 5 pixels wide. The surface area of the ROIs depended on the vertebral size and varied from 1.18 to 2.93 cm^2 for the cortical and 3.05 to 6.63 cm^2 for the trabecular ROIs. The CT values obtained were converted to equivalent concentrations of dipotassium phosphate (mg K_2HPO_4 per ml, BMD) using the CT values of a simultaneously measured phantom placed underneath the subjects. The phantom contains tubes with various concentrations of K_2HPO_4 (25–400 mg/ml) representing the density range to be expected in human vertebral bone.

The (short-term) coefficient of variation for the QCT measurement was obtained by scanning 10 osteoporotic women twice with a interval of 30–60 minutes. This procedure included repositioning of the patient on the CT table. The whole group was scanned within 4 months. Under these conditions the coefficient of variation for duplicate cortical and trabecular QCT measurements is 2.5 and 2.7%, respectively, for L2–L3.

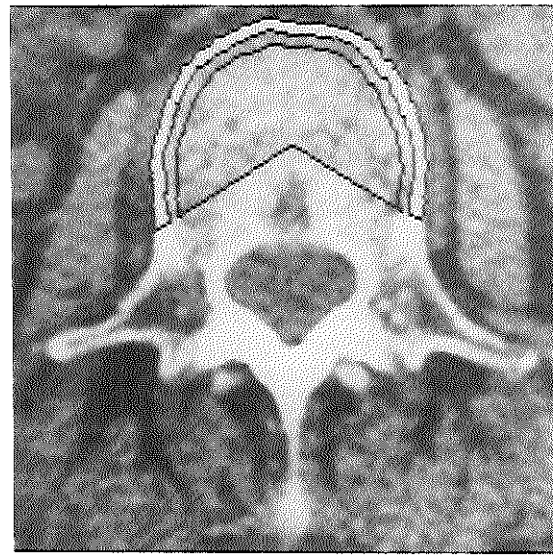

FIG. 1. CT scan of L3 showing the cortical and trabecular ROI, respectively. For details see Materials and Methods.

Quantitative Roentgen microdensitometry of the phalanx

The BMD at the middle phalanx of digital II of the right hand was measured by QMD.[14] This technique uses two standardized radiographs of the selected phalanx and a simultaneously radiographed aluminum reference wedge. Because the two radiographs are made in planes perpendicular to each other, an estimation of the bone mineral content per unit of volume can be achieved. The radiographs are analyzed by an optical microdensitometer. The results are expressed in mm aluminum Eq/mm³. In normal people the coefficient of variation was found to be less than 1%.[15]

Statistical analyses

Comparisons of the results of the various methods of bone mineral measurement were done with Wilcoxon's two-sample test. The significance of the trend in the mean BMD of L1–L3 as measured by QCT was assessed by the rank test of Friedman. To investigate whether combinations of the various techniques of bone mineral assessment perform better in detecting spinal osteoporosis than each technique on its own, Fisher's linear discriminant analysis method was used. Finally, standard (Pearson) correlation coefficients were calculated between the results of the densitometric measurements. P values smaller than 0.05 were considered significant. All P values are two-tailed.

RESULTS

Table 2 shows the mean values for each type of measurement in the osteoporotic and normal groups. Because of technical difficulties, such as inadequacy in the localization of the ROI or vertebral collapse (in the osteoporotic group only), the number of observations may be lower than the number of participants. As can be seen in Table 2, all means of the axial measurements were (highly) significantly lower in the group with spinal osteoporosis. The means of the appendicular measurements were also lower in the osteoporotic women; however, the difference was only significant for SPA_{dist}. The individual data of the axial measurements are depicted in Fig. 2.

To investigate the potential contribution of combinations of the various techniques in detecting spinal osteoporosis, several discriminant analyses were performed. The

TABLE 2. ASSESSMENT OF MINERAL BONE MASS[a]

	Normals	*Osteoporotics*
Axial		
DPA		
BMC (g Ha per L2–L4)	36.9 ± 5.7 (22)	28.9 ± 7.2 (23)[b]
BMD (g Ha per cm²)	0.82 ± 0.10 (22)	0.66 ± 0.11 (23)[b]
QCT (mg K_2HPO_4 per ml)		
Trabecular L1	91.1 ± 27.0 (22)	45.9 ± 25.4 (12)[b]
Trabecular L2	83.5 ± 29.0 (23)	40.8 ± 20.3 (23)[b]
Trabecular L3	78.7 ± 26.6 (23)	36.2 ± 22.5 (24)[b]
Mean trabecular L2 + L3	81.1 ± 27.4 (23)	40.3 ± 19.4 (22)[b]
Cortical L1	261.9 ± 36.1 (23)	205.3 ± 35.2 (12)[b]
Cortical L2	305.4 ± 38.5 (23)	242.8 ± 55.6 (23)[b]
Cortical L3	314.3 ± 49.8 (23)	248.5 ± 44.4 (24)[b]
Mean cortical L2 + L3	309.8 ± 42.6 (23)	247.1 ± 47.8 (22)[b]
Peripheral		
SPA (U/cm²)		
Distal	0.89 ± 0.18 (23)	0.78 ± 0.13 (24)[c]
Proximal	1.21 ± 0.23 (23)	1.13 ± 0.18 (24) NS
QMD (mm Al Eq/mm²)	0.490 ± 0.52 (23)	0.462 ± 0.39 (25) NS

[a]Mean values ± SD. Number of observations in parentheses. Significance determined by Mann-Whitney U test.
[b]$p < 0.001$.
[c]$p < 0.05$.
NS = not significant. Mean trabecular L2 + L3 denotes to the mean of the trabecular QCT measurement of L2 and L3. Mean cortical L2 + L3 denotes to the mean of the cortical QCT measurement of L2 and L3.

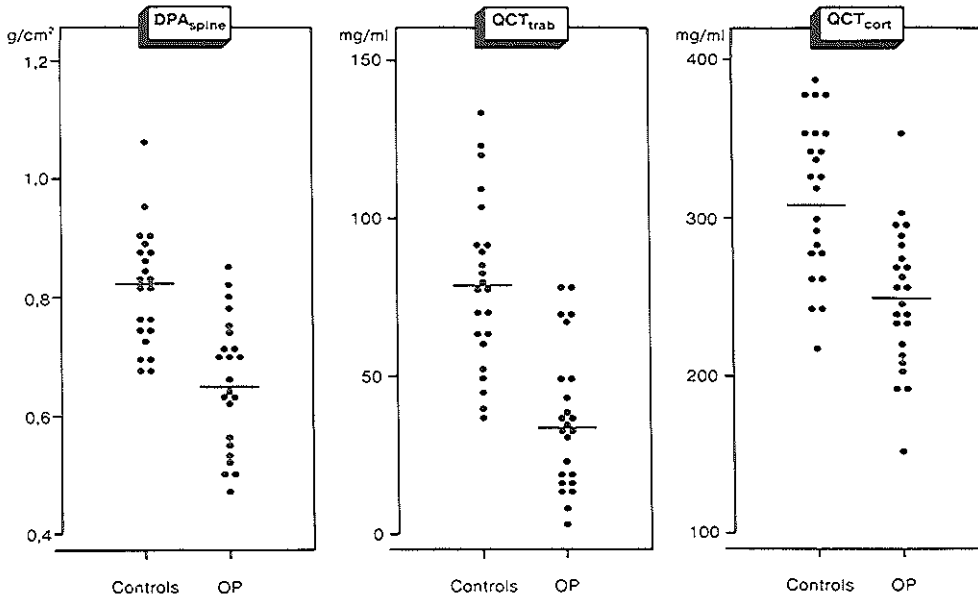

FIG. 2. The results of the individual axial densitometric measurements. The horizontal lines denote the means. Details are given in Table 2.

QCT values of L1 were not included, leaving 23 cases in the osteoporotic and 22 in the control group. The best discriminating combination of the appendicular measurements could classify only 59% of the subjects correctly. Of the axial measurements, QCT_{trab} of L2 and L3 appeared to have the highest percentage correctly classified (79–81%), followed by DPA_{spine} with 70%. Adding more variables in a discriminant model already containing QCT_{trab} did not result in essential improvements.

Table 3 shows the correlations among the results obtained with the densitometric techniques. QCT_{trab} results showed a good correlation with DPA results for normal women ($r = 0.76$) and a moderate correlation for the osteoporotic women ($r = 0.45$). On the other hand, QCT_{cort} versus DPA showed the opposite trend ($r = 0.49$ and 0.70, respectively). For both groups a moderate correlation was found between QCT_{trab} and QCT_{cort} ($r = 0.57$ and 0.49, respectively). Except for SPA_{dist} versus SPA_{prox} ($r = 0.88$ and 0.69), the results of the various appendicular measurements correlated moderately, at best. In the osteoporotic women the correlations between QMD and both SPA measurements were even very low. In normal women both DPA_{spine} and QCT_{trab} correlated with SPA_{dist} and SPA_{prox} ($0.62 < r < 0.70$). The results of none of the appendicular measurements showed a significant correlation with QCT_{cort}.

The results of the QCT measurements of the trabecular part of the vertebrae show a significant decrease in the mean BMD from L1 to L3 (Table 2). In contrast, the results of the cortical measurements show an increase in the mean BMD from L1 to L3. For the trabecular ROI the mean BMD decreased significant from L1 to L3 for the two groups combined as well as for the control group. The results of the cortical ROI showed a significant increase in the mean BMD for both groups. The QCT densities of L1–L3 were ranked for each subject to assess individual trends. The mean ranks, which are given in Table 4, were compared with Friedman's test.

DISCUSSION

The current study confirms earlier reports[1,3,16–19] that BMD measurements of the axial skeleton discriminate women with spinal osteoporosis from normal women better than do measurements of the appendicular bone mass, like SPA and QMD. Of the axial measurements QCT_{trab} appears to have the highest predictive value with approximately 80%, followed by DPA_{spine} with 70%. Nevertheless, such a difference in diagnostic capabilities of QCT_{trab} and DPA_{spine} must be confirmed in larger series of osteoporotic women and matched controls.

The substantially larger decrement observed with QCT_{trab} (−50%) compared with DPA_{spine} (−20%) was in agreement with that found by several other investigators[19–21] and suggests once more the higher diagnostic potential of direct trabecular measurements in detecting spinal osteoporosis. Although our study differs from the studies quoted by the fact that our normal subjects were matched to the osteoporotic women according to age and years since menopause, still the differences found between the two groups are as large as found by others. Furthermore, a significant difference of 20% in the cortical vertebral BMD was observed. That Jones et al.[22] were not able to detect such a difference between normal women and osteoporotic patients is probably because they used a completely different method to estimate compact bone density values. Additionally, differences in the selection and number of participants may have been important. Despite these differences it is clear that QCT_{cort} does not provide important additional information in this cross-sectional study. The significance of this parameter, however, needs to be assessed in larger series.

Previous reports suggested that the average CT values of spongious bone of a single slice from various vertebral bodies are relatively constant.[20,22] However, our data indicate a systematic decrease in trabecular BMD from L1 to L3; on the other hand, the cortical BMD appears to in-

TABLE 3. CORRELATIONS BETWEEN THE VARIOUS MEASUREMENTS IN BOTH GROUPS[a]

	DPA_{spine}	QCT_{trab}	QCT_{cort}	SPA_{dist}	SPA_{prox}	QMD
DPA_{spine}	–					
QCT_{trab}	0.76 (0.45)*	–				
QCT_{cort}	0.49* (0.70)	0.57 (0.49)*	–			
SPA_{dist}	0.62 (0.47)*	0.70 (0.44)*	0.16 NS (0.40) NS	–		
SPA_{prox}	0.66 (0.34) NS	0.69 (0.43)*	0.22 NS (0.34) NS	0.88 (0.69)*	–	
QMD	0.29 NS (0.05) NS	0.41* (0.23) NS	0.29 NS (0.24) NS	0.53* (0.15) NS	0.58 (0.27) NS	–

[a]All correlations $p < 0.01$ except (*) $p < 0.05$; NS = not significant. The correlation coefficients of the osteoporotic group are in parentheses. QCT_{trab} represents the mean trabecular density of L2 and L3; QCT_{cort} represents the mean cortical density of L2 and L3.

TABLE 4. RESULTS OF FRIEDMAN'S TEST PERFORMED ON THE QCT MEASUREMENTS OF L1 TO L3

	Group	N	*Mean rank: L1-L2-L3*	p
Trabecular	Combined	32	2.56-1.94-1.50	0.0001
	Controls	22	2.64-1.86-1.50	0.001
	Osteoporotics	10	2.40-2.10-1.50	NS
Cortical	Combined	32	1.09-2.19-2.72	0.00001
	Controls	22	1.05-2.18-2.77	0.0001
	Osteoporotics	10	1.20-2.20-2.60	0.006

crease. In our CT system a correction for beam hardening is implemented for the total range of possible attenuation values (for all detectors). This is achieved by using plexiglass (PMMA) bars of increasing thickness that cover the whole fan array. Therefore, differences in CT values cannot be explained by differences in beam hardening associated with changes in overall cross-sectional thickness of the body. In addition, preliminary results obtained with DPA also showed an increase in BMD from L2 to L4 (data not shown). It remains to be elucidated whether there exists a parallel between our data and those obtained by Nottestad et al.[24] They observed in human cadaver vertebrae an increase in the mean total body calcium content of the whole vertebral body from L1 to L3 and simultaneously a decrease in the percentage of trabecular bone calcium.

Widely differing correlations among the results of the axial measurements and between the results of the axial and appendicular measurements have been reported in apparently similar groups of patients.[17,19,20] In general, as is the case in our study, the best correlations have been found between the results of various axial measurements, but moderate to even low correlations have been observed between the data derived from the axial and appendicular skeleton, respectively. It may be of significance that in osteoporotic subjects a better correlation between the results of DPA and QCT_{cort} was observed than in normal woman. This may indicate that in established spinal osteoporosis DPA results reflect mainly vertebral cortical bone.

In our study the highest correlation between the results of a peripheral and an axial measurement is 0.70 (SPA_{dist} versus QCT_{trab}). However, the implication of this apparently reasonably good correlation is that a measurement at one site can account for approximately 49% of the variability (r^2) at the other site. Therefore, peripheral measurements are not suitable to predict axial BMD.

In conclusion, measurements of spinal trabecular bone density by QCT allow the best discrimination between healthy women and women with spinal osteoporosis. Furthermore, in this study peripheral and axial cortical measurements added little information on the degree of spinal osteoporosis.

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CHAPTER 7

ESTROGENS, ANDROSTENEDIONE, SEX HORMONE BINDING GLOBULIN AND BODY MASS INDEX AS DETERMINANTS OF BONE MINERAL MASS IN ELDERLY POSTMENOPAUSAL WOMEN.

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ABSTRACT

Endogenous estrogen, androstenedione and sex hormone binding globulin (SHBG) levels were studied in relation to peripheral and axial bone mineral density (BMD) in 43 postmenopausal women (aged 68-72 years). From a larger population study two groups of women were selected with low and high endogenous estrone (E_1) levels, respectively. The group with low estrone levels showed a lower BMD at all measurement sites, significantly so at the peripheral sites. Each group was divided further into 2 groups based on their SHBG levels. The BMD of the resulting 4 groups was tested along a ranking of increasing estrogen bio-availability. In the low-E_1/high-SHBG-group a significantly lower forearm BMD was found than in the other groups. The body mass index (BMI) was significantly higher in the high-E_1 group. Correction for the differences in BMI led to the loss of the differences in BMD between the low- and high-E_1 groups and also of the differences in BMD between the low-E_1/high-SHBG and the high-E_1/low-SHBG subgroups. When the low- and high-E_1 groups were subdivided according to their BMI values the BMD of the low-E_1/low-BMI subgroup was at all sites and with all methods considerably lower than that of the other three subgroups. In women around 70 years of age BMI is a main determinant of bone mass acting through its influence on estrogen and SHBG formation as well as through other mechanism(s).

INTRODUCTION

In the perimenopausal years endogenous estrogens are important for the conservation of the bone mineral mass[1]. In the early postmenopausal years bone mineral density (BMD) appears to be more related to estrogen deficiency than to age[2], but this relationship is less clear in the late postmenopausal years[3,4]. Riis et al[5] found no differences in the levels of estrone (E_1), estradiol (E_2) and androstenedione (A) nor in fat mass between groups of 70 year old women with and without osteoporotic fractures, whereas among early postmenopausal women (45-54 years old) the subjects with rapid forearm bone mineral loss had significantly lower E_1, E_2 and fat mass than the slow losers of bone mineral.

Apart from the postmenopausal endogenous estrogen level itself the estrogen binding protein (sex hormone binding globulin; SHBG) may be of importance for the bone conserving activity of estrogens as the fraction of circulating sex steroids that is bound to SHBG is not available for receptor binding nor for metabolism[6]. Comparing elderly women (average age 75.6 years) with hip fractures to age-matched controls Davidson et al.[7] found no differences in E_2, E_1 and testosterone (T). However, SHBG levels were significantly higher and free E_2 and free T and percent ideal weight were lower in the osteoporotic group. The differences in SHBG , free E_2 and free T disappeared when a subgroup of the fracture patients was matched according to percent ideal body weight. Subsequently, they reported on 30 women (aged 63 ± 1 years) with and without spinal fractures and found no lower levels of sex steroids (E_2, E_1, T, A and DHEA(S)) and no higher SHBG in the osteoporotic group[4]. Based on a population study van Hemert et al. observed an inverse relationship between the level of SHBG and metacarpal bone mass in 746 normal women aged 53-76 years[8].In a subgroup of women of 65 years and over a significantly higher SHBG level was found in women with osteoporotic fractures (mainly vertebral) compared to a group without fractures, while age and body mass index (BMI) did not differ between the 2 groups. In adults the SHBG level is

rather strongly inversely correlated to body weight and positively to age[9,10]. Exogenous estrogen raises the SHBG level, while exogenous androgen lowers it[11,12].

In the present study we investigated the influence of the SHBG level and BMI on peripheral and axial bone mineral mass in two groups of women, aged 68-72 years, selected from a normal population[8,13] according to their low and high serum E1 level, respectively.

TABLE I: Characteristics of the participants.

	low serum E_1 n = 23	high serum E_1 n = 20	p-value
Age (years)	68.3 (1.9)	68.2 (1.9)	NS
Years since menopause	17.8 (1.0)	15.4 (0.8)	NS
Height (cm)	164.3 (1.2)	162.3 (1.5)	NS
Weight (kg)	68.3 (1.9)	75.4 (1.9)	0.02
Body Mass Index (kg/m^2)	25.7 (0.6)	29.7 (0.7)	0.0002
Estradiol (pmol/l)	17.8 (3.9)	49.1 (6.1)	0.0001
Androstenedione (nmol/l)	2.5 (0.3)	4.7 (0.5)	0.0004
SHBG (nmol/l)	99.9 (9.5)	76.4 (15.7)	NS

Characteristics of the participants in the low (65.1 ± 4.3 pmol/l) and high E_1 (288.9 ± 10.1 pmol/l) group, respectively. Values are means. Standard errors of the mean between parentheses.
Two-sided p-values calculated by t-test.

TABLE II: Results of the bone mineral mass assessments in 43 healthy postmenopausal women.

	low estrone n = 23	high estrone n = 20	p-value
SPA dist. (units/cm²)	0.84 (0.04)	0.96 (0.04)	0.05
SPA-prox (units/cm²)	1.11 (0.05)	1.26 (0.05)	0.03
DPA spine (g HA/cm²)	0.77 (0.02)	0.83 (0.03)	NS
QCT trab (mg/ml)	76.1 (6.0)	85.5 (9.2)	NS
QCT cort (mg/ml)	259.9 (12.7)	278.7 (12.8)	NS

Peripheral and axial bone mineral densities of the high and low estrone groups. Values are means. Standard errors of the mean between parentheses. Two-sided p-values calculated by t-test.

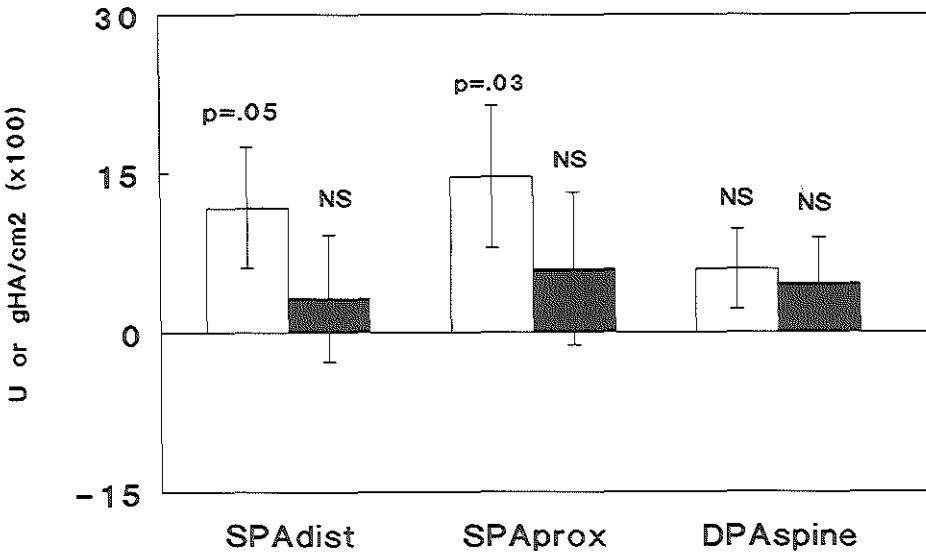

Fig. 1: Difference in BMD between the high- and low-E_1 groups. Open bars: without correction, closed bars: after correction for BMI. Means ± SEM

MATERIALS AND METHODS

43 Healthy women of 68-72 years were selected from a larger epidemiologic study comprising 746 women aged 58 to 77 years[8,13]. The selection was based on serum E_1 levels. According to Cauley et al.[14] one single measurement of E_1 is reproducible and reliable in characterizing a postmenopausal woman for epidemiologic research. One group (n=23) with low E_1 levels was selected at random from the 10th to 20th percentile and a second group (n=20) with high E_1 levels from the 80th to 90th percentile. None of them used glucocorticoids or hormonal substitution. Previous use of these drugs never had exceeded 3 months. All women were volunteers and gave informed consent.

Peripheral bone measurements were done at the right forearm according to the Single Photon Absorptiometry (SPA) method described by Nilas et al[15], using a Nuclear Data 1100a bone density scanner. Measurements were performed both distally (SPA-dist) and proximally (SPA-prox) in the forearm. With this technique the bone measured distally consists to a larger extent of trabecular bone than proximally[16]. The results are expressed as BMD in arbitrary units (U/cm^2). A correction for the variability of the amount of fat in the forearm has been used[17].

For the Dual Photon Absorptiometric (DPA) measurements of the lumbar spine (DPA-spine) L_2 through L_4 was the region of interest. Measurements were done with a Novo BMC-lab 22a scanning device as described by Krølner and Nielsen[18]. The results are expressed as BMD in gram hydroxyapatite (HA) per cm^2.

For the Quantitative Computed Tomographic (QCT) densitometric measurements a Philips Tomoscan-350 was used. Trabecular and cortical measurements (QCT-trab and QCT-cort) were performed as described previously[19]. Scans, with a slice thickness of 6 mm, were made in the midplane of L_1 through L_3 as selected from a lateral scanogram. Results were converted to equivalent concentrations of di-potassium phosphate (mg K_2HPO_4/ml) by means of a simultaneously scanned phantom placed underneath the patient. The coefficient of variation was for SPA-prox and -dist (both BMD) 1.0 and 1.9 %, respectively, for DPA-spine (BMD) in osteoporotic patients 2.3 % and for QCT-trab and -cort in normal women 2.5 % and 2.7 %, respectively.

E_1 concentrations were measured by radioimmunoassay (RIA) as described by van Landeghem et al[20], estradiol (E_2) concentrations by

TABLE III: Body mass index and results of various measurements of bone mass (BMD) in the four subgroups based on serum E_1 and SHBG levels.

Group	low E_1 high SHBG	low E_1 low SHBG	high E_1 high SHBG	High E_1 low SHBG
N	11	12	10	10
BMI (kg/m^2)	24.4 (1.00)#	26.4 (0.85)	28.3 (1.09)	29.1 (1.12)
SPA dist (U/cm^2)	0.78 (0.05)#*	0.90 (0.05)	0.90 (0.08)	1.01 (0.04)
SPA prox (U/cm^2)	1.06 (0.05)#*	1.16 (0.08)	1.17 (0.08)	1.33 (0.05)
DPA spine (g HA/cm^2)	0.75 (0.04)	0.80 (0.02)	0.83 (0.05)	0.84 (0.04)
QCT trab mg K_2HPO_4/ml)	71.0 (6.9)	80.2 (9.5)	80.2 (13.0)	90.8 (13.8)
QCT cort mg K_2HPO_4)	251.3 (18.3)	267.0 (18.2)	275.5 (20.9)	281.8 (16.3)

Values are means. Between parentheses SEM.
* $p < 0.01$ compared with high E_1 / low SHBG group (analysis of variance).
# $p < 0.05$ vs. the other groups (t-test).

TABLE IV: Results of various bone mass measurements (BMD) in the four subgroups based on serum E_1 and BMI.

group	low E_1 low BMI	low E_1 high BMI	high E_1 low BMI	high E_1 high BMI
BMI (kg/cm^2)	22.7 (1.8)	27.7 (2.3)	26.6 (1.4)	31.1 (3.1)
N	11	12	10	10
SPA dist (U/cm^2)	0.75 (0.05)#	0.92 (0.05)	0.95 (0.06)	0.96 (0.07)
SPA prox (U/cm^2)	1.00 (0.06)#	1.21 (0.06)	1.22 (0.06)	1.29 (0.08)
DPA spine (g HA/cm^2)	0.72 (0.04)#	0.82 (0.03)	0.84 (0.04)	0.83 (0.05)
QCT trab (mg K_2HPO_4/ml)	58.5 (6.4)#	87.7 (7.5)	83.3 (9.2)	88.4 (18.8)
QCT cort (mg K_2HPO_4/ml)	227.4 (22.2)#	281.6 (12.6)	269.5 (19.6)	290.9 (14.9)

Values are means. Between parentheses SEM.
$p \leq 0.01$ vs. the other groups (t-test).

a RIA kit of Diagnostic Products Corporation (Los Angeles, California, USA) and androstenedione (A) levels by a RIA kit from Eurodiagnostics (Apeldoorn, The Netherlands). SHBG was measured as described by Hammond et al[21]. The inter- and intraasay variations of these determinations varied from 10.8-14.6 and 16.5-18.4 %, respectively[8].

DATA ANALYSIS

The data were analyzed in two ways. First, group means comparisons were made using a t-test for unpaired observations. The results for various comparisons are expressed as means and standard errors of the mean for each of the groups. Second, to test the mediating effect of plasma SHBG level the low and high estrone group were each divided in two subgroups with high and low SHBG levels, based on the median level of plasma SHBG. Similarly, the low and high E_1 groups were each subdivided in two subgroups with low and high BMI values, according to the BMI median value. The differences between the resulting two times four groups were again studied with a t-test and differences across groups using analysis of variance. Two-sided p-values are used throughout. When applicable adjustments for confounding variables were made using multiple linear regression analysis.

RESULTS

The general characteristics of the two study groups and their blood analysis are given in Table I. As could be expected the serum gonadal hormone levels differ significantly between the groups. All the values of the bone mineral assessments (Table II) in the low-E_1 group are lower than in the high-E_1 group, significantly so for the forearm measurements

Because the BMI was also significantly lower in the low-E_1 group (Table I) the BMD data were -by regression analysis- corrected for body mass. Subsequently, the difference in forearm BMD between the low- and high-E_1 groups were no longer observed (Fig. 1). On the other hand the significant differences in E_2 and A between the two groups of women did not disappear after correction for BMI. To investigate whether the SHBG level modulates the effect of low and high estrogen levels on BMD, the two groups of women were divided in subgroups on the basis of the serum SHBG level. The forearm BMD was in the first (low-E_1/high-SHBG) subgroup significantly lower than in the fourth (high-E_1/low-SHBG) subgroup (Fig. 2, Table III). Because also the relationship between the SHBG level and BMD disappeared, when the data for the four subgroups were corrected for body mass, we again subdivided the low- and high-E_1 groups, this time according to low and high BMI values. As can be seen in Fig. 3 and Table IV the BMD was in the low-E_1/low-BMI subgroup of women considerably lower than in the other three subgroups. This applied to the results of all types of measurement and at all sites measured.

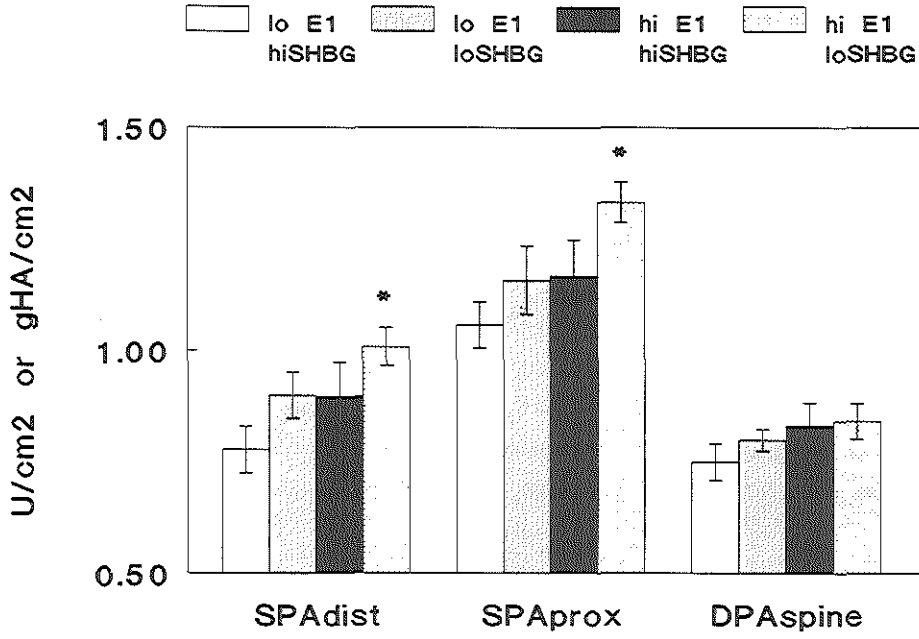

Fig. 2: BMD of the forearm and lumbar spine. Subdivision of the low (lo)- and high (hi)-E_1 groups as to the SHBG - level. *p < 0.01 versus lo-E_1/hi-SHBG

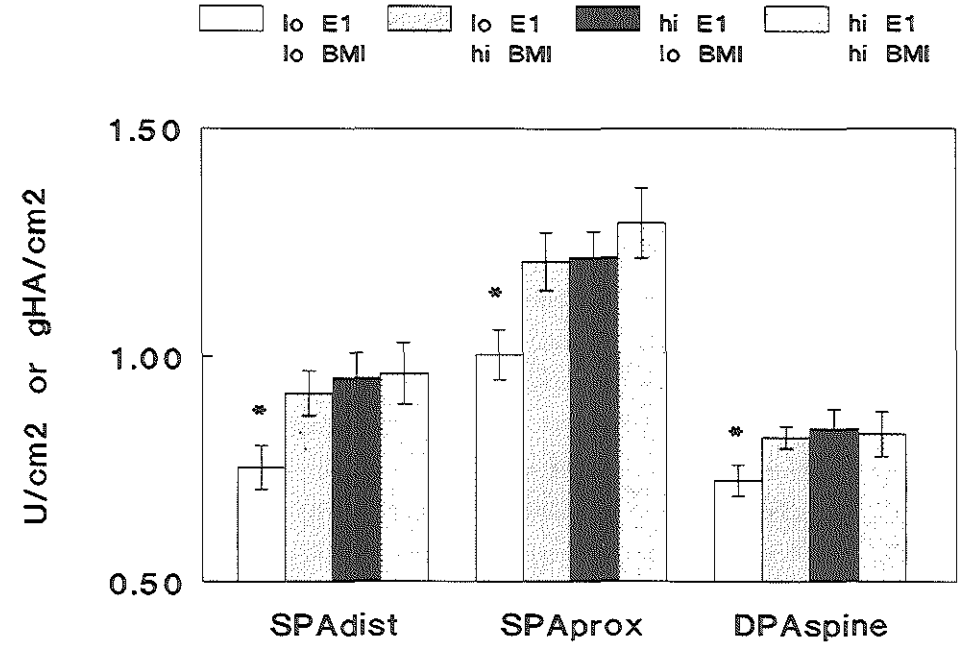

Fig. 3: BMD of the forearm and lumbar spine. Subdivision of the low- and high-E_1 groups according to the BMI value. *p ≤ 0.01 versus the other groups.

DISCUSSION

Using bone mass as a selection criterium several authors have established a rather strong correlation between the levels of estrogens and bone mass[14,22]. We decided to study this relationship, in the open population, by an opposite approach, i.e. using estrogen level as the selection criterium. In this way we found that the women selected with regard to low (from the 10th to the 20th percentile) and high (from the 80th to the 90th percentile) serum E_1 had significantly different forearm BMD (two sites). The fact that in the lumbar vertebrae the BMD was not significantly different between the low- and high-E_1 groups may reflect the lower precision of the methods used for that region as compared with those used at the forearm. To further analyze the importance of estrogen levels one has to consider factors influencing those levels and estrogen bioavailability, such as androstenedione (A), fat or body mass and SHBG.

Postmenopausal estrogen levels are largely dependent on the adipose tissue aromatization of A secreted by the adrenal cortex. Accordingly, a correlation between the serum estrogen level and the adipose tissue mass (or the body weight) has repeatedly been demonstrated in pre- and postmenopausal women[23,24]. Serum E_1 was in this situation also dependent on the plasma A level[25]. Selection on the basis of low and high E_1 levels in our hands resulted in a selection according to low and high body mass and serum A. Therefore, we had to exclude the possibility that the observed differences in BMD between the two groups had to be partly attributed to differences in these variables. In the population-based study, from which our subjects were afterwards selected, van Hemert et al[8] demonstrated an independent relationship between age, SHBG, E_2 and BMI on the one hand and peripheral bone mass on the other. In the present study the difference in A between the groups with low and high serum E_1 was still observed after correction for body mass. However, no correlation between BMD at the various sites and serum A was found (data not shown).

The biological effects of a steroid hormone are determined by the binding of the free hormone to the receptor. In the case of a constant concentration of estradiol an increased SHBG level will in the steady state be accompanied by a lowered free hormone concentration. In postmenopausal women the influence of SHBG is especially important because feed-back control of estrogen production is lacking. The results obtained in this study appeared to support this concept (Fig. 2 and Table III): When the patients of the two groups were ranked in categories of supposedly increasing estrogen activity a difference in BMD was observed. However, as mentioned we found a parallel significant difference in BMI between the low- and high-E_1 groups. In adults body weight and serum SHBG are inversely correlated[8,9,10]. Correction of our data for the differences in BMI

led to a loss of the significant differences in BMD between the low- and high-E_1 groups as well as between the low-E_1/high-SHBG and high-E_1/low-SHBG subgroups. Subdivision of the low- and high-E_1 groups as to the BMI values revealed at all sites measured a considerable difference in BMD between the low-E_1/low-BMI group and the other groups. Therefore, one may conclude that in the postmenopausal women selected BMI is a main determinant of bone mass acting by influencing the serum estrogen and SHBG levels, but in addition independently from these mechanisms.

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CHAPTER 8

BONE MASS IN WOMEN WITH PRIMARY BILIARY CIRRHOSIS: THE RELATION WITH HISTOLOGICAL STAGE AND THE USE OF GLUCOCORTICOIDS

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Bone Mass in Women With Primary Biliary Cirrhosis: The Relation With Histological Stage and Use of Glucocorticoids

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To assess the impact of primary biliary cirrhosis on bone mass in general and the relative importance of the stage of the liver disease and of treatment with glucocorticoids for the possible development of osteoporosis, bone mineral mass was measured by single and dual photon absorptiometry in 55 unselected female patients with longstanding primary biliary cirrhosis. Although most of the patients had a bone mineral density within the normal range, the bone mineral densities of the lumbar spine and distal and proximal forearm were 8% ($P < 0.004$), 8% ($P < 0.03$), and 5% (NS) respectively, lower than in age-matched healthy women. Multiple regression analysis showed that the histological stage of the liver disease (early stage vs. late stage) was an independent determinant of axial bone mineral density, whereas the use of glucocorticoids resulted in only a moderate and not significant bone loss. Serum calcium proved to be significantly lower in the patients with late-stage primary biliary cirrhosis than in those with early-stage disease, whereas no significant differences were found in these groups with regard to several biochemical parameters of bone metabolism. In conclusion, in patients with primary biliary cirrhosis, bone loss was only moderate and related to the histological stage. The effect of low-dose glucocorticoids on bone mass seemed not significant.

Primary biliary cirrhosis (PBC) is a chronic disease of the liver typically encountered in middle-aged women; it is characterized by an inflammatory process affecting the intrahepatic bile ducts. This inflammation is accompanied by cholestasis and may eventually result in biliary cirrhosis and death of hepatic failure (1).

Like other cholestatic liver diseases, PBC may be complicated by metabolic bone disease. Both osteomalacia and osteopenia have been described in PBC (2–12). Nowadays, it is generally agreed that osteoporosis is the more common and clinically more important lesion in PBC. In patients with PBC, prevalence rates of osteoporosis, based on histological criteria, have been reported to vary from 0%–17% (8,10,11,13). The cause of osteoporosis in PBC is unknown.

Currently there is no effective treatment for PBC, and results with various immunosuppressive or antiinflammatory drugs have been disappointing (14). Especially in PBC, glucocorticoids are assumed to aggravate osteoporosis (1,15), but this has never been extensively studied.

The current study investigated the determinants of bone mineral density in 55 unselected female patients with PBC. Furthermore, we investigated whether glucocorticoids cause a further decrease of the bone mineral density in PBC, and if so, to what extent.

Materials and Methods

Patients

From 1973 to 1988, a diagnosis of PBC was made in our department in 102 patients (89 women). Fourteen patients (all women) were lost to follow-up and 22 (18 women) died. Of the 66 patients still followed up, 57 are women. Of these women, one was excluded because of severe polymyositis and consequent immobilization; the other was excluded

Abbreviations used in this paper: BMD, bone mineral density; DPA_{spine}, dual photon absorptiometry of the lumbar spine; Ha, hydroxyapatite; OH-prol, hydroxyproline; $1,25-(OH)_2D_3$, 1,25-dihydroxyvitamin D_3; $25-(OH)D_3$, 25-hydroxyvitamin D_3; PBC, primary biliary cirrhosis; PTH, parathyroid hormone; SPA_{dist}, single photon absorptiometry of the distal forearm; SPA_{prox}, single photon absorptiometry of the proximal forearm.

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because incomplete data were obtained. The remaining 55 patients (aged 39–75 years) were entered to the study. All patients' liver biopsy results were consistent with PBC, and all had positive tests for antimitochondrial antibodies. None of the patients had evidence of bone disease in their history or at physical examination. All patients received a diet containing at least 1.5 g of calcium daily, and vitamin D_3 (400 IU/day orally) was supplemented, when indicated by serum 25-hydroxyvitamin D_3 [25-(OH)D_3] levels (six patients). In principle, therefore, all patients may be considered to have had an adequate intake of calcium and vitamin D.

Thirty patients had been treated for their PBC with D-penicillamine, azathioprine, colchicine, cyclosporin A, prednisone, or combinations of these drugs. Of these patients, only five had been treated with azathioprine or cyclosporine A. Twenty-three patients had received glucocorticoids or were still treated with glucocorticoids. All patients were initially administered 30 mg of prednisone which was tapered off within 6 weeks to a maintenance dose of 10 mg. The mean duration of treatment was 6.3 years (range, 0.3–14.5 years). For the calculation of the cumulative glucocorticoid dose, one patient with chronic asthma was excluded because reliable data could not be obtained.

To determine the relationship between the histological stage of PBC [assessed according to Scheuer (16)] and parameters of bone metabolism and bone mineral density (BMD), the patients were divided into groups of early-stage (stage I and II, n = 30) or late-stage (stage III and IV, n = 25) disease (Table 1). Furthermore, the effects of treatment with glucocorticoids on the same parameters were studied, by subdividing the PBC patients in a group who used or had used glucocorticoids (n = 23) and a group who had never used this type of drug (n = 32) (Table 2). Informed consent was obtained from all participants.

Biochemistry

Serum concentrations of calcium, creatinine, inorganic phosphorus, bilirubin, and albumin were measured by standard methods. Serum calcium levels were corrected for the serum albumin concentration as described by Payne et al. (17). Urinary hydroxyproline (OH-prol) excretion was measured according to a previously described method (18). Serum 25-(OH)D_3 levels were measured by a competitive protein binding assay, whereas 1,25-dihydroxyvitamin D_3 [1,25-$(OH)_2D_3$], immunoreactive intact parathyroid hormone [PTH(1-84)] and osteocalcin were measured with commercially available kits (Incstar Corp., Stillwater, MN).

Assessment of Bone Mineral Mass

All patients were measured with photon absorptiometry, as described elsewhere (19). Peripheral bone measurements were carried out at the right forearm according to the method described by Nilas et al. (20), using a Nuclear Data

Table 1. Patient Characteristics, Bone Mineral Densities, and Biochemical Data According to the Classification Based on Histological Stage of the Liver Disease

	Early stages	Late stages	*P*	Normal values
No.	30	25		
Age (yr)	59.2 ± 7.6	56.1 ± 9.7	NS	
Height (*cm*)	162.6 ± 7.8	161.1 ± 5.7	NS	
Mean menopausal age[a]	48.3	50.2	NS	
Weight (*kg*)	68.1 ± 11.8	61.7 ± 7.6	<0.05	
Quetelet index (kg/cm^2)	25.7 ± 4.10	23.7 ± 3.1	NS	
Duration of PBC (yr)	8.2 ± 3.6	7.2 ± 2.9	NS	
Corticoids (*n*)	12	11		
Cumulative dose (*g*)	25.8 ± 25.5	22.8 ± 15.0	NS	
BMD[b]				
DPA_{spine} (%)	94.8 ± 14.7	85.4 ± 10.6		
SPA_{dist} (%)	96.1 ± 20.2	85.8 ± 17.5		
SPA_{prox} (%)	100.2 ± 17.2	91.5 ± 16.2		
Serum				
Bilirubin (*μmol/L*)	15 ± 17	34 ± 44	0.05	2–12
Calcium (*mmol/L*)[c]	2.35 ± 0.07	2.29 ± 0.15	0.002	2.20–2.65
Albumin (*g/L*)	42.6 ± 2.1	39.2 ± 6.2	NS	36–48
PTH (*pg/mL*)	19 ± 10	20 ± 10	NS	10–55
Osteocalcin (*ng/mL*)	3.5 ± 1.4	3.5 ± 1.6	NS	1.8–6.6
25-$(OH)D_3$ (*nmol/L*)	63.2 ± 46.3	70.9 ± 41.0	NS	>30
1,25-$(OH)_2D_3$ (*pmol/L*)	61.2 ± 18.9	59.3 ± 17.6	NS	40–101
Urine				
Calcium/creatinine (*mol/mol*)	0.30 ± 0.16	0.35 ± 0.22	NS	0.28 ± 0.06
OH-prol/creatinine (*mol/mol*)	0.02 ± 0.01	0.02 ± 0.009	NS	0.02 ± 0.005
TMP/GFR (*mmol/L*)	1.1 ± 0.2	1.1 ± 0.2	NS	0.81–1.35

NOTE. The values are expressed as mean ± SD. The cumulative dose of corticoids is expressed as prednisone equivalents.
[a]For both groups, the mean age at menopause was calculated.
[b]The BMDs are presented as percentages of age-matched control subjects.
[c]Corrected for serum albumin. For statistical evaluation, multiple linear regression analysis was used, as described in Materials and Methods.
GFR, glomerular filtration rate; TMP, maximal renal reabsorption of inorganic phosphate.

Table 2. Patient Characteristics, Bone Mineral Densities and Biochemical Data According to the Classification Based on Use of Glucocorticoids

	No steroids	Steroids	P
No.	32	23	
Age (yr)	59.2 ± 8.5	55.9 ± 8.7	NS
Mean menopausal age[a]	48.9	49.0	NS
Height (cm)	160 ± 6.1	163 ± 7.5	NS
Weight (kg)	64.7 ± 8.4	65.9 ± 13.4	NS
Quetelet index (kg/cm^2)	25.1 ± 3.1	24.5 ± 8.7	NS
Duration of PBC (yr)	6.9 ± 3.0	8.9 ± 3.5	NS
Early/late stage	19/13	11/12	
BMD[b]			
DPA_{spine} (%)	92.9 ± 15.5	87.5 ± 10.6	
SPA_{dist} (%)	95.5 ± 21.9	86.1 ± 14.9	
SPA_{prox} (%)	101.1 ± 18.8	90.0 ± 12.6	
Serum			
Bilirubin ($\mu mol/L$)	24 ± 40	23 ± 23	NS
Calcium ($mmol/L$)[c]	2.35 ± 0.16	2.34 ± 0.81	NS
Albumin (g/L)	40.9 ± 5.8	41.4 ± 2.6	NS
PTH (pg/mL)	23 ± 7	27 ± 12	NS
Osteocalcin (ng/mL)	3.7 ± 1.4	3.2 ± 1.5	NS
25-$(OH)D_3$ ($nmol/L$)	58.2 ± 21.3	78.0 ± 61.4	NS
1,25-$(OH)_2D_3$ ($pmol/L$)	61.9 ± 18.9	58.2 ± 17.8	NS
Urine			
Calcium/creatinine (mol/mol)	0.33 ± 0.20	0.32 ± 0.17	NS
OH-prol/creatinine (mol/mol)	0.02 ± 0.09	0.03 ± 0.01	NS
TMP/GFR ($mmol/L$)	1.1 ± 0.2	1.1 ± 0.2	NS

NOTE: The values are expressed as the mean ± SD.
[a]For both groups, the mean age at menopause was calculated.
[b]The BMDs are presented as percentages of age-matched control subjects.
[c]Corrected for serum albumin. For statistical evaluation, multiple linear regression analysis was used as described in Materials and Methods. For normal values, see Table 1.

(Hørsholm, Denmark) 1100a bone density scanner. Measurements were performed both distally (SPA_{dist}) and proximally (SPA_{prox}). With this technique, the bone measured distally consists of trabecular bone in a higher proportion than when measured proximally (21). The results are expressed as BMD in arbitrary units (U/cm^2). In our laboratory, the coefficient of variation, based on 50 duplicate measurements in normal subjects, is 1.9% for the distal site and 1.0% for the proximal site.

For the dual energy photon absorptiometric measurements of the lumbar spine (DPA_{spine}), L2-4 was the region of interest. Measurements were carried out with a Novo (Bagsvaerd, Denmark) BMC-lab 22a scanning device, as described by Krolner and Nielsen (22). Results were expressed as grams hydroxyapatite (Ha) per square centimeter (BMD). The coefficient of variation calculated on the basis of duplicate measurements of the lumbar BMD of 20 patients with osteoporosis in our laboratory is 2.3%.

Statistical Methods

Bone densitometric values of the PBC patients (n = 55) were compared with values obtained from a group of age-matched healthy subjects, randomly sampled from a reference group described previously (19). Differences were analyzed by Mann-Whitney's test.

Multiple linear regression analyses were performed to evaluate the dependency of the various densitometric values on age, histological stage of PBC, and the use of glucocorticoids. In this way, the influence of disease stage, glucocorticoids, and age, respectively, on bone mass was evaluated independently. Adding the variables (corrected) serum calcium and Quetelet index (or weight) in the regression model had no significant influence. The participants were classified to subgroups according to use of glucocorticoids and the histological stage. The Mann-Whitney test was used to compare the differences among the various parameters in the subgroups.

Results

All Patients

Mean BMDs at both the distal region of the forearm and in the lumbar spine were 8% lower in patients with PBC than in normal women of the same age ($P < 0.03$ and $P < 0.004$, respectively; Table 3). However, no significant difference was observed in the proximal forearm. In Figure 1*A-C*, the axial and peripheral BMD values of the patients are plotted against age. Although the mean DPA_{spine} and SPA_{dist} were significantly lower, most of the individual BMD values of the patients are within the normal range. For all biochemical parameters, no differences between the total PBC group and our reference values were found, including vitamin D metabolites, PTH, and osteocalcin.

Early and Late Stage

Using the criteria of Scheuer (16), the patients were subdivided in groups with early stages (I and II) and late stages of PBC (III and IV). With this approach, the only significant difference in clinical characteristics between these two groups was weight, which was lower in the late-stage group (Table 1). Late stage PBC appeared not to be associated with a longer duration of the liver disease. Of the biochemical parameters measured, only bilirubin was higher in the late-stage

Table 3. Bone Mineral Densities in Patients With PBC and Age-Matched Control Subjects

	DPA_{spine}	SPA_{dist}	SPA_{prox}
Control subjects (n = 55)	0.85 ± 0.14	0.97 ± 0.19	1.30 ± 0.25
PBC (n = 55)	0.78 ± 0.12	0.89 ± 0.20	1.24 ± 0.22
P value	<0.004	<0.03	0.18

NOTE. BMDs are expressed in grams hydroxyapatite or units per square centimeter ± SD (see Materials and Methods). The reference group is also described in the Materials and Methods section.

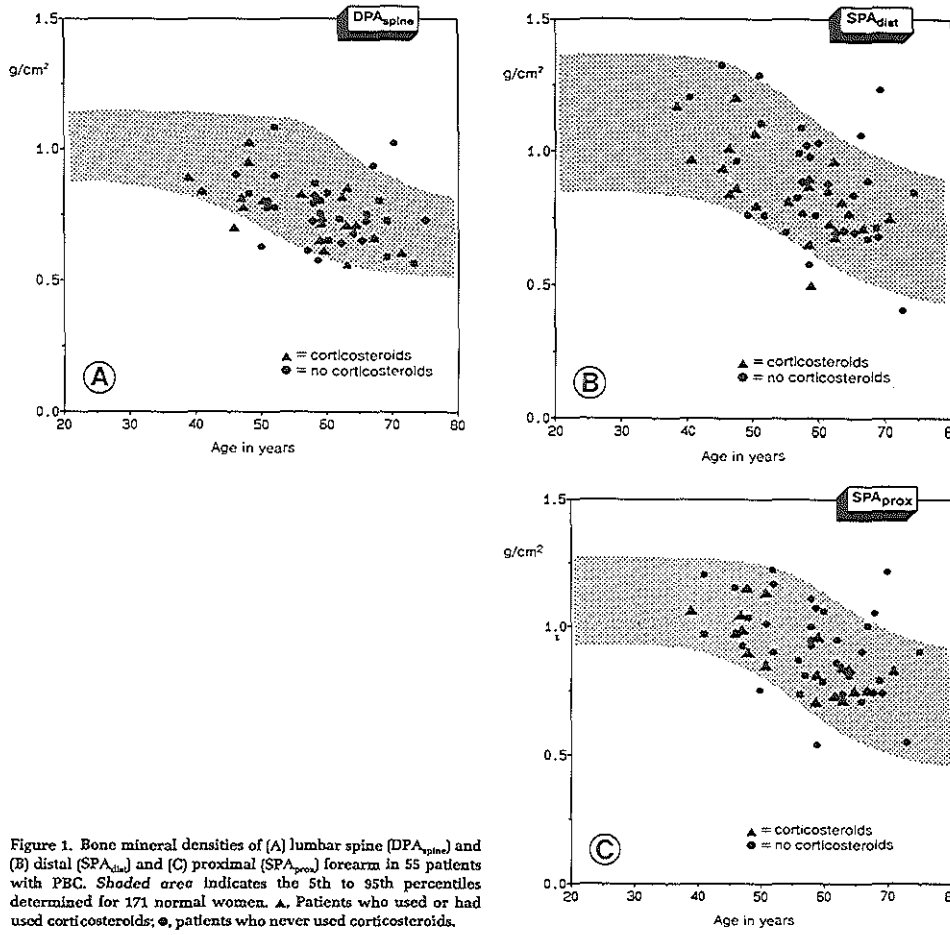

Figure 1. Bone mineral densities of (A) lumbar spine (DPA_{spine}) and (B) distal (SPA_{dist}) and (C) proximal (SPA_{prox}) forearm in 55 patients with PBC. *Shaded area* indicates the 5th to 95th percentiles determined for 171 normal women. ▲, Patients who used or had used corticosteroids; ●, patients who never used corticosteroids.

group, whereas on the other hand serum calcium and corrected calcium levels were significantly lower in this group (Table 1). Using the multiple regression method, we observed a tendency to lower age-corrected peripheral and axial BMD values in the late-stage group. However, this difference reached significance ($P < 0.002$) only for DPA_{spine}. Weight or Quetelet index could not be identified as independent determinants of BMD in these groups.

Glucocorticoids

The patients with PBC who used or had used glucocorticoids were also compared with those who had never used this type of drug. As shown in Table 1, no significant differences between both groups could be observed. Also, the cumulative dose of glucocorticoids was not correlated with the histological stage of PBC. Nevertheless, the steroid group tended to have lower age-corrected BMDs than the nonsteroid group. Multiple regression analysis indicated that for SPA_{prox} this trend just reached significance ($P = 0.05$).

Discussion

The results presented in this report confirm earlier reports that the peripheral BMD at the distal forearm is lower in female patients with PBC than in

age-matched control subjects (6,8). Furthermore, axial BMD, another parameter of trabecular bone mass, was also significantly lower in the patients with PBC. Only BMD measurements at the proximal forearm, largely reflecting cortical bone, did not show a significant difference with our reference group. Therefore, these results suggest a preferential loss of trabecular bone compared with cortical bone in PBC-related bone disease.

However, our findings are not in agreement with the severe form of bone loss as described by Hodgson et al. (10). These investigators reported that in approximately 50% of their patients with PBC, axial BMD values were even below the theoretical fracture threshold, whereas we found a mean reduction of BMD of only 8% both in the lumbar spine and distally in the forearm compared with the results in age-matched control subjects. This discrepancy may be explained by differences in the populations of patients studied and in the statistical methods used. For instance, Hodgson et al. used a linear relationship for the age-related axial bone loss in control subjects, whereas the current report used the more common nonlinear function with an accelerated bone loss around the menopause (Figure 1A–C and reference 19).

At the presentation of PBC, there is little evidence for metabolic bone disease (13); it remains to be seen whether early substitution with vitamin D and calcium, as applied in our patients, prevents bone loss. In this respect, the available data are not conclusive, because only the effect of relatively short-term treatment with vitamin D on bone loss has been reported (4,5).

The importance of the histological stage of PBC for bone mass is illustrated by the significant difference between the axial BMD of our early-stage and late-stage groups. To our knowledge, this is the first report of such a relationship. Another interesting observation in the current study was the slightly but significantly lower mean serum calcium level in patients with histological evidence of late-stage PBC. This was not accompanied by differences in the concentration of vitamin D metabolites or PTH. The latter observation might indicate a certain degree of hypoparathyroidism in this patient group, because the lower mean serum calcium level should have resulted in a higher mean PTH concentration. Also in other studies, normal or even subnormal serum immunoreactive PTH levels have been found (5,6).

Unfortunately, we had no opportunity to measure parameters of calcium absorption to investigate a possible relationship with serum calcium levels and bone mass. However, it has been reported that chronic intestinal calcium malabsorption seems to be implicated in the pathogenesis of bone loss in patients with PBC (6). Consequently, our findings could be a reflection of this phenomenon.

Several recent studies have shown that not osteomalacia, but osteoporosis in the most frequently found metabolic bone disease in patients with PBC (5–12). Furthermore, histological analyses of bone biopsies have shown impaired osteoblastic function with decreased bone formation (9,10). Although we have not performed bone biopsies, the slightly lowered serum osteocalcin levels in our PBC patients, as compared with reference values, do not indicate a severely impaired osteoblast function. This is in agreement with the very moderate lowering of bone mass in our patients.

The recently proposed hypothesis that toxic substances related to hepatic disease and cholestasis play a role in PBC-related bone disease remains attractive (10,12). For instance, copper and bile salts are known to have cytotoxic effects and are found in high concentrations in hepatocytes and other tissues of patients with PBC (10). In patients with Wilson's disease, copper may be implicated in the development of hypoparathyroidism (23). Toxic substances might not only interfere with osteoblast activity but might also depress parathyroid function (24,25).

Several investigators consider the use of glucocorticoids in the treatment of PBC disadvantageous because of the induced bone loss (1,15). However, our observations do not indicate a clinically important long-term influence of glucocorticoids, in the doses used, on bone mass or biochemical parameters of bone turnover. A recent study by Diamond et al. (12) of patients with hepatic osteodystrophy points in the same direction. An explanation for this finding could be that most of our patients were kept on a relatively low maintenance dose of prednisone (10 mg daily). We did not observe lower serum osteocalcin levels as others did in glucocorticoid-treated patients (26). However, we have to emphasize that not all patients in the steroid group were treated at the time of measurement. Because only a limited number of patients have been treated with azathioprine or cyclosporine A, it may be assumed that the potential negative effects of these substances on bone mass could not have influenced our overall results significantly.

In patients with rheumatoid arthritis, low-dose glucocorticoids also did not significantly diminish bone mineral content (27). Similar data were obtained by our group in patients with chronic obstructive lung disease (28). In this respect, the importance of the cumulative dose of corticoids has been stressed by Dykman et al. (29). Indeed, in our patients the mean cumulative dose was below the critical level (30 g equivalent of prednisone) indicated by these authors for the occurrence of fractures. Therefore, we believe that relatively low doses do not strongly accelerate the

progression of osteoporosis in patients with PBC. This conclusion may have relevance for future studies, because long-term prospective controlled trials of corticosteroids in PBC are lacking.

In conclusion, our study does not indicate the occurrence of a severe degree of bone loss in our patients with PBC, although we found a moderately lower BMD in patients with a late histological stage of PBC. Furthermore, the assumed deleterious effect of long-term (low-dose) glucocorticoids on BMD seemed to be minor in our patients. It remains to be determined whether the early substitution with vitamin D and calcium in our patients has had a beneficial effect. Finally, our data provide evidence for a lower serum calcium in the late-stage group. This phenomenon has to be studied in more detail, especially with regard to parathyroid function.

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CHAPTER 9

BONE LOSS IN PATIENTS WITH LOW MAINTENANCE GLUCOCORTICOID TREATMENT FOR CHRONIC OBSTRUCTIVE LUNG DISEASE. IS TREATMENT WITH 1α-HYDROXYVITAMIN D_3 INDICATED?

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9.1 Introduction

Chronic administration of glucocorticoids may induce bone loss and ultimately osteoporosis[1]. Despite the extensive use of glucocorticoids and occurrence of glucocorticoid-induced osteoporosis, little is known about the possible means to prevent this syndrome. Histological studies show decreased bone formation and increased bone resorption. This latter condition is probably due to an elevated parathyroid hormone (PTH) secretion[2,3,4] or activity[5]. The first may be secondary to a low calcium absorption[6] and increased renal loss of calcium[7]. The negative effect of glucocorticoids on intestinal calcium absorption can be counteracted to some extend by activated vitamin D[8,9,10]. It is, therefore, of clinical interest whether active vitamin D derivatives can decrease glucocorticoid induced bone loss. In a previous study we showed a positive effect of six months treatment with 2 ug 1α-hydroxyvitamin D_3 per day (1α-$(OH)D_3$) on the calcium absorption and on trabecular bone volume in bone biopsies taken from patients treated with glucocorticoids[10]. In the present study the long-term effect of a lower dose 1α-$(OH)D_3$ (1 ug/day) on the mineral bone mass was evaluated by photon absorptiometry of the lumbar spine and radius.

9.2 Patients and methods

After informed consent was obtained 30 asthmatic patients (26 males and 4 premenopausal females), who had received for more than 6 months and still received at least 7.5 mg prednisone per day entered the study and were followed during 2 years. The patients were matched according to age, sex, dose and duration of prednisone treatment. After matching, the patients were randomly divided and received either a placebo or a daily dose of 1 ug 1α-$(OH)D_3$ (double blind). Before treatment the average peripheral and axial bone mineral mass proved to be the same in both groups. Patients characteristics are given in Table I.

During the study period the prednisone dose was reduced in most patients, largely due to the increasing use of inhalation corticosteroids. This reduction resulted in a mean daily prednisone dose of 8.7 mg per day (range 5-15 mg per day).

Peripheral bone measurements were performed by single photon absorptiometry (SPA) at the right forearm using a Norland-Cameron bone density scanner. The radius at one third of the length from the distal end was transversely scanned. The results are expressed as Bone Mineral Content (BMC in U/cm)[11]. Axial bone mass was assessed by dual photon absorptiometry (Novo BMC-lab 22a) at the lumbar spine (DPA_{spine}) with L_2-L_4 as the region of interest[12]. The results are expressed in g Ha per region of interest. In our laboratory the coefficients of variation of SPA and DPA are 1 and 2.3%, respectively (the latter in osteoporotic patients).

Table I

Pre-treatment patient characteristics and prednisone dose during treatment.

	Placebo	$1\alpha(OH)D_3$
Age (years)	40±2.4	40±2.3
Height (cm)	175±1.7	173±2.5
Weight (kg)	78±2.7	76±3.6
Cumulative dose before study in g prednisone	10.5±2.0	9.5±1.6
Mean daily dose mg	8.7±2.8	8.7±2.3
Range in mg	5-15	5-12.5
BMC_{radius} (U/cm)	786±18	772±21
BMC_{spine} (gHa/L_2-L_4)	34.64±2.1	33.39±2.3

The data are expressed as means ± SD. There were no significant differences between the two groups. Mean daily dose and range expressed in mg prednisone per day during the study period.

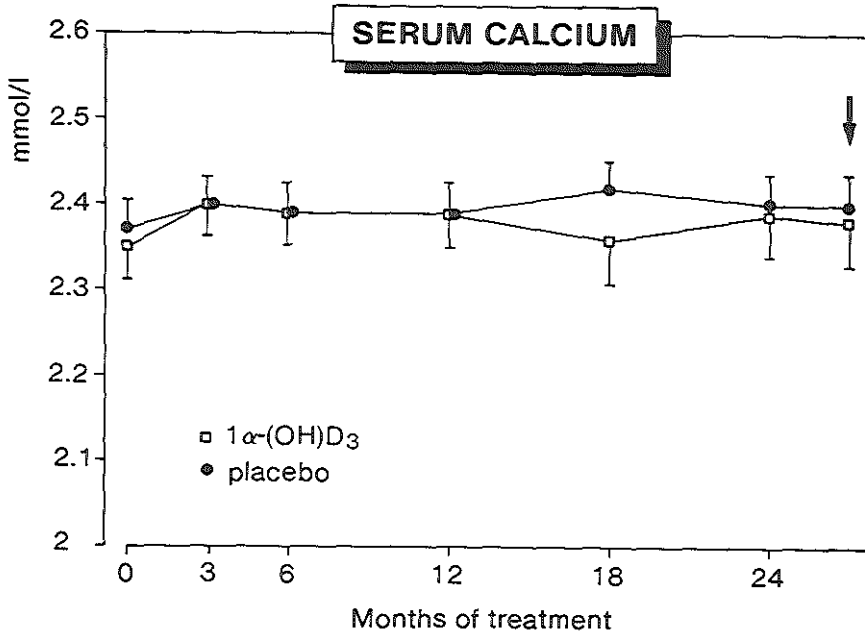


Fig. 1 Mean serum calcium values ± SD. The arrow indicates the value 3 months after discontuation of treatment.

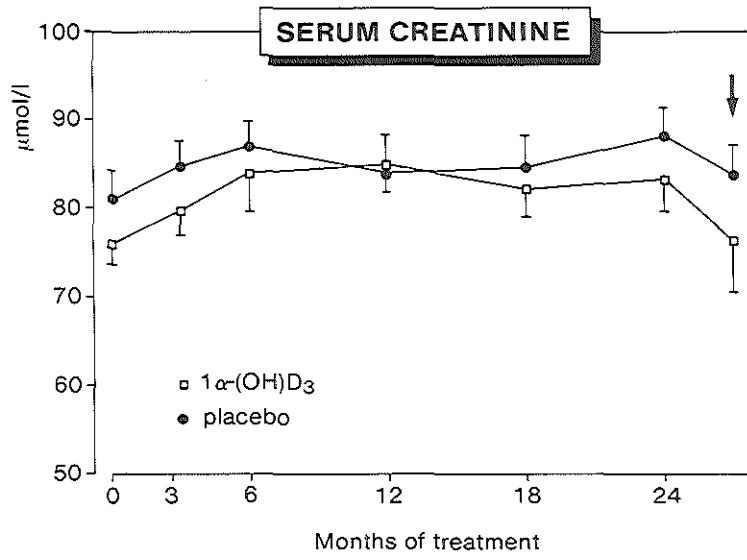


Fig. 2 Mean serum creatinine values ± SD. The arrow indicates the value 3 months after discontuation of treatment.

Table II

Results of bone mineral mass assessments and the maen daily dose of prednisone of both groups after treatment period.

	Placebo	1α(OH)D_3	p
BMC_{radius} (U/cm)	783±21 (-0.004%)	775±23 (+0.004%)	NS
BMC_{spine} (gHa/L_2-L_4)	33.68±2.4 (-2.6%)	32.49±2.4 (-2.7%)	NS

Mean values ± SD. Between paracenteses the percentile differences with the pretreatment values. None of the parameters showed a significant difference between the two groups.

Every three months serum calcium, creatinine, phosphate, albumin, alkaline phosphatase and 24 h urinary calcium and creatinine were determined. 24 H-urinary hydroxyproline was measured according to Goverde et al.[13]

Statistical analysis was done using the Wilcoxon matched-pairs signed-rank test, $p< 0.05$ being regarded as significant.

Results of the bone measurements were analyzed by linear regression. For each pair the difference of the slopes was tested by the Wilcoxon matched-pairs signed-rank test.

9.3 Results

The results of the biochemical determinants are calculated as the means for both groups and the results of the serum calcium and creatinine measurements are depicted in the figures 1-2. At zero time the pre-treatment results are given, while the last measurements were performed after the treatment was stopped for three months (indicated by an arrow). The other serum assessments showed no differences between the groups before, during or after treatment (data not shown). The 24-h urinary excretion of calcium and creatinine are presented as the ratio calcium/creatinine in figure 3.

Because the subjects were paired (placebo versus active treatment) the results of the bone mineral assessments are expressed as the difference between the regression coefficients of the pairs of patients (figures 4-5). The results of the axial measurements showed for 7 pairs a higher loss of bone mineral in the 1α-$(OH)D_3$ treated patients, while in the other 7 pairs the 1α-$(OH)D_3$ treated patients had lower bone loss or more bone gain than the placebo treated patients. These results differ not significantly. For the peripheral measurements the results were slightly better for the 1α-$(OH)D_3$ treated patients. 4 Pairs showed more loss or less gain in bone mineral in the 1α-$(OH)D_3$ treated patients. The other 10 pairs showed less bone loss or more bone gain for the 1α-$(OH)D_3$ treated patients. Also these differences were not statistically different.

Table II gives the overall results of the mean bone mineral assessments for both groups after treatment. There was only a very moderate bone loss of 1.3-1.4% per year for the axial measurements in both groups, while the peripheral measurements showed no bone loss or bone gain during the study period.

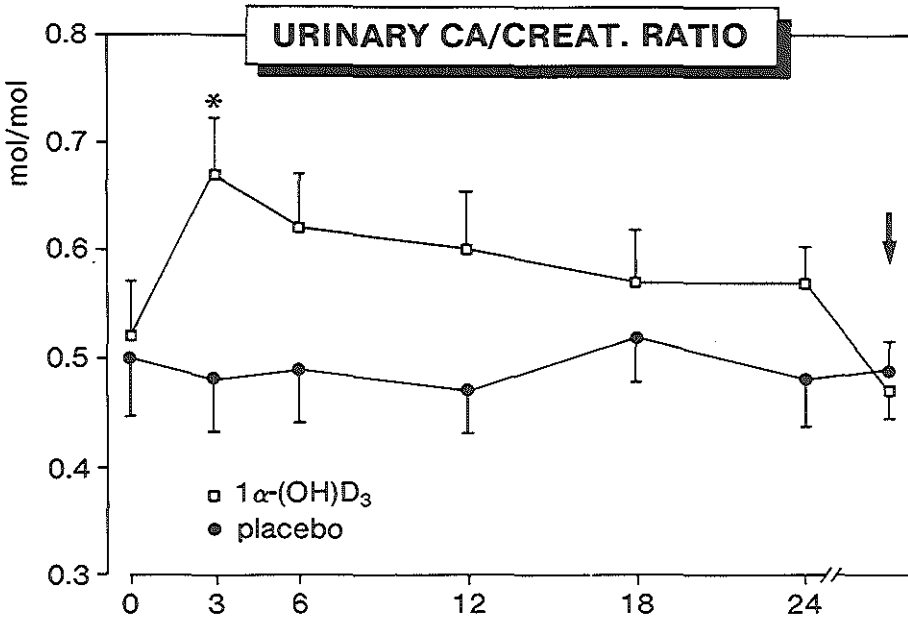


Fig. 3 Mean urinary calcium/creatinine ratio values ± SD. The arrow indicates the value 3 months after discontinuation of treatment.

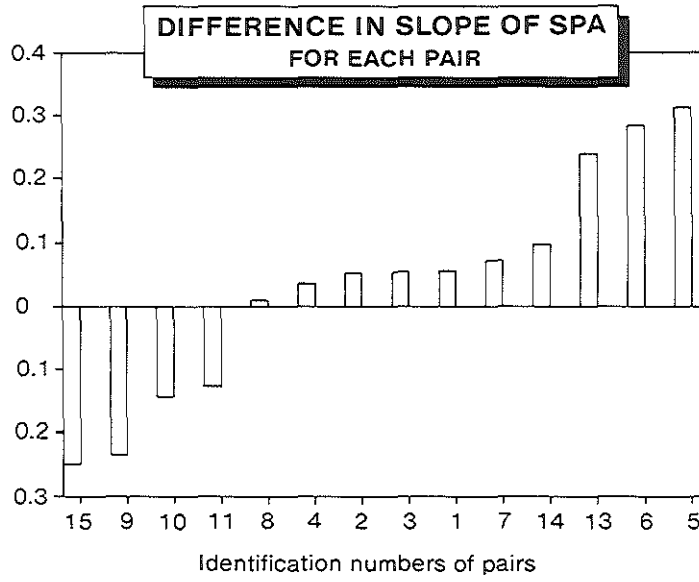
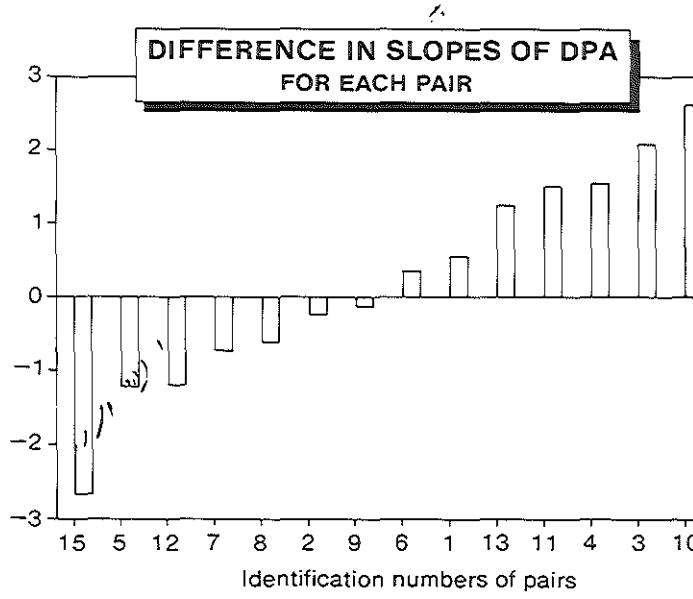


Fig. 4 and 5. Ranged histograms of the differences of the regression coefficients of SPA and DPA of the matched pairs. The identification numbers of the pairs are given on the horizontal axis.



9.4 Discussion

The results presented in this paper do not show a beneficial effect of treatment with 1 μg 1α-(OH)D_3 daily on both peripheral and axial bone mass in patients on maintenance therapy with glucocorticoids. However, it is important to emphasize that the bone loss was moderate. In the lumbar spine, only bone mass measurements showed a loss of 1,3-1,4% per year, while no loss was found in the appendicular skeleton. In other words it seems reasonable to suggest that a treatment a maintenance dose of prednisone of approximately 8.5 mg daily as used in our patients, do not induce an important loss of bone mass in the axial and appendicular skeleton. Recently we observed a similar phenomenon in patients with primary biliary cirrhosis kept on a low maintenance dose of prednisone[14]. Sambrook et al[15] also reported that low dose glucocorticoids do not significantly diminish bone mineral content in patients with rheumatoid arthritis, while in a longitudinal study Ruegsegger et al[16] only observed appendicular bone loss with the use of an average daily dose of 15 mg prednisone and over. In retrospect, taking these considerations into account, it is questionable whether one could expect a beneficial effect of treatment with 1α-(OH)D_3 in the patients included in this study. Of course this does not imply there is no favourable effect of active vitamin D in patients on higher maintenance doses of glucocorticoids. The results of the study of Braun et al[10] point in this direction.

During the 2 years follow up there were no periods of hypercalcemia nor indications for the induction of a decrease of renal function. Therefore, a daily dose of 1 microgram 1α-(OH)D_3 given for 2 years in these glucocorticoid treated patients seems to be save with regard to the occurrence of hypercalcemia and with regard to the renal function. As could be expected the average 24 hours urinary calcium/creatinine ratio in the 1α-(OH)D_3 treated patients exceeded the values in the placebo treated group, indicating the compliance of the patients. Only at three months the difference was significant. An interesting phenomenon is the gradual decline in the 24 hours urinary calcium/creatinine ratio, which might suggests that during treatment with 1α-(OH)D_3 some kind of adaptation of calcium homeostasis may occur. One may even speculate if adaptation of the dosage of 1α-(OH)D_3 during this study was warranted. Another explanation for the decline in calcium/creatinine ratio, might be a lower calcium intake by the patients on active treatment during the study period. In other longitudinal studies with vitamin D derivatives no such decline has been observed or reported[17,18].

We conclude that this dose of 1α-(OH)D_3 used appears not to have a prominent role in the prevention of glucocorticoid-induced mineral bone loss, when the daily maintenance dose of prednisone does not exceed 7.5 mg per day. This does not imply that a higher dose of 1α-(OH)D_3

(e.g. 2 ug/day) is not beneficial in patients using higher doses of prednisone[10]. However, these last results were obtained during a shorter period of treatment. It is important that maintenance treatment with prednisone in an average daily dose of between 7.5 and 10 mg may be of only limited harm to the bone (mineral) mass.

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CHAPTER 10

PREDICTION OF FUTURE FRACTURES AND SCREENING FOR OSTEOPOROSIS

10.1 Introduction

The increasing availability of effective preventive strategies for osteoporosis have raised the issue whether women should routinely have some kind of assessment in order to identify those at risk for osteoporotic fractures. There exists a reluctance on the part of physicians and the general public to implement a prophylactic program (e.g. calcium supplements, estrogen replacement therapy) on a widespread basis without making some attempt to identify those subjects who are at greatest risk for osteoporotic fractures and thereby will benefit most from treatment. There are several methods to assess putative risk factors, but the most appropriate experimental design is a prospective study in which the risk factors are identified and subsequently related to the occurrence of osteoporotic fractures. Or better: the end-point should include some kind of estimation of quality of life (as related to the incidence of fractures). One of the models to assess risk factors is the logistic regression analysis. With this procedure it is possible to investigate independently the influence of various variables like life-style, dietary factors, biochemical parameters and bone mineral mass assessments. Adjustments for potential confounders can be made (e.g. age). By comparing cases to controls one can calculate the fracture risk for each variable measured. This is mostly done by the method of the odds ratio (OR), which represents the odds (probability) of a fracture at one level of exposure (e.g. one SD below the mean) divided by the odds at another exposure level (e.g. one SD above the mean). This implies that an OR of 1.0 indicates that there is no correlation of a variable with the outcome (i.c. the occurrence of fractures), while an OR of 5.0 for a difference in BMC of 2 SD indicates that there is a fivefold increase in risk for fractures.

The first studies dealing with fracture risks were cross-sectional, case-controlled and/or of a too limited size to investigate risk factors independently. During the last five years however, several prospective studies have been published. In this chapter a survey is made of the usefulness of markers or determinants with regard to the prediction of osteoporotic fractures in the individual. Furthermore, several aspects of screening for osteoporosis will be discussed and recommendations will be put forward with regard to possible future screening programs.

10.2 Prediction of osteoporotic fractures.

Factors influencing and determining bone mineral mass and bone strength are discussed in section 3.7. Naturally, these variables are taken into account in putative risk profiles. We can divide those variables into 5 groups:

1) Clinical history.
2) Anthropometric measurements.
3) Biochemical measurements.
4) Bone mineral mineral mass or density assessments.
5) Prevalence of osteoporotic fractures.

These five groups are discussed in further detail in the next paragraphs. Because clinical history and anthropometric data are mostly studied in combination they will not be discussed separately.

10.2.1 Clinical history and anthropometric data

A screening test should be simple, reasonably inexpensive, safe and acceptable to the general public. This is all true for the clinical history and the measurements of height and weight. But most important, a test for screening must have adequate predictive value, in other words predict future fractures. This has been investigated for the clinical history by several authors. Kleerekoper et al showed, in a retrospective study of 663 postmenopausal women, that in comparison with women without fractures, osteoporotic women reported a higher prevalence of a positive family history of osteoporosis and had fewer children, but no differences were observed with regard to cigarette smoking, alcohol consumption, exercise habits, menstrual or menopausal history, dietary intake of milk or calcium[1]. They concluded that an assessment of the risk of osteoporosis cannot be based with sufficient sensitivity on the risk factors studied. This was confirmed by van Hemert et al[2] in a prospective study of 742 women with one follow-up assessment after 9-years. They studied 12 historical, anthropometric and radiological risk factors and none were found to be strong indicators of future fractures. Even for the upper risk score quintile (the risk score being composed of up to 5 selected variables) turned out to have a low sensitivity (0.48) and specificity (0.84) as to the prediction of osteoporotic fractures.

In the studies mentioned above, the possible risk factors studied are related to the prevalence or incidence of fractures. An other approach to investigate risk profiles is based on the association of various putative risk factors (independent or combined) with bone mineral mass, under the assumption that bone mineral mass is strongly negatively correlated with the development

of osteoporotic fractures. In a group of 286 normal perimenopausal women it has cross-sectionally been investigated whether clinically available data (body mass index, reproductive history, menopausal status, calcium intake, physical activity and smoking) could provide an adequate risk profile for low bone mineral mass[3]. No reliable predictions for spinal bone mass could be made. Additional information of the same type has been obtained by others[4 5].

The value of anthropometrics (weight, height, skinfold, calfcircumference and biacromal width) as determinants of bone mass has also been studied[6]. The results suggest that frame size, muscularity and adiposity have independent positive effects on bone mineral mass, but the associations were too weak to predict bone mass for individuals. Several investigators have addressed smoking as a risk factor for low bone mineral mass: some found no correlations[7 8], others reported a negative effect of smoking on bone mineral mass in elderly men and women[9], or a negative effect on endogenous estrogen levels and thereby on bone mass[10]. Physical exercise as a determinant of bone mass has been studied extensively[11 12 13 14 15]. Although bone mineral mass is undoubtly correlated to physical exercise, future fractures cannot be predicted by (the lack of) physical exercise.

Unfortunally, one has to conclude that on the basis of clinical history and anthropometric data no sufficiently sensitive and specific risk factor status to select women for fracture prevention programs can be determined.

10.2.2 Biochemical measurements

There are several biochemical markers of bone turnover. Both osteoblasts and osteoclasts produce bone specific proteins which can be measured in the blood. These cells are also responsible for neosynthesized constituents or fragments of bone matrix which escape into the circulation. These substances can be measured in blood or urine. Markers of bone formation or osteoblastic activity are: alkaline phosphatase, serum osteocalcin (also called bone gla-protein) and the serum level of type I collagen propeptides. Markers of bone resorption include urinary hydroxyproline, plasma tartrate-resistant acid phosphatase, serum free gamma carboxyglutamic acid and urinary desoxypyridinoline. These biochemical markers are used in studies of metabolic bone diseases and proved to be useful in the follow-up of patients and in monitoring the effect of treatment. It has been suggested by the group of Christiansen that postmenopausal osteoporosis is correlated to several of these biochemical markers[16].

It is possible that the rate of bone loss in women with a low peak bone mineral mass is much lower than that in women with a high peak bone (mineral) mass. In this connection, it is of importance to quantify the rate of bone loss by multiple bone mineral measurements over a certain period of time. Based on densitometric results obtained at the forearm "slow and fast-losers" have been discerned by Christiansen et al[17]. They found that with the results of biochemical

measurements "slow and fast-losers" could be identified in approximately 80% of the cases. In another study the same group presented data about prediction of postmenopausal bone loss by measurements of four parameters: serum alkaline phosphatase, osteocalcin, fasting urinary calcium and hydroxyproline[18]. At present these findings are not confirmed by others[5]. Moreover, the rate of bone loss differs between the peripheral and axial measurements sites[19 20 21]. Therefore, it is possible that a subject can be a "fast loser" at one skeletal site, while being a "slow loser" at another. Furthermore, Hui et al. demonstrated that, because of biological variability in long-term rates of bone loss, it was difficult or even impossible to identify long-term "fast losers"[22].

At present, no reliable distinction between individuals with high or low bone (mineral) mass can be made by measuring biochemical markers of bone turnover.

10.2.3 Bone mineral mass or density measurements

Because there exists a strong positive correlation between BMD and bone strength[23 24], one would expect that the results of bone mineral mass or density measurements strongly predict bone fractures. In this paragraph an overview will be given how the relationship between bone mass data and future fractures have been explored.

As is described in paragraph 3.6 it appeared to be impossible, in the individual, to predict BMD of the lumbar vertebrae or the hip from information obtained at other skeletal sites. Consequently, the next step was to study whether one could predict (already existing) osteoporosis (fractures) on the basis of densitometric measurements at the various fracture regions[25 26 27] (see also Chapter 6). Cross-sectional studies have reported a positive correlation between low BMC and osteoporotic fractures[28 29]. Although the differences were small, vertebral BMD was more reduced than forearm BMD in the case of vertebral fractures and forearm BMD was more reduced than spinal BMD in peripheral fracture cases[30]. On a group basis the results were encouraging, but for the individual the results of these investigations were disappointing: no reliable information was obtained by peripheral and/or axial measurements on the degree of spinal osteopenia or the presence of fractures. However, the usefulness of a risk factor (in this case bone mineral mass or density) is not so much determined by how well it can diagnose existing disease (fractures), but rather how well it can predict future fractures. This cannot be demonstrated with a cross-sectional study design and several longitudinal studies addressing this issues have been published and will be discussed later on.

It seems reasonable to assume that a middle-aged woman or man with a low bone mineral mass, will bear a greater risk of sustaining osteoporotic fractures than a woman or man of the same age with a high-normal bone mineral mass. The best way to test this assumption is to monitor

(without selection) a cohort of women (or men) for a reasonably long period of time, perform at the outset of the study non-invasive measurements of bone mass at peripheral and/or axial sites in the skeleton and subsequently diagnose and quantify all fracture events. Using the distal and proximal forearm site for bone mineral density measurements it was found that in subjects aged 50-69 years the risk of a fracture (spinal or other) was over 10-16 years 3 to 6 times higher in the lowest BMC decile than in the highest decile[31].

In another prospective study it was shown that even a measurement site in the skeleton which is not prone to osteoporotic fractures (the calcaneus) can predict osteoporotic fractures elsewhere in the skeleton[32]. In this latter study a sevenfold greater probability of spinal fracture was observed in women at or below -1 SD from the mean at that age for calcaneus BMC than in women at or above +1 SD. Another prospective study using forearm densitometry demonstrated an increase of the fracture risk ratio of nonspinal fractures of 2.2 for each SD below the mean[33].

An interesting review has been published by Ross et al[34]. They analyzed 27 cross-sectional and 7 longitudinal studies on bone mass and fracture risk. The data were, if possible, recalculated to evaluate the relationship between bone mass and fractures by a logistic regression procedure. Finally, the authors selected 4 prospective studies in which valid data have been provided to calculate the risk of fractures expressed as the odds ratio. The odds ratio (OR) for a 2 SD difference in BMC (for 1 decade) appeared to be 2-4 for nonspinal fractures, and 4-8 for spinal fractures, varying somewhat as to the site of measurement. Most of these longitudinal studies lasted for an average of up to 10 years and the measurement devices have been highly improved during that period, e.g. it became possible to measure selectively cortical or cancellous bone and at sites prone to fractures. It may be expected that by using these newer techniques and methods a better fracture prediction may be possible.

Based on these data, it seems reasonable to advise that if there is already a low bone mineral mass (e.g. 1 SD below normal) and a suspicion of a high rate of bone loss (e.g. because of immobilization, the use of glucocorticoids etc.) prophylactic (therapeutic) measures should be started.

10.2.4 Prevalence of osteoporotic fractures.

Non-traumatic wrist, hip and vertebral fractures are called osteoporotic and having such a fracture will label a subject (by definition) as osteoporotic (specific processes like tumour metastasis being excluded). Hence, it is not surprising that such an individual is prone to future fractures. In one study it was shown that the prevalence of one of these osteoporotic fractures was a strong predictor of future osteoporotic fractures[35]. This observation, of course, can not be used for screening purposes but it underlines the necessity of therapy aimed at improvement of bone mass and quality in order to prevent future fractures.

10.2.5 Conclusion

Current evidence suggests that bone mineral mass measurement is the most reliable method to predict future fractures, while several studies have shown that no item from an individual subject's history, physical examination or biochemical assessment is sensitive enough to predict fractures.

10.3. Screening for osteoporosis.

10.3.1 Introduction

The purpose of screening is to select individuals with low bone mass and, subsequently, to treat them in order to prevent future osteoporotic fractures. This chain of events raises the following questions: Which bone mineral mass or density measurements is suitable for screening the general population? Is treatment effective, and acceptable to most individuals? Is screening and the subsequent treatment cost-effective?

10.3.2 Which bone mass measurement device is suitable for screening?

Photon absorptiometry and (conditionally) DEXA have a good accuracy and precision and thus are adequate to select women with a low bone mineral mass (see Table 1., chapter 2). Single energy QCT has a lower accuracy than absorptiometry and because of the higher radiation exposure and the higher costs, QCT appears not to be suitable for general screening purposes. Photon absorptiometry and DEXA are relatively easy to perform, have low costs and a low radiation exposure. One single measurement at a peripheral or axial skeletal site (for instance performed perimenopausally) can predict future fractures at other sites. Especially with axial measurements (for example DEXA as a successor to DPA) better results as to predictability of osteoporotic fractures may be expected. Although different OR's are reported for the various measurement sites and osteoporotic fractures, at present no single measurement site appeared to be significantly better than the others in predicting future fractures[36]. SPA and (probably) DEXA are the methods of choice for screening. Based on present data no definitive choice can be made between SPA and DEXA, although it might be expected that, because of its better precision and lower radiation dose (as compared to DPA) DEXA will be the best candidate for screening the general population.

10.3.3 Treatment and the fracture risk

Many case control studies have indicated the protective role of the postmenopausal use of estrogen[37 38 39 40]. Controlled prospective studies, that have shown the same, have mainly been carried out in normal postmenopausal women[41 42 43]. In a cohort study a distinct reduction of the incidence of vertebral fractures in postmenopausal osteoporosis have been observed[44]. However, no long-term large scale prospective controlled studies have been published in which peri-or postmenopausal women with low bone mass (selected by screening from the general population) or with postmenopausal osteoporosis are treated with hormonal replacement therapy (HRT) and monitored for side effects and fracture incidence. It seems quite logical to start HRT directly after the menses cease, because most of the total bone loss occurs in the early postmenopausal years[45]. No data exist about the optimal duration of this therapy. Even in elderly postmenopausal women (up to the age of 74 years) estrogens may be protective[40]. When estrogens were stopped after the age of 65 years bone was (at the forearm) lost more rapidly than women of similar age who had never taken estrogens[43]. In other words the early postmenopausal bone loss appeared to have been postponed. Based on the prevention of bone loss one can recommend a life long duration for estrogen or hormonal replacement therapy, started as soon as possible after menopause. However, the optimal duration of HRT is not determined by its effects on bone alone. The long-term use of estrogen must also be considered in the light of a possible reduction of the risk of atherosclerotic cardiovascular disease[46] and the possible increased risk of breast cancer[47 48]. The combined use of estrogen and progestagen in women with an uterus will not lead to an increased risk of endometrial cancer[49]. It is more likely that other aspects (side effects and the outcome of cost-benefit analyses) will be of importance in determining the optimal duration of this kind of therapy. Until these data become available, it seems to be reasonable to use this preventive treatment at least for 10 years[50].

In established osteoporosis several other therapeutics have been investigated and have been shown to reduce fracture incidence (bisphosphonates[51 52] and vitamin D derivatives[53]). Although (long-term) fluoride therapy in the usual therapeutic doses will increase axial bone mineral mass[54 55], the effect on fracture incidence is disappointing[55]. It has been demonstrated that intranasal calcitonin can counteract early postmenopausal bone loss[56], but there is no information on the prevention of fractures by calcitonin. The effectiveness and safety of these therapeutics are not as well documented as the effectiveness of estrogens. Therefore, these therapies cannot as yet be recommended for preventive treatment in normal women who are selected by screening as to low bone mass.

10.3.4 Is therapy safe and will women accept preventive treatment?

This is a difficult issue. Estrogen therapy has beneficial effects on bone mass and (if not combined with a progestagen) also on atherosclerotic cardiovascular disease[46 57]. To protect the endometrium against the induction of hyperplasia and carcinoma HRT has to consist of a combination of (continuous) estrogen and cyclical progestagen. When the uterus is still present HRT will inevitably result in vaginal bleeding. This is a major drawback of this kind of hormonal treatment and will result a high percentage of subjects ceasing to take it. There exists controversy about the increased risk of breast cancer from HRT. The answer to the question whether estrogens or HRT increase the risk of breast cancer has been difficult to obtain. Large epidemiological studies suggest that estrogens enhance the risk for breast cancer[58]. In a recent study, already after six years of follow-up an increased risk of breast cancer with the postmenopausal use of oestradiol was demonstrated[59]. In contrast, from other studies a reduction of the risk of breast cancer by HRT[60 61] has been reported. Recently, it has been shown by combining the results from multiple studies that menopausal therapy consisting of 0.625 mg/d or less of conjugated estrogens does not increase breast cancer risk[62].
Although the relation between HRT and the increased risk of breast cancer is delicate, there is no conclusive evidence that the relative risk of breast cancer outweighs the benefits of HRT in postmenopausal women.

Acceptance of a preventive treatment with regard to osteoporosis might be better if a woman is well informed on the fracture risk she bears. This might be achieved by a bone mass measurement. The knowledge of a low bone mass and consequently a higher fracture risk for an individual may outweigh the negative aspects of HRT.

10.3.5 Screening, treatment and cost-effectiveness

This is of interest only if the answers to the other questions are favourable. Indeed, screening is possible and at least one effective preventive treatment (estrogens) is available for women with low bone mass. However, it is not known how well this therapy will be accepted in the general population.
Ross et al. calculated a reduction of osteoporotic fractures by 33% if the women with the lowest 47% of bone mass were selectively treated with an agent that is assumed to slow the rate of loss of bone by 50%[63]. In an early study (without bone mass measurements) it was concluded that the cost for each quality-adjusted year of life gained was comparable to the benefits of treating hypertension[64]. Tosteson and colleagues[65], have calculated that performing a single measurement of

bone density of the hip in perimenopausal women who did not have a hysterectomy, and prescribing a combination of estrogen and progestagen to those whose bone density is low, would -depending on BMD cut-off points at 0.9 or 1.0 g/cm^2- cost $12000 to $22000 per quality adjusted year of life saved by prevention of deaths from hip fracture.

All these estimates are aimed at estrogen use and osteoporosis, but in postmenopausal women there are also beneficial effects of estrogen if not combined with progestagen on atherosclerotic cardiovascular disease. These positive effects are much more important with respect to years of life gained and may outweigh the possible negative aspects of this preventive strategy. For these reasons it is mandatory to evaluate all the positive and negative effects of estrogens in the chain of screening and subsequent treatment in the case of low bone mass. The overall financial impact of starting HRT based on perimenopausal bone mineral mass measurements remains an issue not yet settled.

10.4 Final conclusions

The various determinants of bone mineral mass and putative risk factors for osteoporotic fractures are of no predictive value. Only the results of bone mass measurement can predict future fractures to some extent, and of the various measurements available only SPA and DEXA are suitable for screening the general population. Generally, early postmenopausal women (for screening purposes simplified to: women at the age of 50) will start to lose bone at a considerably higher rate than premenopausal women do. These women will therefore benefit most of bone sparing preventive interventions. For this reason screening would probably be best performed around this age. However, no consensus has yet been reached on specific screening programs in the general population[66]. Only a well designed screening program and treatment protocol will give information about the effectiveness of fracture prevention and improvement of the quality of life.

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CHAPTER 11

SUMMARY

Summary

It has now became possible to measure the bone mineral content in the axial as well as the peripheral skeleton. Moreover, with the use of computed tomography a selective assessment can be made of cancellous (trabecular) versus cortical bone mineral density. These technical achievements have led to a better understanding of the pathophysiology of osteoporosis and provided information on the effects of therapeutic interventions. Despite these sophisticated methods for bone mineral assessment the diagnosis of osteoporosis remains based on the occurrence of non-traumatic fractures and for that purpose an ordinary X-ray will be sufficient.

For investigational use several non-invasive methods for measuring bone mineral mass have been developed, although only photonabsorptiometry (Single and Dual energy: SPA and DPA, respectively) and Quantitative Computed Tomography (QCT) are operational in large scale clinical practice. The advantages of photonabsorptiometry and the more recently developed Dual Energy X-ray Absorptiometry (DEXA) over QCT are the lower radiation exposure, lower costs, better accuracy and precision and easier operation. The great advantage of QCT is the unique possibility to measure cancellous and cortical bone separately.

With these non-invasive methods of bone mineral assessment is has been shown that women will lose during their lifes about 35 percent of their cortical and about 50 percent of their cancellous bone. We studied this pattern of age-related bone loss cross-sectionally in 171 healthy Dutch women and observed an accelerated bone loss around the menopause at all measurement sites (see Chapter 5). Further analyses showed that the onset of cortical bone loss as measured by SPA occurs on the average at least a decade later than the onset of cancellous bone loss which already manifests itself before the menopause. This pattern of cancellous and cortical bone loss during aging shows a parrallelism with the observed patterns of incidence of age-related fractures. The incidence of Colles fractures in women rises soon after the menopause and a plateau is reached around the age of 65. This type of fracture (distal forearm) occurs at a site containing a relatively high proportion of cancellous bone. On the other hand, the incidence of hip fractures increases slowly with age, which rise accelerates late in life in both men and women. This type of fracture characteristically is one of cortical bone. Somewhere between these two types of fractures the vertebral compression fractures take position. They occur soon after the menopause and the incidence apppears to rise over the two decades after menopause. The vertebral body contains about equal amounts of cancellous and cortical bone.

An important issue about the relationship between bone mineral mass and fractures is the "quality versus quantity" concept. The importance of this concept is already demonstrated by the fact that individuals with a bone mineral mass or density within the normal range may have typical osteoporotic fractures, while on the contrary individuals with a low bone mineral mass may sustain no fracture at all. These observations (among other evidence) have led to the hypothesis of a three-dimensional fracture space with bone mineral mass, loss of bone connectivity and fatigue damage as important determinants of fracture (Chapter 3).

The treatment (or secundary prevention) of osteoporosis is reviewed in Chapter 4. Treatment is based on modulation of one of two aspects of bone remodelling: increasing bone formation and decreasing bone resorption. In practice there are at the moment only two therapeutics available which may increase bone formation: fluoride and possibly anabolic steroids.

The role of calcitonin and bisphosphonates as inhibitors of bone resorption in the treatment

of osteoporosis has to be investigated further, but these agents appear to be useful tools in future treatment regimes.

For both normal or osteoporotic postmenopausal women oestrogens are beneficial in maintaining bone mass and in reducing fracture rate. Besides positive effects on bone, the long-term use of oestrogen must also be considered in the light of a possible reduction in the risk of cardiovascular disease and with regard to a possible increased risk of breast cancer. For women with a uterus, the combined use of oestrogen and progestagen will not lead to an increassed risk for endometrial cancer.

In Chapter 7, we report on the hormonal determinants of bone mineral density in elderly postmenopausal women. A positive correlation between (endogenous) serum estrone and bone mineral mass was observed. We found a significant negative correlation (by linear trend) between the level of Sex Hormone Binding Globulin (SHBG) in the serum and bone mineral density. However, correction for the difference in body mass index (BMI) led to the loss of differences in BMD between all groups. It was concluded that in elderly postmenopausal women BMI is a main determinant of bone mass.

Because of its complexity the pathophysiology of glucocorticosteroid induced bone loss is not well understood, although it is assumed that stimulation of bone resorption has a prominant role in the process. In Chapter 9, we report a longitudinal double-blind placebo controlled trial of the effect of 1α-(OH) vitamin D_3 over two years on bone los in glucocorticoid treated patients with chronic obstructive lung disease. No beneficial effect could be observed, but it was concluded that in the placebo-treated patients the average axial (lumbar vertebral) bone loss during treatment with an average daily dose of 8.7 mg prednisone was only about 1.3% yearly, while in the same group over two years no loss of bone mineral was found at the forearm. In a cross-sectional study in patients with Primary Biliary Cirrhosis (PBC) (Chapter 8) we found only a moderate and not significant decrease in axial and peripheral bone mass in the patients who had used or were still using glucocorticoids as compared to those who never had been treated with glucocorticoids. These data are comparable with the results obtained in our asthmatic patients and support the view that relatively low doses of glucocorticoids (7.5-10 mg prednisone daily) on the long run have at most only a moderately negative influence on bone mineral mass.

Another observation made in the patients with PBC is the negative influence of the histological stage of the liver disease on bone mineral mass. Furthermore the patients with the more severe histological grades of PBC and the lowest bone mineral mass had also a significantly lower serum calcium level. The lower serum calcium was not accompanied by a higher serum immunoreactive parathyroid hormone (iPTH), which suggests an impairment in the PTH production or secretion in these patients.

One of the most interesting questions in the management of osteoporosis is: will it be possible to predict future fractures? This issue is discussed in detail in Chapter 10. We could not discriminate between a group of patients with postmenopausal osteoporosis and a group of healthy postmenopausal women of the same calender and postmenopausal age with various types of peripheral and axial measurement of bone mineral mass or density (Chapter 6). These results appeared to lead to the conclusion that it would be impossible to predict future fractures by bone mineral mass or density measurements. From 1986 onwards, however, several prospective studies have been published which showed a relationship between a low initial bone mineral density at a certain skeletal site measured by photon absorptiometry and a high relative risk of osteoporotic fractures. This relationship between low bone mineral mass and a subsequent high fracture incidence appears

to be strong enough for screening purposes in the general population. Therefore, despite the low correlation coefficients between the results obtained at the various measurement sites and despite the considerable overlap between the results of measurements in normals and osteoporotics there is evidence that the result of one single bone mineral mass measurement (preferably with SPA or DEXA) may indeed predict to some extent future fracture risk.

It is concluded that non-invasive bone mineral measurements have been most helpful in elucidating the course of the natural occurring bone (mineral) loss during life. In controlled investigations these measurement techniques made it possible to study bone mineral loss and gain under various pathologic conditions and during therapeutic interventions.

Samenvatting

De laatste 20 jaar is het mogelijk om de minerale botmassa zowel in het perifere skelet als in het axiale skelet op niet-invasieve wijze te meten. Met de komst van de "computed tomography" is nu ook zeer selectief het trabeculaire en het corticale bot te meten. Deze nieuwe technieken hebben geleid tot een gedetailleerd inzicht in de pathofysiologie van osteoporose en in de resultaten van diverse therapieën voor osteoporose. Echter, de diagnose osteoporose wordt nog steeds gesteld door het aantonen van fracturen door middel van een gewone röntgenfoto.

Voor wetenschappelijk onderzoek zijn verscheidene niet-invasieve methoden om de minerale botmassa te meten ontwikkeld, alleen fotonabsorptiometrie (Single en Dual energy: SPA en DPA) en Quantitative Computed Tomography (QCT) worden gebruikt voor de dagelijkse patiëntenzorg. Het voordeel van fotonabsorptiometrie (en de recent ontwikkelde methode Röntgen absorptiometrie DEXA) boven QCT zijn de lagere radiatie dosis, de geringere kosten, de betere nauwkeurigheid (accuracy) en reproduceerbaarheid (precision). Voorts is de meetmethode van QCT ingewikkelder. Het grote voordeel van QCT is daarentegen, dat alleen deze techniek zowel trabeculair als corticaal bot onafhankelijk van elkaar kan kwantificeren!

Met bovenstaande technieken is veel onderzoek gedaan naar het normale (fysiologische) botverlies bij vrouwen. Zo is aangetoond dat vrouwen gedurende hun leven gemiddeld 35% corticaal en 50% trabeculair bot verliezen. Wij bestudeerden in een transversaal onderzoek bij 171 gezonde vrouwen het verlies van bot op diverse plaatsen in het skelet (zie hoofdstuk 5), en vonden een versneld botverlies rond de menopauze terwijl het verlies van corticaal bot een decade later optrad dan het trabeculaire. Het trabeculaire botverlies lijkt reeds voor de menopauze te beginnen. Dit patroon van botverlies vertoond interessante overeenkomsten met de incidentie van de verschillende osteoporotische fracturen. De incidentie van Colles-fracturen bij vrouwen stijgt direct na de menopauze totdat een plateau rond het 65ste jaar wordt bereikt. Deze fracturen van de onderarm ontstaan op een plaats die relatief veel trabeculair bot bevat. Dit is in tegenstelling met de incidentie van heupfracturen die geleidelijk aan toeneemt met het ouder worden en vooral sterk toeneemt na het 70ste jaar. Dit type fractuur is typisch voor corticaal botverlies. Tussen deze twee typen fracturen in bevinden zich de wervelfracturen (infracties of compressie-fracturen). Osteoporotische wervelfracturen treden op vrij kort na de menopauze en blijven toenemen tot ongeveer 20 jaar na de menopauze. Ook qua botsamenstelling nemen de wervellichamen een tussen-positie in: gelijke delen corticaal en trabeculair bot.

De relatie tussen de minerale botmassa en het optreden van fracturen wordt zowel door de kwaliteit als kwantiteit van die minerale botmassa bepaald. Dit zogenaamde "quality versus quantity" concept wordt geïllustreerd met de observatie dat patiënten met een normale minerale botmassa typische osteoporotische fracturen kunnen hebben, terwijl mensen met een lage minerale botmassa in het geheel geen fracturen vertonen. Deze bevindingen en andere gegevens hebben geleid tot de hypothese van de drie-dimensionale "fracture space". De drie assen de het fractuur risico bepalen zijn minerale botmassa, de onderlinge verbinding van de botbalkjes en -plaatjes ("bone connectivity") en materiaal moeheid ("fatigue damage"). In hoofdstuk 3 wordt deze hypothese besproken.

De behandeling (of secundaire preventie) van osteoporose is gebaseerd op het beïnvloeden van twee aspecten van de botombouw: het verhogen van de botaanmaak en verminderen van de botafbraak. De diverse therapieën worden besproken in hoofdstuk 4. Alleen van fluoride (en

mogelijk ook van anabolica) is het bekend dat de botaanmaak gestimuleerd kan worden. Remmers van de botresorptie zijn calcitonine en de bisfosfonaten, de rol van deze middelen in de behandeling van osteoporose wordt momenteel uitvoerig onderzocht, de eerste resultaten zijn hoopvol.

Oestrogenen zijn zowel voor normale als osteoporotische postmenopauzale vrouwen zinvol om botverlies tegen te gaan; tevens is overtuigend aangetoond dat zij het fractuurrisisco verlagen. Het langdurig gebruik van oestrogenen kent naast positieve effecten op de botmassa ook andere werkingen: er zijn aanwijzingen dat het cardiovasculaire risico gunstig wordt beïnvloed, daarentegen wordt mogelijk een licht verhoogde incidentie van borstkanker waargenomen. Indien de oestrogeentherapie wordt gecombineerd met een progestativum is het risico op baarmoederkanker niet verhoogd.

De relatie tussen de hormonale status en de minerale botmassa in oudere postmenopauzale vrouwen werd door ons onderzocht in een transversaal uitgevoerd onderzoek (zie hoofdstuk 7). Een positieve correlatie tussen endogeen oestron en botmassa werd aangetoond, terwijl het "Sex Hormone Binding Globuline" (SHBG) een significante negatieve relatie vertoonde met de minerale botmassa. Echter, wanneer er werd gecorrigeerd voor het lichaamsgewicht (in ons geval "body mass index", BMI) verdween het verschil in botmassa tussen de groepen. De conclusie was dan ook dat de BMI voor oudere postmenopauzale vrouwen een belangrijke determinant is van de minerale botmassa.

De pathofysiologie van glucocorticoïd geïnduceerde osteoporose is ingewikkeld en onvoldoende begrepen. Algemeen wordt aangenomen dat een gestimuleerde botafbraak een belangrijke rol speelt bij het ontstaan van deze vorm van osteoporose. In hoofdstuk 9 maken wij melding van een longitudinale studie, dubbel blind en placebo-gecontroleerd, naar het effect van 1α-(OH) vitamine D_3 (gegeven in een periode van twee jaar) op de botmassa van met glucocorticoïden behandelde astmapatiënten. Een positief effect kon niet worden vastgesteld. Dit kan deels worden verklaard door het feit dat de gemiddelde prednison-dosis laag was (8.7 mg per dag) en met een relatief gering gemiddelde botverlies (1.3% per jaar in het axiale skelet en nauwelijks botverlies in de onderarm). In een andere studie-opzet werd het effect van glucocorticoïden bestudeerd in patiënten met primaire biliaire cirrhose (PBC) (hoofdstuk 8). In deze groep patiënten vonden wij slechts een matige en niet significante daling van de minerale botmassa ter plaatse van de lumbale wervelkolom en de onderarm in PBC patiënten, die glucocorticoïden gebruikten of hadden gebruikt, vergeleken met PBC patiënten, die nooit glucocorticoïden hadden gebruikt. Deze resultaten steunen de de conclusie verkregen uit het onderzoek verricht bij onze astma-patiënten dat relatief lage doses glucocorticoïden (7,5-10 mg prednison per dag) gedurende langere tijd op zijn hoogst slechts een matig negatief effect hebben op de minerale botmassa.

Een andere observatie uit het PBC onderzoek betreft de negatieve relatie tussen het histologische stadium van de lever ziekte en de minerale botmassa. Tevens bleek dat patiënten met de histologisch meer ernstige stadia van PBC en met een lagere minerale botmassa ook een significant lager calciumgehalte van het serum hadden. Het verlaagde serum calcium ging echter niet gepaard met een hoger gehalte immuno-reactief parathyroied hormoon (iPTH), hetgeen wijst op een onvoldoende produktie of secretie van PTH bij deze patiënten.

De vraag of het mogelijk is om toekomstige fracturen te voorspellen heeft tot veel onderzoek geleid. In hoofdstuk 10 wordt op de verschillende aspecten hiervan dieper ingegaan. Wij onderzochten met de meest gangbare niet-invasieve meettechnieken twee groepen vrouwen: één groep postmenopauzale vrouwen met osteoporotische wervelinfracties en één groep gezonde vrouwen vergelijkbaar wat betreft kalender- en postmenopauzale leeftijd. Het bleek, op basis van botmassametingen, onmogelijk alle vrouwen in één van beide groepen te classificeren (hoofdstuk 6).

Deze resultaten en de matige correlaties tussen de resultaten van de perifere en axiale metingen hebben aanvankelijk tot de veronderstelling geleid dat het onmogelijk zou zijn met behulp van botmassametingen toekomstige fracturen te voorspellen. Echter, vanaf 1986 tot heden zijn diverse prospectieve onderzoekingen gerapporteerd waarin een lage initiële botmassameting gecorreleerd bleek te zijn met een hogere incidentie van osteoporotische fractuur. Deze relatie blijkt zelfs sterk genoeg te zijn om eventuele screening van de vrouwelijke bevolking serieus te overwegen.

De niet-invasieve botmassametingen zijn van grote waarde gebleken voor het onderzoek naar en in kaart brengen van het natuurlijk verlopend botverlies gedurende het leven. Tevens is het mogelijk met deze meettechnieken het verlies of de toename van bot(mineraal) nauwkeurig te bestuderen tijdens ziekte of behandeling.

APPENDIX

A COMPARISON OF TWO METHODS FOR CACULATING LUMBUR BONE MINERAL CONTENT

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submitted for publication

Abstract

Dual photon absorptiometry of the lumbar spine is widely used to determine bone mineral content. A modified software program for calculating the bone mineral mass of the lumbar spine is reported here. Comparing this program with the original one it appeared that the program gives a two-fold reduction of the time needed for the analysis of the patient data. The program has a similar interobserver variability with regard to the total bone mineral content, while the interobserver variability of the bone mineral density is significantly improved. Furthermore, with the modified program the repositioning of the baseline and side cursors in follow-up studies is easier because of the reduced number of variables.

Introduction

Measurement of the lumbar spine by dual photon absorptiometry is used as a tool in the detection and monitoring of patients with osteopenia or osteoporosis[1]. Nowadays, several dual photon scanners are commercially available. Most scanners use a Gadolinium (Gd-153) source, but they differ considerably in their algorithms for calculating bone mineral mass[2]. There exist diversities in the edge-detection routines, the baseline calculation and positioning, calibration procedures and in precision and accuracy. A disadvantage of our DPA system is the complex and time-consuming calculation procedure, which may take up to 15 minutes. The costs of the measurement of one patient consist mainly of personnel costs based on time needed for both measuring and calculation. A reduction of one of these periods would be most welcome.

Tothill et. all introduced[3] a method in which they use a summation technique to calculate bone mineral content for a low activity Gd-153 source. In this paper we describe for our scanner a modification of the original calculation routine in which we use a summation technique as well. The activity of the source we used was according to the specifications (37-8 GBq) indicated by the manufacturer of the scanner. The program results in a two-fold reduction of the time needed for the analysis of the patient data. Moreover, the interobserver variability with regard to bone mineral density is slightly improved. Image quality is improved by introducing the possiblity to subtract a background. Thus it is easier to delineate the top of L2 and the bottom of L4.

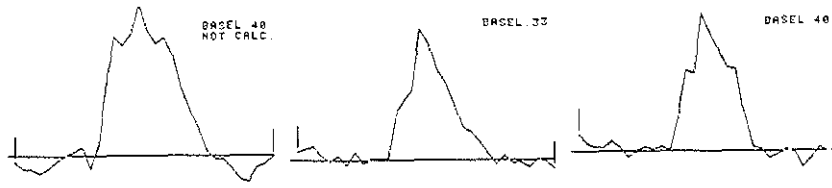

Figure 1. Examples of intervertebral scanprofiles. The profiles correspond to respectivily scan 17, 25 and 33 in Fig.3.

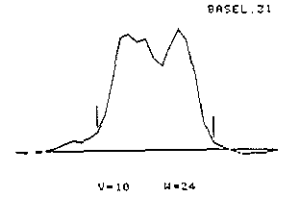

Figure 2. Summated scanprofile over the ROI (L2-L4). The scanprofile corresponds to the ROI in Fig.3.

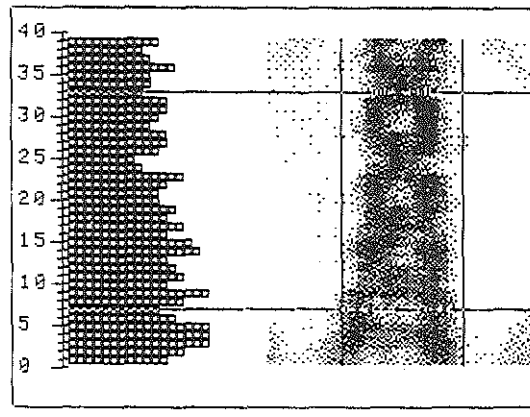

Figure 3. Total scan image. On the right side the scan image with the delimiters for the ROI. On the left side the histogram representing the BMC values for each scanprofile.

Materials and methods

Our DPA system (BMC-Lab 22A, Novo Diagnostic Systems) is equipped with a standard computer and floppy discdrive (HP-85A, Hewlett Packard Co.). The scanner device uses a 4x4 mm pixel size. Each scan profile has a width of 12.8 cm, thus there are 32 pixels per scan profile. The numeric value measured in each pixel is plotted as a function of its position (Fig. 1). Over the region of interest (ROI) (L2-L4) there are generally 22-26 scan profiles.

The original program (Fig. 5, left side) offers the possibility to position the side delimiters and delineate the baseline by the operator on each scan profile. The side delimiters are positioned on all scans in the ROI. This leads to an irregular ROI along the lumbar spine. The scans recommended to use to delineate a baseline are the scans containing the intervertebral discs. In Fig.1 examples of such a scan profile are depicted. The original program includes an algorithm to calculate automatically the baselines, which have to be accorded or readjusted (and then accorded) by the observer. Not all scan profiles can be used to determine a baseline. Therefore, for the remaining scan profiles the baselines are automatically calculated using a linear regression analysis on the accorded baselines. The next step is the calculation of the area under the curve (AUC) for each scanline. Subsequently the observer determines the ROI (mostly L2 to L4). A summation of the results of the individual AUC's in the ROI is performed. Finally, after calibration, the results are expressed as bone mineral content (BMC) in grams hydroxyapatite (g HA) for the ROI. Dividing the BMC by the surface of the projected ROI results in bone mineral density (BMD) expressed in g Ha/cm^2. As the average ROI contains about 24 scanlines the number of variables may be up to 74 with a minimum of 5 (one baseline, two side delimiters and two delimiters for the ROI).

In the new program (Fig. 5, right side) the calculation is done as follows. First the ROI (L2-L4) is defined by the observer. The computer program then summates all pixels for each column in this ROI and plots the summated curve of all 32 columns (Fig. 2). In this curve the side delimiters have to be placed by the observer. The baseline is automatically calculated by the program using the same algorithm as in the original program, and may eventually be readjusted before accordation. With the accorded baseline and the adjusted side delimiters, which are thus all three the same for all scanprofiles, the bone mineral content is calculated for each scan profile. Like in the original program this profile is displayed on the screen as a histogram together with the total scan image (Fig. 3). It is possible to adjust the ROI at this stage. If the ROI is adjusted the program continues with the calculation of the summated curve for the new ROI. If the ROI is not adjusted

the program prints the final scan report.

As a consequence of our program the total ROI is always rectangular (Fig. 3) and the number of variables always equals five.

Another modification in the new program is the possibility to subtract a background as a percentage of the maximal pixel value in the scan, which improves the quality of the scan image and makes the localization of the ROI easier (Fig. 4).

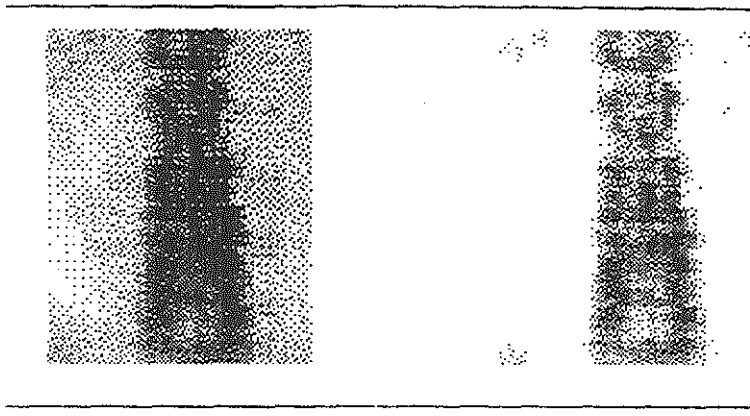

Figure 4. Left : The original scan image.
Right: The same image with a lower threshold of 20%. Note for example the improved image quality in L2. This vertebrae is, in contrast to the original image, clearly asymmetric on this image.

Results

We measured the bone mineral mass of the lumbar spine per L2 to L4 in 49 women, randomly chosen from a larger group of normal women described elsewhere[4]. Individual data of these patients were analyzed by one observer using both calculation programs and expressed as bone mineral content (BMC) and as bone mineral density (BMD). The results of both programs show very high correlation coefficients (for BMC: r=0.9966 ; for BMD: r=0.9957). The regression lines relating the results of the original and new program do not pass through zero. The BMC and BMD values obtained with the new program are somewhat higher. The conversion formulas from original to new program and vice versa are given in Table I.

In order to compare the interobserver variability of the two calculation methods, the BMC and BMD of 20 patients, out of the group of 49, were calculated by 4 observers with both programs. As a measure for interobserver variability the standard deviation between the measurements of the 4 observers was chosen. For each of the twenty patients two standard deviations were calculated, one based on the measurements of the 4 observers with the original program, and one based on the new calculation program. The means of these standard deviations over the twenty patients were for BMC 0.66 (original program) and 0.51 (new program), and for BMD 0.010 (original) and 0.006 (new). The values of the standard deviations of the two calculation programs were compared by means of Wilcoxon's signed rank test. For BMC the result was not significant, while for BMD the interobserver variability for the new method appeared to be significantly lower ($p<0.01$) than for the original program. Looking at the coefficients of variation instead of the standard deviations give comparable results.

Another advantage of the new program is the reduction of the time needed for the analysis and print-out of the scan results. Using the original software program this takes about 15 minutes per patient. In contrast the new program takes 8 minutes per patient. In the original and the new program the time needed for the computer to calculate, display the images and print the scan report amounts 6 and 5.5 minutes respectivily. The reduction in the time needed for the analysis is thus almost completely due to the reduced number of actions, that have to be done by the observer.

Table I. Conversion formulas for data obtained with the original and the new program.

	BMC (g Ha/L2-L4)	BMD (g Ha/cm^2)
ori—>new	-1.79 + 1.02*new	-0.02 + 1.01*new
new—>ori	2.03 + 0.97*ori	0.03 + 0.98*ori

ori=original program new=new program

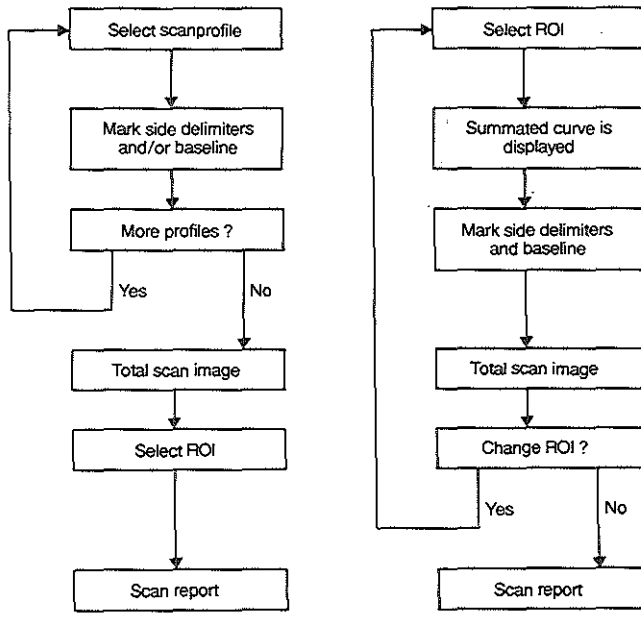

Figure 5. Flowchart of the original (left) and the new program (right).

Discussion

The accuracy and precision of lumbar spine scanning for measuring the bone mineral content by DPA depend on variations in the technical approach of the scanning procedure, and also on the computational routines. Problems arising by variations in the source strength and by soft tissue calcifications, osteoarthritic lesions and other interfering lesions are well known[5 6 7 8 9].

Only a few reports consider the problems of the analysis of the raw data, such as edge detection, baseline positioning and calculation time[3 10 11].

Another important issue is the inter- and intra-observer variation[12]. These variations are mainly due to the interpretation of the scanprofiles. In practice it appears that the automatic calculation of the baseline, especially in adipose patients with low bone mineral mass and in osteoporotics, often fails. In such cases the observer has to determine the baseline. This can introduce variations of the baseline of 5 to 20% and variations in the final results of 1 to 20% (data not shown).

In order to reduce these variations we developed a calculation program based on an average baseline detection over the ROI (L2-L4). Our results show that an average baseline over the ROI is reproducible, even in the hands of several operators. The inter-observer variations were of the same order of magnitude as in the original software program (for BMC) or better (for BMD) in our group of normals. However, the most important advantages of the new program in comparison with the original program are the shorter time for the analysis of the scan results and the diminished observer actions. Because of these improvements it is possible to analyze two patients simultaneously using two computers.

In follow-up studies the new software furthermore turned out to have the advantage that the curve obtained at a later stage shows impressive similarity with earlier curves of the individual studied. This enables the operator to obtain more precise positioning of baseline and side cursors, in comparison with the previous scans. This might greatly improve the long-term precision. In a longitudinal study the original and the new software program are compared in this respect.

We realize that the computer equipment we used is not up to date with respect to the time needed for both the calculation and the displaying of the scan images. With more modern equipment these times will be markedly reduced. We think however that the method itself deserves consideration for more modern equipment as well.

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NAWOORD

Graag wil ik allen danken die door hun hulp en steun hebben bijgedragen tot het tot stand komen van dit proefschrift.

Allereerst mijn opleider en promotor prof. dr. J.C. Birkenhäger, die mij enthousiast wist te maken voor het moeilijke gebied van het patiënt-gebonden onderzoek. Zijn stimulerende en optimistische begeleiding, met name ook in het geval van teleurstellende resultaten, zijn essentieel geweest voor het afronden van dit proefschrift.

Huib Pols heeft mij op plezierige wijze ingewijd in het zinvol en leerzaam bezoeken van congressen ("wie is wie in osteoporose-land"). Naast de vele discussies die wij samen voerden, heb ik van hem geleerd dat de "ivoren toren van de wetenschap" in tijden van universitaire bezuinigen alleen met goed management (en contacten buiten de eigen universitaire gemeenschap) kan worden behouden of uitgebouwd.

De metingen van de minerale botmassa werden op voortreffelijke wijze verricht door de medewerkers van de afdeling nucleaire geneeskunde en de afdeling experimentele radiologie. Peter Kooij heeft met zijn "kritische" en mathematische aanpak de fotonabsorptiometrie begeleid, hetgeen resulteerde in een verbeterde rekenmethode.

Zonder de medewerking van gezonde vrijwilligers en de vele patiënten was dit promotie-onderzoek niet mogelijk, hen ben ik veel dank verschuldigd.

Mijn "maten" Herman Gertrouw en Cees Geers wil ik bedanken omdat zij altijd voor mij klaar stonden om waar te nemen, wanneer ik ons ziekenhuis verliet om de universiteit te bezoeken.

Aan Trees Steenhorst, onze secretaresse, beloof ik dat het vele kopiëren nu echt voorbij is.

Hoe belangrijk ook, dit proefschrift is slechts een stap in de opleiding tot volwaardig mens. De eerste stappen werden gemaakt onder leiding van mijn ouders, zij hebben het klimaat gecreëerd waarin het plezierig en vanzelfsprekend was om hobbies te hebben, te sporten en te studeren. Tijdens het schrijven van het manuscript hebben zij mij gesteund met hun interesse en aanmoedigingen. Van praktisch nut bleek hun grote vriendenkring: vrijwel alle gezonde proefpersonen werden daaruit geacquireerd.

Penny, liet mij werken, maar haalde mij op de juiste momenten achter het beeldscherm vandaan, en wist daarmee duidelijk te maken dat ons gezinsleven nog vele malen boeiender is dan de wetenschap.

CURRICULUM VITAE

De schrijver van dit proefschrift werd geboren op 3 december 1956 te Rotterdam. Na het behalen van het Atheneum B diploma aan het Sint Montfort college te Rotterdam werd in 1975 met de studie geneeskunde aangevangen aan de Erasmus Universiteit Rotterdam. Gedurende deze studie werd ervaring opgedaan in wetenschappelijk onderzoek op de afdeling chemische endocrinologie (hoofd prof. dr. H.J. van der Molen.) Tevens was hij student-lid van de Vaste Commissie Wetenschapsbeoefening. In januari 1981 werd het artsenexamen afgelegd (met lof). In afwachting van zijn opleiding tot internist werkte hij als arts-assistent op de afdeling Interne Geneeskunde in het Bergweg Ziekenhuis (hoofd Dr. G.J.H. den Ottolander) en op de afdeling Cardiologie van het Zuiderziekenhuis (opleider X.H. Krauss). Vanaf 1983 tot 1988 werd de opleiding tot internist gevolgd in de afdeling Inwendige Geneeskunde III van het Academisch Ziekenhuis "Dijkzigt" te Rotterdam (hoofd prof. dr.J.C. Birkenhäger). Het onderzoek beschreven in dit proefschrift werd op deze afdeling en de afdeling Nucleaire Geneeskunde verricht (in samenwerking met de afdelingen Radiodiagnostiek, Pathologie en Inwendige Geneeskunde II). Na zijn registratie als internist in 1988 werkte hij in het van Dam-Bethesda ziekenhuis te Rotterdam. In juni 1990 volgde de overgang naar Spijkenisse, alwaar het Ruwaard van Putten Ziekenhuis werd geopend.