EXTENDED REPORTS

Validated measurement of periarticular bone mineral density at the knee joint by dual energy x ray absorptiometry

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Abstract

Objective—The association of inflammatory arthritis with loss of periarticular bone mineral density (BMD) has been well established. However, changes in bone density cannot be quantified by conventional radiography. This study aimed at developing a new technique for measurement of periarticular bone density at the knee joint by dual energy x ray absorptiometry (DXA) and assessing the precision of this technique for selected areas around the knee.

Methods—To validate this technique for bone density assessment in both patient and control subjects, knee joints from healthy subjects and patients with inflammatory arthritis were selected for study. Posteroanterior (PA) and lateral scans of both knees were acquired with the Hologic 4500 elite bone densitometer. Each scan was repeated three times, with repositioning between scans. Knee scans were obtained with the forearm software and evaluated by subregion analysis. Seven femoral and seven tibial subregions of interest (ROIs) were selected on PA scans. Six ROIs were selected on lateral scans. Precision was determined for each ROI selected.

Results—14 knee joints were studied in each group. Precision, expressed as percentage coefficient of variation (CV%), varied widely between subregions. PA scans were most appropriate for measurement of femoral bone density (CV% = 1.89–2.64%), whereas the best value obtained for ROIs within the tibia was on the lateral scan, where CV% for measurement of the proximal 5 mm was 2.67% in the patient group. CV% for BMD of the patella was excellent at 0.84% in the patient group.

Conclusion—This new application of DXA can be used to measure periarticular bone density at the knee joint. Regions within the distal femur and patella have been identified as the optimal areas to study

Dual energy x ray absorptiometry (DXA) is considered to be the most advanced currently available technique for measurement of bone mineral density (BMD). It is a non-invasive technique that uses very low doses of ionising radiation. Thus it has been shown to be a fast, safe, accurate, and reproducible means of assessing BMD.¹ DXA has been widely used to quantify change in generalised BMD, with the lumbar spine, hip, and distal radius being the sites conventionally measured.

The association of rheumatoid arthritis (RA) with both generalised and periarticular osteoporosis has been well documented.^{2–6} Although loss of periarticular BMD is one of the earliest radiological signs of joint damage in inflammatory arthritis, osteopenia only becomes apparent radiographically when a considerable proportion of bone density has been lost. Furthermore, conventional radiography is a subjective and non-quantitative method of assessing bone density. Several studies have measured peripheral bone loss in patients with RA, but to date such studies have concentrated mainly on total hand and forearm measurements. Loss of bone density in the hand occurs in early disease and has been suggested as a predictor of joint destruction in RA.⁷ Single photon absorptiometry⁸ and peripheral quantitative computed tomography⁹ have been used to measure BMD of the distal radius. The precision (represented as the percentage coefficient of variation (CV%)) for these techniques varies from approximately 2.0% to 3.7%. Neutron activation analysis has been used to measure bone mineral content (BMC) of the hand, but this technique is limited by the high radiation doses required.^{10, 11} Single photon absorptiometry has also been used to measure hand BMC.¹² More recently, total hand BMC has been measured by DXA¹³ and this technique applied to patients with RA.^{7, 14, 15} Although the precision of this technique is good, with a CV% of 1.5% for BMC and 1.0% for BMD of the total hand,¹³ the ability to quantify reliably the degree of periarticular bone loss around individual peripheral joints has not yet been developed.

Although the earliest radiological change is commonly seen around the small joints of the hands and feet, periarticular bone loss may be

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seen around any inflamed joint in patients with inflammatory arthritis. This study was undertaken to develop a protocol for measurement of periarticular bone density at the knee joint. The development of such a technique would make it possible to monitor periarticular bone density over time, thus providing a useful marker of disease progression. The knee joint was selected as the optimal joint in which to study periarticular bone loss as it is commonly affected in both seropositive and seronegative arthropathies. Furthermore, synovial biopsy of the knee joint is a simple procedure and correlation of histological and other measures of inflammation with local bone loss around the joint should provide further insight into the pathogenesis of periarticular osteopenia in these conditions. Short term precision of the technique was evaluated for several regions of interest, both in healthy control subjects and in patients with inflammatory knee arthritis. The distal 4 mm of femur on the posteroanterior (PA) scan (R4) and patella on the lateral scan (R6) were selected as the optimal regions of interest (ROIs) to select for periarticular bone density measurement. In healthy control subjects, precision values (CV%) of 1.89% and 1.21%, respectively, were obtained for these ROIs. The potential clinical application of the technique was confirmed in the patient group, where precision values of 2.36% and 0.84% were obtained for measurement of these regions. Precision values of this order confirm that the technique can be reliably used to detect relatively small changes in periarticular bone density.

Methods

STUDY SUBJECTS

Seven healthy female subjects with no history of recurrent knee pain were selected for study. To validate the technique in a patient population, as well as in healthy control subjects, a second group consisting of seven patients with inflammatory arthritis affecting at least one knee joint was also selected. The healthy subjects were female hospital staff ranging from 21 to 48 years of age. The patient group included three women and four men ranging from 15 to 59 years of age. All had inflammatory arthritis with knee involvement. Disease duration ranged from one month to six years. C reactive protein concentrations ranged from 0 to 65 mg/l (normal 0–5.9 mg/l).

MEASUREMENT OF BONE MINERAL DENSITY AT THE KNEE JOINT

Knee scans were acquired on a Hologic 4500 elite fan beam bone densitometer. PA and lateral views were performed on each knee. For PA scans the subject was positioned in the supine position while lateral scans of the left and right knees were performed in the left and right lateral positions respectively. Custom-made modified thermoplastic leg braces were used as positioning devices to stabilise the joint and improve precision. Preliminary evaluations were performed with the lumbar spine software, which has been shown to be dependent on soft tissue thickness.¹⁶ Owing to lack of soft

tissue around the knee joint, bone detection was incomplete, and scans acquired in this way could not be properly analysed. Thus using this programme it was necessary to simulate soft tissue by placing rice bags around the knee joint. This technique was quite cumbersome, prolonged the time taken to position the patient, and, because of difficulty in using the joint positioning devices, had the potential to affect precision adversely. To eliminate these factors, scans were then obtained with the forearm software, which allows for air, in addition to soft tissue, detection. Scan width was large enough to accommodate all the joints studied. In two cases it was necessary to increase the height of the scan in order to include enough reference material to allow for analysis. Each joint was scanned in this way three times in immediate succession, with repositioning between scans by removing the positioning device and taking the subject off the table.

Scans were evaluated by subregion analysis. On the PA scan, 14 subregions of interest were selected for analysis. These included seven

Figure 1 Posteroanterior knee scan. The subregion area increases from R1 to R7. The lower border of the regions of interest (ROIs) is distal to the femur and remains constant for all ROIs. The upper border of R1 is placed 1 mm above the intercondylar notch. The height of subsequent subregions is increased in 1 mm increments from this reference point. Thus R1 represents the distal 1 mm of femur and R7 represents the distal 7 mm of femur. Labels for each ROI are randomly placed by the computer at different points on the ROI boxes. Table 1 shows the results for bone mineral content and bone mineral density for each of the subregions.

Table 1 Results for subregions of interest on posteroanterior scans of the femur

Region	Area (cm ²)	BMC* (g)	BMD* (g/cm ²)
Global	70.43	56.48	0.802
R1	4.47	3.70	0.827
R2	5.74	5.07	0.883
R3	7.05	6.49	0.920
R4	8.37	7.88	0.942
R5	9.70	9.22	0.951
R6	11.03	10.56	0.957
R7	12.37	11.90	0.962
Net average	12.37	11.90	0.962

*BMC = bone mineral content; BMD = bone mineral density.

Figure 2 Lateral knee scan with six subregions of interest—R1, R2 (distal 2 mm and 5 mm femur respectively), R3, R4 (proximal 2 mm and 5 mm tibia respectively), R5 (region of interest includes an area 5 mm above and below the joint line), R6 (patella). Table 2 shows the results for bone mineral content and bone mineral density for each of the subregions.

Table 2 Results for subregions of interest on lateral scan

Region	Area (cm ²)	BMC* (g)	BMD* (g/cm ²)
Global	66.76	64.68	0.969
R1	1.28	1.08	0.844
R2	3.46	3.55	1.026
R3	1.55	1.87	1.212
R4	4.15	4.73	1.141
R5	7.64	7.94	1.040
R6	5.53	5.11	0.925
Net average	14.18	14.16	0.998

*BMC = bone mineral content; BMD = bone mineral density.

ROIs in the distal femur and seven in the proximal tibia. The width of the ROIs was constant, exceeding the width of the bone being scanned. On the femoral scan, R1 represents the most distal part of the femur with the height of the region of interest set at 1 mm above the intercondylar notch. The height of each subsequent subregion was increased by 1 mm from the same reference point, with R7 therefore representing the distal 7 mm of femur on the scan (fig 1, table 1). Use of the compare facility in scan acquisition ensured that the angle of the femur was similar on serial scans, thus making it possible to reproduce the subregions of interest. The seven ROIs in the tibia were determined in the same way on the PA scan, with R1 representing the proximal 1 mm of tibia and R7 representing the proximal 7 mm of tibia on the scan. The top of the tibial condyles was used as the proximal reference point for tibial ROIs. The tibial ROIs were analysed independently of the femoral ROIs for two reasons. Firstly, the forearm software only allows analysis of seven ROIs at a time. Secondly, the analysis programme does not allow angulation of the ROI around the intercondylar notch of femur. To include the most distal part of the femur, it is therefore necessary to position the base of the femoral regions of interest in a straight line below the femoral condyles. As a

result, the proximal part of the tibia is included in the femoral regions of interest, and this tibial bone must be deleted from the scan so that it is not included as femoral bone. Similarly, the distal femur must be deleted from the scan during independent analysis of tibial bone density. Thus the most distal part of femur and proximal region of tibia cannot be analysed simultaneously.

Six ROIs were selected for analysis on the lateral scans. R1 and R2 represent the distal 2 mm and 5 mm of the femur, respectively. R3 and R4 represent the proximal 2 mm and 5 mm of the tibia, respectively. R5 was determined by selecting an area 5 mm above and below the centre of the joint. Finally, R6 includes the total patella (fig 2, table 2).

Accurate edge detection was achieved by manual editing for both femoral and tibial ROIs.

STATISTICS

Short term precision for each ROI was calculated as the CV% according to the formula recommended by Gluer *et al.*¹⁷ $CV_{SD}\% = (SD/means/n) \times 100\%$, where n = the number of subjects. The precision for each ROI for the group as a whole was calculated by finding the root mean square (RMS) average for the 14 subjects according to the following formula: $CV = \sqrt{\sum CV^2/n}$, where n = the number of subjects.

The least significant change (LSC) for each ROI was calculated by multiplying the CV% for each ROI by 2.8 (95% confidence interval).

Table 3 Precision of periarticular bone mineral density measurements at selected regions of interest in the knee joints of normal subjects

Region of interest	PA femur* (%)	PA tibia* (%)	Lateral scan* (%)
R1	2.40	3.89	7.14
R2	2.16	3.90	4.29
R3	1.99	3.41	6.19
R4	1.89	3.41	3.14
R5	1.98	3.24	3.87
R6	1.96	3.20	1.21
R7	1.94	3.21	

*All results expressed as percentage coefficient of variation.

Figure 3 Individual bone mineral density (BMD) measurements for R4 femur on posteroanterior scans—healthy subjects. Where BMD values are similar, points may be superimposed on each other.

Figure 4 Individual bone mineral density measurements for patella on lateral scans—healthy subjects. Where BMD values are similar, points may be superimposed on each other.

Results

Seven healthy subjects were selected for study. Each knee joint was evaluated three times in both PA and lateral positions, with precision values derived from a total of 42 BMD analyses/ROI. Fourteen subregions of interest were studied on PA scans and six on lateral scans. Thus 84 knee scans and 840 subregion analyses were evaluated in these subjects. An additional 84 knee scans and 840 subregion analyses were evaluated in the patient group.

Table 3 shows the precision obtained for each of the seven femoral ROIs in the healthy subjects, represented as the CV%. The CV% values for these subregions were low, ranging from 1.89% to 2.40%, a difference of only 0.51%. The optimal values were observed for R3 to R7, all within a range of 0.10%. LSC values for these regions ranged from 5.29% to 5.57%. Figure 3 illustrates the individual femoral R4 BMD measurements for each of the subjects in order of increasing BMD.

Table 3 also shows the CV% values for tibial ROIs in healthy control subjects. The range of CV% values was greater for tibial than femoral ROIs, ranging from 3.20% to 3.90%. The best precision was obtained for R6 (proximal 6 mm of tibia) with CV% values of 3.20%. The LSC value for this ROI was 8.96%.

Among healthy control subjects, CV% values were high for femoral and tibial ROIs on the lateral scans but improved considerably as the area of analysis increased (table 3). Thus the CV% for lateral ROIs was 7.14% for R1 and 4.29% for R2 (femur) and 6.19% and 3.14% for R3 and R4 respectively (tibia). Precision for measurement of R5, which includes an area 5 mm above and below the joint line, was 3.87%. Excellent results were obtained for measurement of patellar bone density (R6, lateral scan). CV% for this ROI was 1.21% giving an LSC value of 3.39%. Figure 4 shows the individual values obtained for bone density of the patella in this group.

Table 4 shows precision values for the same ROIs in the patient group. Precision values for femoral ROIs on the PA scans ranged from 2.31% to 2.64% (a difference of 0.33%). The lowest precision values for these ROIs were

Table 4 Precision of periarticular bone mineral density measurements at selected regions of interest (ROIs) in the knee joints of patients with arthritis

Region of interest	PA femur (%)	PA tibia (%)	Lateral ROIs (%)
R1	2.49	4.52	6.89
R2	2.37	3.99	3.67
R3	2.31	3.84	6.07
R4	2.36	3.84	2.67
R5	2.44	3.57	2.76
R6	2.53	3.44	0.84
R7	2.64	3.44	

*All results expressed as percentage coefficient of variation.

observed for R2 to R5, with CV% values ranging from 2.31 to 2.44%, a difference of only 0.13%. LSC values for these regions ranged from 6.47% to 6.83%. As with healthy subjects, the range of CV% values was greater for tibial than for femoral ROIs, ranging from 3.44% to 4.52% (a difference of 1.08%). The degree of precision for tibial ROIs on the PA scans improved as the area of the ROI increased, with the best precision being obtained for R6 and R7 (CV% = 3.44%; LSC = 9.63%). Again, CV% values for femoral and tibial ROIs on the lateral scans improved considerably as the area of analysis increased, with CV% values of 6.89% for R1, 3.67% for R2 (femur), and 6.07% and 2.67% for R3 and R4 (tibia) respectively. CV% in this group for measurement of R5 on the lateral scan, which includes an area 5 mm above and below the joint line, was 2.76%. Excellent results were obtained for measurement of patellar bone density (R6). CV% for this ROI was 0.84%, giving an LSC value of 2.35%. Thus measurement of bone density of the patella in the patient group provided the best precision value for any of the ROIs studied.

Discussion

Periarticular bone density around the knee joint was measured by dual energy x ray absorptiometry using this new technique. Precision of the technique varied widely between different regions within the knee joint. Precision was good for all femoral ROIs on PA scans, particularly R3, R4, and R5. CV% values for femoral ROIs on the PA scans approximated those for hip measurement,¹⁸ ranging from 1.89% to 2.40% in control subjects and from 2.31% to 2.64% in patients. CV% for measurement of ROIs within the tibia was better on lateral scans (CV% R4 tibia = 2.67%, patient group) than on PA scans where CV% was >3% for all subregions selected. CV% for measurement of BMD of patella on the lateral scans was excellent. Least significant change values for this ROI were such that the technique could be reliably used to detect changes in bone density of 2.4%.

Precision on the PA scans was better overall for femoral ROIs than tibial ROIs. In both groups precision for measurement of tibial ROIs improved as the area of analysis increased. These results were similar to those in previous studies, in which CV% for tibial subchondral bone varied from 2.9 to 4.3%.¹⁹ As with femoral ROIs, precision for measurement of tibial ROIs in the patient group may be

adversely affected by the effect of synovitis on joint position. Knee scans are acquired with the leg extended in the supine position. In this position, flexion and extension of the leg are associated with rotation of the tibia, whereas rotation of the femur only occurs when the foot is fixed on the ground.²⁰ Thus in the supine position, inability to extend the leg fully owing to knee synovitis will adversely affect precision of tibial measurements to a greater extent than that of femoral measurements. The effect of knee synovitis on the ability to extend the leg fully may also partially explain why precision for measurement of tibial bone density is better in the control group than in the patient group. Furthermore, as the precision values are expressed as a percentage (CV%), the poor precision for measurement of tibial compared with femoral subregions is partly a reflection of the lower BMD of the tibia compared with the femur (for example, in the patient group, mean BMD of R4 femur is 1.032 g/cm³ compared with 0.985 g/cm³ for R4 tibia.)

Although CV% values for femoral ROIs on the PA scans were lower overall in control subjects than in patients, the range of values was similar in both groups. Differences between the two groups may be partly due to the effect of synovitis in the patient group. This could compromise the patient's ability to extend the leg fully, adversely affecting reproducibility of joint position. On the lateral scans, precision values were better overall in the patient group than in healthy subjects. Correct positioning of the knee joint is more difficult for lateral than for PA scans. As the patients were scanned at a later stage than the control subjects this probably reflects improved operator technique rather than a real difference between the two groups.

Thus joint position is one of the factors most likely to affect precision of BMD measurement. The use of modified leg braces as joint positioning devices was more important for lateral than for PA scans as the leg position was more variable for lateral scans. The same braces were used for every patient. Although the brace can be tightened around the leg it was not always possible to tighten the brace fully around the joint and therefore eliminate any free movement of the knee. It may therefore be more effective to have braces of different sizes available.

Femoral values on the lateral scans were not as good as those obtained on PA scans. However, the lateral scan has been shown to be useful for measurement of tibial bone density, with CV% in the patients studied of 2.67% for tibial R4 and 2.76% for R5, which includes both distal femur and proximal tibia. The lateral scan was most relevant for measurement of patella, where excellent results were obtained—CV% was 0.84% for measurement of bone density of patella in the patient group. This reflects the ease with which the total patella can be identified on the lateral scan, particularly in the patient group in whom joint swelling may increase the distance between the patella and the femur making it easier to include only the total patella within the ROI.

Thus periarticular bone density at the knee joint can be measured by DXA. The precision of this technique is good enough to allow small changes in bone density to be detected, with LSC values in the patient group of 2.35% for patella on lateral scans and 6.61% for R4 femur on PA scans. LSC values calculated in this way represent the 95% confidence limits for the measured change. Although 95% confidence is considered ideal, it has been suggested that for clinical decision-making a confidence level of 90% may be adequate.²¹ At the 90% confidence level, the LSC value is calculated by multiplying the CV% $\times$ 2.3, which would give smaller LSC values for our ROIs than those outlined above. The ability to measure periarticular bone density at the knee joint is particularly relevant in patients with inflammatory arthritis, in whom such bone loss may predict joint damage. DXA is non-invasive, accurate, fast (approximate scanning time for the knee is 40 seconds), and uses low doses of ionising radiation. Thus DXA of the knee joint is acceptable to both patient and operator. The technique has been validated in healthy control subjects and patients. Precision has been shown to vary significantly between different regions of interest. While bone density of tibia should only be measured on lateral knee scans, precision is acceptable for several femoral ROIs on PA scans. However, of all the ROIs studied, CV% is lowest for measurement of bone density of the patella, which thus provides the most sensitive index of periarticular bone loss at the knee. PA femoral R4 and lateral R6 (patella) have been selected as the most reliable ROIs to measure in future studies of periarticular bone loss.

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