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34

Sulin Cheng

Bone Mineral Density and Quality in Older People

UNIVERSITY OF JYVÄSKYLÄ

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A Study in Relation to Exercise and Fracture Occurrence, and the Assessment of Mechanical Properties

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献给养育我的父母和尊师良友们

To my parents and mentors

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ABBREVIATIONS

ABSTRACT

Sulin Cheng
Bone mineral density and quality in older people - a study in relation to exercise and fracture occurrence, and the assessment of mechanical properties. Jyväskylä: University of Jyväskylä, 1994 - (Studies in Sport, Physical Education and Health,
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The study examined bone mineral content (BMC) and density (BMD) in older men and women. The purpose was to relate BMD to physical exercise, to examine the association between BMD and the risk of fractures and to assess the biomechanical properties of bone. Bone measurements were performed at the calcaneus by ^{125}I-photon absorption in 160 men and 324 women aged 75 and 80 and 108 women aged 50-60. In addition, the elastic wave propagation technique and computerized tomography were developed for studying the mechanical properties of the tibia in two groups of 78-year-old women (n=37) with high and low calcaneus BMD. Higher calcaneus BMC and BMD values were obtained for the men than women and for the younger than older age groups among the women. Body weight correlated positively with BMC and BMD in the older age groups, especially in the women. High BMD was associated with vigorous physical activity in the middle-aged women and with moderate physical activity in the elderly men and women. In 75-year-old men and women, BMD also correlated with previous physical activity and smoking history. Both retrospective and prospective fracture cases among the 75- and 80-year-olds had lower BMC and BMD than non-fracture subjects. With increased BMC and BMD values the probability of fractures showed a similar decrease in both sexes. The low calcaneus BMD group also had lower tibia BMD and moments of inertia. The analyses on bone mass distribution showed that the low BMD group had lost bone mainly from the endosteal surface of the tibia shaft, especially in the direction of greatest strength. Moreover, elastic wave propagation measurements indicated harder and less elastic bone in the low BMD group. The results show that calcaneus BMC and BMD are adequate predictors of fractures in the elderly. Combining elastic wave velocity with cross-sectional geometry provides a good estimate of bone mechanical properties in studying bone fragility and assessing the resistance of long bones to bending.

Keywords: aging, bones, computed tomography, density, elastic wave velocity, exercise, fractures, mass distribution, moment of inertia, osteoporosis, photon absorption

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LIST OF ORIGINAL ARTICLES

The thesis is based on the following papers which will be referred to in the text by their Roman numerals:

I Cheng, S., Suominen, H., Rantanen, T., Parkatti, T., Heikkinen, E. 1991. Bone mineral density and physical activity in 50-60-year-old women. Bone and Mineral 12, 123-132.

II Cheng, S., Suominen, H., Heikkinen, E. 1993. Bone mineral density in relation to anthropometric properties, physical activity and smoking in 75-year-old men and women. Aging Clinical and Experimental Research 5, 55-62.

III Cheng, S., Suominen, H., Era, P., Heikkinen, E. 1994. Bone density of the calcaneus and fractures in 75- and 80-year-old men and women. Osteoporosis International 4, 48-54.

IV Cheng, S., Timonen, J., Suominen, H. Elastic wave propagation in bone in vivo: Methodology. Journal of Biomechanics (accepted for publication).

V Cheng, S., Toivanen, J.A., Suominen, H., Toivanen, J.T., Timonen, J. Estimation of mechanical and geometrical properties of cortical bone by computerized tomography in 78-year-old women (submitted for publication).

LINKS TO ORIGINAL ARTICLES

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V https://doi.org/10.1002/jbmr.5650100120

ABBREVIATIONS

BMC	Bone mineral content
BMD	Bone mineral density
CSA	Cross-sectional area
CV	Coefficient of variation
DPA	Dual-photon absorptiometry
DXA	Dual energy X-ray absorptiometry
E	Young's modulus
EWP	Elastic wave propagation
I_{ap}	Moment of inertia (anterior-posterior direction)
I_{ml}	Moment of inertia (medial-lateral direction)
I_{max}	Principal moment of inertia (maximum direction)
I_{min}	Principal moment of inertia (minimum direction)
K	A measure for an average value of Young's modulus
PTH	parathyroid hormone
P	A measure which assumes that Young's modulus is proportional to density squared
R	A measure of (average values of) Young's modulus and area moment of inertia combined
SPA	Single-photon absorptiometry
v	Velocity
ρ	Density.
CT	Quantitative computerized tomography

1 GENERAL INTRODUCTION

Osteoporosis involves a reduction in bone mass and bone mineral density that leads to increased risk of fractures, especially in women (Hui et al. 1987, Cummings et al. 1990, Falch et al. 1990, 1993, Marcus 1991). In Finland, the number of new femoral neck fractures among Finns aged 50 years and over doubled between 1970 and 1985. This is due to an aging population as well as to increased rates of incidence (Simonen 1991). Because of this major public health problem, an understanding of age-related changes in bone structure and strength in both normal individuals and patients with osteoporosis is crucial. The factors affecting bones, such as physical exercise and other living habits should also be considered.

Bone mineral content and density measurements have been widely used in vivo to predict the incidence of fractures. However, the occurrence of a fracture is not dependent on bone mass and density alone; bone architecture and geometry also contribute to the integrity of the skeleton. Therefore new methods are needed for assessing the quality and important geometric features of bone. Such methods will contribute to improving the accuracy of clinical assessment of fracture risk.

This study examines bone mineral density in older men and women. The purpose was to relate bone mineral density to physical exercise, to assess the biomechanical properties of bone, and to examine the association between bone mineral density and the risk of fractures in elderly people.

2 REVIEW OF THE LITERATURE

2.1 Properties of bone

2.1.1 The organization of bone, bone cells and matrix

Bone is a specialized connective tissue that, together with cartilage, makes up the skeletal system. The skeletal system basically has three functions: mechanical, protective and metabolic. The hardness and rigidity of the bone tissue provide protection for soft and vulnerable organs and tissues, thus enabling the skeleton to maintain the shape of the body and transmit the force of muscular contraction from one part of the body to another (Suominen 1993).

Bone as a tissue includes organic matrix and mineral components. Bone is physiologically mineralized with tiny crystals of hydroxyapatite and is unique among the classical connective tissues. The organic matrix of bone consists of approximately 90% type I collagen, the remainder being non-collagenous proteins (Parfitt 1988). The collagenous network provides the substrate for the incorporation of the hydroxyapatite crystals in bone. Consequently, the organic and mineral components of bone are closely related, although the exact nature of this relationship is far from being understood.

Bone as an organ can be divided into two types: cortical and trabecular. Although they are constituted from the same cells and the same matrix elements, there are structural and functional differences between them. The functional differences are a consequence of the structural differences, and vice versa: cortical bone mainly fulfills the mechanical and protective functions, and trabecular bone the metabolic function (Parfitt 1988, Baron 1993).

Various bone cells are involved in the process of bone metabolism. However, the dynamic processes in bone are largely controlled by four types of bone cells: the lining cells, osteoblasts, osteoclasts and osteocytes (Chambers & Fuller 1985).

The osteoblasts, which originate from local mesenchymal stem cells, secrete collagen and ground substance into the bone matrix. The osteoblasts control the bone formation process, e.g. synthesis and intracellular processing of type I collagen, secretion and extracellular processing of collagen, the formation of collagen microfibrils, fibrils, and fibers, and maturation of the collagen matrix with subsequent nucleation and growth of hydroxyapatite crystals. During the process of bone formation, approximately 10-20% of osteoblasts eventually become osteocytes and lie on the surface of bone or in the lacunae in mineralized bone. Toward the end of the secretion period part of the osteoblasts become flat lining cells on the resting bone surface (Baron 1993).

The osteoclasts contain multiple nuclei, with prominent Golgi stacks around each nucleus, and a high number of mitochondria. Accordingly, they are well adapted to the high metabolic activity needed in the bone resorption process. During the resorption phase, osteoclasts are capable of dissolving collagen and minerals, as well as osteocytes.

2.1.2 Bone remodeling

In order to understand osteoporosis it is necessary to know how normal bone remodeling takes place. From childhood throughout the whole of adult life the skeleton passes through three phases: growth, modeling and remodeling. During these processes, the skeleton can change size and shape or simply renew old structures without changing shape (Eriksen et al. 1994). During the growth process, in childhood and the early years of adulthood, the skeleton grows in length, and the bones expand in diameter and are modeled. During the modeling process, peak bone mass is reached, and the skeleton changes in response to physiological and mechanical influences. The osteoblasts and osteoclasts work independently on the different bone surfaces. The new layers of bone are added at the periosteal surface, while removal of old bone occurs at the endosteal surface. Both the growth and modeling processes are controlled by mechanical usage (Frost 1990).

Bone remodeling takes place throughout adult life. During the remodeling process, bone is renewed through the continuous removal and replacement of discrete amounts of old bone by the synthesis of new bone matrix and its subsequent mineralization (Väänänen 1991, 1993, Erikson et al. 1994). In the normal adult skeleton, bone formation occurs only where bone resorption has previously occurred (Baron 1993). The osteoclasts and osteoblasts work closely together. In "coupling", which takes place between the resorption and formation of bone during the remodeling process, they work in parallel. The mechanical stimulation of bone cells appears to be an important prerequisite for coupling to take place. Without this mechanical stress on bones, as in the case of immobilization, a negative bone balance is induced more rapidly as a result of the uncoupling of resorption and formation. Moreover, during the normal aging process there is always a negative balance after each remodeling cycle. The remodeling process is also controlled by hormonal stimuli (Parfitt 1984, 1987, Mosekilde 1990).

During the remodeling process, cortical bone is remodeled through the activity of the bone remodeling units, which are more active at the endosteal surface, leading to the expansion of the marrow space in long bone. On the other hand, trabecular bone is remodeled much more rapidly than cortical bone. After trabecular bone loss, the trabecular network becomes thin and disconnected, leading to the disruption of the network. Signs of this uncoupling of the resorptive and formative activities can be seen in the weight-bearing skeleton where trabeculae lack connections with other trabeculae (Eriksen et al. 1994).

2.1.3 Bone loss

Bone changes occurring during normal aging are a universal phenomenon of biology regardless of sex, race, life style, economic development, geographic location, and historical epoch (Parfitt 1988, Kiebzak 1991). The changes are both quantitative and qualitative in nature. Bone mass rises through puberty to reach maximal peak adult bone mass during the second to third decade (Snow-Harter & Marcus 1991, Barquero et al. 1992). At that time, there is little difference between the sexes at the axial sites of bone mass (Kelly & Eisman 1993). Thereafter, a gradual loss begins, which is faster in the trabecular bones and is further accelerated in women during the menopause (Riggs & Melton 1986, Wasnich et al. 1989).

Involutional osteoporosis, that is, gradual, progressive bone loss, can be categorized into two types: postmenopausal osteoporosis and senile osteoporosis (Riggs & Melton 1986). Postmenopausal osteoporosis mostly occurs between the ages of 50-65 years. Here trabecular bone accelerates resorption related to estrogen deficiency, and is often manifest in a fracture in the spine or wrist. Senile osteoporosis usually occurs in both men and women at the age of 75 or older, with a proportionate loss of both trabecular and cortical bone, seen in fractures in the hip, proximal end of the humerus, tibia, and pelvis (Genant 1993). If the sex difference in the fracture rate in elderly people is mainly the result of postmenopausal bone loss, reducing fracture incidence implies different strategies for men and women. On the other hand, the environmental risk factors for bone loss probably do not differ greatly between men and women (Slemenda et al. 1992).

It is well established that the age-related decrease in bone mineral content (BMC) or density (BMD) structurally weakens bone and thus predisposes bone to fractures. However, old bone is more highly mineralized than young bone, and thus bone substance density changes much less with age than bone matrix volume (Hayes & Gerhart 1985, Parfitt 1988). The problem remains that trabecular BMD accounts for about 75-85% of the variance in bone strength in normal individuals (Melton et al. 1988), while cortical bone mineral density may not correlate with strength (McCalden et al. 1993). Factors such as bone size, shape, and the amount and orientation of the organic matrix, collagen, also exert an influence on the structural integrity of bone (Hayes & Gerhart 1985, Suominen 1993).

It is also well known that the mechanism of bone loss varies in different types of bone tissue. A disruption of the trabecular network in vertebrae with age is mainly caused by perforation of horizontal supporting struts. These structural changes cannot be reversed (Mosekilde 1993). Cortical bone, on the other hand, has a different pattern of loss. Cortical bone is lost mostly from the endosteal surfaces so that the marrow cavity of bone is expanded, leading to a net reduction of as much as 30 to 50% in the thickness of cortical bone in women (Melton et al. 1988, Einhorn 1992). Such changes are much greater in the lower extremities than in the upper, and may vary according to age, sex and skeletal site (Melton et al. 1988). Moreover, there is evidence that cortical thickness may be preferentially maintained in bone segments subjected to high bending and torsional stresses, while metaphyseal bone becomes progressively weaker (Ruff & Hayes 1982). Examples of trabecular and cortical bone loss are shown in Figures 1 and 2.

Although there is mounting evidence to indicate that genetic factors have a strong role in determining peak bone mass and influence the rates of change of bone mass at particular sites during ageing, life-style and environment appear to interact with the powerful genetic regulators of bone metabolism to determine net bone mass (Kelly & Eisman 1993, Krall & Danson-Hughes 1993).

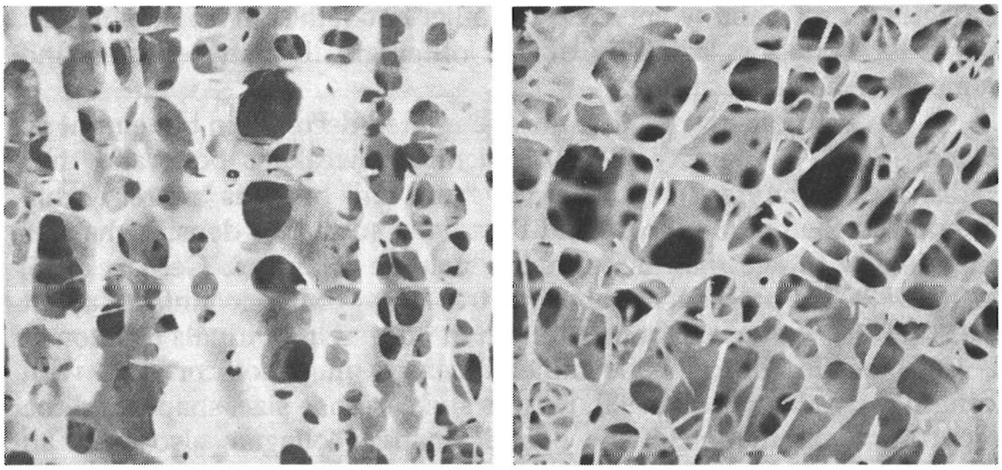


FIGURE 1 Trabecular bone in vertebrae of normal (left) and osteoporotic (right) subjects (Reproduced with permission from Eriksen, E.F., Axclrod, D.W. & Melsen, F. 1994. Bone histomorphometry. Chapter four: bone remodeling and changes in bone mass. New York: Raven Press, 26-27).

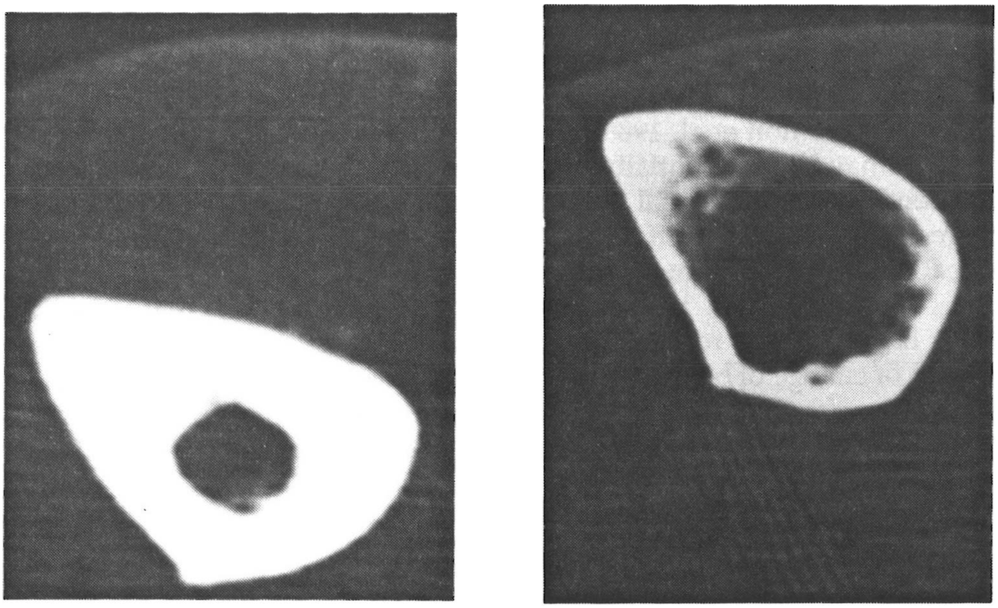


FIGURE 2 Cross-section of cortical bone in middle shaft of tibia, of women with high BMD (left) and osteoporotic women (right). Image from CT scan.

2.2 Measurements of bone characteristics

Several non-invasive methods for assessing bone properties in vivo have been developed since the 1970s. These methods include densitometric measurements which measure bone mineral content and density, and biomechanical measurements which measure the material and structural properties of bone.

2.2.1 Densitometric measurements

The major techniques in clinical use include: 1) single-photon absorptiometry (SPA); 2) dual-photon absorptiometry (DPA); 3) dual energy X-ray absorptiometry (DXA); and 4) quantitative computed tomography (CT). Differences between these techniques exist in terms of the type of bone measured, precision, accuracy, scanning time, and radiation dose as well as costs (Mazess et al. 1989, Alhava 1991, Faulkner et al. 1991). In general, no one technique is considered superior to another (Ott 1993).

SPA (Cameron & Sorensen 1963) uses the transmission of a narrow beam of monoenergetic radiation to measure appendicular bone. The source is usually a low-energy radionuclide such as ^{125}I (27 Kev). The radiation beam is monitored with a sensitive detector, usually a NaI (Tl) scintillation detector. The source and detector are coupled on a yoke and moved together across the bone (Mazess et al. 1989). The mineral mass of the bone is calculated from the integrated logarithmic ratio of the transmission value of water (soft tissue equivalent) to that of bone ($\Sigma \ln I_o/I_i$). SPA devices have also been developed that can move the source-detector device horizontally across the heel from two orthogonal directions to measure both the "width" and "depth" of the bone and enable the results to be expressed per volume unit of bone (Suominen & Rahkila 1991).

DPA (Dunn et al. 1980, Wahner et al. 1985) is generally similar to SPA in theory but a dual-energy radionuclide source is used. The high energy allows the total thickness of bone (spinal and appendicular bone) and soft tissue to be measured at any point without crossing the area of interest, thus removing the need for water baths and gels (Mazess et al. 1989). DXA (Mazess et al. 1990), which can measure the spine, hip and total body, has essentially replaced the isotope-based DPA systems, owing to its increased precision and reduced radiation dose, and also does not require frequent changes in the radiation source (Faulkner et al. 1991).

CT has been developed to enable the determination of true bone density and the distribution of bone mass at any skeletal site (Cann 1987, Crawley 1990). The basic methodology employed in CT scanning involves the computation of the cross-sectional distribution of X-ray attenuation in a body by back-projecting the X-ray transmission measurements acquired at many angles around the body until the spatial arrangement of the absorbing structures can be determined (Stytz & Frieder 1990).

Usually, there are three ways of expressing the results, depending on how the bone measurements have been performed. First, linear density (rectilinear cross-sectional scan), which expresses BMC as $g{\cdot}cm^{-1}$. Second, area density (rectilinear two dimensional scan), which expresses BMC or BMD as $g{\cdot}cm^{-2}$. Third, volume density (transmissive three-dimensional reconstruction computed density of the volume of bone), which expresses BMD as $g{\cdot}cm^{-3}$ (Washich et al. 1989, Faulkner et al. 1991). When comparing different studies, it is important to check which definition of BMC and BMD has been used, since there are currently two different ways of determining each. In the present study, the following definitions have been used: BMC is expressed as $g{\cdot}cm^{-2}$ and BMD as $g{\cdot}cm^{-3}$.

2.2.2 Biomechanical measurements

The biomechanical properties of bone can be described at two levels: material and structural (Hayes & Gerhart 1985, Melton et al. 1988, Martin 1991, Einhorn 1992). The material properties of bone are only tested under laboratory conditions (Mosekilde 1993, Turner & Burr 1993). These properties are strength, stiffness, energy-absorptive capacity, and deformation. The structural properties, which function as a complete anatomical unit, are the architecture and the geometry of the bone (Hayes & Gerhart 1985, Melton et al. 1988, Einhorn 1992). The form, size, density and strength of the skeleton at any age are dependent on its mechanical usage (Frost 1988, Einhorn 1992).

Because of the methodological difficulties, basic biomechanical measurements of bone, except for bone density measurements, are made in vitro (Tuner & Burr 1993). The present, in vivo measurements can only use CT, sound or elastic waves to indicate some of the mechanical properties of bone. Ultrasonic methods, for instance, have been introduced into clinical use (Langton et al. 1984, 1990, Kaufman & Einhorn 1993). Ultrasonic methods measure either the attenuation or the velocity of ultrasound in bone. The bulk sound velocity is equal to the square root of the ratio of the elastic modulus to density. These methods can thus provide information not only about the density but also about the mechanical properties of bone.

In addition to ultrasonic methods, acoustic or elastic wave propagation along the bone, generated by an impact force, and received by accelerometers, has also been suggested as a diagnostic tool (Chen & Saha 1987, Pelker & Saha 1983). These methods measure the velocity of elastic waves through the long bones (tibia and ulna), and are also radiation free. Measurements are simple, inexpensive, and permit the evaluation of changes in mechanical properties along the bone. However, it is difficult to extract a unique factor which would explain the behavior of the velocity along the bone. Velocities cannot be interpreted simply as the results of bone density measurements (Glüer et al. 1992). Consequently, these methods are still under development. Velocity measurements can also be complemented with measurements of bone geometrical properties such as bending stiffness (Myburgh et al. 1992, Harrington et al. 1993).

2.3 Bone mineral density, body weight and physical exercise

2.3.1 Body weight and exercise

Today it is widely accepted that bone is a highly adaptive tissue which develops in structure and function in response to mechanical forces and metabolic demands (Frost 1988, Smith & Gilligan 1989, Turner 1992). Yet there is still considerable debate as to how bone adaptation should be modeled (Turner 1992). It has been proposed that the homeostatic regulation of bone structure, which is characterized by negative feedback such that the system is driven toward a net bone formation rate of zero, occurs in growing bone, and that the epigenetic regulation, which is characterized by positive feedback and is driven to an attractor state of maximal bone formation, is more important during bone development phases in the adult skeleton (Turner 1992).

In bone, the homeostatically regulated variable is skeletal rigidity, which is maintained at a level that is adequate for functional needs but minimal mass (Turner 1991). Epigenetic regulation, on the other hand, tends to drive a system to one of multiple steady-state levels (Turner 1992). Mechanical loads resulting from activity produce strains within bones which are thought to provide the stimulus for the functional adaptation of bones (Forwood & Burr 1993, Turner et al. 1994). If mechanical loads, such as body weight and exercise, are the stimulator for the functional adaptation of bones, the benefits of these factors for bones should be seen either before skeletal maturity or throughout adulthood into very old age.

It is known that mechanical stress and weight-bearing activity on bone bring about increasing mineralization and bone mass (Bailey et al. 1986). For bone growth, as well as to slow the process of bone loss, special stimulus (pressure stress) is needed. If physical activity is too light, it cannot reach the threshold level required for changing the bone metabolism. If physical activity is too intensive, it may cause adverse effects (Schoutens et al. 1989, Forwood & Burr 1993).

Animal studies have shown that a growing bone has a greater capacity to respond to mechanical loads and add new bone to the skeleton than an adult bone. Young bone has a greater potential for periosteal expansion than aging bone, allowing it to adapt more rapidly and efficiently to an acute need for increased strength (Frost 1987). The effects of exercise in the adult skeleton is conservation and not acquisition (Forwood & Burr 1993). Tuukkanen et al. (1991) found that moderate treadmill exercise partially prevented bone loss in ovariectomized rat. On the basis of animal studies, we may assume that earlier habitual physical activity contributes a great deal to maximal peak bone mass, and that continuing physical activity through life has great importance for maintaining bone mass.

The most extensive evidence in human studies in support of exercise has so far been obtained from in cross-sectional studies of athletes (Suominen 1993, Forwood & Burr 1993). Evidence from previous studies clearly showed that athletes from various sports have significantly higher BMC and BMD values in several bone sites when compared with non-athletes (Nilsson & Westlin 1971, Dalén & Olsson 1974, Jacobson et al. 1984, Lane et al. 1986, Suominen et al. 1989). Suominen and Rahkila (1991) found that elderly male athletes, e.g. long-distance runners, cross-country skiers, sprinters, jumpers, throwers, and weightlifters, had higher calcaneus BMD values than controls. Higher BMC and BMD values have also been shown in long-distance runners and swimmers in the lumbar spine (Lane et al. 1986, Orwoll et al. 1989), and in the distal forearm and humeral head (Dalén & Olsson 1974) in comparison with non-runners. The dominant hands and forearms of tennis players also seemed to undergo greater hypertrophy than the non-dominant limb (Huddleston et al. 1980, Montoye et al. 1980). The greatest differences in bone mineral mass between male athletes and non-athletes seem to occur in trabecular bone sites, the differences being somewhat smaller in older people (Suominen 1993).

Most of the experimental exercise intervention studies have been undertaken in young and middle-aged adults. There have been few experimental trials carried out in older people which have shown positive effects on bones after training. So far the net results of exercise interventions have shown differences in change between exercisers and controls ranging from - 6% to + 7% in BMC or BMD (for a review see Smith & Gilligan 1991, Snow-Harter & Marcus 1991, Marcus et al. 1992, Suominen 1994). Dalsky et al. (1988) found that after 22 months low-intensity weight-bearing exercise training spine BMC increased by 7% in postmenopausal women aged 55-70 years. Rikli and McManis (1990) also showed that BMC in the radius increased 4% after 10 months' exercise in 57-83-year-old postmenopausal women. Smith et al. (1981) obtained increased BMC after 3 years' exercise in a study of women 69-95 years old. Rundgen et al. (1984) also showed that after a 9-month exercise program, calcaneus BMC increased about 6% in 63-84-year-old women. Suominen et al. (1986) found an increase in calcaneus BMD after 2 months training in 74-78-year-old men.

However, many other studies in elderly women have not found significant differences after exercise. A study (Martin & Notelovitz 1993) of the effects of aerobic training on bone mineral density in postmenopausal women did not find significant increases in arm or lumbar BMD after 12 months of training, but the training did attenuate lumbar BMD loss in those women who were ≤6 years of onset of the menopause. A recent intervention study (Suominen et al. 1993) of the effects of various types of exercise on various bone sites in 76-78-year-old women did not find any changes in BMD after 18 weeks of training. Some studies have even shown exercise to have negative effects on BMC and BMD (Sandler et al. 1987, Simkin et al. 1987, Cavanaugh & Cann 1988, Sinaki et al. 1989). It is not clear whether exercise commenced at older ages has any major effects on bone mass and so helps to prevent osteoporosis and related fractures (Suominen 1994).

In addition to exercise, body weight has also shown associations with BMD. A recent study (Edelstein & Barrett-Connor 1993) of 55-84-year-old men and women showed that by using multiple linear regression models adjusted for age, smoking, exercise, alcohol, thiazide use, and estrogen use (in women), body weight was the most consistent marker of BMD overall. Rundgren et al. (1984) suggested that body weight must be taken into account when studying the changes in bone mineral content (BMC) of the lower extremities, especially in cross-sectional studies. Yano et al. (1984) showed that body weight was strongly related to BMC for all skeletal sites in both sexes. Moreover, BMC and BMD of the calcaneus and the spine correlated equally with body weight, whereas no correlations were found between BMC of the forearm and body weight (Svendsen et al. 1992). The effect of body weight on BMD was more noticeable in weight-bearing sites than in non-weight-bearing sites (Edelstein & Barrett-Connor 1993, Felson et al. 1993). Also, in general, this effect was much less in elderly men (Suominen et al. 1984, Suominen & Rahkila 1991, Felson et al. 1993). Women usually have much higher body fat content than men. Fat mass may have greater effect among postmenopausal women because it is responsible for the conversion of adrenal steroid precursors to estrogens (Lindsay et al. 1992).

2.3.2 Other factors affecting bone mineral density

In addition to physical activity, muscle mass showed an association with BMD in 20-80-year-old women (Aloia et al. 1991). Pocock et al. (1989) showed that biceps and quadriceps muscle strength was associated with BMD in the femur, forearm, and spine in 20-75-year-old women. They also found that in postmenopausal women muscle strength was a significant predictor of bone mass in the femur and forearm, but not in the spine. Another study (Zimmermann et al. 1990) showed that hip flexor torque was related to BMD in the lumbar vertebrae and hip in postmenopausal women. Bevier et al. (1989) found that grip strength significantly predicts lumbar spine and mid-radius bone density in elderly women, and that grip strength is a marker for overall fragility and general health and for the adequacy of skeletal loading exercise (Kritz-Silverstein & Barrett-Connor 1994). Back strength predicts axial bone density in elderly men (Bevier et al. 1989) and women (Sinaki & Offord 1988). Back strength was also the most robust predictor of BMD at the trochanter, Ward's triangle, whole body, and tibia in adult men, and the effects of muscle strength on bone was greater in men than in women (Snow-Harter et al. 1992). Although muscle strength has a greater impact on bone, the mechanism remains nuclear; possibly muscle strength relates to muscle mass via the circulatory system which brings nutrition to bone.

Bone loss being multifactorial, it can be assumed that environmental factors such as physical exercise, dietary calcium intake, smoking and drinking habits interact with each other to determine bone status (Suominen 1993). Information about the effects of diet on BMD, however, remains contradictory. High calcium intake was associated with high BMC and BMD during late adolescence and early adulthood (Anderson & Metz 1993). Elders et al. (1989) showed in their study that lower lumbar BMD was observed in low calcium intake (≤900 mg/day) premenopausal women compared to their high calcium intake (≥1200 mg/day) counterparts. However, this difference was not shown in the peri- and postmenopausal women. It seems that dietary calcium intake is more important in the development and /or maintenance of peak bone mass, than in the modulation of postmenopausal bone loss. Calcium supplementation (1000 mg/day) decreased the serum parathyroid hormone (PTH) level in elderly women, and the suggestion that increased calcium intake decreases PTH may have implications for the management of a subset of patients with involutional osteoporosis (Kochersberger et al. 1990). Several studies did not observe significant effects on bone mineral density from calcium intake or milk consumption in either young adults (McCulloch et al. 1990, Mazess & Barden 1991), or postmenopausal women, female college athletes, and nonathletic college women (Riis et al. 1987, Frederick & Hawkins 1992). High dietary calcium intake was associated with a slightly increased risk of hip fracture, but decreased risk of wrist fracture (Kreiger et al. 1992). Although BMC and BMD do not correlate well with recent dietary intakes of calcium, long term adequacy of calcium intake may influence bone mass (Weaver 1990).

Besides the above factors, smokers have shown lower BMC and BMD values than non-smokers (Daniell 1972, 1976, Lindquist & Bengtsson 1979, Suominen et al. 1984, McDermott & Witte 1988, Mazess & Barden 1991, Mannius et al. 1992, Sowers et al. 1992, Krall & Dawson-Hughes 1993). A high consumption of coffee was associated with a lower bone mass, but was not an independent risk factor for low bone mass and fractures in 70-year-old men and women (Johansson et al. 1992). Alcohol consumption did not show effects on bones (Vecchia et al. 1991, Sowers et al. 1992). Among postmenopausal women, moderate alcohol consumption was found to correlate positively with BMC and BMD (Laitinen & Välimäki 1991).

2.4 Biomechanical properties of bone

The biomechanical concepts of bone are based on those of mechanical engineering. However, different interpretations and definitions make it difficult to compare the results from different studies. It is thus important to clarify the terms which are used in bone studies and facilitate the comparability of the results from different laboratories.

2.4.1 Stress-strain

The fundamental factors of bone biomechanics are stress and strain. These variables can only be tested in vitro at present. Stress is usually defined as force per unit area and, depending upon how loads are applied, it can be classified into three types: 1) compressive stress, which is developed if loads are applied so that the material under consideration becomes shorter, e.g. the effect of body weight on the calcaneus bone in the standing position; 2) tensile stress, which is developed when the material is stretched, e.g. the stress which is applied to the forearms when a person is hanging on a bar; and 3) shear stress, which is developed when one region of the material slides relative to an adjacent region, e.g. in up and down jumps, where shear stress appears in the proximal femur end. Strain is usually defined as a percentage change in the length, or relative deformation. When the bone length is changed, its width will also change. If loads are transmitted from different directions, materials like bone express a property known as anisotropy (Hayes & Gerhart 1985).

The relationship between stress and strain in bone follows a stress-strain curve (Figure 3). The slope of the linear part of the curve is called the elastic, or Young's modulus. It is a measure of the intrinsic stiffness or rigidity of bone. The linear part of the curve is also know as the elastic region. Physiologically this means that forces applied to the bone in this region will only deform the bone temporarily. After the load is removed, bone will return to its original shape. Loading beyond the linear part of the stress-strain curve will bring the bone into the plastic region, which results in a permanent deformation of the bone. The point which separates the two regions is called the yield point, and the stress at this point (the elastic limit) is known as the yield strength. The maximum stress the bone can sustain is called the ultimate strength, and the breaking strength is the stress at which the bone actually breaks (Hayes & Gerhart 1985, Turner & Burr 1993). The strain at the point of failure is known as the ductility of the bone. The area of the stress-strain curve is a measure of the energy absorptive capacity of bone. This energy is dissipated when the bone is fractured, and is lost at the point of failure.

2.4.2 Strength

In investigating bone properties, the term strength is usually used instead of the term stress. In fact, the strength of bone tissue is determined by calculating the maximum stress at the point where the bone fails (Figure 3). In the life sciences bone strength is often referred to in units of force. In engineering studies bone strength is usually reported in terms of stress or as intrinsic strength (Turner & Burr 1993). It should be noted that strength is an intrinsic property of bone. Strength is a variable independent of the size and shape of the bone. Failure force is different from intrinsic strength because the breaking load (fracture force) will vary with bone size. Therefore, it is important to distinguish these two concepts because of the different reactions to intrinsic strength and breaking load in drug studies (Einhorn 1992, Turner & Burr 1993).

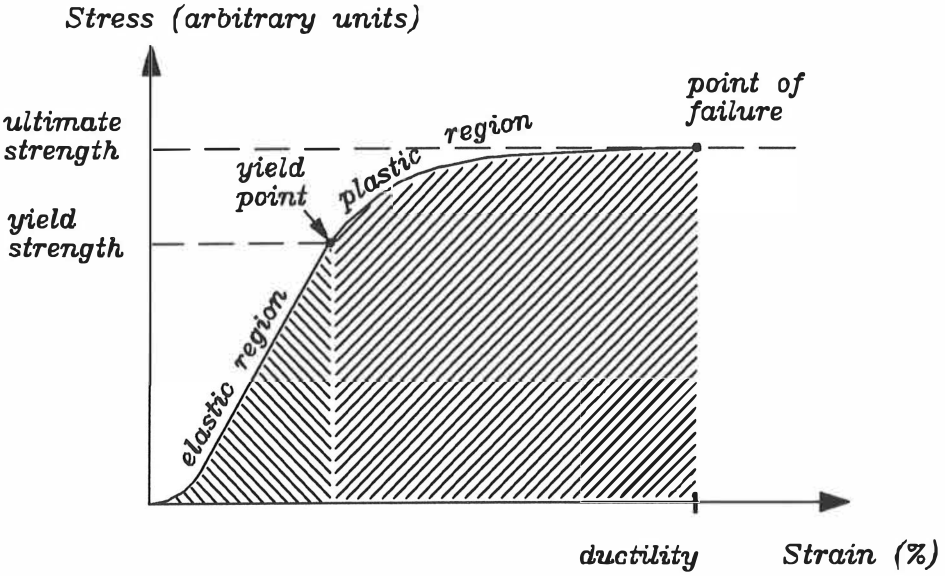


FIGURE 3 A schematic stress-strain curve of bone. The linear part of the curve represents bone stiffness. The area under the curve represents the strain energy (elastic region) and the total energy stored at the point of failure (plastic region). The maximum strain at the point of failure is called bone ductility.

The strength of human cortical bone varies depending on the kind of stress applied to the bone. For example, in specimens of age 20-89 years, the ultimate tensile strength of the femur was 120-140 MPa and, of the tibia 145-170 MPa (Burstein et al. 1976). The corresponding figures for ultimate compressive strength were 179-209 MPa and 183-213 MPa (Burstein et al. 1976), respectively. The mean shear strength of the femur was 67 MPa (Reilly & Burstein 1975). A recent study in 235 cortical specimens of age 20-102 years (McCalden et al. 1993) showed that the tensile properties of cortical bone deteriorated markedly with age. Ultimate stress decreased by 5 percent per decade. The porosity of bone increased significantly with age and accounted for 76 percent of the reduction in strength, while the mineral content and elastic modulus were not affected. McCalden et al. (1993) concluded that the quantitative changes in aging bone tissue, rather than the qualitative changes, influence the mechanical competence of bone. Strength in cancellous bone can also vary from 1 MPa to over 20 MPa, and is strongly dependent on the apparent density and trabecular orientation (Turner 1989). Moreover, in a metaphyseal shell structure, such as proximal tibial bone, the ultimate strength was also found to vary from 58 GPa to 121 GPa with changing distance from the proximal to the distal direction along the tibia (Hayes & Gerhart 1985).

2.4.3 Moments of inertia

Moments of inertia are measures of the mass and its distribution around a given axis (Figure 4). For a bone cross section, moments of inertia can be measured using a digitizing system or point counting techniques, or by CT scans. Usually, a moment of inertia can be expressed as a polar moment of inertia if the calculation is based on how the bone mass is distributed around a torsional axis, a principal (area) moment of inertia if the calculation is based on how the bone mass is distributed around a principal axis, or an anatomic moment of inertia if the calculation is based on how the bone mass is distributed around an anatomical axis (Harrington et al. 1993). These moments of inertia relate to structural stiffness and increase with stiffness (Melton et al. 1988, Einhorn 1992).

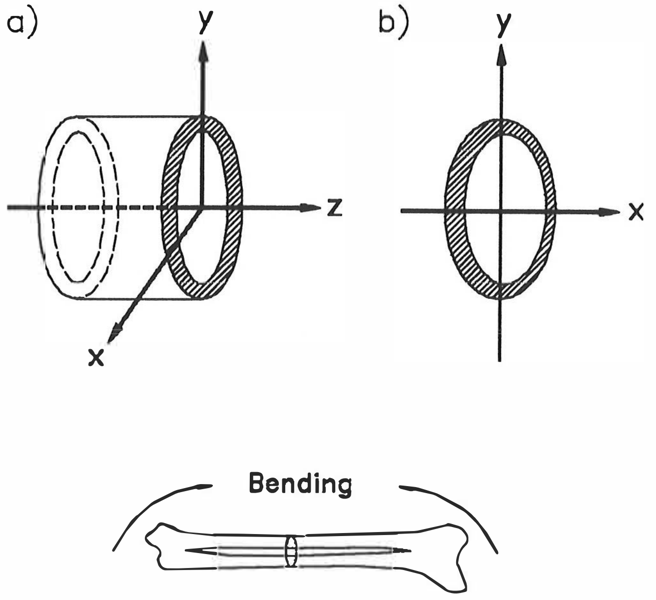


FIGURE 4 Schematic presentation of axes which are used in determining cross-sectional moments of inertia (I). a) illustrates the principal axes relevant for bending. The principal moment of inertia, I_{max} and I_{min} can be calculated from an equation given in our paper V. b) illustrates the anatomical axes. The anatomical moment of inertia, I_{ap} and I_{ml} can be calculated by an equation given in our paper V.

2.4.4 Sound and elastic wave velocity

Sound, whether it be ultrasound or audible sound, results from a mechanical disturbance in a medium such that each particle in the medium exhibits oscillatory movements (Kaufman & Einhorn 1993). The rate at which (longitudinal) sound travels through the bulk of solid matter, such as bone, is dependent on its elastic properties and density such that, for homogeneous matter,

$$v = \sqrt{\frac{E}{\rho}} \ ,$$

where v is velocity, E is Young's modulus, and ρ is density.

When the sound or elastic wave is propagated parallel to the direction of oscillation, the mode of the wave is called longitudinal. If the wave propagation is perpendicular to the direction of oscillation, the mode of the wave is called transverse or shear (Figure 5). The velocity of sound and other elastic waves depends on the properties of the medium through which it is being propagated and on its mode of propagation. Longitudinal waves are generally faster than shear waves or other elastic waves such as bending waves which may appear in finite material bodies (Figure 5). The velocity of elastic waves also depends on the cross section through which the waves travel.

Because of anatomical considerations, the most accessible sites for ultrasound measurements are the calcaneus and patella (Kaufman & Einhorn 1993). Acoustic or elastic wave propagation is usually measured along the long bones (tibia, radius, ulna, and phalanges).

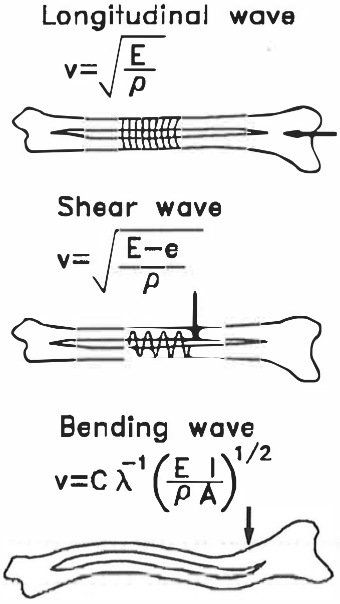


FIGURE 5 Schematic presentation of propagation of sound and other elastic waves in bone. The wave is longitudinal (bulk mode) when it propagates parallel to the direction of oscillation. The wave is transverse or shear wave (bulk mode) when it propagates perpendicular to the direction of oscillation. The wave is a bending wave when it constitutes a collective motion of the whole material body and propagates perpendicular to the oscillation. In the equations v is velocity, $E = Y(1-\sigma)/(1+\sigma)(1-2\sigma)$, where Y is Young's modulus and σ is Poisson's ratio, $e = E/2(1-\sigma)$, and I is the area moment of inertia for the cross section of the bone. In the text we usually call E the Young's modulus for simplicity. C is a numerical factor, λ is the wave length of the mode, A means A_2-A_1, A_2 being the outer cross-sectional area and A_1 the cross-sectional area of the hollow core. ρ is bone density which is assumed to be homogeneous, together with the other quantities, for the equations to hold true.

2.5 Bone properties and risk of fractures

Fracture risk refers to the probability that a fracture will occur. The most considerable risk factors altering the probability of fracture are age and low bone mass (Wasnich et al. 1989). However, age has an effect on fracture incidence which may be independent of bone mass (Ott 1993). Fracture risk may also be influenced by diet, genetics, and physical activity (Wasnich et al. 1989, Ott 1993).

2.5.1 Bone mineral density in relation to risk of fractures

Studies on different age groups have shown that appendicular BMD such as that of the calcaneus can be used as a predictor of fractures (Ross et al. 1987, 1989, Hui et al. 1989, Cummings et al. 1990, Black et al. 1992), and that its predictive power is similar to that of other measurements made at the hip, spine and vertebra (Hui et al. 1989, Black et al. 1992). The overall risk of diverse types of fractures, such as fractures of the ribs, metacarpi, and forearm, is highest among women who have the lowest bone mass in the radius and calcaneus (Ross et al. 1987, Kotzki et al. 1993). A recent follow-up (8-10 years) study by Melton et al. (1993) also showed that after adjusting for age, BMD measured at various bone sites predicted the likelihood of any incident fracture due to moderate trauma.

Cummings et al. (1993) showed that in women aged 65 and over femoral neck BMD was a better predictor of hip fracture than measurements of the spine or radius, and moderately better than the calcaneus. There are few studies relating BMC and BMD to fractures in old age. Gärdsell et al. (1989, 1990) found that in both men and women over the age of 70 BMC at the distal forearm site had no predictive value for fractures. Ito et al. (1993) showed that in women in their 60s with spinal fractures both the trabecular and cortical BMD of the spine were significantly lower than their counterparts without spinal fractures. In women in their 70s, only trabecular BMD differed between the fracture and non-fracture cases. In women in their 80s, neither trabecular nor cortical BMD differed between the fracture and non-fracture cases.

2.5.2 Biomechanical aspects of fractures

When whole bones are subjected to experimental or physiological loading conditions, fracture represents the failure of the whole bone. The mechanical behavior of bone depends not only on its mass and material properties but also on its geometry and architecture (Hayes & Gerhart 1985, Alho et al. 1988, Faulkner et al. 1991, Einhorn 1992, Ott 1993).

Because of technical limitations, all measurements of material properties and some structural properties are done in vitro or in vivo indirectly. In vitro studies, trabecular bone density at different bone sites showed a high correlation with the ultimate strength of bone (Smith et al. 1976, Mosekilde et al. 1987, Alho et al. 1988, Esses et al. 1989, Lotz & Hayes 1990, Hayes et al. 1991). In cortical bone, on the other hand, BMD correlated only weekly or not at all with strength (Alho et al. 1988, Hayes et al. 1991, Snyder & Schneider 1991). McCalden et al. (1993) showed that changes in the porosity of cortical bone accounted for 76 percent of the reduction in strength, and that mineral content did not play a major role. Moreover, changes in the composition of bone marrow, cross-sectional geometry, distribution of bone mass and loading condition on bones may be more important in altering the skeletal strength of cortical bone than BMD alone (Hayes et al. 1991, Einhorn 1992, Myburgh et al. 1992, Danielsen et al. 1993).

Most clinical fractures occur as a result of a combination of axial compression, bending and torsion. In bending or torsion, the cross-sectional area of a structure is more important in resisting loads than its mass or density (Alho et al. 1988, Melton et al. 1988). In bone, the ideal situation is for the mass of the bone to be distributed as far away as possible from the neutral axis. Evidence from rat femur (Ferretti et al. 1993) showed that the strength and stiffness of the integrated diaphyses depend on both cross-sectional moment of inertia and body weight but not on BMD. Myers et al. (1993) found that the failure force of the distal radius assessed in vitro correlated with distal radius width, cross-sectional area and the principal area moments of inertia, but not with BMC or BMD. In an in vivo study, recruits with low area moments of inertia of the tibia were found to have higher stress fracture morbidity than those with a high area moment of inertia (Milgrom et al. 1989). It seems that the geometric properties of bone may offer a better predictive capacity for fracture than BMC and BMD alone.

2.5.3 Other aspects of fractures

A fall is generally the main reason for fractures in the elderly (Nevitt et al. 1992), but only persons with low BMC and BMD values frequently develop fractures (Melton et al. 1993). Moreover, whether an increased risk of fractures can be shown to be related to body weight or living habits such as physical activity or the effect of smoking and drinking remains unclear.

Several studies have shown that fractures are related to a lower body mass and body mass index (Elmståhl et al. 1993, Mellström et al. 1993, Johansson et al. 1993, Meyer et al. 1993). Body height seems to have an independent influence on hip fracture in middle-aged men and women (Meyer et al. 1993). A case control study of 70-75-year-olds also showed that hip fracture patients had a lower body mass index, lower BMC and higher prevalence of vertebral compression fractures (Mannius et al. 1992).

The relationship between the risk of fracture and physical activity in the elderly is a complex issue. Physical activity may, through mechanical stimulation, improve the resistance of bone to fracture, as well as joint flexibility, balance, and muscle force, while reducing the risk of falling (Melton & Riggs 1985, Wickham et al. 1989, Smith & Gilligan 1991).

against fracture in older people (Sorock et al. 1988). However, participating in certain physical activities may also increase the possibility of a fall, thereby increasing the risk of fracture (Sorock et al. 1988). A negative association has been found between a medium or high level of participation in outdoor games and hip fractures (Paganini-Hill et al. 1981).

Smokers have a high fracture risk (Vecchia et al. 1991, Johansson et al. 1993, Mellström et al. 1993). A high consumption of coffee and alcohol was not an independent risk factor for fractures (Vecchia et al. 1991, Johansson et al. 1992, Kreiger et al. 1992, Sowers et al. 1992, Laitinen et al. 1993). According to Hernandez-Avila et al. (1991) caffeine and alcohol consumption increase the risk of osteoporotic fractures in middle-aged women.

3 AIMS OF THE STUDY

The present study examines bone mineral density in older men and women. The purpose was to relate bone mineral density to physical exercise, to assess the biomechanical properties of bone, and to examine the association between BMD and the risk of fractures in elderly people. More specifically, the aims were:

1) To examine BMC and BMD of the calcaneus by single-photon absorptiometry in relation to anthropometric properties and physical activity in different sex and age groups of older people (I, II).

2) To evaluate the BMD of the tibia in relation to its mechanical and geometrical properties by computerized tomography in elderly women (V).

3) To investigate the association of BMC and BMD in the calcaneus with the incidence of non-spinal fractures in elderly men and women (III).

4) To find an alternative inexpensive, sensitive and non-invasive way of evaluating the mechanical properties of bone (IV).

4 MATERIAL AND METHODS

4.1 Subjects, sampling procedures and participation rates

The study comprises several parts of larger research projects. Two papers (II, III) are part of the Evergreen project, a larger research program on functional capacity and health among 75- and 80-year-old residents of Jyväskylä. The study is also part of a study of middle aged women (I). The mechanical properties of bone were studied among 78-year-old women as a subgroup of a previous sample of 75-year-old women living in Jyväskylä (IV and V).

A description of the subjects and participation rates in the different studies is schematically presented in Table 1. Detailed information on participation rates, the reasons for non-participation and sampling procedures are given in the original reports referred to.

4.2 Questionnaires

Information on background factors such as the subjects' habitual physical activity, smoking and drinking habits, dietary habits, menopausal history, fracture history and medication as well as information about educational level and socio-economic status were collected by a postal questionnaire and interviews. The questionnaire was completed at home, and checked at an interview when the subjects came for the laboratory examination. Detailed information about background factors is given in the original reports (I, II and III).

TABLE 1 Subjects and participation rates in studies I-V

Study	Subjects	Age (years)	Target population N	Interview & postal questionnaire n	(%)	Bone measurements n	(%)
I	Women	50-60		193		108	(61)
II	Men	75	126	119	(94)	103	(82)
	women		262	236	(90)	188	(72)
III	Men	75	126	119	(94)	103	(82)
	Women		262	231	(88)	188	(72)
	Men	80	78	74	(95)	57	(73)
	Women		213	188	(88)	131	(62)
IV, V	Women	78		45		37	(82)

Information regarding current physical activity by the 75-year-olds (II) was requested by questionnaire twice. 75% of the men and the 65% of women gave the same answers in both surveys. The validity and reliability of the questionnaire concerning fracture occurrence were examined by analyzing the level of agreement between the self-reports and medical records (including radiographs) of all the subjects who had sustained a fracture during the 5-year period preceding the laboratory examinations. Detailed information is given in study III. In studies IV and V all the fractures were confirmed by radiography.

4.3 Physical characteristics of the groups studied

The anthropometric properties of the groups studied and the methods used are shown in Tables 2 and 3, respectively. There were significant differences between the 75-year-old men and women in all the anthropometric properties studied (II). The same was true for the 80-year-olds. Body mass and fat content were significantly lower in the 80-year-old women compared with the 75-year-old women (III). However, no differences were found between the 75- and 80-year-old men in any of the anthropometric properties (III). The study on 50-60-year-old women showed that only body fat content differed significantly between the sedentary group and the physically active group (I). Body mass was significantly different between the high and low BMD groups of 78-year-old women (IV and V).

TABLE 2 Physical characteristics of the different groups studied (Mean ± SD)

Groups	n	Body height (cm)	Body mass (kg)		Lean body mass (kg)	Body fat (%)	
<u>Women</u>							
50-60-year-old							
Sedentary	41	162.4 ± 6.6	70.2 ± 12.0	*		37.8 ± 4.6	**
Active	66	162.2 ± 6.1	64.6 ± 8.6			34.9 ± 4.6	
75-year-old	188	155.8 ± 5.6	67.6 ± 10.6	*	44.7 ± 4.1	32.7 ± 6.8	**
80-year-old	131-133	155.5 ± 5.2	64.7 ± 10.1		44.3 ± 4.6	30.7 ± 7.0	
78-year-old							
High BMD	19		69.4 ± 10.5	*			
Low BMD	17		60.5 ± 12.9				
<u>Men</u>							
75-year-old	103	169.5 ± 6.2	73.8 ± 10.3		57.3 ± 6.3	21.8 ± 5.9	
80-year-old	55-57	168.9 ± 6.4	74.8 ± 12.8		57.3 ± 6.8	23.0 ± 5.9	

* $p<0.05$, ** $p<0.01$, significant difference between age, physical activity or BMD groups.

4.4 Laboratory assessments of bone properties

For the measurement of bone mineral density, mechanical properties and functional capacity standardized methods were used under standardized laboratory conditions. The laboratory assessments and the variables investigated in the different studies are listed in Table 3.

4.4.1 Bone density

Single-photon absorption

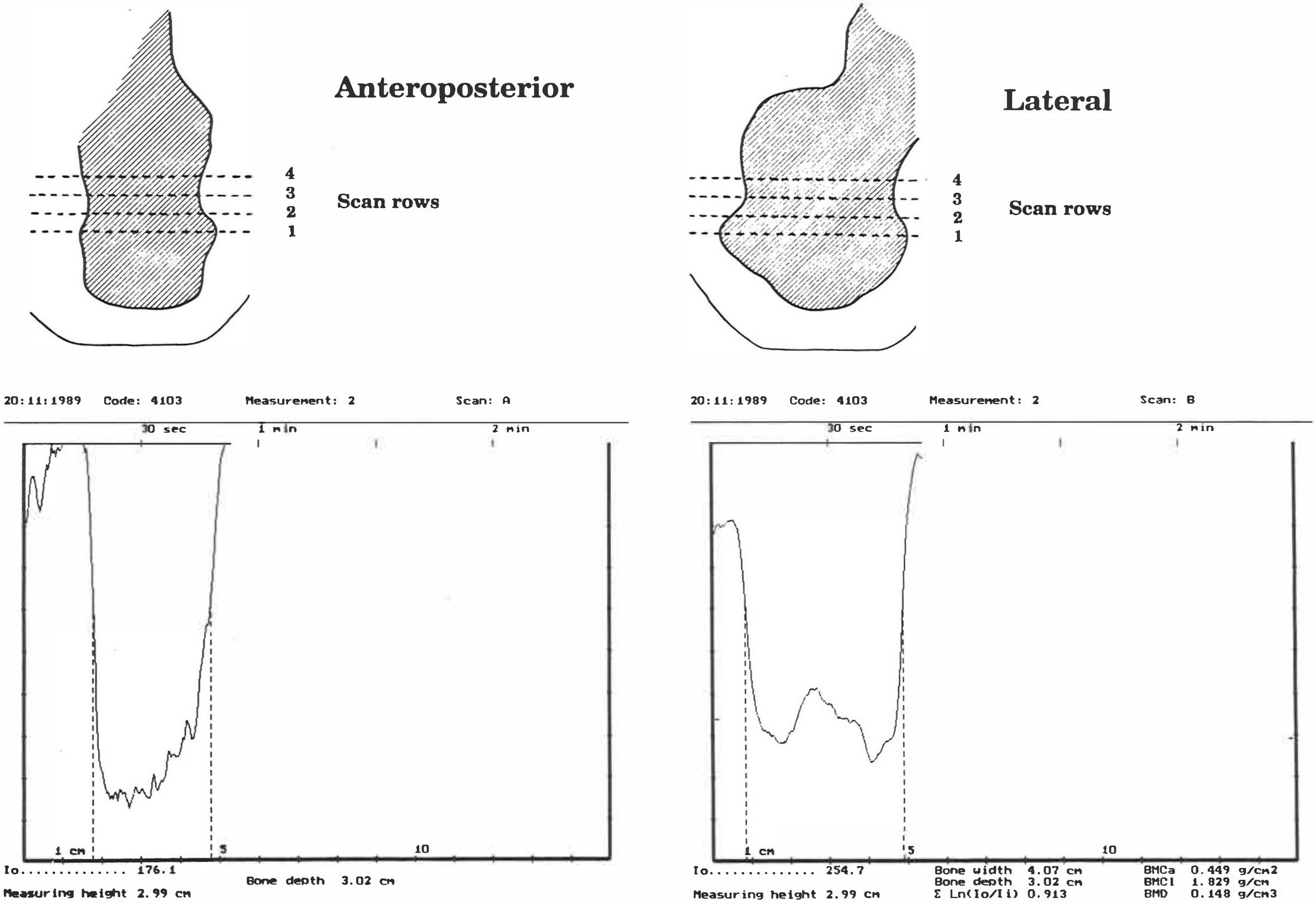
The SPA technique was used in our population studies (I, II, III) to measure the BMC and BMD at calcaneus. The radioactive source was ^{125}I, and the mean energy approx. 27 KeV. The scanning time for total four scans was less than 15 min. The measurements were done from two orthogonal directions (lateral and anteroposterior) to measure both the "width" and "depth" of the calcaneus (Figure 6) and to enable the results to be expressed per volume unit of bone ($g \cdot cm^{-3}$). In the study of 50-60-year-old women, only one scan was measured (middle-part of the calcaneus, which corresponded the third scan in later studies II and III). In studies II and III, the mean of four different scanning sites was taken as the result. The coefficients of variation (CV) between the repeated measurements of calcaneus BMC and BMD were less than 2%. Detailed information about the measurements is given in the original reports referred to.

Computerized tomography

A CT scanner (Siemens SOMATOM CR) was used to measure the BMD and geometrical properties of tibia bone in the subgroups of 78-year-old women (IV and V). Bone densities, cross-sectional areas, and moments of inertia of three scans were determined from the proximal and middle shaft of the tibia in which the same (intersection) points were used as in measuring elastic wave velocity. The system parameters employed were as follows: pixel size at X and Y of 0.2mm, a slice thickness of 2mm, a pixel matrix of 256 x 256; and exposure factors of 125 kV, 500 mA and 7s. The reproducibility of the BMD measured by CT was 3.2%. The CV of the whole cross-sectional area (CSA) was 1.4% and of bone CSA 4.9% (IV). Detailed information is given in the original reports referred to.

TABLE 3 The variables measured in the original studies and the methods used

Variables	Studies	Method/Reference
Anthropometry and physical capacity:		
Body height	I, II, III	
Body mass	I-V	
Body fat and lean body mass	I, II, III	Durnin et al. 1974, Lukaski et al. 1985
Body mass index	I	Weight·height^{-2}
Calcaneus width and depth	I, II	Suominen & Rahkila 1991
Leg extension force	I	Heikkinen et al. 1984, Viitasalo et al. 1985
VO_2max	I	Rusko et al. 1980 Heikkinen et al. 1984,
Bone densitometry:		
BMC and BMD in calcaneus	I, II, III	Single energy photon absorption, Suominen & Rahkila 1991
BMD in tibia	IV, V	CT, Siemens SOMATOM CR
Tibia bone cross-sectional area	IV, V	CT, Siemens SOMATOM CR
Tibia bone mass and density distribution	V	Mass and density spectrum. CT, Siemens SOMATOM CR
Mechanical properties:		
Velocity of elastic wave	IV	Abramson et al. 1958, Landau et al. 1959
Elastic factor R	IV	A measure of (average values of) Young's modulus and area moment of inertia combined
Elastic factor K	IV	A measure for an average value of Young's modulus
Elastic factor P	IV	A measure which assumes that Young's modulus is proportional to density squared
Moments of inertia	V	Milgrom et al. 1989, Harrington et al. 1993
Flexural rigidity angle R	V	The angle between the I_{max} axis and the ap axis in the clockwise direction



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20:11:1989    Code: 4103          Measurement: 2              Scan: A

Io.............. 176.1
                                  Bone depth   3.02 cm
Measuring height 2.99 cm
```

```
20:11:1989    Code: 4103          Measurement: 2              Scan: B

Io.............. 254.7            Bone width   4.07 cm        BMCa   0.449 g/cm2
                                  Bone depth   3.02 cm        BMCl   1.829 g/cm
Measuring height 2.99 cm          Σ Ln(Io/Ii)  0.913          BMD    0.148 g/cm3
```

FIGURE 6 Schematic presentation and sample of print-out of transmission of radiation in anteroposterior and lateral scanning of the calcaneus (from Suominen et al. 1991, with permission).

4.4.2 Elastic wave propagation

The elastic wave propagation (EWP) measurements in vivo were performed on the right tibia. The experimental arrangement was such that the subject was seated on a chair and the subcutaneous surface of the tibia was placed horizontally on a table. Selected points on the skin surface were chosen for the hammer strike and for the accelerometer contacts. The hammer was dropped from a fixed height of 4 cm on to the tibia tubercular. The accelerometers A and B were positioned on the tibia distally to the prescribed distances from the point of the hammer strike. The force and acceleration outputs were collected simultaneously using a DT 2821 Data Translation software package (sampling frequency 40 kHz per channel). The velocity of the pulse in vivo was calculated from the measured signals by using calibrated time intervals determined for the first detected peak of the acceleration curves (F to A, F to B and A to B) and from the known distances between the three points. Detailed information about the measurements are given in original report IV.

The timing accuracy of the apparatus was tested on nylon and acrylic rods (D=50 mm) and found to be ± 16 µs. The results for nylon and acrylic were also used for calibrating the measured time intervals in order to exclude the effect of the apparent slowing of a pulse of bending waves caused by dispersion. The CV of measured velocities ranged from 2.5% to 4.8% for human tibia bone.

We also tested the relationship between velocity and cross-sectional area (velocity is proportional to the square root of the sum of the outer and inner cross-sectional areas) in polyvinyl chloride (density 1.4 $g \cdot cm^{-3}$) tubes of varying inner and outer diameters. The results of these measurements show the above relationship to hold very well with our assumption. Detailed information is given in original report IV.

It is difficult to name a unique factor which would explain the behavior of the velocity along the bone. Therefore, we constructed three factors which included different kinds of dependence on velocity (IV): factor R, a measure of (average values of) Young's modulus and area moment of inertia combined, which incorporates the effect of changing bone mass; factor K, a measure for an average value of Young's modulus, which includes changes along the bone in both density and area moment of inertia; and factor P, a measure which assumes that Young's modulus is proportional to density squared and includes the changes in density, Young's modulus and area moment of inertia.

4.5 Statistical methods

Student's t-test (two-tailed, I-V) was used as the basic tool in the statistical analyses. One-way analysis of variance followed by the LSD test was employed to test the differences between the means of three groups (II), and two-way analysis of variance followed by the LSD-test was used to test BMD in relation to smoking and drinking at different levels of physical activity (I). Pearson's and Polyserial correlation coefficients and partial correlation coefficients, as well as the analysis of covariance, were applied to examine the relationships between bone mineral density, level of physical activity, and other variables (I, II and III). Chi-square (X^2) was used to test the physical activity differences between the men and women, and between the high and low BMD groups (II, V). A stepwise logistic regression analysis was performed to estimate the interrelationship between fracture and BMD, age, and lean body mass (III). The relative risk (RR) of fracture in relation to different levels of BMD for both sexes was also calculated (III). The statistical analyses were employed using an SPSS-X software package.

5 RESULTS

5.1 Bone mineral density in men and women

The results of the BMC and BMD measurements in the 75-and 80 year-old men and women are shown in Figures 7 and 8. The men had on average 36% higher BMC and 16% higher BMD values than the women at the age of 75. The corresponding figures for the 80-year-olds were 33% and 21%. When the BMC and BMD values were compared between the groups, significant differences were found among the women, but not among the men. The BMD values (one scan) of the 50-60-year-old women (I) were clearly higher than those of the 75- and 80-year-old women.

5.2 Bone mineral density in relation to body weight and physical exercise

The correlations between BMC, BMD and body weight in the groups studied are summarized in Table 4. BMC correlated with body weight in the 75- and 80-year-old men and women. BMD correlated positively with body weight in the 80-year-old men and in both the 75- and 80-year-old women, but in the 50-60-year-old women the correlation was negative. The extremely low BMD group of 78-year-old women had significantly lower body weight than the high BMD group. However, when the correlation analyses were carried out separately in these two homogenous groups, no correlations were obtained between BMD and body weight.

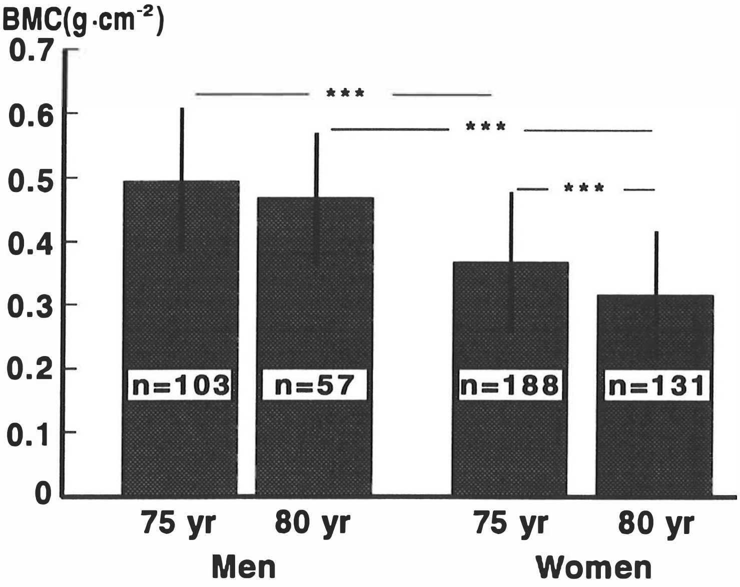

FIGURE 7 Bone mineral content in 75- and 80-year-old men and women (*** $p<0.001$).

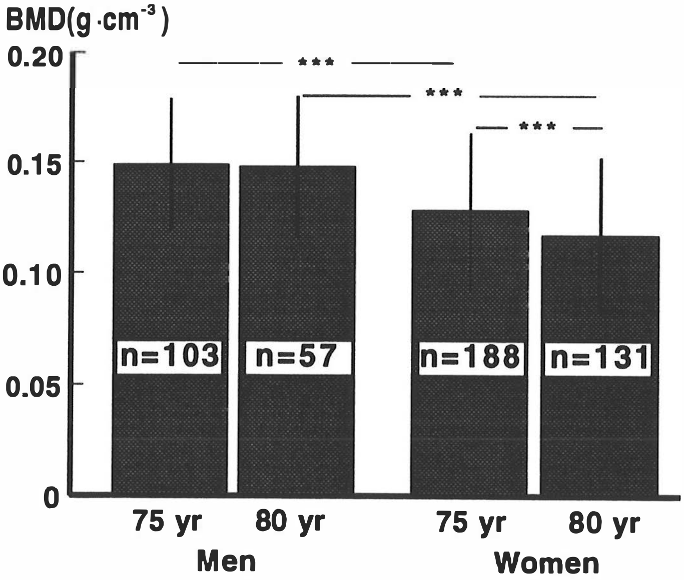

FIGURE 8 Bone mineral density in 75- and 80-year-old men and women (*** $p<0.001$).

The study of the 50-60-year-old women (I) showed that women who participated in vigorous exercise two or more times a week or whose total physical activity amounted to four hours a week had significantly higher BMD than those who exercised less. When the subjects were classified into three groups according to level of physical activity and the effect of body weight was controlled, moderate physical activity was related to higher BMC among the 75-year-old men (II) and to higher BMC and BMD in the 80-year-old men and women (Table 5).

Table 4. Correlations between BMC/BMD and body weight in the groups studied (r values, 2-tailed p in brackets)

Variable	Studied Groups	
	50-60-year-old	
		Women (n=108)
$BMD_{calcaneus}$		-0.162 (0.047)
	75-year-old	
	Men (n=103)	Women (n=188)
$BMC_{calcaneus}$	0.325 (0.001)	0.311 (<0.001)
$BMD_{calcaneus}$	0.189 (0.056)	0.241 (0.001)
	80-year-old	
	Men (n=55-57)	Women (n=131)
$BMC_{calcaneus}$	0.412 (0.001)	0.455 (<0.001)
$BMD_{calcaneus}$	0.319 (0.015)	0.468 (<0.001)
	78-year-old women	
	High BMD group (n=19)	Low BMD group (n=17)
$BMD_{tibia\ trabecular}$	0.023 (0.925)	0.117 (0.656)
$BMD_{tibia\ cortical}$	-0.097 (0.694)	0.103 (0.693)
$BMD_{tibia\ cortical}$	-0.112 (0.648)	0.132 (0.614)

TABLE 5 BMC and BMD in relation to current physical activity among 80-year-old men and women using body weight as a covariate (Mean ± SD)

Physical activity	Men				Women			
	BMC ($g\cdot cm^{-2}$)		BMD ($g\cdot cm^{-3}$)		BMC ($g\cdot cm^{-2}$)		BMD ($g\cdot cm^{-3}$)	
Low	0.428 ± 0.128		0.137 ± 0.039		0.304 ± 0.096		0.114 ± 0.034	
	(n=22)				(n=44)			
Moderate	0.497 ± 0.087		0.156 ± 0.026		0.317 ± 0.105		0.118 ± 0.036	
	(n=32)				(n=88)			
Analysis of covariance	F	p	F	p	F	p	F	p
Physical activity	5.130	0.028	3.975	0.052	4.422	0.037	5.012	0.027
Body weight	12.303	0.001	6.280	0.015	34.006	<0.001	36.448	<0.001

Figures 9 and 10 illustrate the interrelationship between exercise, body weight and BMD. Even though there were no differences in BMD between the different physical activity-level groups, when we combined body weight and physical activity, dividing body weight into four classes and physical activity into three classes in the 75- and 80-year-old women, the results showed a tendency in the 80-year-olds for BMD to increase with level of physical activity and body weight. However, only body weight showed a significant effect on BMD in all groups.

Those 75-year-old men and women who had been physically active in their earlier life span tended to show higher BMD values than those who had been more sedentary (II). The same phenomenon was obtained in the subgroup of 78-year-olds (IV and V): the high BMD group had been physically more active in their earlier life span than the low BMD group (age periods 20-49, p<0.01-0.05).

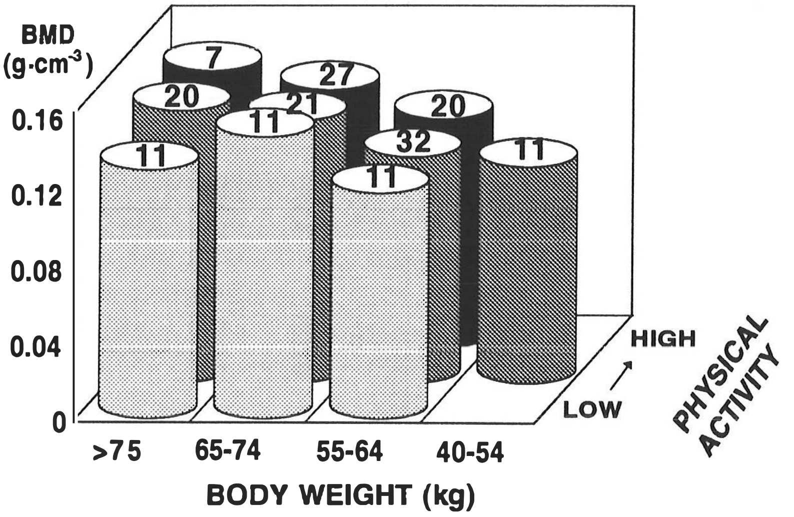

FIGURE 9 Bone mineral density at different levels of physical activity with different body weight among 75-year-old women (two-way analysis of variance, p=0.975 for physical activity, and p=0.002 for body weight).

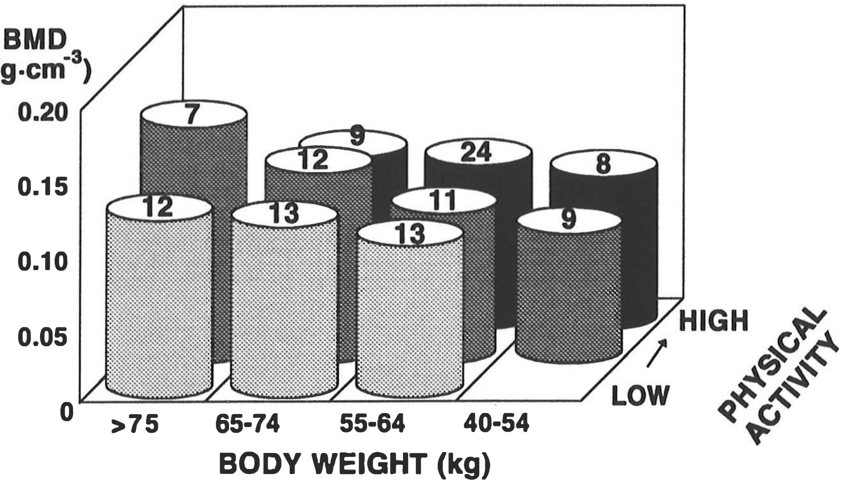

FIGURE 10 Bone mineral density at different levels of physical activity with different body weight among 80-year-old women (two-way analysis of variance, $p=0.090$ for physical activity, and $p<0.001$ for body weight).

5.3 Bone mineral density and mechanical properties

The bone density and cross-sectional geometry properties of the tibia shaft were measured by CT at the same intersection points as the elastic bending wave velocity recordings (IV, V) in the 78-year-old women. The results (V) showed that the high calcaneus BMD group had higher tibia BMD and bone cross-sectional area (CSA) than the low BMD group. The distribution of bone mass indicated that the low BMD group had lost their bone mainly from the endosteal surface, especially in the direction of greatest strength (Figure 11). However, both groups had a similar mass distribution curve at the measured sections (V).

The high BMD group also had higher cross-sectional moments of inertia (anterior-posterior: I_{ap}, medial-lateral: I_{ml}) and principal moments of inertia (I_{max} and I_{min}) at the upper middle shaft section (A) in comparison with the low BMD group. The differences between the groups were more pronounced when only the high density areas were included. At the lower middle shaft section (B), the differences between the groups also appeared significant at the higher BMD levels (V). There were no differences in the area moments of inertia between these two groups (V).

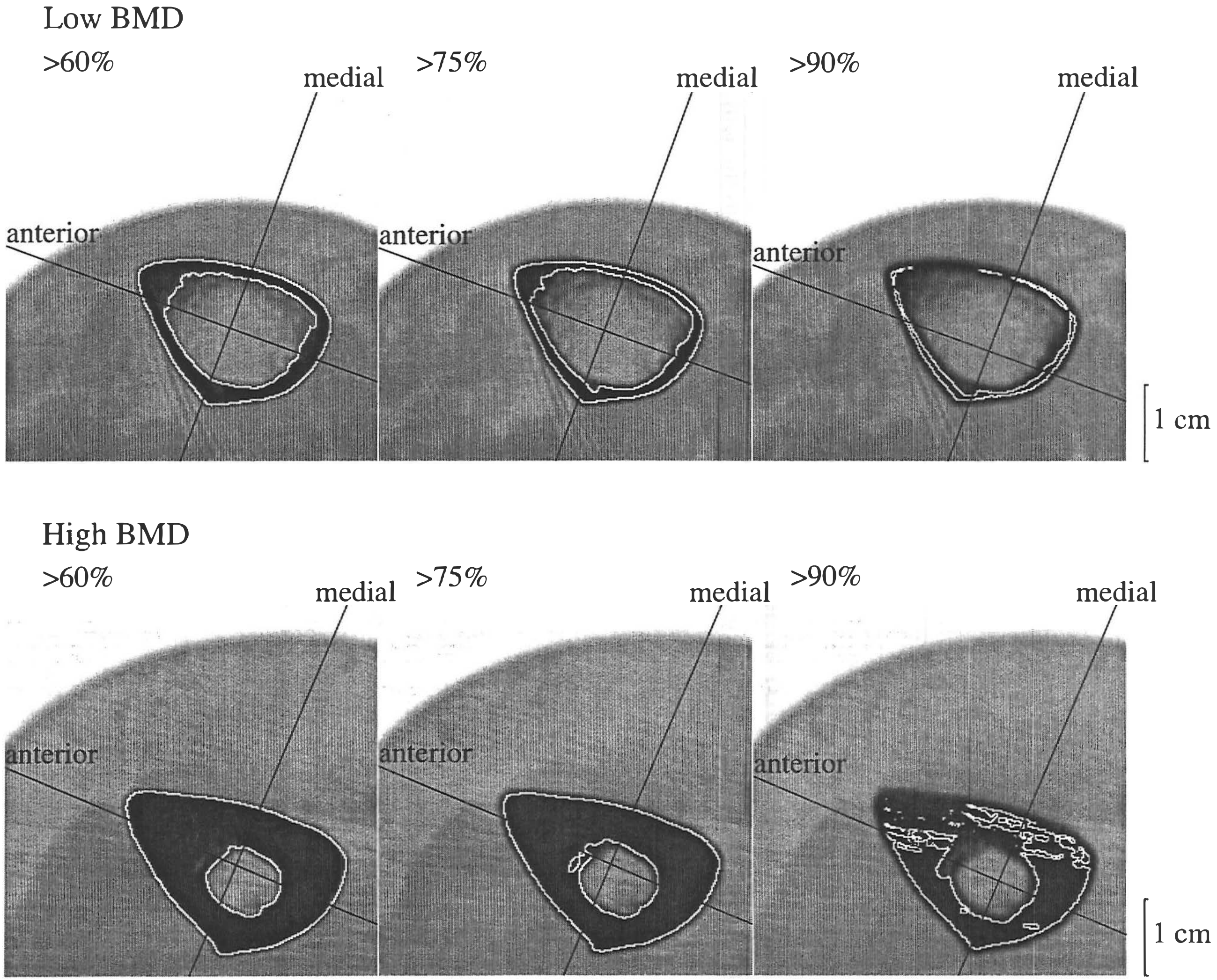

FIGURE 11 Example of bone mass distribution around center axis for cross-sectional areas representing different density levels (percentages of maximum value of BMD) in the CT scan. Low BMD woman (above) and high BMD woman (below). Cross section through the middle shaft of the right leg. Sectioned surfaces viewed from distal.

BMD correlated with I_{ap} and I_{min} in the low BMD group, but not in the high BMD group (V). There were no correlations between BMD and CSA in either section and either group. Tibia BMD correlated with calcaneus BMD only at section A in the high BMD group (r=0.490, p=0.033).

The results for the velocity of elastic bending waves through the tibia shaft and the corresponding BMD values are shown in paper IV, Table 1. The low calcaneus BMD group had a higher velocity at proximal tibia (between sections F and A), and lower velocity at the middle tibia (between A and B), in comparison with the high BMD group.

The correlations between BMD, velocity of elastic (bending) waves and elastic factors of cortical tibia bone (IV, V) are shown in Table 6. The results indicate that the velocity along the tibia middle shaft (A-B) was dependent on the combination of Young's modulus and the area moment of inertia in the high BMD group. The higher the BMD, the lower the velocity. In the low BMD group, the velocity related mainly to Young's modulus. The higher the BMD, the higher the velocity. In both groups the elastic factor R correlated with the cross-sectional moments of inertia and principal moments of inertia (r range 0.520-0.658, p =0.010-0.057 for the high BMD group, and r=0.535-0.783, p <0.001-0.033 for the low BMD group).

TABLE 6 Correlations between BMD, velocity of elastic wave (v) and elastic factors (R, K, P) of cortical tibia bone in high and low calcaneus BMD groups of 78-year-old women (r values, 2-tailed p in brackets)

	High BMD group (n=14-19)					Low BMD group (n=16-17)				
Variable	v	BMD	CSA	R	K	v	BMD	CSA	R	K
BMD	-0.373 (0.189)					0.337 (0.202)				
CSA	0.412 (0.143)	-0.414 (0.141)				0.244 (0.362)	0.168 (0.534)			
R	0.980 (<0.001)	-0.327 (0.253)	0.556 (0.039)			0.908 (<0.001)	0.552 (0.027)	0.447 (0.082)		
K	0.330 (0.249)	0.220 (0.450)	-0.033 (0.910)	0.318 (0.268)		0.624 (0.010)	0.308 (0.246)	0.142 (0.601)	0.576 (0.020)	
P	0.541 (0.046)	-0.184 (0.530)	0.106 (0.720)	0.502 (0.067)	0.803 (0.001)	0.210 (0.435)	0.171 (0.527)	-0.302 (0.256)	0.016 (0.954)	-0.013 (0.961)

5.4 Bone mineral density and risk of fractures

In the retrospective fracture study (III), 22% (n=22) of the men and 45% (n=84) of the women among the 75-year-olds sustained (at least) one fracture after age 50. The corresponding figures for the 80-year-olds were 16% (n=9) and 35% (n=48), respectively. Over half of the fractures were of the wrist/hand or ankle/leg. Prospective fractures (III) were recorded over periods of 29-34 months. Twenty of the 75-year-olds (3 men and 17 women) and 16 of the 80-year-olds (6 men and 10 women) sustained a fracture during the follow-up period.

The incidence of fractures in relation to BMD in the 75- and 80-year-olds showed that both the retrospective and prospective fracture subjects in both age groups had lower BMC and BMD values when compared with the non-fracture subjects, especially among the women. During the follow-up period, there were no fractures in either of the sex or age groups among those with BMC and BMD values greater than 1 SD above the mean. When using logistic regression analysis, BMD alone explained about 60% of the overall fracture probability among the women studied.

Figures 12 and 13 show the probability of fractures. When the absolute levels of BMC and BMD were related to fracture occurrence, the results clearly showed that with increased BMC and BMD values the probability of fracture decreased. Where men and women have similar BMC and BMD values, they also have a similar probability for fracture occurrence.

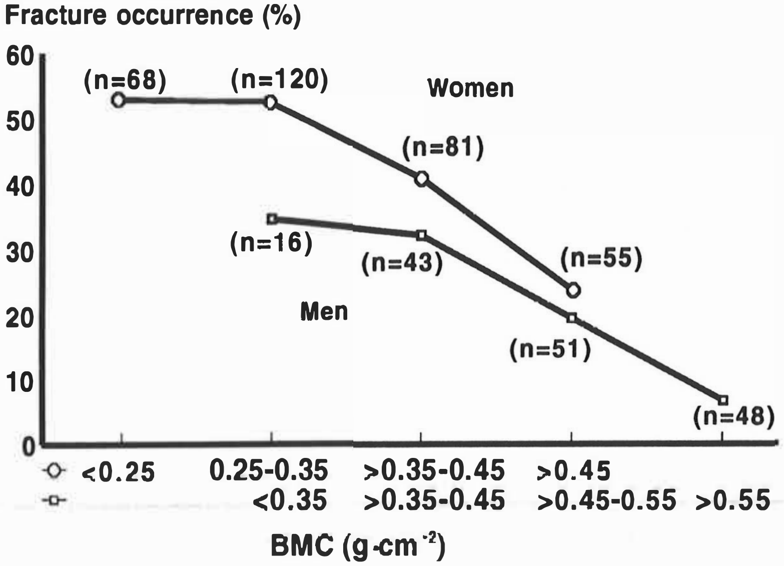

FIGURE 12 Fracture occurrence after age 50 for 75- and 80-year-old men and women with different BMC levels.

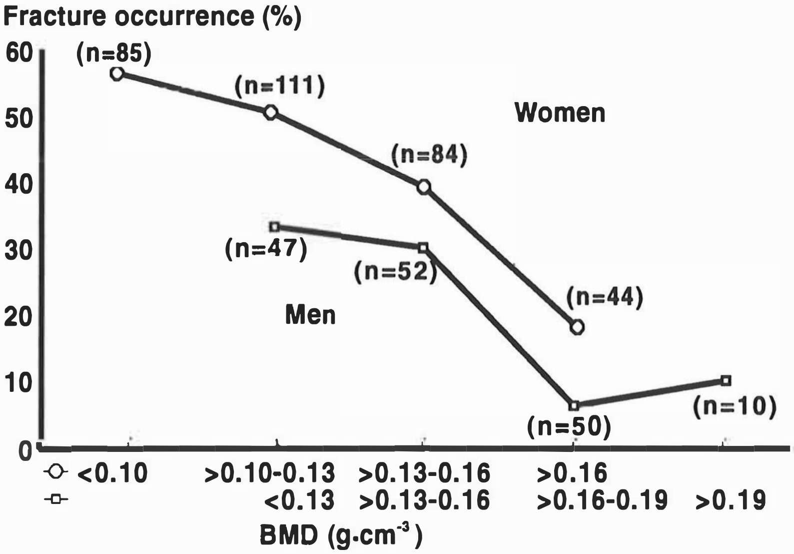

FIGURE 13 Fracture occurrence after age 50 for 75- and 80-year-old men and women with different BMD levels.

6 DISCUSSION

6.1 Methodological issues

The present research has mostly been carried out using cross-sectional studies. The techniques which have been used included SPA, CT and EWP. The advantages and disadvantages of the various designs and techniques used are described below.

The SPA technique was used in our population studies (I, II, III) to measure the BMC and BMD at the calcaneus. The major advantage of SPA is low radiation, high precision (less than 2%) and short scanning time (less than 15 min). On the basis of the literature SPA is also very accurate (2-6% error, Mazess et al. 1989, Faulkner et al. 1991). Because the measurements were done from two orthogonal directions (lateral and anteroposterior) to measure both the "width" and "depth" of the calcaneus, it was also possible to express the results per unit volume of bone ($g \cdot cm^{-3}$) in our studies.

The calcaneus contains mostly trabecular bone (95%), and the mineral density in the calcaneus correlated highly with total body mineral density (Suominen et al. 1991). The calcaneus also seems to be the most sensitive bone site in response to change of loading condition (Leblanc et al. 1990). However, trabecular bone may not be metabolically active at this site in comparison with trabecular bone in the spine (Mazess et al. 1989). Therefore, it may not be sensitive enough to predict fractures of the spine and hip (Mazess et al. 1989, Cummings et al. 1993).

An attempt to find out what other characteristics of bone associated with BMD in relation to fractures, we also sampled the subjects by groups

(IV and V) according to the BMD values of the population studied (II). The groups represent the extremes of the population. This has the advantage of showing the differences more clearly. However, because of the homogeneity of the groups, which was due to the selection procedure, the correlation analysis within the groups becomes somewhat complex.

CT was used to measure the BMD and geometrical properties of tibia bone in the subgroups. The CT method has the advantage of measuring the true density and distribution of bone mass. It also makes it possible to calculate the geometric properties of bone. It not only measures BMD but also gives information about at the various surfaces within the bone cortex. Therefore, it can provide more information for clinical use in predicting fracture incidence. The precision of CT was 3% for tibia BMD in our study. The results were standardized by using K_2HPO_4 and cow bone ash density. However, CT is expensive and emits high radiation compared with other bone densitometry methods.

EWP (IV) was used to measure the velocity of the bending wave through tibia bone, on the basis of elasticity theory. It is radiation-free, and has the advantage of providing information not only about the density but also about the mechanical properties of bone. Measurement in this way is also simple and inexpensive. However, it is difficult to name a unique factor which would explain the behavior of the velocity along the bone. Therefore, we worked out three factors which included different kinds of dependence on velocity. It is conceivable that some of these factors, when combined with the measured velocities of elastic waves, could be used as indicators of the mechanical properties of bone. This work also has value for the further development of methods for studying the biomechanical properties of bone in vivo, so contributing to our understanding of the causes of bone fractures.

In reality, bone mass is not homogeneously distributed, so that true bone mass and its distribution should be taken into account in determining e.g. the moments of inertia. If true bone mass and its distribution are not taken into account, which is the case when scaled moments of inertia and area moments of inertia are used, the results will not distinguish the high and low BMD groups (V).

6.2 Bone mineral density in older men and women

The results of the calcaneus mineral measurements in 75-and 80-year-old men and women show, in accordance with previous studies (Rundgren et al. 1984, Yano et al. 1984, Barquero et al. 1992, Jonsson et al. 1993), that the men had higher bone mineral mass. The difference between the men and the women, however, was clearly smaller for BMD. The differences between the sexes in BMC and BMD in elderly people may be due to anthropometric factors and steroid hormone metabolism (unpublished data). For instance, body mass and lean body mass were significantly higher in the men than the women in both age groups. However, the sex difference in BMD disappeared after controlling for lean body mass. This indicates that lean body mass may be one of the important factors associated with BMD in elderly people in relation to sex differences. We also found that the 75-year-old men had higher testosterone values and lower sex hormone-binding globulin values than the women (data not shown).

When the results of BMC and BMD between the age groups were compared, the differences were found only among the women but not among the men. These findings may be due to selective mortality, as the 80-year-old men were still in good health.

Rico et al. (1992) suggested that it is more relevant to measure BMC than BMD, because BMD values minimize sex-related differences as opposed to BMC values. However, BMC gives an idea about the amount of bone mass in one bone site while BMD takes into account bone size and gives an idea about the density of that bone site. An animal study showed that increases in bone volume may occur without a corresponding change in bone quality (Woo et al. 1981). Buckwalter & Cooper (1987) stated that the shapes and sizes of bones are largely predetermined by genetic factors which cannot be changed. Given that bone mineral density rather than bone size can be influenced by environmental factors, it is therefore important to measure both BMC and BMD in studying bone properties. Even where older people have the same BMC and BMD values as younger adults, their bone quality will not be the same. They may differ in bone mass distribution and geometrical properties as well as in the metabolic status of bone.

6.3 Bone mineral density and the interaction of body weight and physical exercise

The results of the study in the 50-60-year-old women showed that BMD was associated with the level of physical activity. BMD also correlated with muscle force (I). However, the results of the studies in the 75- and 80-year-olds showed that only those with moderate physical activity had higher BMC and BMD values than those with low activity. Older women tend to exercise at a lower intensity than men and younger women. For example, according to self-reported walking distance and frequency, the 75-year-old women walked on average about 70% fewer km/week than the men. But there were no differences in walking times per week between the men and women. Supposing that both groups walk one hour per day and cover the distance they reported, then the men must clearly walk much faster than the women. If we further take into account the differences in body weight between the men and the women, the men will have had more load on the calcaneus than the women during the same time period.

Moreover, BMD correlated negatively with body weight in the younger women but positively with body weight in the older women. This may be due to the fact that physically active women have a lower percentage of fat and a lower body weight than sedentary women. For older women, even when they are active, the intensity of physical activity is less than for younger women. Consequently, body weight in the elderly becomes an important source of bone mechanical stress. Thus we cannot use either body weight or physical activity as an independent variable in studying bone density in relation to loading history (Whalen et al 1988). When we categorized body weight into four classes and physical activity into three classes among the 75- and 80-year-old women, only body weight showed a significant effect on BMD. It can be seen that the 80-year-old women with high body weight who were moderately physically active had high BMD values in comparison with the women with low body weight who were physically inactive. This suggests that for older people, the interaction between body weight and physical activity contributes to the maintenance of bone mass and density. The best way to slow down the loss of bone would appear to be to keep moving with moderate intensity and to retain a moderate body weight.

The question, however, remains whether a small percentage gain in bone mineral density, possibly achieved by increased exercise, is of clinical significance for bone strength or whether there are other changes in bone structure, geometry or metabolic properties that are more important, and whether physical exercise can inhibit the occurrence of fractures (Suominen 1994). The study (III) in 75- and 80-year-old men and women did not show any associations between self-reported physical activity or other living habits and fracture occurrences. It must also be kept in mind that physical activity could not be very accurately measured by the present method. Individuals may interpret the same criteria regarding level of activity differently.

There have been very few studies of elderly people that have focused on the effects of physical activity practised during different periods of their lives. Investigating the history of physical activity in elderly people would provide useful information about the role of physical activity in relation to bone properties. It would also show what kind of timing of physical activity is the most beneficial for late age bone properties. The study of the 75-year-olds showed that the men had been more physically active during the earlier periods of their life span than the women (below age 40). After age 40, the level of physical activity was reported to be lower than previously by both sexes (II). In agreement with Kriska et al. (1988), BMD seemed to be related to the amount of physical activity practised during earlier periods of the life span in both sexes. The same was also true for the 78-year-old women in the high and low BMD groups (IV and V). The high BMD group had been physically more active during earlier life than the low BMD group. These findings suggest that physical activity during the earlier life span can be beneficial for high bone density throughout later life.

6.4 The relationship between bone mineral density and biomechanical properties

Strength is the key word in studying the relationship between BMD and the biomechanical properties of bone. However, up till now it has not been possible to measure bone strength in vivo; the best way to estimate bone strength indirectly has been to measure the velocity of sound or elastic waves, or cross-sectional moments of inertia. According to elasticity theory, Young's modulus (stiffness of bone) is proportional to the density multiplied the longitudinal velocity squared. However, the relationship between Young's modulus, density and velocity cannot always be explained in such a simple way. Moreover, if a bone is under a bending load then, according to the relationship between failure stress and moment of inertia, the larger the (cross-sectional) moment of inertia the smaller the stress on the bone (Milgrom et al. 1989). A large (cross-sectional) moment of inertia means a good resistance capacity to the bending load on the bone.

The study of the relationship between the geometric properties of the tibia and bone mineral density in 78-year-old women showed that the inner cross-sectional area had expanded more in the low BMD group and that they had a smaller bone cross-sectional area than the high BMD group. The results also showed that the low BMD group had smaller moments of inertia than the high BMD group, especially in the direction of greatest strength. Accordingly, our findings indicate that these two groups have a different resistance to the bending load, especially in the direction of greatest strength of the tibia. The high BMD group has obviously adapted quite well to mechanical usage, and their bones have good mechanical properties. On the other hand, the low BMD group had lost their bone mass mainly from the direction of greatest strength, thus incurring a higher risk of fractures.

In addition, our results showed that the principal angle R, which indicates the direction of the greatest flexural rigidity of the tibia, had rotated on the average more in the low BMD group than in the high BMD group. For maintaining the resistance of bone to bending, the bone mass seems to be better maintained in the periosteal area. It seems that the altered distribution of bone mass takes place only in some parts of the bone, although the factors which control the local biomechanical requirements are still unknown. The relative redistribution of bone mass compensates for the loss in bone structural strength (Myburgh et al. 1992), and thus the supportive function of bone and its resistance to bending are better maintained.

The results of EWP (IV) showed that the velocities of bending waves along tibia bone can for the most part be explained by the density and area moment of inertia of bone, the density depending on the elastic constants of the bone (Young's modulus). When the correlations between cortical tibia BMD, velocity and elastic factors were calculated in the high and low calcaneus BMD groups separately, it was found that the mechanical behavior of the tibia was different in these two groups regardless of the factor used. In the high BMD group, the velocity of elastic waves depends on the combination of Young's modulus and area moment of inertia. The higher the BMD, the lower the velocity, which follows basic elasticity theory. In the low BMD group, on the other hand, the velocity related mainly to Young's modulus. The higher the BMD, the higher the velocity, which indicates that bone in the low BMD group is harder (more fragile) and that it has lost much of its elastic properties. Moreover, the different behavior of the velocity between proximal part (F-A) and middle part (A-B) of the tibia in these two groups may be due to the fact that the structure of the proximal part resembles a metaphyseal shell, the changes in geometry as well as in the ratio between cortical and trabecular bone are quite dramatic. But thereafter, between the A and B sections, the bone becomes more homogeneous and mostly contains cortical bone.

Except for the bone material and geometrical properties, fracture occurrence is dependent on loading conditions as well as on loading history. Loading changes the configuration of deformable objects through the development of internal forces within the object (Hayes & Gerhart 1985, Melton et al. 1988). For most people, daily activities together with body weight are the principal sources of external loads on bone (Whalen et al. 1988). Although the specific loading conditions were unknown in our study, we may speculate, on the basis of the differences in the history of physical activity and in body mass, that the loading histories were different in these two groups.

6.5 Bone mineral density as a predictor of fractures

The validity of cross-sectional studies depends on how well the sample represents the population as a whole. We used the total population in our fracture study (III). The same subjects participated in both the retrospective and prospective studies. Similar results were obtained for both the retrospective and prospective studies, which gives the predictor (BMD) more power to predict the outcome (fractures). The same age cohort was used and the participation rates were high. However, the results did not include persons who were housebound, living in institutions, or hospitalized. Consequently, the results cannot give a true picture of the age-specific incidence of fractures. Nevertheless, our findings are generalizable to 75- and 80-year-old people living in their own homes in an urban environment.

Both the retrospective and prospective studies showed that those persons who had BMD values clearly higher than average for their age had the lowest fracture risk. Fractures occurred more frequently among those with BMD values below the mean. During the prospective follow-up no fractures occurred among those with high BMD values. These findings are in agreement with earlier prospective studies (Ross et al. 1987, 1988, Hui et al. 1989, Cummings et al. 1990, Black et al. 1992) indicating that calcaneus BMD values provide useful information on the probability of fractures even in old age.

When the absolute levels of BMC and BMD were used in calculating the probability of fracture occurrence, the results clearly showed that with increased BMC and BMD values the probability of a fracture decreased in both sexes. Where the levels of BMC and BMD are the same for men and women, the difference between the sexes in the probability of sustaining fractures is reduced, and both men and women have a similar fracture probability.

6.6 Future studies

This study strengthens the idea that bone is a highly complex material. The integrity of the skeleton involves the amount of bone mass, the distribution of bone mass within a bone site, and bone quality. Fracture occurrence seems to be related not only to loss of bone mass but also to change in bone geometry and mechanical properties. Physical activity and moderate body weight may contribute both to slowing down the loss of bone and the strengthening of bone. However, several questions still need to be clarified.

We do not know why fractures do not occur in some bones, even in persons with very low BMC and BMD values at those bone sites. We do not know how mechanical stress stimulates the bone cells while the bone is adapting to mechanical usage. We do not know why bone activation occurs only at a particular location and at a particular time of life. We do not know how bone mass is redistributed after its loss, and under what conditions this occurs. Neither do we know the nature of the mechanism by which bone mineral and collagen metabolism are related to the mechanical properties of bone thus enabling stress on bone to be translated into biological transformations inside the bone. We do not know what role is placed by hormones in maintaining bone properties in elderly people. We do not know the optimum intensities and types of physical exercise useful for maintaining bone mass and slowing down the process of bone loss after peak bone mass has been attained.

Future studies, therefore, should be focused on the above-mentioned questions with the aim of developing methods for testing the material and geometric properties of bone independently and discriminating the material and geometric changes in bone. The mechanism of these changes might then be understood, opening the way towards finding means to prevent and treat negative changes in bone structure and metabolism. Future research should also pay more attention to the timing of physical exercise during the life-course and to identifying optimum exercise programs for young, middle-aged and elderly people, respectively, so that exercise can be used to more efficiently effect on bone. The reason why weight-bearing trabecular bone, such as the calcaneus, does not fracture should be investigated. Studies are also needed to quantify the changes in cortical bone, since cortical bone fractures cost more in hospitalization and are more complicated to treat.

7 SUMMARY

The present study examined bone mineral density in older men and women. The purpose was to relate bone mineral density to physical exercise, to assess the biomechanical properties of bone, and to examine the association between BMD and the risk of fractures in elderly people.

The study covered all the men and women born in 1910 and 1914 who were resident in the city of Jyväskylä in 1989 (75 years old, N=388) and 1990 (80 years old, N=285) (II,III). In addition, 193 women who were 50-60 years old in 1988, also from the city of Jyväskylä and selected on the basis of their physical activity and educational background, participated in the study (I). Altogether 160 men and 432 women took part in the bone measurements performed at the calcaneus using a ^{125}I-photon absorption method. Furthermore, 57 women who were 78 years old in 1992 and who constituted subgroups of the previously studied 75-year-old women living in Jyväskylä were selected on the basis of their calcaneus BMD value (>0.160 g·cm^{-3}, n=30, and <0.100 g·cm^{-3}, n=27). Finally, 20 women with high calcaneus BMD, and 17 women with low BMD took part in the studies of the mechanical properties of the tibia using elastic wave propagation and computerized tomography (IV, V). Retrospective and prospective fracture study was carried out in the 75- and 80-year-olds (III). Retrospective fracture history after age 50 was obtained by questionnaire and interview, and reported fractures were checked from medical records. Prospective fractures were recorded over periods of 29-34 months.

The results can be summarized as follows:

1) Among the 75-80-year-olds, the men had on average 33-36% higher BMC and 16-21% higher BMD values than the women. Among the men there were no differences in either BMC or BMD between the ages of 75 and 80. Among the women, BMD was clearly higher in the 50-60-year-old age group in comparison with the older age groups, and BMC and BMD also differed significantly between the ages of 75 and 80.

2) The 78-year-old women with a higher calcaneus BMD also had on average 20-21% higher BMD of the cortical tibia and 9-12% greater CSA of the tibia at the measured sections compared with the low calcaneus BMD group. The distribution of bone mass showed that the low BMD group had lost their bone mainly from the endosteal surface of the tibia shaft, especially in the direction of greatest strength. However, both groups had a similar mass distribution curve at the measured sections. The high BMD group also had 16% higher cross-sectional moments of inertia at the upper section than the low BMD group. The differences between the groups were more pronounced when only the high BMD parts were included. At the lower section, the differences in moments of inertia between the groups also appeared significant at the higher BMD level.

3) The low BMD group of the 78-year-old women showed a higher elastic wave velocity in the proximal tibia between sections F and A, and a lower velocity in the middle tibia between A and B, in comparison with the high BMD group. The correlations between BMD, velocity of elastic bending wave and the elastic factors of cortical tibia bone showed that the velocity of the elastic bending wave was dependent on the combination of Young's modulus and the area moment of inertia in the high BMD group. The higher the BMD, the lower the velocity, which follows basic elasticity theory and indicates good bone mechanical properties. In the low BMD group, the velocity related mainly to Young's modulus. The higher the BMD, the higher the velocity, which indicates that in the low BMD group, the bone was harder and had lost much of its elastic properties. Accordingly, the results suggest that the mechanical behavior of bone is different in the high and low BMD groups.

4) The middle-aged women who participated in vigorous exercise two or more times a week or whose total physical activity amounted to four hours a week had significantly higher BMD than

those who exercised less. Moderate physical activity related to higher BMC and BMD among the elderly men and women. Those 75-year-old men and women who had been physically active earlier in their life span tended to show higher BMD values than those who had been more sedentary. BMC and BMD correlated positively with body weight in both sexes among the 75- and 80-year-olds. A negative correlation was found among the middle-aged women. Body weight became an important source of stress on bone in the older ages, especially in the women. The interaction of physical activity and body weight exerts more impact on bone. There was a negative correlation between the BMD values and the number of cigarettes smoked over the entire life course among the 75-year-old men and women.

5) The study of bone mineral density of the calcaneus in relation to fractures among the 75- and 80-year-old men and women showed that both retrospective and prospective fracture subjects in both age groups had lower BMC and BMD values compared with non-fracture subjects, especially among the women. On the other hand, during the follow-up period there were no fractures in either of the sex or age groups among those with BMC and BMD values greater than 1 SD above the mean. With increased BMC and BMD values the probability of fractures decreased at a similar rate in both men and women.

6) In respect of the final specific aim, developing a methodology for evaluating the biomechanical properties of bone, it was observed that elastic wave velocity provides an inexpensive way of evaluating the elastic properties of bone and, thereby, osteoporosis. When the study of elastic wave velocity is combined with the study of cross-sectional geometry, it offers a good estimate of bone mechanical properties and has a better discriminatory capability than BMD alone in studying bone fragility and assessing the resistance of a long bone to bending.

In order to obtain reliable values for the elastic wave velocity, it is important to specify the section of the bone over which the velocity is being measured. Useful information may be obtained by comparing the changes in velocity measured along the bone. From the results for the three elastic factors, R, K, and P, we found that the velocities of bending waves can for the most part be explained by changes in bone density and cross-sectional area. In isolating the effect of bone density it is important to include its effect on the elastic constants of bone such as Young's modulus. It is conceivable that some of these factors (R, K and P) combined with the measured velocities of elastic waves could be used as indicators of the mechanical properties of bone. The above consideration may also be useful in ultrasonic measurements.

8 TIIVISTELMÄ

Tutkimuksessa selvitettiin iäkkäiden miesten ja naisten luun mineraalipitoisuutta (BMC) ja -tiheyttä (BMD). Tarkoituksena oli tutkia BMD:n yhteyksiä liikuntaan ja murtumariskiin sekä määrittää luun biomekaanisia ominaisuuksia. Luun tiheysmittaukset tehtiin kantaluusta ^{125}I-gamma-absorptiomenetelmällä 75- ja 80-vuotiailla miehillä (n=160) ja naisilla (n=324) sekä 50-60-vuotiailla naisilla (n=108). Lisäksi kehitettiin elastisten aaltojen etenemiseen perustuvaa tekniikkaa ja tietokonetomografiaa sääriluun mekaanisten ominaisuuksien tutkimiseksi 78-vuotiailla naisilla (n=37), jotka edustivat kantaluun BMD:n osalta kahta ääriryhmää. Naisten kantaluun BMC- ja BMD-arvot olivat pienempiä kuin miesten ja vanhempien ikäryhmien naisten arvot pienempiä kuin nuorempien. Kehon paino korreloi positiivisesti BMC- ja BMD-arvoihin vanhemmissa ikäryhmissä, erityisesti naisilla. Korkea BMD oli yhteydessä intensiiviseen liikuntaan keski-ikäisillä naisilla ja kohtuulliseen fyysiseen aktiivisuuteen iäkkäillä miehillä ja naisilla. 75-vuotiaiden miesten ja naisten BMD korreloi myös aikaisempaan fyysiseen aktiivisuuteen ja tupakointihistoriaan. Sekä retrospektiivisillä että prospektiivisilla murtumatapauksilla oli 75- ja 80-vuotiaiden tutkimuksessa alhaisempi BMC ja BMD kuin niillä, joilla ei ollut murtumia. Murtumien todennäköisyys väheni BMC:n ja BMD:n lisääntyessä miehillä samoin kuin naisillakin. Naiset, joilla oli pieni kantaluun BMD, saivat pienempiä arvoja myös sääriluun BMD:ssä ja sääriluun poikkipinta-alan jäyhyysmomenteissa. Sääriluun massan jakauma-analyysit osoittivat, että alentuneen BMD:n ryhmä oli menettänyt luuta pääasiassa putkiluun sisäpinnasta, erityisesti suurimman taivutuslujuuden suunnassa. Elastisten aaltojen etenemisnopeuden perusteella luu näytti kyseisessä ryhmässä olevan myös kovempaa ja vähemmän elastista. Tutkimuksen tulokset osoittavat, että kantaluun BMC ja BMD ennustavat suhteellisen hyvin iäkkäiden luunmurtumia. Elastisten aaltojen etenemisnopeuden yhdistäminen poikkileikkausgeometriaan antaa hyvän arvion luun mekaanisista ominaisuuksista tutkittaessa luun haurastumista ja taivutuslujuutta.

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