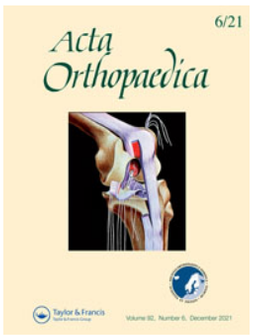

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Bone mineral measurements at the knee using dual photon and dual energy X-ray absorptiometry

Methodological evaluation and clinical studies focusing on adaptive bone remodeling following lower extremity fracture, total knee arthroplasty, and partial versus total meniscectomy

Michael Mørk Petersen

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List of papers

This thesis is based on the following publications:

1. Petersen MM, Olsen C, Lauritzen JB, Lund B. Changes in bone mineral content in the proximal tibia following ankle fracture. Eur J Exp Musculoskel Res 1992; 1: 77-80.

2. Petersen MM, Olsen C, Lauritzen JB, Lund B. Bone mineral content assessed by dual photon absorptiometry in the proximal tibia: normative data and measurements in orthopedic conditions. Eur J Exp Musculoskel Res 1993; 2: 121-6.

3. Svalastoga E, Petersen MM, Wenck A, Strøm H. Measurement of bone mineral content to facilitate an objective evaluation of limb function in the dog. A feasibility study using dual photon absorptiometry. Vet Comp Orthop Trauma 1994; 7: 118-23.

4. Petersen MM, Olsen C, Lauritzen JB, Lund B. Changes in bone mineral density of the distal femur following uncemented total knee arthroplasty. J Arthroplasty 1995a; 10: 7-11.

5. Petersen MM, Nielsen PT, Lauritzen JB, Lund B. Changes in bone mineral density of the proximal tibia following uncemented total knee arthroplasty. A 3-year follow-up of 25 knees. Acta Orthop Scand 1995b; 66: 513-6.

6. Petersen MM, Jensen NC, Gehrchen PM, Nielsen PK, Nielsen PT. The relation between trabecular bone strength and bone mineral density assessed by dual photon and dual energy X-ray absorptiometry in the proximal tibia. Calcif Tissue Int 1996a; 59: 311-4.

7. Petersen MM, Lauritzen JB, Pedersen JG, Lund B. Decreased bone density of the distal femur after uncemented knee arthroplasty. A 1-year follow-up of 29 knees. Acta Orthop Scand 1996b; 67: 339-44.

8. Petersen MM, Olsen C, Lauritzen JB, Lund B, Hede A. Late changes in bone mineral density of the proximal tibia following total or partial medial menisectomy. A randomized study. J Orthop Res 1996c; 14: 16-21.

9. Petersen MM, Gehrchen PM, Nielsen PK, Lund B. Loss of bone mineral of the hip assessed by DEXA following tibial shaft fractures. Bone 1997; 20: 491-5.

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Introduction

During skeletal mineralization and growth, the bones continue modeling and remodeling. Modeling is defined as alterations in the shape of bones through the actions of osteoblasts and osteoclasts, while remodeling is bone turnover without alterations in the shape of bone (Buckwalter et al. 1995). In early adulthood a continuous physiological remodeling of bone takes place without affecting the shape or density of the bones, but after the peak bone mass has been achieved, an age related remodeling results in bone loss (Mazess 1982; Buckwalter et al. 1995). Furthermore according to Wolff's law (Wolff 1892) bones have the ability to model and remodel as a consequence of altered load, and thus adjust their density and structure to the current mechanical demands. In orthopaedic research such change in bone density induced by altered mechanical load has been named adaptive bone remodeling. A special type of adaptive remodeling is the local bone loss observed in close relation to orthopaedic implants such as total hip arthroplasty (THA) (Brown and Ring 1985; Engh et al. 1987), total knee arthroplasty (TKA) (Cameron and Cameron 1987; Mintzer et al. 1990), and spinal fixation devices (McAfee et al. 1989; Smith et al. 1991; Dalenberg et al. 1993). This implant related osteopenia is considered to be a result of stress shielding of the bone. Another type of adaptive remodeling is the loss of bone mineral associated with fractures (Nilsson 1966; Andersson and Nilsson 1979a), and this posttraumatic osteopenia has been very thoroughly examined with respect to quantitative density changes in the peripheral skeleton in close relation to the fracture (Nilsson 1966; Andersson and Nilsson 1979a; Finsen and Benum 1989; Ulivieri et al. 1990). This thesis mainly focus on quantitative measurements of the adaptive remodeling at the knee in relation to different orthopaedic conditions.

The knee is a synovial joint representing the junction between femoral condyles, tibial plateau, and the patella. The knee joint is a weightbearing joint between the two longest bones of the skeleton and it is the largest joint of the body. Great mechanical stresses is acting across the knee joint, and during normal walking compressive forces across the joint have been estimated to reach 2-4 times body weight (Morrison 1970). Thus, the knee is the joint most often involved in pathological changes. Both the distal femur and the proximal tibia consists of epiphysial trabecular bone surrounded by a thin cortical shell. The load across the knee joint is transferred from the femoral condyles through the load contact areas consisting of the cartilage and the menisci (Walker and Erkman 1975; Shrive et al. 1978). The cortical subchondral plates of the proximal tibia distribute the load to the epiphysial subchondral trabecular bone, which in the frontal plane consist of two more condensed trabecular columns medially and laterally (Takechi 1977; Bourne et al. 1984). In the epi- and metaphysis of the proximal tibia, the trabecular bone gradually concentrate and finally transmit the load applied to the tibial joint surface into the cortical bone of the tibial diaphysis (Hayes et al. 1978; Bourne et al. 1984; Orr et al. 1990).

Quantitative measurements of bone mineral and local changes in density of bone cannot be performed by conventional roentgenograms due to poor accuracy and precision. Recent studies evaluating the detection limit of bone loss from conventional roentgenograms compared with quantitative densitometric measurements of bone mineral density (BMD), have shown that a difference in BMD of 25–30% is required (Finsen and Anda 1988; Robertson et al. 1994). Thus a quantitative method for measurement of BMD and bone mineral content (BMC) was required to measure the adaptive bone remodeling at the knee.

Aim of the study

The aims of the present study were as follows:

1. Testing the feasibility of specially designed scanners for measurements of bone mineral at the knee.
2. Description of normal values of BMC in the proximal tibia focusing on:
   – how is BMC influenced by sex, age, height, and weight.
   – the effect of generalized osteoporosis and local pathological conditions at the knee.
3. Quantitatively evaluate posttraumatic bone loss of the proximal tibia following ankle and tibial shaft fractures including examination of whether BMD of the hip is influenced by a tibial fracture.
4. Can treatment with calcitonin prevent the development of posttraumatic bone loss following fractures.
5. Does a local adaptive bone remodeling within the proximal tibia following medial menisectomy take place, and does a different remodeling pattern between total and partial meniscectomy exist.
6. Does uncemented TKA lead to an adaptive remodeling of the distal femur and proximal tibia.
7. Can bone loss of the distal femur after TKA be prevented by an altered design of the femoral component.

Developments in bone densitometry

Photodensitometry was the first quantitative method for determination of bone mineral by measuring bone absorption of ionizing radiation (Jackson 1951; Baker et al. 1959). This technique is based upon a conventional roentgenogram of a peripheral skeletal site including an Aluminum calibration step-wedge on the roentgenogram, and followed by a quantitative measurement of their densities on the exposed film by a photodensitometer. However, errors are introduced in every step of this process, and especially the accuracy is reduced if the measured bone is covered with soft tissue (Jackson 1951; Baker et al. 1959), and attempts to standardize the thickness of soft tissue using a waterbath was not successful (Anderson et al. 1966).

The development of photon absorptiometric measurements for determination of bone mineral have mainly been applied in the diagnosis of postmenopausal osteoporosis including estimation of fracture risk, and evaluation of treatment. Single photon absorptiometry (SPA) was introduced in 1963 (Cameron and Sorenson 1963), and was the first precise and accurate quantitative method available. The technique uses a single energy peak of a radioactive photon source, in most studies either Iodine-125 or Americium-241. The extremity is scanned in a rectilinear fashion, and the intensity of the photon beam after passage of the body is registered by a scintillation detector (Nilsson 1966; Cameron et al. 1968; Christiansen et al. 1975). To achieve a good accuracy with the SPA technique it is necessary for the scanned limb to be submersed in water to obtain a standardized soft tissue covering. Thus the use of SPA is limited to measurements in the peripheral skeleton and have mainly been used for bone mineral measurements of the forearm (Christiansen et al. 1975; Price et al. 1989) or in the lower extremities from the distal femur and below (Nilsson 1966; Andersson and Nilsson 1979a).

During the seventies dual photon absorptiometry (DPA) which is very similar to SPA became available as a method for measurements of bone mineral in the axial skeleton (Roos and Skjöldborn 1974; Wilson and Madsen 1977; Krølner and Pors Nielsen 1980). The first DPA-scanners were developed for measurements of bone mineral in the lumbar spine (Roos and Skjöldborn 1974; Wilson and Madsen 1977; Krølner and Pors Nielsen 1980), and later the method was modified to allow measurements of bone mineral in the hip (Bohr and Schaadt 1983; Bohr and Schaadt 1985), and of the total body (Peppler and Mazess 1981; Gotfredsen et al. 1984a) including soft tissue body composition (Mazess et al. 1984b; Hassager et al. 1989). The DPA technique (Roos and Skjöldborn 1974; Wilson and Madsen 1977; Krølner and Pors Nielsen 1980) rely on a photon source usually gadolinium-153 (^{153}Gd) emitting photons at two radiation energy peak levels. Based on measurements of the absorption curves obtained at the two different energy levels, it is possible to calculate the mass of bone mineral or soft tissue in the scanned area, by solving the two equations describing the transmission of the two photon beams through the body. The body is assumed to consist of a two-component system containing only bone and soft tissue of homogeneous composition. Because the soft tissue is not really a uniform component, but a two component system composed of fat and lean tissue, the assumption is made that the fatty composition adjacent to and overlying the bone is the same. Information about the fat content of the soft tissue is achieved during the scanning of the soft tissue adjacent to the bone, and these information's are used in the calculation of the amount of bone mineral in the pixels containing bone (Krølner and Pors Nielsen 1980; Gotfredsen et al. 1984a). The discrimination between bone pixels and measuring points consisting only of soft tissue rely on different bone edge detection routines depending on the particular scanner used. The determination of bone mineral is thus possible throughout the skel-

eton without the need for a constant soft tissue thickness. Such bone mineral measurements with the DPA-technique could be performed with a radiation dose to the patient below 0.1 mSv (Mazess and Barden 1988; Glüer et al. 1990), which is less than 1/20 of the annual average dose received from the natural background radiation in Denmark.

The next major development in bone densitometry was the introduction of dual energy X-ray absorptiometry (DEXA) (Mazess and Barden 1988; Mazess et al. 1989; Glüer et al. 1990). DEXA is based on exactly the same principle as DPA except that the two photon beams are generated from an X-ray tube instead of a radionuclide source. The higher photon flux available from X-ray sources provides some advantages, especially important for BMD-measurements at the axial skeleton, such as improved spatial resolution, faster scan speed, and reduced exposure to radiation. Furthermore the precision error for measurements of BMD in the axial skeleton have been halved compared to measurements with DPA (Mazess and Barden 1988; Mazess et al. 1989; Glüer et al. 1990).

Quantitative computed tomography (QCT) measure three-dimensional BMD (volume density), and thus allow measurement of exclusively the most metabolically active trabecular bone (Cann 1988; Pacifici et al. 1990). However, compared to DPA and DEXA the QCT also have some important disadvantages, such as relatively poor accuracy when measuring the BMD of trabecular bone (Cann 1988; Jackson 1951), BMD-measurements are disturbed by artifacts when metal implants are located within the scanned area (Seitz and Rüegsegger 1982; Robertson et al. 1989), and the radiation dose to the patient at QCT examination is significantly higher compared to DPA or DEXA (Cann 1988; Kalender 1992). The development of dual energy QCT, using the same principles that apply to DPA and DEXA, has not been successful. Even though the accuracy errors due to fat and soft tissue can be reduced, it is done at the expense of increased precision error and higher radiation dose to the patients (Cann 1988). The QCT technique is thus not suitable for BMD-measurements in prospective studies with repeated measurements and certainly not for measurements of adaptive bone remodeling in relation to orthopaedic implants.

Finally a quite different approach to bone densitometry without the use of ionizing radiation is ultrasound. Ultrasonic properties of bone such as the speed of sound and the broadband ultrasound attenuation are measured. Both parameters are related to bone density, but the speed of sound and the broadband ultrasound attenuation also reflect respectively elasticity and structure of the measured bone (Langton et al. 1984). In general the precision of bone density measurements with ultrasound is 2–4% (Lees and Stevenson 1993; Graafmans et al. 1996). Only superficial bone structures usually the calcaneus, the patella or the tibial shaft can be measured (Heaney et al. 1989; Lees and Stevenson 1993; Foldes et al. 1995), and the technique is still under development.

Methods

Description of BMD scanners

Three different scanners were used for measurements of bone mineral in the present study; two DPA-scanners, custom made with the specific purpose of measuring bone mineral in respectively the proximal tibia and distal femur, and a standard DEXA-scanner used mainly for measurements of bone mineral in the axial skeleton.

Bone mineral measurements in the proximal tibia were performed with a Gammatec GT-50, Tibia-1a scanner (Gammatec A/S, DK-3500 Værløse, Denmark). The scanner was developed on the basis of the experience with bone mineral measurements of the proximal tibia in studies performed by Bohr and coworkers (Bohr and Lund 1987; Bohr and Schaadt 1987). The scanner is a DPA-scanner and uses the radiation peaks of 44 and 100 keV from a ^{153}Gd source with a maximum activity of 200 mCi (half life =242 days). The detector system of the DPA-scanner consist of a NaI-detector with a three channel system; one channel for 44 keV and two channels for 100 keV. The two channels for 100 keV are used for automatic adjustment of high voltage, which is performed every time the system is turned on. The diameter of the active beam size at the bone was 4 mm, and the distance between the photon source and the detector was 20 cm. Scan speed (4–6 mm/s) was automatically adjusted according to the decay of the ^{153}Gd source. Scanning with an old source consequently increases the total scan time, but does not affect the counting statistics. Scanning was performed transversly to the bone axis (in the coronal plane) of the proximal tibia, and during scanning the knee was extented and the foot in an upright position, and placed in a special device designed to secure unaltered rotation of the extremity at follow-up. The scanner has a special facility for automatic identification of the joint line of the knee, thus starting the scanning just above the joint line, but the scanning could also be started manually.

The standard region most often used for bone mineral measurements of the proximal tibia was an 8 mm wide region located between the subchondral plates of the tibial condyles and the head of the fibular bone (Figure 1). Within this region of interest (ROI) the software facility automatically calculates BMC (g/cm) as the total amount of bone mineral between the horizontal lines divided by the distance between the lines. Furthermore a derived BMD-value (g/cm^2) is calculated from the total amount of bone mineral divided by the area of bone within the lines (Figure 1). Area of bone is determined by a threshold calculation performed in each pixel (pixel size: 2 by 2 mm^2) to determine the interface of the bone and the adjacent soft tissue. Pixels with BMD values above 0.27 g/cm^2 are considered to be bone, and thus contribute to the area calculation, while pixels below this threshold are considered to be soft tissue. Further-

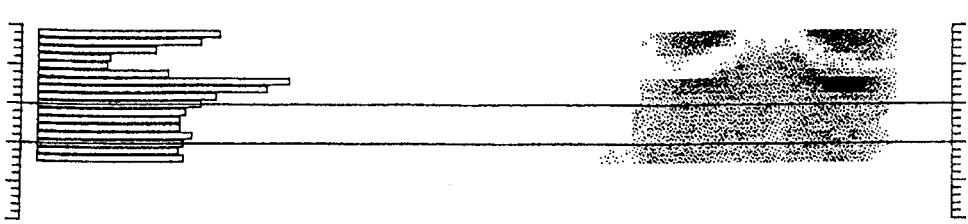

Figure 1. Scan plot of the proximal tibia. The BMC-values of each scan (2 mm wide) is indicated by the histogram to the left. Between the two horizontal lines located 6 mm below the subchondral plates (the scan line with highest BMC value) an 8 mm wide ROI is selected for standard BMC measurements. From Petersen et al. J Orthop Res 1996;14:16-21.

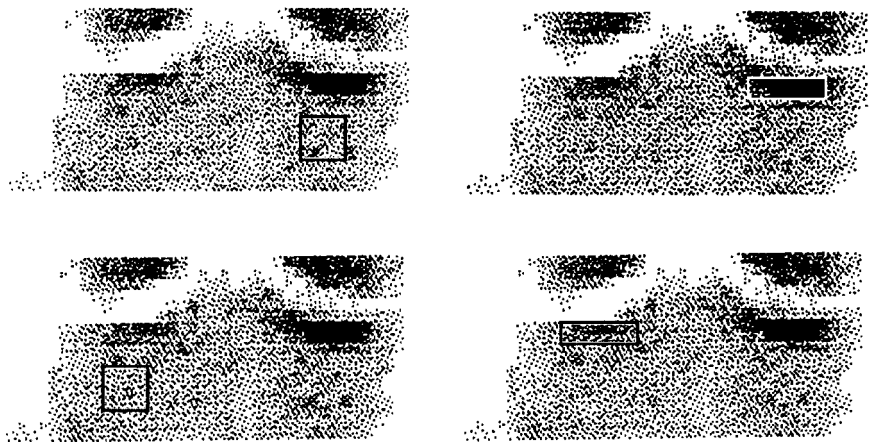

Figure 2. Scan plots of the proximal tibia showing ROI´s used for local measurements of BMD within the proximal tibia. The ROI´s shown were used for evaluation of adaptive bone remodeling of the proximal tibia following medial meniscectomy (Petersen et al.1996c). From Petersen et al. J Orthop Res 1996;14:16-21.

more pixels with BMD-values higher than 3.5 g/cm^2 are considered by the software to be metal and thus excluded from the analysis.

The scanner software also include a local region analysis facility for measuring BMD (g/cm^2) in small ROI within the proximal tibial bone (Figure 2). When using the local region analysis facility for measurements of BMD, it is necessary that the total ROI is kept within the area of bone, since this BMD-value is calculated as the total amount of bone mineral divided by the area of the ROI, thus no algorithm to distinguish between bone pixels and soft tissue pixels is attached to the facility for local region analysis. This facility was mainly used to provide information about regional differences and adaptive remodeling of the proximal tibia.

The second DPA-scanner was a Gammatec GT-50, Femur-1a scanner (Gammatec A/S, DK-3500 Værløse, Denmark), which was developed with one specific purpose; measurements of regional changes in BMD of the distal femur following TKA. The scanner is identical with the tibia scanner described above, except that the scanner arm and scanner table is turned 90 degrees, thus allowing measurements in the medio-lateral plane of the distal femur.

The DEXA-scanner used was a standard bone densitometer NORLAND XR-26 Mark II, dual energy, dual detector, X-ray absorptiometric system (Norland Corp., WI, USA) which uses two radiation peaks of 47 and 80 keV from an X-ray tube for measurements of bone mineral. A more detailed description of the specific DEXA-scanner has been published by Gehrchen et al. (1995). Calibration of the scanner was performed daily before the first scanning, using a 77 step calibration standard according to the manufacturers recommendations. This scanner was primarily used in a study (Petersen et al. 1997), where measurements of bone mineral in the axial skeleton was required. BMD (g/cm^2) in the hip (femoral neck and greater trochanter) using the standard hip scan option and in the lumbar spine (L_2–L_4) using the standard option for measurement of bone mineral in the lumbar spine was used in the study evaluating the effect of tibial shaft fractures on bone mineral in the axial skeleton (Petersen et al. 1997). In the same study BMC (g/cm) was measured in the anteroposterior plane of the tibia using the flexible research scan option with a pixel size of 1 by 1 mm^2 and a scan speed of 45 mm/s. The BMC measurements were performed in the coronal plane in a 1 cm long region in the trabecular bone of the proximal tibia between the subchondral plates and the head of the fibular bone, and few patients had their bilateral tibial BMC measurements performed in a 2 cm wide region in the distal part of the tibia and fibular bone just above the ankle joint. In the study evaluating the relation between trabecular bone strength and BMD (Petersen et al. 1996a), scanning was performed by both DPA and DEXA. DEXA scanning was performed using the

flexible research scan option and the pixel size and scan speed selected were respectively 0.5 x 0.5 mm^2 and 45 mm/s.

Accuracy

The term accuracy is defined as the ability of a method for estimating the true value (Gotfredsen 1990; Knudsen 1994). The accuracy of a method is often evaluated by a linear regression analysis with calculation of the slope and intercept of the regression line, the coefficient of correlation (r) or determination (r^2), the level of significance (p-value or confidence limits for the regression line), and a measure of the individual variability around the regression line (standard error of the estimate (SEE) or prediction limits for the regression line). It is the measure of individual variability, which is normally used as an estimate of the accuracy error (Gotfredsen 1990). The accuracy error of the application of both DPA and DEXA for measurements of bone mineral have previously been evaluated by other investigators. Normally the accuracy error is evaluated from measurements performed on specimens of dried bone, ashed bone or bone mineral equivalent material. Generally the accuracy error *in vitro* assessed as SEE is between 1.3% and 5% for DPA measurements of BMD or BMC (Krølner and Pors Nielsen 1980; Gotfredsen et al. 1984b; Wahner et al. 1985; Gotfredsen et al. 1988; Szücs et al. 1992), and using DEXA the error could be further reduced (Mazess et al. 1989; Gehrchen et al. 1995).

Own results (study 3)

Since our DPA-scanners were custom made scanners, we evaluated the accuracy by examining the relation between the weight of ashed bone meal and measurements of BMD and BMC (Svalastoga et al. 1994). The bone mineral measurements were performed with the DPA-scanner used for the tibial measurements (GT-50, Tibia-1a). BMC (r=0.997) and BMD (r=0.9996) were closely related to the weight of ashed bone and the accuracy error assessed as the SEE was respectively 3.2% and 1.1% (Svalastoga et al. 1994).

Because one of our previous studies (Petersen et al. 1993) had indicated that a nonlinear relationship between BMD and BMC existed, the lower detection limit of the DPA-scanner was evaluated. An *in vitro* study (Svalastoga et al. 1994) using two series of defatted dogs bone meal stored in polycarbonate straight side jars with two different diameters (two different, but constant areas of bone) showed that when BMD was higher than 0.4 g/cm^2 a low accuracy error (and precision error) was obtained for both BMC and BMD. If BMD was below this limit, and BMD was used, bone mineral was overestimated due to incorrect area calculation (underestimated) (Figure 3).

Discussion

The advantage of using BMD is that the adjustment for bone size reduces the inter-individual variance (Christensen et al. 1981; Krølner 1982; Nilas et al. 1986). However, most of our clinical studies were of prospective design with repeated measurements performed in individuals often undergoing a considerable loss of bone mineral. Thus the decreased accuracy, when BMD was used for standard analysis of bone mineral of the proximal tibia (Figure 1) in patients with low bone mass, was considered so important, that BMC was preferred as a measure of bone mineral. Since the newer DEXA-scanners possesses the same error (Fisher and Kempers 1993; Gehrchen et al. 1995) BMC was also used, when bone mineral of the tibia was measured by DEXA.

Precision

The precision of a method is a measure of the reproducibility of the method - the error of repeating the same measurement in the same individual (Gotfredsen 1990; Knudsen 1994). The precision error is normally calculated as the coefficient of variation (CV = standard deviation/mean x 100%) and is evaluated from multiple measurements performed in a single subject or few repeated measurements in several subjects or a combination of both (Gotfredsen 1990). In prospective studies with repeated measurements in the same individuals a low precision error is important. When follow-up of changes in a single individual are performed a change between two measurements of 2 x CV% x squared root of 2 is required for the dif-

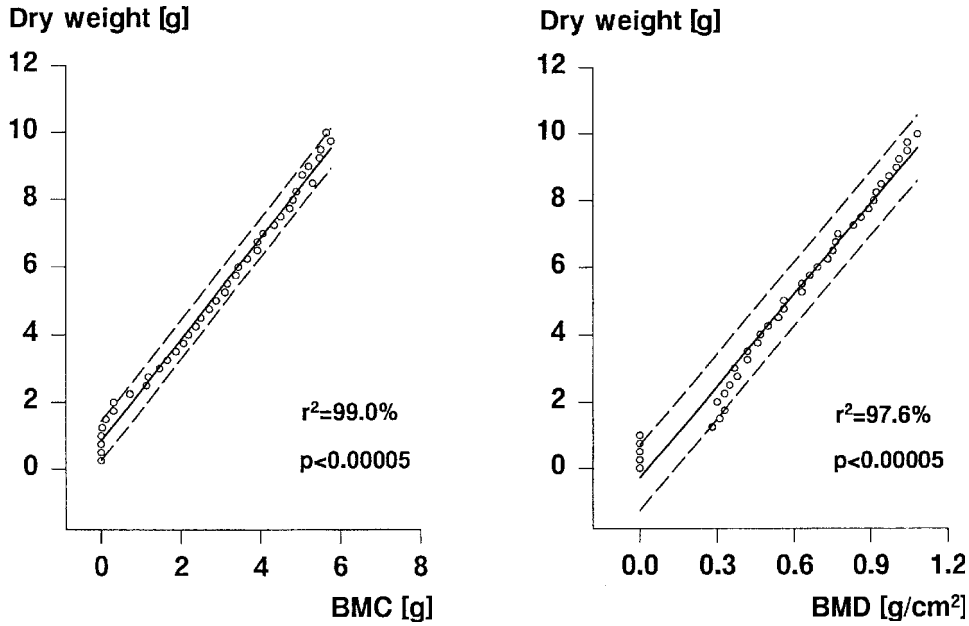

Figure 3 . The relation between fat-free dry weight of bone meal (jar diameter of 2.6 cm) and respectively BMC and BMD measured by DPA. Results of the linear regression analysis are presented as the regression line with the 95%-prediction limits for the line together with a scatter diagram of the raw data. Furthermore the p-value and r^2-value are shown. All data points, also those obviously below the detection limit of the scanner (n=4 and n=5 for respectively BMC and BMD), were included in the regression analysis.

ference to be statistically significant. When changes in a group of patients are studied the CV is an important determinant for the number of participants necessary to detect a significant change with an appropriate statistical power (Nilas et al. 1988).

The precision for measurements of bone mineral of the axial skeleton (hip and lumbar spine) and total body by DPA has been evaluated by several authors and a CV of 2–3% is seen (Mazess and Wahner 1988). Since the DPA-technique has mainly been used for bone mineral measurements of the axial skeleton and total body, only relatively few authors have evaluated the precision of this technique for measurements in the peripheral skeleton.

Own results (study 2 and 9)

The short-term (1 month) and long-term (1 year) precision *in vitro* for standard analysis (with threshold calculation for determination of area) with the tibia scanner was evaluated from repeated measurements performed on a plexi-glass calibration standard containing hydroxyapatite (Petersen et al. 1993). The short-term and long-term precisions expressed as the CV were respectively 0.5% and 0.8% for BMC and 1.7% and 2.0% for BMD. In the same study (Petersen et al. 1993) the precision was evaluated from 8 healthy subjects scanned 3 times in both legs within one week. Using the standard region analysis (Figure 1) the average precision *in vivo* was 1.8 % and 1.1% for respectively BMC and BMD. Our evaluation of precision *in vivo* for DEXA-measurements of BMC in the tibia revealed CV-values of 0.8% and 1.4% for measurements in respectively the proximal and distal part of the bone (Petersen et al. 1997).

Own results (study 5, 7 and 8)

When BMD was measured by DPA in the proximal tibia using the local region facility for bone mineral measurements in small ROI of the trabecular bone or cortical bone of the subchondral plates the precision error is expected to be higher compared to measurements with the standard analysis option. Just as it is seen when regional bone mineral measurements of the arms, head, chest, spine, or legs are derived from a total body bone mineral measurement (Mazess et al. 1984a;

Gotfredsen et al. 1986). We found average precision errors for regional tibial BMD measurements of 3.4–5.2% with the highest CV´s for ROI located in the subchondral cortical bone (Petersen et al. 1996c), and in the trabecular bone of knees with a TKA implanted the average errors for different locations of the ROI was 2.8–4.7% (Petersen et al. 1995a). Repeated measurements of regional BMD in the distal femur in patients with TKA using the femur-scanner revealed mean precision errors of 3.2% and 2.2% for measurements of BMD in the two ROI´s selected for the BMD-measurements distally behind the anterior flange of the femoral component and posteriorly above the fixation pegs (Petersen et al. 1996b).

Discussion

The precision *in vivo* obtained in our studies (Petersen et al. 1993; Petersen et al. 1997), when using the standard region analysis for measurements of BMC of the proximal tibia by DPA or DEXA, was very similar to the level of precision error for measurements of bone mineral in the peripheral skeleton found in other studies using DPA (Bohr and Schaadt 1987; Jonson et al. 1990; Szücs et al. 1992; Schaadt and Madsen.1992; Madsen et al. 1994) or DEXA (Sievänen et al. 1992; Sievänen et al. 1993).

Only few investigators have evaluated the precision for regional measurements of BMD in small regions within the proximal tibia. Bohr and Schaadt (1987) found a CV of 3.0%, but if the ROI was kept in the trabecular bone just below the subchondral plates the CV decreased to 2.5%. Madsen et al. (1994), using a similar tibia-scanner as in our studies, found a CV of 2.2–3.5% for repeated measurements of regional BMD in the proximal tibia of normal knees, while the CV for measurements in knees with osteoarthrosis was slightly higher (2.6–3.7%).

It is generally accepted that the DEXA technique represents a methodological improvement compared to DPA, and typically the precision error for bone mineral measurements is halved (Mazess and Barden 1988; Glüer et al. 1990). Precision errors for measurements *in vivo* of BMD in the hip (femoral neck and greater trochanter, but not Ward's triangle) and lumbar spine (L_2–L_4) by DEXA are below 2% (Mazess et al. 1989; Glüer et al. 1990; Sievänen et al. 1992; Lees and Stevenson 1992). When measurements *in vivo* of BMD are performed in patients with THA the precision that can be obtained using DEXA around the femoral component in uncemented THA is between 1.8-4.7% (Kiratli et al. 1992; Kilgus et al. 1993; Trevisan et al. 1993; Cohen and Rushton 1995a). Data regarding precision of DEXA-measurements of bone mineral around TKA exist mainly for the femoral component. The average CV measured *in vitro* is 1.2% (Robertson et al. 1994), and for BMD measurements *in vivo,* respectively 3.1–3.7% (Liu et al. 1995), and 2.3% (Trevisan et al. 1998). The study by Trevisan et al. (1998) also evaluated the precision for measurements of BMD below the tibial component and found and average CV of 0.9–2.2%.

Relation to bone strength

Another important parameter in the interpretation of the bone mineral measurements in clinical studies is the relation of BMD to the mechanical strength of bone. Low BMD is an important risk factor for hip fractures in the elderly (Melton et al. 1986; Cummings et al. 1993), and previous studies have shown that BMD is closely correlated to the breaking strength of the femoral neck (Dalén et al. 1976; Courtney et al. 1994). Furthermore the mechanical properties of the trabecular bone in the proximal part of the tibia are considered to be an important biological determinant for the failure rate in TKA (Hvid 1988; Hvid and Hansen 1986; Christensen et al. 1982; Zysset et al. 1994), and a significant negative correlation between bone mineral of the proximal tibia and late migration of the tibial component in uncemented TKA has been found (Petersen et al. 1999).

Several authors have measured the relation between bone strength of small specimens of trabecular bone obtained from the proximal tibia and bone mineral measured by photon or X-ray absorptiometric techniques, but without testing the feasibility of measuring these parameters *in vivo* (Behrens et al. 1974; Christensen et al. 1982; Hvid et al. 1985). Also QCT have been applied in the determination of biomechanical parameters within the proximal tibia (Bentzen et al. 1987; Zysset

et al. 1994). The failure rate following TKA has decreased during the past years, but the main problem is still the early fixation of the the tibial component (Windsor et al. 1989; Moran et al. 1991). Methods which provide non-invasive *in vivo* evaluations of the mechanical properties of the trabecular bone at the proximal tibia are of interest. They make it possible to evaluate quantitative variations in bone biomechanical characteristics at the knee before operation with insertion of TKA and prospectively in individuals after TKA. Theoretically such measurements also make it possible to design improved tibial components and to choose the optimal type of tibial component for TKA in the individual patient. Several previous studies have evaluated the variations in trabecular bone strength within the proximal tibia, but most studies have been cadaver studies using mechanical testing of trabecular bone specimens (Zysset et al. 1994; Goldstein et al. 1983; Behrens et al. 1974) or penetration strength measurements with an osteopenetrometer (Hvid et al. 1984; Sneppen et al. 1981; Hvid and Hansen 1986). The penetration strength measurements have also been performed *in vivo* during TKA-operations (Hvid 1988).

Own results (study 6)

In 14 cadaver knees we evaluated the feasibility of DPA and DEXA for prediction *in vivo* of regional trabecular bone strength within the proximal tibia (Petersen et al. 1996a). Trabecular bone strength was evaluated using an osteopenetrometer and from destructive penetration testing performed on bone cylinders, thus measuring the average penetration strength and ultimate strength in respectively the medial, lateral and central part of the tibial bone specimens. Linear regression analysis showed significant relations between BMD measured by DPA (r^2 =72%) or DEXA (r^2 =73%) and ultimate strength (Figure 4). Even closer relations between BMD (DPA: r^2 =80%, DEXA: r^2=81%) and penetration strength of trabecular bone were found (Figure 4).

Discussion

The relations between bone strength and BMD found in our study were comparable with other studies evaluating the relations in larger and more well defined parts of the skeleton such as the femoral neck (Dalén et al. 1976; Courtney et al. 1994) and lumbar vertebrae (Hansson et al. 1980; Oyster and Smith 1988). Thus the use of small ROI within the proximal part of the tibia did not seem to influence the degree of correlation between bone strength and BMD. In a methodological study Hvid et al. (1987) evaluated the relation between bone mineral measured by DPA and respectively ultimate strength and penetration strength. The resolution used when scanning with this DPA scanner, was not on the same level as could be obtained with the scanners in the present study, and the average amount of bone mineral in respectively the medial and lateral tibial condyle was measured and not BMD in small regions. The relation between bone mineral and bone strength measured as ultimate strength was on the same level as in the present study, while significantly closer relations between penetration strength and bone mineral and between the two methods used for strength measurements were found in the present study. However, direct comparison between the studies is difficult since no parameters for the individual variability about the regression line was calculated in the study by Hvid et al. (1987).

In our study (Petersen et al. 1996a) the scatter of data points around the regression line and thus the prediction limits for measurements of local trabecular bone strength from bone density measurements were quite wide. The scatter of data points when comparing BMD measured by DPA and DEXA was also larger than one would expect from the accuracy and precision that are normally obtained with these techniques in studies designed to evaluate this specific purpose (Svalastoga et al. 1994; Gehrchen et al. 1995). It is thus obvious that the design of the present study itself introduces different sources of error, which are all included in the prediction limits. However, many of these errors are eliminated when the BMD measurements are used as a single non-destructive and non-invasive method to predict bone strength, and thus we find that DPA and DEXA are suitable methods to evaluate *in vivo*, local variations of trabecular bone strength within the proximal tibia.

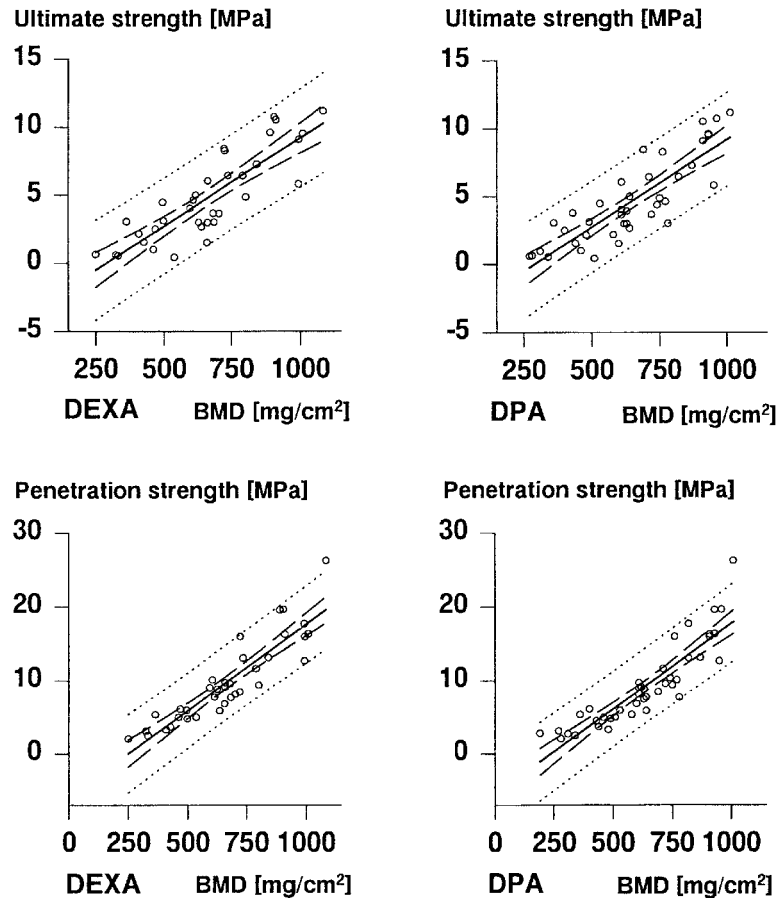

Figure 4 . The relation between ultimate strength and BMD measured respectively by DEXA and DPA (upper) and the relation between penetration strength and BMD measured by respectively DEXA and DPA. The relations are shown as scatter plots with the regression line (solid lines), the 95%-confidence limits (dashed lines), and the 95%-prediction limits (dotted lines). From Petersen et al. Calcif Tissue Int 1996;59:311-4.

Statistics

The statistical methods for evaluation of precision, accuracy, and relation to bone strength have been described in the relevant paragraphs. In the clinical studies we mainly used nonparametric tests. When two groups of observations were available for analysis we performed either a Wilcoxon test when data were paired or a Mann-Whitney test if data in the groups were independent. Intragroup changes over time with more than two observational groups were evaluated by a nonparametric two-way analysis of variance (Friedman). With the aim of showing where the significant changes were located, we frequently performed either repeated Wilcoxon tests or calculation of the 95% confidence limits (95%-CL) for the percentage changes. In the randomized studies the difference between groups was evaluated by comparing relevant intragroup changes using either a Mann-Whitney test or calculation of 95%-CL for the difference between means. Furthermore, statistical power analysis with calculation of the probability of type 2 error (ß) or the statistical power (1–ß) were performed with a fixed type 1 error probability of 5%. In all studies two-tailed p-values below 0.05 were considered significant.

Normal values for BMC of the proximal tibia

It is well known that various different determinants for the level of bone mineral at different skeletal measuring sites exist (Mazess and Wahner 1988). To be able to interpret the BMC measurements performed in later clinical studies, we investigated the influence of the parameters sex, age, weight, and height on the level of BMC in the proximal tibia (Petersen et al. 1993).

Own results (study 2)

We found that BMC of the proximal tibia in 102 healthy women showed an almost 50% decrease from an average of 5.30 g/cm in women aged 20–29 years to 2.85 g/cm in women aged 80–89 years, and an accelerated bone loss was seen subsequent to the menopause (Petersen et al. 1993). Furthermore linear regression analysis showed that BMC had a significant but very moderate (r=0.20, p=0.04) relation to height, but not to weight. Among young healthy men (n=10, mean age 31 years) and women (n=10, mean age 32 years) BMC was almost 30% higher in men compared with women. Height and weight was much more important determinants of BMC in these young people with r-values of 0.6–0.7. In the same study (Petersen et al. 1993) we evaluated in a cross-sectional design the influence of osteoporosis (Colles' fracture), knee arthrosis and immobilization of the extremity because of ankle fracture, lesion of the anterior cruciate ligament of the knee (ACL-lesion), and hip arthrosis on BMC in the proximal tibia. Age adjusted BMC was lower in women with osteoporosis (p=0.003) compared with controls and in women with knee arthrosis BMC was higher (p=0.0002) compared with controls. Women with hip arthrosis had BMC in the affected legs 19.4% below the value in the healthy contralateral legs (p=0.004), and the BMC-value was also lower compared with BMC in healthy women, while BMC in the healthy legs was within normal range. Women with earlier ACL-lesions had BMC in the injured legs not different from average values in normal women, but it was decreased by 8.6% (p=0.002) compared with their healthy contralateral legs.

Discussion

The age-related decay in BMC of the proximal tibia shows similar age-related trends as in other skeletal sites (Mazess 1982), and both Bohr and Schaadt (1987) and Checovich et al. (1989) found similar age related decreases in bone mineral in the proximal tibia. Postmenopausal osteoporosis was clearly visible in the proximal tibia. As shown in other studies previous ligamental injury was associated with a deceased bone mass in the affected limb (Andersson and Nilsson 1979b; Kannus et al. 1992), while patients with osteoarthrosis had a normal or slightly increased bone mass (Alhava et al. 1975; Carlsson et al. 1979; Hart et al. 1994). However, decreased BMC in the affected limbs in patients with hip arthrosis was in agreement with later findings by Madsen et al.(1997) and possibly a consequence of disuse. The increased BMC in the proximal tibia in women suffering from knee arthrosis might be caused by the well known histological and radiological changes associated with knee arthrosis (Ahlbäck 1968; Havdrup et al. 1976). When measurements in the proximal tibia are performed for diagnosis or evaluation of treatment in osteoporosis, the results could be strongly influenced by earlier periods of immobilization or local pathological conditions at the knee.

Bone loss following fractures of the lower extremities

Quantitative densitometric measurements

Several decades ago bone loss following musculoskeletal trauma has been described in studies using plain roentgenograms (Noble and Hauser 1926; Fontaine and Herrmann 1933; Key et al. 1934). Later, such bone density changes in the lower extremities following fractures (Table 1, Table 2), and ligamental or meniscal injuries (Nilsson and Westlin 1969; Andersson and Nilsson 1979b; Kannus et al. 1992) have been measured quantitatively by photon or X-ray absorptiometric techniques. Most of the studies have been of cross-sectional design estimating bone loss by comparing bone mineral values in previous fractured legs with values in the healthy contralateral legs (Table 1). These studies have indicated that bone loss following fractures is not a fully reversible event, even though some restoration of bone mineral can be detected in prospective studies (Table 2). The design of the cross-sectional studies is based on two important assumptions. In healthy subjects there is no difference in bone mass between dominant and nondominant legs, and the bone mineral of the healthy con-

Table 1. Cross-sectional studies using quatitative densitometric measurements of bone mineral for evaluation of bone loss following lower extremity fractures in adults. Some of the studies containing both cross-sectional and prospective data are also included in table 2.

Author	Fracture site	Time after fracture (years)	Technique	Measuring site	Bone loss (%)
Nilsson (1966)	tibia	0.5–15	SPA	distal femur	25
Finsen & Haave (1987)	tibia	2.5	SPA	various	3–8
Ahl et al. (1988)[a]	ankle	1.5	SPA	calcaneus	6
Finsen et al. (1988)[a]	femur	2.5 / 4.5	SPA	distal femur	12/12
				proximal tibia	5/7
				tibial shaft	5/2
Caniggia et al. (1992)[a]	tibia	0.17	DPA	foot	25/9
Bråten et al. (1992)	femur	21/4	QCT	femoral/tibial condyles	19/17
Karlsson et al. (1993b)	tibia	21	DEXA	distal femur	4
				greater trochanter	4
Sarangi et al. (1993)	tibia	4	DEXA	distal tibia/calcaneus	39/31
Janes et al. (1993)	tibia	11/4	DEXA	distal tibia	8
Kannus et al. (1994b)[b]	tibia	9	DEXA	femoral neck	2/2
				distal femur	4/10
				patella	4/11
				proximal tibia	5/9
Kannus et al. (1994a)	femur	10	DEXA	trochanter area	6
				distal femur	7
				patella/proximal tibia	5/5
Eyres & Kanis (1995)	tibia	8	DEXA	distal tibia	54
Neander et al. (1997b)	femoral neck	1.5	QCT	distal femur	10
				proximal tibia	19
Petersen et al. (1997)	tibia (nonunion or infection)	3	DEXA	proximal/distal tibia	43
				greater trochanter	24
				femoral neck	22
Van Der Poest Clement et al. (1999)	tibia	1-19	DEXA	greater trochanter	5
				femoral neck	3

[a] Studies with 2 different groups evaluating the prevention of postfracture osteoporosis.
[b] 2 groups of patients with respectively primarily united fractures and primarily nonunion were studied.

Table 2. Prospective studies using quatitative densitometric measurements of bone mineral for evaluation of bone loss following lower extremity fractures in adults. Some of the studies contains both prospective and cross-sectional data and are included also in table 1.

Author	Fracture site	Follow-up (years)	Technique	Measuring site	Bone loss (%) Maximal	FInal
Andersson & Nilsson (1979a)	tibia	2	SPA	proximal tibia	45	25
Andersson & Nilsson (1979c)[a]	tibia	1	SPA	proximal tibia	44/46	24/29
Finsen & Benum (1989)[b]	ankle	2	SPA	distal femur	9	5
				proximal tibia	8	9
				distal tibia	11	6
Ulivieri et al. (1990)	tibia	0.5	DPA	distal tibia	51	51
Petersen et al. (1992)	ankle	3	DPA	proximal tibia	15	11
Van Der Viel et al. (1994)	tibia	1	DEXA	hip (neck/trochanter)	6/14	6/14
Eyres and Kanis (1995)	tibia	0.5	DEXA	distal tibia	48	47
Karlsson et al. (1996)	hip	1	DEXA	lower extremities	7	3
Neander et al. (1997a)	hip	0.5	QCT	femur (middel/distal)	2/11	2/11
				proximal tibia	22	19
Petersen et al. (1997)	tibia	0.5	DEXA	proximal tibia	33	27
				hip (neck/trochanter)	3/10	7/14
Cattermole et al. (1997)	tibia	<0.5	DEXA	tibia	47	-
Petersen et al. (1998)[a]	ankle	0.5	DPA	proximal tibia	14/7	10/7
Zerahn et al. (1998)	hip	1	DEXA	proximal tibia	16	16
				contralateral hip: neck/trochanter/Wards	5/5/7	5/4/6
Van Der Poest Clement et al. (1999)	tibia	5	DEXA	hip (neck/trochanter)	5/13	3/5

[a] Radomized studies with 2 different treatment groups evaluating the effect of respectively early weight-bearing (Andersson and Nilsson 1979c) and calcitonin (Petersen et al. 1998) for prevention of postfracture osteoporosis.
[b] Randomized study with 3 different postoperative treatment regims for prevention of postfracture osteoporosis.

tralateral legs is unaffected by a contralateral fracture. Previous studies have shown, that a difference in bone mass between dominant and non-dominant legs does not exist in the tibia (Vuori et al. 1994; Sarangi et al. 1993; Petersen et al. 1996c) or the hip (Balseiro et al. 1988; Lilley et al. 1992; Vuori et al. 1994). Theoretically a part of the decrease in bone mineral after lower extremity fractures measured in cross-sectional studies could have developed as a consequence of hypertrophy of the healthy contralateral legs. However, several previous studies have shown that an unilateral musculoskeletal injury will lead to the development of significant posttraumatic osteopenia, while the bone mass in the healthy contralateral legs usually remain unchanged or show minor decreases (Andersson and Nilsson 1979a; Petersen et al. 1992; Van Der Wiel et al. 1994; Zerahn et al. 1998).

Own results (study 1 and 9)

In a prospective 3 year follow-up study Petersen et al. (1992) measured BMC of the proximal tibia using the DPA scanner in 12 patients with ankle fractures. All fractures were treated operatively ad modum Cedell (Cedell and Wiberg 1962) and the affected limbs were immobilized in a plaster cast for 6 weeks. Peak bone loss of 15.4% (p=0.003) was reached 6 months after the fracture, and here after a slow restoration of bone mineral took place. Three years after the fracture BMC was still 10.7% (p=0.003) lower than the initial value. In the healthy contralateral legs a significant bone loss of 5.3% (p=0.004) was observed 1 year after the fracture, and after 3 years BMC was only 2.3% (p=0.08) below initial value.

Only few investigators have evaluated the influence of tibial shaft fracture on BMD in the hip (Karlsson et al. 1993b; Kannus et al. 1994b; Van Der Wiel et al. 1994; Petersen et al. 1997), and only two of these studies are of prospective design (Van Der Wiel et al. 1994; Petersen et al. 1997). In our study (Petersen et al. 1997) using DEXA, we measured the early (0–6 months) changes in bone mineral of the lumbar spine, the hip and tibia following tibial shaft fractures (n=12). Furthermore a

cross-sectional study (Petersen et al. 1997) evaluating the maximal amount of bone loss possible following long-term (average 3 years) impaired limb function as a consequence of complicated tibial shaft fractures (delayed union or non union (n=7), chronic osteomyelitis (n=5), decreased limb length (n=1) or bone defect (n=1)) was performed. Following tibial shaft fractures a prospective decrease in BMD was seen at the hip reaching 7% (95%-CL: -10.2%; -3.5%) and 14% (95%-CL: -19.6%; -7.8%) after 6 months for respectively the femoral neck and greater trochanter. In the proximal tibia BMC decreased and was 19% (95%-CL: -27.4%; -9.9%) below the initial value after six months. BMD of the lumbar spine remained unchanged. In the cross-sectional study BMC in the tibia of the injured legs was 43% (95%-CL: -53.2%; -31.9%) below the value in the healthy contralateral legs, and BMD in respectively the femoral neck and greater trochanter was 22% (95%-CL: -27.4%; -17.6%) and 24% (95%-CL: -36.3%; -12.1%) below the values in the healthy contralateral legs.

Discussion

Finsen and Benum (1989) using SPA also measured BMC following ankle fractures, and found a maximum bone loss of 8–11%, which was slightly less compared with our study (Petersen et al. 1992). Previous studies (Andersson and Nilsson 1979a; Ulivieri et al. 1990; Eyres and Kanis 1995) measuring prospective changes in peripheral bone density following tibial shaft fractures have shown a bone loss of approximately 50% during the first 6 months after the fracture. Van Der Viel et al. (1994) measured the BMD-changes in elderly (mean age 60 years) having sustained a mixture of fractures of the tibia, including both fractures of the tibial plateau, the tibial shaft, and ankle fracture. The fractures healed relatively fast and without complications, and the amount of bone loss after 6 months of follow-up was in the same range as in our study. As in our study (Petersen et al. 1997) no significant changes in BMD of the lumbar spine was observed. No measurements of bone mineral were performed in the tibia. The study (Van Der Wiel et al. 1994) was continued with a follow-up one year after the fracture, and furthermore in a recent publication (Van Der Post Clement et al. 1999) the results of measurements performed in the same patients 5 years after the fracture were presented. One year after the fracture BMD was still decreased by 14% and 5% for respectively the greater trochanter and femoral neck, while 5 years after the frature BMD was decreased by respectively 5% and 3%.

Our cross-sectional study (Petersen et al. 1997) showed that the amount of bone mineral lost during the first 6 months following a tibial shaft fracture was far from the maximal amount of bone loss possible after long-term impaired limb function. If the healing of the fracture is compromized by i.e. non-union or chronic osteomyelitis the bone loss continues in both the fractured bone and in the ipsilateral hip. The decrease in bone mineral at the hip and in the proximal tibia was comparable with the bone loss seen in the proximal tibia and femoral neck following spinal cord injury (Biering-Sørensen et al. 1990) and in the femoral neck following above knee amputation (Rush et al. 1994).

The prospective one year follow-up study by Van Der Viel et al. (1994) suggested that the post-fracture bone loss at the hip might be permanent, and measurements in the same patients 5 years after the fracture showed that only a partial remineralization had taken place during the study period (Van Der Post Clement et al. 1999). Furthermore cross-sectional studies (Karlsson et al. 1993b; Kannus et al. 1994b) have shown that decreased BMD of the hip and also at peripheral measuring sites persists several years after a primarily united tibial shaft fracture. In the study by Kannus et al. (1994b) an additional group of 12 patients with earlier primarily nonunited tibial shaft fracture treated with a bone grafting operation and an average time of plaster cast immobilization of 27 weeks were studied. With the exception of BMD at the femoral neck the estimated bone loss in this group was greater at all peripheral measuring sites (distal femur, proximal tibia, patella, distal tibia and calcaneus) compared to the study group (n=20) with primarily united tibial fractures. However, the size of the study group (n=12) might be insufficient and thus without the necessary statistical power to detect a relatively small decrease in bone mineral of the femoral neck, where the bone is mainly cortical. In the

above mentioned study by Kannus et al. (1994b) significant correlation's were found between the amount of bone loss measured at the knee and immobilization time and the actual function of the injured extremity at follow-up. Thus, it is not surprising that the bone loss in our cross-sectional patients was higher compared with the bone loss seen in the prospective group (Petersen et al. 1997).

BMD is highly correlated to the breaking strength of the femoral neck (Dalén et al. 1976; Courtney et al. 1994), and low BMD is an important risk factor for hip fractures (Melton et al. 1986; Cummings et al. 1993; Marshall et al. 1996). There is good evidence that previous fragility fractures are associated with an increased risk of subsequent hip fracture (Owen et al. 1982; Lauritzen and Lund 1993), but also individuals who has sustained tibial fractures has an increased risk for later fragility fracture (Karlsson et al. 1993a), and in an epidemiologic study by Finsen et al. (1989) it was found that new lower extremity fractures of the tibia or femur in patients with a history of previous tibial shaft fractures were mainly ipsilateral. The loss of bone mineral of the hip and tibia associated with tibial shaft fractures may be considered of clinical importance with respect to the expected age related annual decay of bone mineral at these measuring sites (Schaadt and Bohr 1988; Aloia et al. 1990; Bohr and Schaadt 1987; Checovich et al. 1989; Petersen et al. 1993). The early bone loss seems to be at least partially permanent (Karlsson et al. 1993b; Kannus et al. 1994b), and the potential for recovery have been considered to be even smaller following long-term immobilization (Jaworski and Uhthoff 1986; Minaire 1989). Patients with uncomplicated tibial fractures, even though they have regained full function of the extremity, are a decade or more ahead in the osteoporotic process and osteoporotic fractures later in life, may be expected to occur earlier in these patients. The decreased bone mineral in the injured extremity of the patients in our cross-sectional study (Petersen et al. 1997) was on the same level as in 70-80 year-old subjects and occurrence of osteoporotic fractures following minor traumas could be expected in these patients.

Prevention of posttraumatic osteopenia

The development of posttraumatic osteopenia is considered to occur as a consequence of the trauma itself and the effect of the immobilization which is often an important part of the treatment. The keys to the posttraumatic repair and accelerated restoration of musculoskeletal tissue are considered to consist of a short period of immobilization and early weight-bearing (Buckwalter 1995; Järvinen and Kannus 1997). However, the experimental data with respect to the preventive effect of this treatment on the posttraumatic osteopenia are relatively sparse. Two randomized prospective studies using quantitative densitometric measurements of bone mineral by SPA in patients with respectively tibial shaft fractures (Andersson and Nilsson 1979c) and ankle fractures (Finsen and Benum 1989) did not reveal any significant effect of early weight-bearing. Furthermore two cross-sectional SPA studies (Ahl et al. 1988; Finsen et al. 1988) did not indicate any benefit of early weight-bearing with regard to prevention of post-fracture osteopenia of the lower extremities. In a cross-sectional study comparing bilateral BMD of the feet measured by DPA two months after a tibial shaft fracture, Caniggia et al. (1992) found a partial protective effect on postfracture osteopenia in patients treated with external fixation and early weight-bearing with dynamic loading compared to cast immobilization. Tandon et al. (1995) also found a reduction in post-traumatic osteopenia after external fixation and early weight-bearing compared with immobilization in a plaster cast, but unfortunately the study was not randomized and the evaluation of osteopenia was based only on plain X-rays and thus no quantitative measurements of bone mineral were performed.

The histomorphologic changes in the proximal tibia following tibial shaft fracture consist of an increased number of both osteoclasts and osteoblasts, and thus has the histomorphology of a high turn-over bone disease (Obrant and Nilsson 1984). Inhibition of bone resorption by a direct effect on the osteoclasts is a well known action of calcitonin (Chambers and Azria 1988). The preventive effect of calcitonin on immobilization osteopenia has been evaluated in several experimental animal studies. The reported effect varies from

no effect (Ekeland et al. 1983; Skerry and Lanyon 1993) to increased mechanical properties of both intact and fractured bones (Karachalios et al. 1992) and a preventive effect on bone loss measured as ash weight (Tuukkanen et al. 1990). Three previous human studies (Mallet et al. 1986; Tsakalakos et al. 1993; Crespo et al. 1997) have indicated a possible preventive effect of calcitonin on posttraumatic osteopenia. Generally, calcitonin is well tolerated with transient and mild side effects (Reginster and Franchimont 1985; Azria et al. 1995), and as calcitonin recently has become available as a nasal spray (Kurose et al. 1987; Reginster et al. 1987) it was a relevant drug of choice for evaluation with respect to prevention of posttraumatic osteopenia.

Table 3. Comparison of the mean (standard error) changes in BMC (g/cm) between placebo and sCT groups using calculation of the 95%-CL for the difference between the means (Petersen et al. 1998). From Petersen et al. Acta Orthop Scand 1998; 69: 347-50.

ΔBMC, months	Placebo (n=11)	Calcitonin (n=10)	Diff. (95%-CL)
Injured legs			
1.5–0	-0.39 (0.13)	-0.24 (0.21)	0.15 (-0.36; 0.66)
3–1.5	-0.20 (0.12)	-0.04 (0.15)	0.16 (-0.25; 0.57)
3–0	-0.59 (0.16)	-0.28 (0.21)	0.31 (-0.23; 0.85)
Healthy legs			
1.5–0	-0.18 (0.07	0.17 (0.15)	0.35 (0.20; 0.68)
3–1.5	0.08 (0.12)[a]	0.09 (0.14)	0.01 (-0.38; 0.41)
3–0	-0.12 (0.15)[a]	0.27 (0.17)	0.39 (-0.09; 0.86)

[a] n=10

Own results (study 10)

We performed a study of the preventive effect of nasal salmon calcitonin (sCT) on postfracture osteopenia in 24 patients with ankle fracture treated by open reduction and internal fixation (Petersen et al. 1998). The patients were randomized to postoperative treatment with either 200 IU sCT given daily for three months or placebo in a prospective, double-blind design. The fractures were classified according to the Lauge Hansens' system (Lindsjö 1985) and all were either supination-eversion or pronation-eversion types. The inclusion in this study did not influence the clinical management of the patients and after surgery all injured extremities were immobilized in a plaster cast for 6–8 weeks. During follow-up three patients were excluded from the study and 11 patients in the placebo group and 10 in the sCT group were left for the study. Bilateral measurements of BMC in the proximal tibia were performed by the DPA scanner postoperatively within 7 days after the fracture and after 1.5, 3, and 6 months.

Three months after the fracture BMC in the injured legs was decreased by 14% (95%-CL: -26%; -1.4%) in the placebo group, and only 2.1% (95%-CL: -16%; 12%) in the sCT group. In the healthy legs a tendency towards a decrease in BMC of 2.2% (95%-CL: -14%; 9.7%) was seen in the placebo group 3 months after the fracture, while BMC in the sCT group increased by 8.6% (95%-CL: -5.3%; 23%). When evaluating the effect of sCT on postoperative changes in BMC following ankle fractures, no significant effect was observed in the injured legs, but in the healthy legs a significant difference between the sCT and placebo group regarding the changes in BMC from baseline to 6 weeks postoperatively was observed (Table 3).

The present study was designed with the aim of evaluating if sCT was a potent inhibitor of postfracture bone loss. If the decrease in BMC (0-3 months) was totally prevented by sCT the number of patients needed in each group to reach a statistical power of 72% or 80% was respectively 10 and 12. If the difference in BMC of 0.31 g/cm actually found in the present study was used as the minimal relevant difference between groups with 10 patients in each group a statistical power of only 25% was obtained. Thus the design of the present study was suitable to evaluate an almost total preventive effect of sCT, but without sufficient statistical power to rule out a moderate effect of sCT.

Discussion

The decrease in BMC of the injured legs in the placebo group of respectively 11% and 14% 1.5 and 3 months postoperatively was in good agreement with the amount of bone loss found in previous studies (Finsen and Benum 1989; Petersen et al. 1992) evaluating bone loss following ankle fractures. In the injured legs of the sCT group the decrease in BMC was not significant and below half of what was seen in the placebo group, but no

statistically significant intergroup difference regarding the changes in BMC could be detected.

To our knowledge no previous studies using quantitative densitometric measurements of bone mineral have evaluated the effect of sCT on posttraumatic bone loss following fractures in humans, but there has been other studies using different techniques. In an open non-placebo-controlled randomized study Tsakalakos et al. (1993) evaluated the effect of two weeks treatment with daily intramuscularly injections of 100 IU sCT in 40 elderly with recent hip fracture. Blood and urine parameters of bone turnover were measured, but no measurements of bone mineral were performed. No changes in S-calcium, S-phosphorous or S-alkaline phosphatases were found, but it was concluded that a hip fracture induced an increase in markers of bone resorption (U-hydroxyprolin-creatinine-ratio and U-calcium) and sCT reversed this effect.

In a study by Mallet et al. (1986) 19 children with femoral fractures were randomized to 4 weeks of treatment with sCT injections or no treatment. No effect of sCT on biochemical markers of bone turnover was observed, but the treatment prevented bone loss as it could be judged from plain X-rays. The effect of sCT injections combined with oral calcium supplementation 10 successive days each month for one year with the aim of preventing postfracture osteopenia in postmenopausal women with Colles' fracture was evaluated in a recent study by Crespo et al. (1997). Radiogrammetric measurements of metacarpal index, which measure only cortical bone mass, were performed at baseline and after one year of treatment. A significant effect of sCT was found, and in the treatment group metacarpal index increased by 12.8% while in the placebo group a 7.0% decrease was found. Since no measurements were performed between baseline and the one year follow-up and no measurements were performed in the healthy contralateral extremities the data are difficult to interpret or to directly compare with the present study.

Adaptive bone remodeling of the proximal tibia after medial meniscectomy

Shock absorption and load transmission are the main functions of the menisci and 40–60 % of the load through a normal knee joint is carried by the menisci (Distefano 1980; King 1936; Seedholm et al. 1974; Shrive 1974; Shrive et al. 1978; Walker and Erkman 1975) by increasing the area of load-bearing (Walker and Erkman 1975). Following a meniscectomy the tibio-femoral contact area is decreased and the load acting across the contact area of the knee joint is increased by 2–3 times (Baratz et al. 1986; Fukubayashi and Kurosawa 1980; Krause et al. 1976; Kurosawa et al. 1980). A medial meniscectomy results in reduced compressive strains in the lateral part of the tibia, while on the medial side compressive strains are increased at all levels beyond 7 cm distal to the joint line. At levels within 5 cm from the joint line a significant reduction in compressive strains of the medial part of the cortex are seen (Bourne et al. 1984). This strain reduction was explained as a transmission of the increased medial load from the subchondral plate through the underlying cancellous bone to the cortex of the medial metaphysis and diaphysis. Bone scintigraphy in patients with a suspected meniscus tear has shown an increased radionuclide uptake in many patients, and a pattern of uptake claimed to be specific for meniscus pathology was seen in the subchrondral bone of the proximal tibia (Marymont et al. 1983; Mooar et al. 1987), and might be the first sign of adaptive bone remodeling leading to degenerative changes of the postmeniscectomized knee. These changes seen roentgenographically following meniscectomy was first described by Fairbank (1948). Further studies have shown that degenerative changes or even more pronounced roentgenographic signs of osteoarthrosis of the knee (Ahlbäck 1968) are seen in 46–89% of patients more than 10 years after total meniscectomy (Allen et al. 1984; Huckell 1965; Jørgensen et al. 1987; Tapper and Hoover 1969). However, roentgenographic studies have only provided qualitative information about the adaptive bone remodeling following meniscectomy (Ahlbäck 1968; Allen et al. 1984; Fairbank 1948; Huckell 1965; Jørgensen et al. 1987; Tapper and Hoover 1969).

Own results (study 8)

We have measured quantitatively the adaptive bone remodeling in the proximal tibia following medial meniscectomy using the DPA-scanner (Petersen et al. 1996c). A total of 33 patients who had sustained an isolated tear of the medial meniscus, treated with partial (n=14) or total meniscectomy (n=19) by open joint surgery 12 years earlier, were included in the study. The meniscectomized patients in this study were randomly allocated to either partial or total meniscectomy (Hede et al. 1986; Hede et al. 1992), and all patients had a healthy contralateral leg, and no previous fractures, ligamental or meniscal injuries before meniscectomy or during the time between meniscectomy and the bone mineral measurements. None of the patients had been reoperated on. Measurements of BMD were done in the previously injured legs and the healthy contralateral legs. The ROI´s selected for BMD-measurements were located medially and laterally in the cortical bone of the subchondral plates and below in the trabecular bone of the medial and lateral tibial condyles (Figure 2). The distribution of bone mineral within the proximal tibia showed a characteristic and significant pattern (Figure 5). In the trabecular bone of the healthy contralateral knees, BMD was 15% higher in the medial tibial condyles compared with the lateral BMD values, whereas a total (p=0.004) or a partial (p=0.01) meniscectomy had increased this difference to 25%. Focusing on the BMD in the cortical bone of the subchondral plates, the medial density in the healthy knees was 25–29% higher compared with the lateral density, whereas in total and partial meniscectomy the differences were respectively 38% (p=0.04) and 41% (p=0.03). No significant differ-

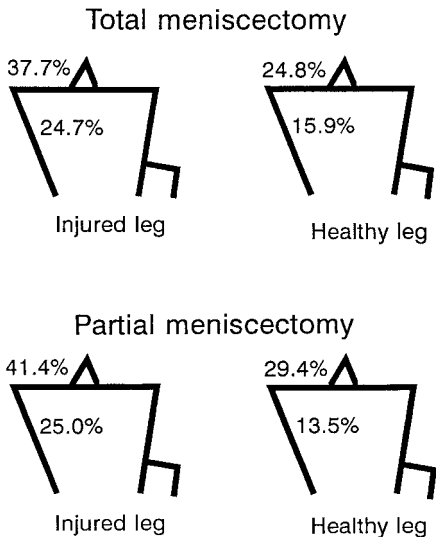

Figure 5 . The distribution of BMD in the cortical and trabecular bone of the proximal tibia following respectively total (n=19) and partial medial (n=14) meniscectomy calculated as the percentage difference between BMD at medial and lateral measuring sites ((BMD_{medial} - $BMD_{lateral}$)/$BMD_{lateral}$ x 100%). From Petersen et al. J Orthop Res 1996;14:16-21.

ences in the distribution of BMD either at cortical (p=1.0) or trabecular (p=0.5) measuring sites, were found between totally and partially meniscectomized knees.

Discussion

The design of our study (Petersen et al. 1996c) was based on the assumption, that in a healthy subject there is no difference between dominant and nondominant legs regarding the distribution of the bone mineral within the proximal tibia. According to a study by Odgaard et al. (1989), a recent study by Madsen et al. (1994), and our own measurements in 10 healthy subjects (Petersen et al. 1996c), the distribution of the bone mineral within the proximal tibia could be considered to be identical in dominant and nondominant legs.

Odgaard et al. (1989) evaluated bone remodeling in the proximal tibia following meniscectomy using QCT. Bone density was measured in small areas (0.2 cm^2) covering slices 0.2 cm wide at 6 different levels in the proximal tibia. A posteromedial displacement of 0.4 cm of the area of maximal density in the medial tibial condyle was found in patients with partial and total medial meniscectomy performed 5 and 10 years earlier. Density in the region of tibiofemoral contact in the medial tibial condyle was higher, compared to density in the same region in the contralateral healthy knees in both partially and totally meniscectomized patients. The patients were not randomized to total or partial meniscectomy and the overall changes in local density were basically identical in the two groups.

The adaptive bone remodeling observed in our study (Petersen et al. 1996c) confirmed what was expected from studies on the biomechanical consequences of medial meniscectomy (Baratz et al. 1986; Bourne et al. 1984; Fukubayashi and Kurosawa 1980; King 1936; Kurosawa et al. 1980; Seedholm et al. 1974; Shrive 1974; Shrive et al. 1978; Walker and Erkman 1975) and the roentgenographic degenerative changes in the postmeniscectomized knee (Ahlbäck 1968; Allen et al. 1984; Fairbank 1948; Huckell 1965; Jørgensen et al. 1987; Tapper and Hoover 1969). Due to different methodology and difference in measuring sites it is difficult to compare the results from our study (Petersen et al. 1996c) directly to the results obtained in the study by Odgaard et al. (1989), but a tendency to increased BMD in the medial part of the proximal tibia following both partial and total meniscectomy was seen in both studies, and no significant difference could be detected between total and partial meniscectomy regarding the adaptive bone remodeling pattern.

A recent study by Pastoureau et al. (1999) evaluated early subchondral bone changes of the distal femur in partial medial meniscectomized guinea pigs. BMD was measured by high resolution DEXA measurements in 2 ROI in respectively the medial and lateral part of the subchondral bone. After a temporary decrease in BMD in both medial and lateral ROI 1 month after surgery, a significant increase of 3.6% in BMD medially compared to the healthy contralateral legs was seen 3 months after medial menisectomy. The results of this animal experimental study (Pastoureau et al. 1999) was in good agreement with with our results and it showed that the reaction of the subchondral bone after meniscectomy with increased density is, at least in guinea pigs a relatively fast response visible within 3 months after meniscectomy.

Previous studies (Behrens et al. 1974; Christensen et al. 1982) have shown that in a knee with

varus or valgus deformity, a highly increased mineral content existed in the trabecular bone of the tibial condyle with the highest load, compared to the mineral content of the less loaded condyle. Several biomechanical studies (Baratz et al. 1986; Bourne et al. 1984; Fukubayashi and Kurosawa 1980; Krause et al. 1976; Kurosawa et al. 1980) have documented that the load is increased in the medial part of the knee joint following a medial meniscectomy, and we believe that the altered distribution of BMD in the proximal tibia with a higher proportion of bone mineral in the medial part of the trabecular bone, mainly was a consequence of the altered loading of the knee joint after the meniscus tear or the meniscectomy. The high bone density in the cortical bone of the medial subchondral plates may be considered to reflect the initial changes in the development of osteoarthrosis in the knee joint (Madsen et al. 1994; Noble and Alexander 1985; Radin and Rose 1986). The adaptive bone remodeling in the proximal tibia was the same in both partial and total meniscectomy, and though arthroscopic partial meniscectomy now is the treatment of choice, it may also alter the biomechanics of the knee joint leading to the same degenerative changes as seen following open meniscectomy.

Adaptive bone remodeling after knee arthroplasty

Tibial component

Operation with implantation of TKA because of arthrosis represents an immediate and significant change in the biomechanical stresses to the surrounding bones (Huiskes et al. 1987; Orr et al. 1990; Tissakht et al. 1996). As a consequence of the TKA-operation, the mechanical axis of the knee is often altered significantly and the proximal tibia start acting as an endo-prosthesis bearing surface. According to Wolffs' law (Wolff 1892) the bones will react with an adaptive bone remodeling, thus adjusting their density to the altered mechanical demands. Operation with insertion of a knee or a hip arthroplasty represents a significant trauma to the bone, and several studies have shown, that even though the level of activity of these patients is increased postoperatively, no permanent increase in bone mineral occurs (Lindberg and Nilsson 1984; Rüegsegger et al. 1986; Bohr and Lund 1987; Hvid et al. 1988; Adolphson et al. 1993). Thus, some degree of posttraumatic osteopenia (Andersson and Nilsson 1979a; Petersen et al. 1992) must be considered to develop in the operated extremity, and might influence the early changes in bone mineral of the periprosthetic bone. Later, also wear debris mediated osteolysis may contribute to the measured bone loss (Harris 1994; Kim et al. 1995).

Own results (study 5)

In a study using DPA (Petersen et al. 1995a) we measured the changes in BMD of the proximal tibia following uncemented TKA (PCA Modular®) because of osteoarthrosis. Repeated measurements were performed for three years after TKA in 25 knees, and BMD was measured in the trabecular bone in small ROI below the tibial component (Figure 6). All knees had pre- and postoperative measurements of the mechanical axis calculated as the hip-knee-ankle angle on long standing roentgenograms. Average BMD in all ROI of the proximal tibia following uncemented TKA was an overall loss of bone mineral of 22% during the first three postoperative years. 23 knees had a change in knee alignment as a consequence of the operation. In the tibial condyles, where the change in knee alignment indicated, that the load was decreased postoperatively, a rapid bone loss of 7–20 % was seen during the first 6 months after surgery. A small but temporary increase in BMD of 2–7 % was seen in the tibial condyles, where load was increased.

Discussion

Hvid et al. (1988) measured trabecular bone remodeling of the proximal tibia using QCT following TKA with a cemented non-metal-backed tibial component in 18 patients (9 with arthrosis and 9 with rheumatoid arthritis). During the two-year observation period, the mean bone density decreased significantly in the preoperatively more loaded tibial condyle, while the density in the preoperatively less loaded condyles was unchanged. The average decrease in bone density after two years was 32 % in rheumatoid arthritis and 11 % in arthrosis. We consider the adaptive bone re-

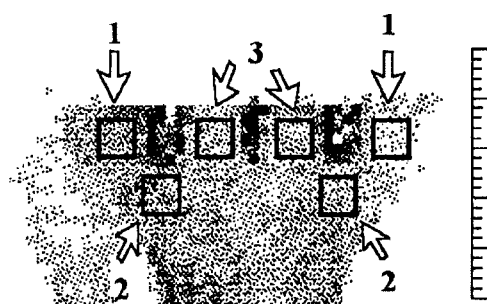

Figure 6 . Scan plot from a DPA-scanning performed in the proximal tibia after implantation of an uncemented total knee arthroplasty (PCA Modular"). The location of the ROI used for the measurements of BMD medially and laterally below the tibial component is shown. ROI 1 is the area located proximally between the fixation peg and the medial/lateral peripherial rim of the bone, ROI 2 is the area located distally just below the fixation peg in the medial/lateral fixation peg, and ROI 3 is the area located proximally in the central part of the bone between the fixation screw and the medial/lateral fixation peg. From Petersen et al. Acta Orthop Scand 1995;66:513-6.

modeling and the average bone loss in this study (Hvid et al. 1988) to be in agreement with our results.

In a study by Bohr and Lund (1987), a temporary increase in average BMD in the proximal tibia was found 6 months after uncemented arthroplasty. During the next year BMD decreased to the initial level. However, this study was of partly cross-sectional design and thus the results could be quite strongly influenced by age and sex related inter-individual differences in bone mineral of the proximal tibia (Bohr and Schaadt 1987; Petersen et al. 1993). Seitz et al. (1987) estimated the local changes in trabecular bone density of the proximal tibia following cemented TKA using a QCT-method modified to reduce artifacts caused by metal implants. From 10 paired measurements performed in 8 patients within 6 months after TKA a bone loss rate of 1.6% per month was estimated. Levitz et al (1995) measured the changes in BMD of the proximal tibia following TKA. Measurements were performed by DPA in 31 patients 6 weeks, 6 months and one year after surgery. Furthermore, 7 patients had an additional measurement performed 8 years postoperatively using DEXA. The implant type and fixation mode were not mentioned in the article. BMD was decreased by 5% at 6 months, but after one year BMD was not significantly different from initial values. However, since the initial measurements were performed 6 weeks after surgery, a significant decrease at one year compared to the immediate postoperative BMD could easily have been overlooked. From the DEXA-measurements a total bone loss of 40% after 8 years was estimated. Although the change of scanning-technique during the study could have influenced the estimated bone loss, the long-term results was in good agreement with our study (Petersen et al. 1995a).

In a recent publication Regnér et al. (1999) measured BMD in the medial part of the proximal tibia (an area with a diameter of 0.8 cm) in 38 knees stratified to two different types of uncemented TKA. BMD measurements were performed by triple energy X-ray absorptiometry, an experimental technique using a continuous X-ray spectrum as a photon source (Swanpalmer et al. 1998). At follow-up 4–5 years postoperatively average BMD had decreased by 26% and furthermore the changes in the load of the medial tibial condyle influenced the amount of bone loss in this region.

In 1999 the first prospective studies (Karbowski et al. 1999; Spittlehouse et al. 1999) using DEXA for quantitative evaluation of adaptive bone remodeling of the proximal tibia after uncemented TKA were published. In the study by Karbowski et al. (1999) scannings were performed in both anteroposterior and lateral projections and with each scannning including both the proximal tibia and distal femur. No software for exclusion of metal was used when the scannings were analyzed. BMD was only measured in 2 ROI including respectively the proximal tibia and distal femur. Both the anteroposterior and lateral measurements in 12 patients showed that BMD had decreased by approximately 10% in the proximal tibia 9 months after surgery. In the study by Spittlehouse et al. (1999) no significant changes in BMD of the proximal tibia was found during the first 6 months after surgery in either lateral or anteroposterior projections.

There is a close relation between BMD and the strength of trabecular bone (Hansson et al. 1980; Hvid et al. 1985; Petersen et al. 1996a), and theoretically an increased risk of fractures or loosening of the tibial component might be expected in patients with a high postoperative bone loss. But generally the long-term results following TKA is quite satisfactory with a low revision rate and periprostetic fractures are rare (Knutson et al. 1994). Preoperatively most patients with arthrosis of the knee has bone mineral values of the proximal tibia above average in normals (Petersen et al. 1993; Madsen et al. 1994) and a part of the bone loss after TKA might represent a return to normal of the relatively high density osteoarthrotic bone.

Femoral component

Previous and recent finite element models of the distal femur following TKA (Walker et al. 1982; Tissakht et al. 1996; Van Lenthe et al. 1997) have shown, that the strain in the anterior part of the distal femur is altered from a high stress region to a stress shielded region following implantation of

the TKA. The bone loss is expected to occur especially in the anterior distal femur, and the highest degree of stress shielding could be expected, if the anterior and posterior flange surfaces are bonded to the bone, but on the contrary if the anterior and posterior surfaces are not bonded to the bone some load transfer through the distal anterior femur should be possible, and thus stress shielding leading to the development of bone loss might be reduced (Walker et al. 1982; Tissakht et al. 1996; Van Lenthe et al. 1997). A study by Whiteside and Pafford (1989) indicated that a porous-coated femoral component with smooth anterior and posterior flange surfaces could prevent the roentgenographic appearance of stress shielding, as it could be estimated from plain roentgenograms, and most knees even showed a hypertrophic pattern of the trabecular bone in the anterior distal femur. But no quantitative measurements of bone density were performed in this study. However, a recent finite element study (Tissakht et al. 1996) indicated that even though this modification of porous-coating could be expected to increase the strain in the anterior distal femur to values comparable with those in intact bone, this increase would not extend to the most distal corner corresponding to our anterior ROI.

Own results (study 4 and 7)

We examined the adaptive changes in BMD using DPA following implantation of 4 different femoral components in uncemented TKA. In the first study (Petersen et al. 1995b) we measured density changes of the distal femur in 8 patients with implantation of an uncemented PCA Primary® prosthesis within three months from the initial scanning, and with a second scanning performed at follow-up two years postoperatively. BMD was measured in three relatively small ROI located respectively anterior to the fixation pegs, above the pegs, and posteriorly to the pegs. A decrease in BMD of 36% (p=0.01) was seen in the ROI anterior to the fixation pegs. In the ROI above the pegs BMD increased by 22% (p=0.12), while BMD in the ROI behind the pegs remained unchanged.

In the second study (Petersen et al. 1996b) we measured the early adaptive bone remodeling prospectively for one year after uncemented TKA in 29 knees with primary arthrosis. 18 knees were randomized to receive a PCA Modular" femur component or a modified version of the same prosthesis specially designed for this study. The PCA Modular component has a surface designed to secure permanent fixation by bone ingrowth with the total surface covered with a porous-coating, except on the surface of the two fixation pegs. The modified component had an altered location of the porous-coating, but was otherwise identical with the standard component. The porous-coating was removed from the anterior and posterior flanges and coating was added to the surface of the pegs. The remaining knees (n=11) was a consecutive series with the Duracon® femoral component. In the trabecular bone above the femoral component BMD was measured in two ROI's anteriorly to the fixation pegs and posteriorly above the pegs using DPA. The ROI's selected were often larger and not identical to those used in our previous study (Petersen et al. 1995b), and the small ROI located posteriorly behind the fixation pegs was not used in this study. No significant differences between the Modular component and the modified version regarding the postoperative decrease in BMD was seen. A significant decrease in BMD in both ROI`s and for all three different femoral components was seen. In both ROI the highest bone loss rate was observed during the first three months after surgery (Figure 7). On average (n=29) a significant bone loss of 44% ($p<0.00005$) and 19% ($p<0.00005$) for the ROI`s located respectively anteriorly and posteriorly above the pegs were observed at the 12 months follow-up compared to the initial values.

In our randomized study (Petersen et al. 1996b) no significant effect of the modified porous-coating on the adaptive bone remodeling was found, but it was obvious that both the early bone loss and total bone loss in the ROI anteriorly to the pegs were below what was seen in femurs with the standard femoral component implanted, while the decrease in BMD in the ROI located posteriorly above the pegs was on the same level in the two groups. The randomized study was designed only to detect a large preventive effect of the modified femoral component regarding development of stress shielding, and the differences actually found could not be expected to be significant with only 9 patients in each study group. The type 2

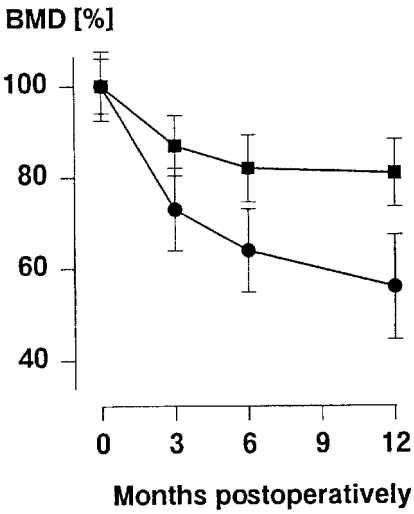

Figure 7. Percentage changes in BMD (mean and standard error of the mean) behind the anterior flange (ROI 1 = l), and above the fixation pegs (ROI 2 = n) for all (n=29) femoral components (three different femoral components; Modular (n=9), modified Modular (n=9), and Duracon (n=11)). From Petersen et al. Acta Orthop Scand 1996; 67:339-344.

error for comparison of the early bone loss (0–3 months) between the two groups using the difference actually found (0.15 g/cm^2) as the relevant minimal difference was 63% with 9 patients in each group.

Discussion

Our studies (Petersen et al. 1995b; Petersen et al. 1996b) confirmed the existence of stress shielding behind the anterior flange of the femoral component following TKA, which was initially suggested by previous roentgenographic and finite element studies (Walker et al. 1982; Cameron and Cameron 1987; Mintzer et al. 1990). The decrease in femoral BMD found in the second study (Petersen et al. 1996b) was significantly higher compared to the average decrease of 8% below the tibial plateau one year after TKA (Petersen et al. 1995a). Previous prospective studies using DEXA for measurements of BMD around cemented or uncemented femoral components after total hip arthroplasty (Cohen and Rushton 1995b; Kiratli et al. 1996) have shown postoperative bone loss below what was seen in our study. When it is taken into consideration that the baseline measurements in our first study (Petersen et al. 1995b) were not performed as close to the time of surgery as in the second study (Petersen et al. 1996b), and thus the initial and very fast bone loss (probably induced by the operative trauma) was not measured in the first study, a good agreement existed between the amount of bone loss found in our two studies (Petersen et al. 1995b; Petersen et al. 1996b).

Liu et al. (1995) measured BMD changes in the distal femur following uncemented TKA using DEXA, but only one of their ROIs' were quite similar to ours. In the ROI comparable with our posterior ROI, an average decrease in BMD of 18% was seen 6 months postoperatively, followed by a partial restoration of bone loss. Thus the total bone loss after one year was only 8%. Using DEXA Spittelhouse et al. (1999) measured early (6 months after surgery) changes in BMD of the distal femur after uncemented TKA in both anteroposterior and lateral projections and found the highest degree of bone loss (16%) in the most distal part of the femur anteriorly on the lateral projections. The baseline measurements were not performed until 6 weeks after the operation and thus the measured decrease in BMD might be underestimated. Karbowski et al. (1999) also used DEXA for measurements of BMD in the anteroposterior and lateral projections of the distal femur after uncemented TKA. An average decrease in BMD of approximately 22% was seen in the distal femur 9 months postoperatively. BMD was only measured in one large ROI including both prosthesis and bone pixels of the distal femur. In our second study (Petersen et al. 1996b) the decrease in BMD after 6 months was on the same level as in the above mentioned DEXA-studies (Liu et al. 1995; Karbowski et al. 1999; Spittlehouse et al. 1999), however, no remineralization was observed at the one year follow-up as shown in the study by Liu et al. (1995).

A some what different approach to quantitative measurements of density changes in the distal femoral bone following TKA have recently been published by Seki et al. (1999). A densitometer was used to quantify changes in bone density on series of plain postoperative lateral radiographs of 114 well-functioning knees. On each radiograph the density in ROI around the femoral component was divided by the density in a reference zone of the femoral shaft. Thus the rate of bone loss was

determined by computing the ratio of the density data on the radiographs at each evaluation time. Four different implant designs using both cemented and uncemented femoral components were examined. The highest bone loss rate was seen in the anterior distal femur after cemented TKA reaching an average decrease in bone density of up to 57% 2 years postoperatively.

Clinical studies have shown that the majority of periprosthetic fractures of the femur following TKA are indeed sustained as a consequence of minor injury (Nielsen et al. 1988; Healy et al. 1993; Garnavos et al. 1994), and often they are associated with radiological evidence of osteopenia (Nielsen et al. 1988; Healy et al. 1993). Supracondylar fractures of the femur following TKA are rare (Nielsen et al. 1988; Figgie et al. 1990), but of clinical importance, because they are difficult to treat and sometimes lead to poor functional results (Nielsen et al. 1988; Figgie et al. 1990; Garnavos et al. 1994). It is well known that there is a close relation between BMD and the strength of trabecular bone (Hvid et al. 1985; Strømsøe et al. 1994), and theoretically an increased risk of periprosthetic fractures or loosening of the femoral component might be expected in patients with a high postoperative bone loss. With respect to the age related annual bone loss of 1% which is normally seen in trabecular bone (Mazess 1982; Petersen et al. 1993), an average decrease in BMD of more than 40% in the anterior distal femur one year after TKA must be considered an important permissive factor for later periprosthetic fracture, and a risk factor for loosening of the femoral component.

Conclusions

The specially designed DPA-scanners provided highly accurate and precise measurements of bone mineral in *in vitro* studies and the precision *in vivo* expressed as the CV for BMC-measurements in the proximal tibia was below 2%. The CV for local BMD-measurements within the proximal tibia and distal femur were respectively 2.8–5.2% and 2.2–3.2%. We found that BMD-measurements by DPA and DEXA were suitable methods for precise evaluation of local variations of trabecular bone strength within the proximal tibia.

The age-related decay in BMC of the proximal tibia showed similar age-related trends as in other skeletal sites and in 102 healthy women an almost 50% decrease form women aged 20–29 years to 80–89 years was found. In young healthy men BMC was almost 30% higher compared to values in women of the same age, and especially in young adults both height and weight showed a significant positive correlation to BMC. Age adjusted BMC was lower in women with osteoporosis compared to controls and in women with knee arthrosis BMC was higher.

Posttraumatic osteopenia was measured following lower extremity fractures. An ankle fracture induced a decrease in BMC of the proximal tibia of 15.3% 6 months after the fracture and after three years BMC was still 10.7% below the preoperative value. A tibial shaft fracture induced a decrease in BMC in the proximal tibia of 19% 6 months after the fracture while BMD of the hip was decreased by 7% and 14% for respectively the femoral neck and the greater trochanter. In patients with complicated tibial shaft fractures cross-sectional data showed that the bone loss continued beyond 6 months. In a randomized double-blind study treatment with nasal sCT for three months in patients with ankle fracture did not show any significant preventive effects on posttraumatic osteopenia, but the bone loss in the sCT group was below half of what was seen in the placebo group, and a statistically significant effect of sCT was observed in the healthy contralateral legs.

BMD-measurements of the proximal tibia 12 years after a total or a partial meniscectomy showed an identical and significant density distribution pattern with increased density medially in both the trabecular bone and in the cortical bone of the subchondral plates compared with the density distribution in the healthy contralateral legs.

BMD of the proximal tibia following TKA showed a tendency towards an adjustment to the altered postoperative alignment of the knee, but on average a progressive decrease in bone mineral of 22% during the first three postoperative years was seen. BMD-measurements of the distal femur in TKA showed an average decrease in bone mineral of 44% in the anterior distal femur during the first postoperative year and thus confirmed the existence of stress shielding. In a randomized study we found no significant preventive effect of a femoral component with an altered porous-coating with regard to stress shielding of the distal anterior femur after TKA.

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List of abbreviations

ACL-lesion	lesion of the anterior cruciate ligament of the knee
1-ß	statistical power
ß	probability of type 2 error
BMC	bone mineral content
BMD	bone mineral density
Ci	Curie
CV	coefficient of variation
DEXA	dual energy x-ray absorptiometry
DPA	dual photon absorptiometry
^{153}GD	Gadolinium-153
keV	10^3 electron volt(s)
QCT	quantitative computed tomography
r	coefficient of correlation
r^2	coefficient of determination
ROI	regions of interest
sCT	salmon calcitonin
SEE	standard error of the estimate
SPA	single photon absorptiometry
Sv	Sievert
THA	total hip arthroplasty
TKA	total knee arthroplasty
95%-CL	95%-confidence limits

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