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Radiographic predictors for bone mineral loss

CORTICAL THICKNESS AND INDEX OF THE DISTAL FEMUR

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Objectives

Researchers continue to seek easier ways to evaluate the quality of bone and screen for osteoporosis and osteopenia. Until recently, radiographic images of various parts of the body, except the distal femur, have been reappraised in the light of dual-energy X-ray absorptiometry (DXA) findings. The incidence of osteoporotic fractures around the knee joint in the elderly continues to increase. The aim of this study was to propose two new radiographic parameters of the distal femur for the assessment of bone quality.

Methods

Anteroposterior radiographs of the knee and bone mineral density (BMD) and T-scores from DXA scans of 361 healthy patients were prospectively analyzed. The mean cortical bone thickness (CBTavg) and the distal femoral cortex index (DFCI) were the two parameters that were proposed and measured. Intra- and interobserver reliabilities were assessed. Correlations between the BMD and T-score and these parameters were investigated and their value in the diagnosis of osteoporosis and osteopenia was evaluated.

Results

The DFCI, as a ratio, had higher reliability than the CBTavg. Both showed significant correlation with BMD and T-score. When compared with DFCI, CBTavg showed better correlation and was better for predicting osteoporosis and osteopenia.

Conclusion

The CBTavg and DFCI are simple and reliable screening tools for the prediction of osteoporosis and osteopenia. The CBTavg is more accurate but the DFCI is easier to use in clinical practice.

Cite this article: *Bone Joint Res* 2018;7:468–475.

Keywords: Osteoporosis, Knee joint, Radiography, Dual-energy X-ray absorptiometry, Prospective study

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doi: 10.1302/2046-3758.77.BJR-2017-0332.R1

Bone Joint Res 2018;7:468–475.

Article focus

- Radiographic images of various parts of the body have been reappraised in light of dual-energy X-ray absorptiometry (DXA) findings.
- No parameter from the distal femur has been proposed and verified to predict changes in bone quality.
- We propose two radiographic parameters of the distal femur that may be used in the diagnosis of osteoporosis and osteopenia.

Key messages

- The mean cortical bone thickness of the distal femur (CBTavg) and the distal femoral cortex index (DFCI) were the two parameters that were assessed in this study.
- Excellent reliability agreements were achieved using both CBTavg and DFCI.
- Both parameters are valuable predictors of change in bone quality.

Strengths and limitations

- This is the first time that new radiographic parameters have been proposed to focus on the distal femur, where the fragility fracture has a high morbidity. They have been compared with the bone mineral density (BMD) measured by DXA.
- The local BMD around the knee using DXA or a specific peripheral quantitative CT was not obtained as a control.

Introduction

Osteoporosis, which is characterized by low bone mass, microarchitectural deterioration of bone, and an increased risk of fracture, is a major threat to health. The incidence of fragility fractures resulting from osteoporosis is expected to increase during the next few decades.[1-3] The costs of diagnosing and treating osteoporosis in both developed and developing countries are very high.[4,5] Currently, the diagnosis of primary osteoporosis without fragility fracture is based on bone mineral density (BMD), which can be measured conveniently and non-invasively by dual-energy X-ray absorptiometry (DXA). Not all physicians, however, have access to this equipment. The cost of DXA and a lack of instruments may limit its widespread use in some communities, and complementary approaches are required in order to develop screening tools to identify patients who are at risk of osteoporosis.

Despite improvements in treatment, osteoporotic fractures remain difficult to treat.[5,6] They may take a long time to heal[7] and are associated with high complication rates and adverse outcomes.[8,9] The surgical treatment of fractures around the knee in elderly patients and those with osteoporosis remains problematic. However, the diagnosis of osteoporosis can be overlooked, as DXA studies may not be routinely undertaken in patients who suffer trauma.[10] Various radiographic parameters have focused on the frequently fractured metaphyseal regions, such as the proximal humerus,[11-15] proximal femur,[16,17] femoral shaft,[18] proximal tibia,[19,20] and the distal tibia,[21] in an attempt to predict osteoporosis. The validity of all of these parameters has been verified, except for those at the distal femur. The purpose of this study, therefore, was to propose and validate two easily available parameters around the knee joint in order to simplify the evaluation of bone quality.

Patients and Methods

After obtaining ethical approval for this study, patients who simultaneously underwent DXA scans and radiographs of the knee were enrolled. Before DXA scans, pelvic and lumbar radiographs were undertaken in order to exclude any problem that might influence the BMD results. The inclusion criteria were: the ability to undertake normal activities; a full range of movement of the lower limbs with no deformity or dysplasia; no pathological change such as periosteal hyperplasia, hyperostosis, or osteolysis of the distal femur; no severe osteoarthritis (OA) of the knee according to the Kellgren–Lawrence grading score,[22] (grade 0 to 2); and no history of trauma or surgery involving the knee. Exclusion criteria included: skeletal immaturity (age $\leqslant$ 16 years); a history or evidence of metabolic bone disease such as diabetes, hyper- or hypoparathyroidism, Paget's disease, osteomalacia, renal osteodystrophy or osteogenesis imperfecta, or other systemic disease such as rheumatoid arthritis, renal failure, and an immune disease; taking a relative's medications; a neoplasia with known metastasis to bone; and a history or the presence of a hip fracture, vertebral fracture or disease, or other osteoporotic fractures and associated surgery including fixation or arthroplasty. After collection of the medical history, examination, DXA scans, and radiographs of the knee, every patient who satisfied the inclusion criteria was randomly enrolled by tossing a coin. In order to avoid the outcome of the coin toss being manipulated by the examiner, it was tossed by the patient. All the screening processes were handled one patient at a time, rather than taking place simultaneously. All patients gave written consent before having DXA scans and radiographs.

Radiological measurement. All patients had weight-bearing anteroposterior (AP) radiographs of the knee, in an extended position, using a standard technique. Which knee was radiographed was also decided by the toss of a coin by the patients. All radiographs were taken on the same X-ray machine (Philips Corp., New York, New York). The exposure was from mid-thigh (25 cm proximal to the joint line) to proximal tibia (5 cm distal to the joint line). The radiation dose was estimated to be 0.01 mSv.

A musculoskeletal radiologist (WWY) and orthopaedic surgeon (C-FL), each with > 20 years of experience, independently screened the radiographs and assigned Kellgren–Lawrence grades.[22] They agreed on a grade by consensus if there was disagreement. There are five grades: 0, normal; 1, doubtful OA; 2, minimal OA; 3, moderate OA; and 4, severe OA.

The images were obtained using picture archiving and communication system workstations, and the measurements were performed using Kingstar Winning TV view software (Shanghai Kingstar Winning Medical Information Technology Co. Ltd., Shanghai, China), which has precision of within 0.01 mm.

Two parameters were measured from the distal femoral cortex: the mean cortical bone thickness (CBTavg) and the distal femoral cortical index (DFCI). The method for calculating the CBTavg of the medial and lateral distal femur was adapted from the methods used for the proximal humerus described by Bloom and Laws[23] and Tingart et al.[11] The anatomical axes of the femur (line P) were initially defined, as described by Luo.[24] The CBTavg and DFCI were measured at two levels in which the lines were perpendicular to the line P. Level 1 was the most distal level of the femoral diaphysis where the tangent line of endosteal borders of the lateral diaphyseal cortices was separated from the diaphysis. Level 2 was 20 mm proximal and parallel to level 1. The distances between levels 1 and 2 were chosen in an effort to capture the transition zone from the diaphyseal to the metaphyseal bone. It has been suggested that this area would be sensitive to bone mineral loss.[25] At these two levels, the

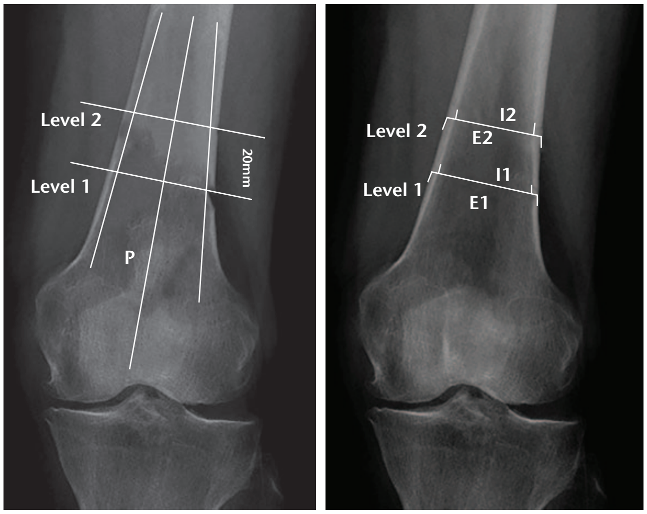

Fig. 1a Fig. 1b

Schematic diagrams of the radiographic parameters on the anteroposterior view of the knee joint: a) the location of the two levels; b) the width of the entire bone and intramedullary canal; the cortical thickness of the medial and lateral side of the distal femur at these levels.

points of intersection of the two lines and the edges of the distal femoral cortex (inner and outer edges) could be confirmed. The width of the entire bone could be measured at these levels from the outer medial cortex of the distal femur to the outer lateral cortex (E1 and E2). At the same level, a measurement of the width of the intramedullary canal was obtained (I1 and I2). The CBTavg was defined as the mean cortical thickness of levels 1 and 2; therefore, it could be calculated by [(E1-I1) + (E2-I2)]/2 for each patient and adjusted automatically for the magnification factor by the software. The measurement of DFCI was similar to the deltoid tuberosity index in the proximal humerus as described by Spross et al.[12] The DFCI was measured at level 1, where the cortical change in the transitional area between the diaphysis and the metaphysis is most obvious. The ratio between the outer cortical (E1) and the inner endosteal diameter (I1) is calculated (E1/I1) as DFCI (Fig. 1).

The mean of three consecutive measurements performed by one investigator was calculated for each patient. All measurements were performed twice, on two different days at four-week intervals by two independent investigators, a trauma surgeon (HS) and a resident doctor (YZ), to determine the intra- and interobserver variability.

BMD measurement. The BMD (g/cm^2) of the lumbar spine (L1-4), and the left femoral neck and hip were measured using a Lunar Prodigy DXA densitometer (Lunar Corp., Madison, Wisconsin) and the data were analyzed using Prodigy Encore software (Ver. 6.70, Lunar Corp., standard array mode). The scanner was set on fan-beam mode and calibrated daily. The coefficient of variation (CV) was obtained from three repeated measurements on 15 patients. The CV for the BMD at L1-4, the left femoral neck, trochanter, and hip were 1.39%, 2.22%, 1.41%, and 0.70%, respectively.[26] The T-score, based on comparisons with the maximum mean BMD found in healthy young adults of the same ethnicity and gender, was automatically calculated by the processor of the Lunar device. The bone quality was defined as: normal if the T-score was $>$-1.0; osteopenic if it was between -1.0 and -2.5; and osteoporotic if it was $<$-2.5.[27] All scans were conducted by the same team with well-trained surveyors (team leader: YW) who were blinded to the study.

For the subset of patients in this analysis, BMD at the left hip including the femoral neck, greater trochanter and proximal femur, was strongly correlated with the value for the spine (L1-4) (Pearson's $r=0.065$, $p=0.0003$). Patients who had osteophytes and/or disc space narrowing were excluded because these values were technically unsuitable for analysis. Thus, analyses with values for the hip are reported, while results were similar to those for the other site.

Statistical analysis. This was performed using Statistical Package for the Social Sciences, version 19.0 software (IBM Corp., Armonk, New York). All parameters were tested for normal distribution. Univariate analysis was performed using the chi-squared test or Fisher's exact test for comparison of proportions between two categorical data. The Mann–Whitney U test was used to compare the non-parametric data between two independent samples. The level of statistical significance was defined as $p \leqslant 0.05$.

Intra- and interobserver reliabilities of the CBTavg and DFCI were assessed by calculating the intraclass correlation coefficients (ICC).[28] The strength of agreement was assessed as described by Landis and Koch[29]: values of 0.81 to 1.00 indicating excellent agreement; 0.61 to 0.80, good agreement; 0.41 to 0.60, moderate agreement; 0.21 to 0.40, fair agreement; and 0 to 0.20, slight agreement. In order to evaluate differences between single ICC values, 95% confidence intervals (CI) were calculated. Differences between single ICC values were considered significant when upper and lower boundaries of the 95% CI did not overlap.[30]

Pearson's correlation coefficient (r) was used to test the relationship between age, BMD, T-score, CBTavg, and DFCI, using the grading suggested by Evans[31]: r with 0.81 to 1.0, very strong correlation; 0.60 to 0.79, strong correlation; 0.40 to 0.59, moderate correlation; 0.20 to 0.39, weak correlation; and 0 to 0.19, very weak correlation.

Receiver operating characteristic (ROC) curve analysis was performed to determine the diagnostic efficiency of the CBTavg and DFCI for osteoporosis and osteopenia.[32] The sensitivity, specificity, negative predictive values, and the area under the curve (AUC) were calculated from ROC. The value of the AUC was interpreted according to the following principle: non-predictive ($AUC < 0.5$); less predictive ($0.5 < AUC \leqslant 0.7$); moderately predictive ($0.7 < AUC \leqslant 0.9$); highly predictive ($0.9 < AUC < 1.0$);

Table I. Summary of descriptive characteristics of the 361 patients in the study

Characteristic	
Mean age, yrs (SD; range)	61.81 (12.31; 21 to 89)
Gender (female/male), n (%)	294 (*81.4*)/67 (*18.6*)
Knee side (left/right), n (%)	212 (*58.7*)/149 (*41.3*)
Mean BMI, kg/m² (SD; range)	24.32 (3.01; 15.39 to 33.87)
Mean BMD, g/cm² (SD; range)	
Lumbar spine (L1 to L4)	1.01 (0.18; 0.56 to 1.91)
Hip	0.88 (0.13; 0.48 to 1.36)
Mean T-score (SD; range)	
Lumbar spine (L1 to L4)	-0.79 (0.39; -2.72 to 3.10)
Hip	-0.65 (1.05; -3.80 to 3.20)
Diagnostic categories, n (%)*†	
Normal	228 (*63.2*)
Osteopenia	99 (*27.4*)
Osteoporosis	34 (*9.4*)

*According to the World Health Organization criteria[35]
†Lowest BMD T-score in the lumbar spine or hip was considered
BMI, body mass index; BMD, bone mineral density

Table II. Intraclass correlation coefficients (ICC) of mean cortical bone thickness of the distal femur (CBTavg) and the distal femoral cortex index (DFCI)

	Intraobserver (95% CI)	**Interobservers (95% CI)**
ICC, CBTavg	0.892 (0.867 to 0.912)	0.890 (0.864 to 0.910)
ICC, DFCI	0.910 (0.889 to 0.927)	0.908 (0.887 to 0.925)
p-value	0.021*	0.018*

*Significant difference ($p < 0.05$)
CI, confidence interval

and perfect prediction (AUC = 1.0).[33] AUC values of > 0.75 are generally considered to represent good performance. The difference between the AUCs under these two dependent ROC curves was tested with the method of DeLong et al.[34]

Statistical significance was set at $p < 0.01$.

Results

Between July 2015 and June 2016, a total of 361 eligible patients were enrolled into the study. Their characteristics, including diagnostic categories according to World Health Organization (WHO) criteria,[35] are shown in Table I. The correlations between age and BMD of the lumbar spine and hip were very weak (r = -0.306, p < 0.001; r = -0.127, p = 0.004).

The mean CBTavg and DFCI for the whole cohort was 4.55 mm (SD 0.73; 2.38 to 6.90) and 1.10 mm (SD 0.03; 1.04 to 1.19), respectively.

The reliability of CBTavg and DFCI. Based on the plain radiographs, excellent intra- and interobserver reliability agreements could be achieved using the CBTavg and DFCI. The DFCI as a ratio showed higher intra- and interobserver reliability than CBTavg (Table II).

Correlation between CBTavg, DFCI, BMD, and T-score. There were strong correlations between the CBTavg and BMD of the hip (r = 0.664, p < 0.01), T-score (r = 0.654, p < 0.01) (Fig. 2). Moderate correlations were found between the DFCI and BMD of the hip (r = 0.457, p < 0.01), T-score (r = 0.464, p < 0.01) (Fig. 3).

ROC and AUC. The ROC and AUC showed a moderate accuracy for predicting osteoporosis using the CBTavg and DFCI, whereas CBTavg was better, as the AUC was larger than for DFCI (0.820 *vs* 0.740, z = 2.432, p = 0.015) (Fig. 4a). The cut-off value for CBTavg for predicting osteoporosis was 4.4 mm, with a sensitivity of 100% and a specificity of 61%. The cut-off value for the DFCI was 1.10, with a sensitivity of 88% and a specificity of 80% (Table III). CBTavg and DFCI were moderately accurate for the diagnosis of osteopenia; the AUC of CBTavg was better than that of DFCI (0.798 *vs* 0.721, z = 4.929, p = 0.019) (Fig. 4b). Selecting a 4.5 mm threshold value for CBTavg resulted in a sensitivity of 78% and a specificity of 67%, and selecting a 1.08 threshold value for DFCI resulted in a sensitivity of 51.52% and a specificity of 80.35% (Table IV).

Discussion

A simple and accurate method of identifying the risk of osteoporosis is essential for the management of orthopaedic patients. Although the BMD from DXA of the lumbar spine, hip, and proximal femur have been the benchmarks to screen for osteoporosis, these methods are not practical for either patients or practitioners, especially in an emergency or outpatient department.[19] In the past, the bone quality has been assessed radiographically.[23,36-40] However, the relationship between the radiographic parameters and BMD have not been reappraised.[11,13,15-21,41] To our knowledge, this is the first study to propose new radiographic parameters focusing on the distal femur, where a fragility fracture has a high morbidity,[42] and compare these parameters with the BMD from DXA.

Except for the BMD from conventional sites such as the lumbar spine, hip, and proximal femur as the reference, other studies have used different control groups[11,12,17] or compared the radiographic parameters between different groups.[14] Tingart et al[11] evaluated the correlation between the BMD of the proximal humerus (the humeral head, the surgical neck, and the greater and lesser tuberosity) using DXA and the cortical thickness of the proximal humeral diaphysis. Peripheral quantitative CT (pQCT) may be used to evaluate the local BMD, but has limited availability. Spross et al[12] defined and validated the deltoid tuberosity index in an attempt to simplify the measurement of bone quality in patients with a proximal humeral fracture using the BMD of the humeral head by pQCT as a control. Hepp et al[14] evaluated the use of the cortical index as a predictor of the risk of failure after locking plate osteosynthesis of displaced proximal humeral fractures by comparing the fracture group with a control group of patients who had fallen on the shoulder without

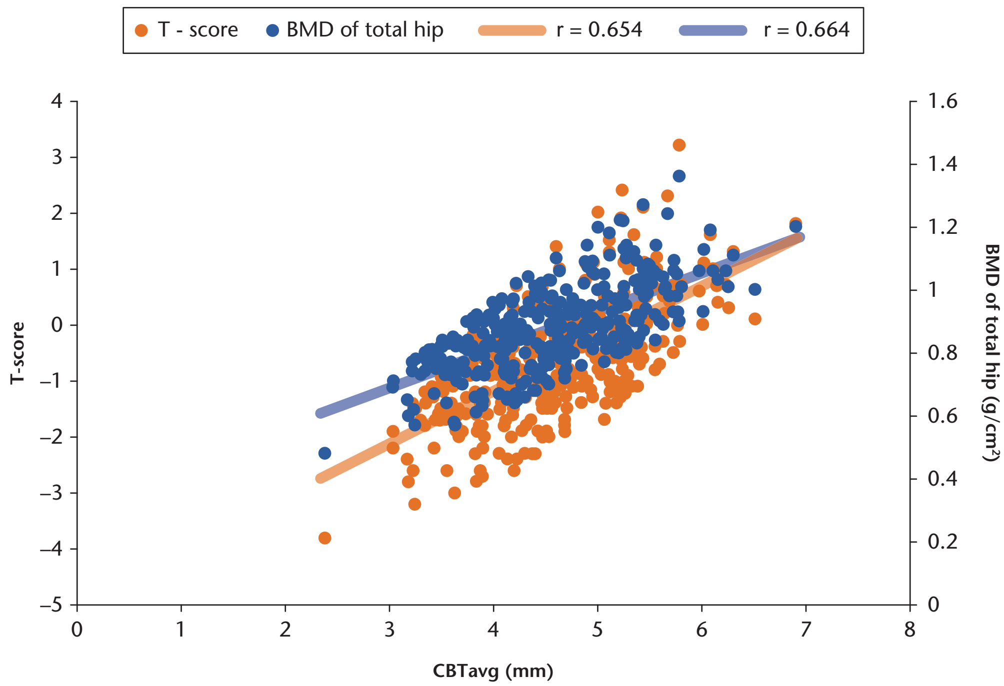

Fig. 2

Graph showing the correlation between the mean cortical bone thickness of the distal femur (CBTavg) and bone mineral density (BMD) of the hip and T-score.

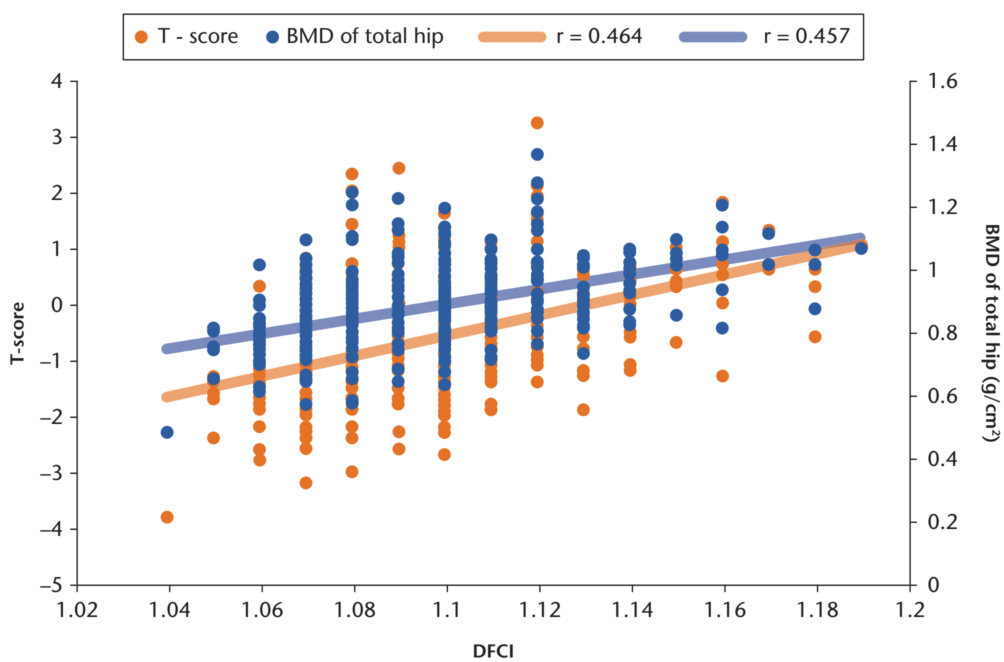

Fig. 3

Graph showing the correlation between the distal femoral cortex index (DFCI) and bone mineral density (BMD) of the hip and T-score.

sustaining a fracture. However, it was subjective because the mechanism of injury, including the degree of violence and the condition of the patient, could not be controlled. Thus, the radiographic parameters or indices verified by local BMD or compared by different groups can only reflect local bone quality, and only the parameters or indices verified by the BMD from DXA could be a used when screening the whole body for osteoporosis.

The aims of this study were: 1) to provide a simple way of determining the bone quality of the whole body and a useful screening tool for osteoporosis without using DXA apparatus; 2) to raise awareness of a screening protocol

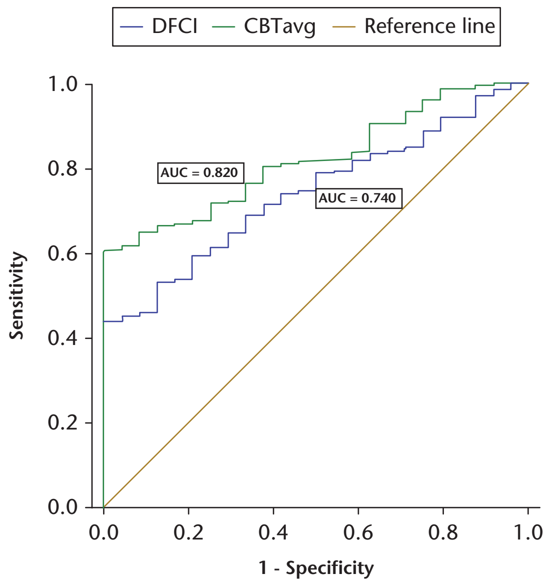

Fig. 4a

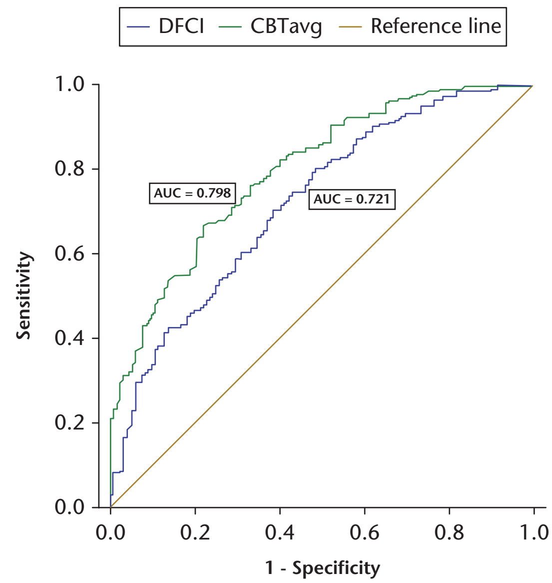

Fig. 4b

Receiver operating characteristic curve analysis was performed to determine the diagnostic efficiency of the mean cortical bone thickness of the distal femur (CBTavg) and distal femoral cortex index (DFCI) for a) osteoporosis and b) osteopenia. AUC, area under the curve.

Table III. Area under the curve (AUC) and the value for osteoporosis

	AUC (95% CI)	Criterion value (95% CI)
CBTavg, mm	0.820 (0.776 to 0.858)	4.40 (4.365 to 4.4)
DFCI, mm	0.740 (0.692 to 0.785)	1.10 (1.093 to 1.097)
p-value	0.015*	N/A

*Significant difference ($p < 0.05$)
CI, confidence interval; CBTavg, mean cortical bone thickness of the distal femur; DFCI, distal femoral cortex index; N/A, not applicable

Table IV. Area under the curve (AUC) and value for osteopenia

	AUC (95% CI)	Criterion value (95% CI)
CBTavg, mm	0.798 (0.753 to 0.838)	4.50 (4.315 to 4.935)
DFCI, mm	0.721 (0.672 to 0.767)	1.08 (1.068 to 1.087)
p-value	0.019*	N/A

*Significant difference ($p < 0.05$)
CI, confidence interval; CBTavg, mean cortical bone thickness of the distal femur; DFCI, distal femoral cortex index; N/A, not applicable

for patients who are at risk of osteoporosis; and 3) to facilitate decision-making in the surgical treatment of patients with fractures or OA of the knee based on radiographic measurements of the uninjured distal femur.

Approximately half of all periarticular fractures about the knee, including distal femoral, tibial plateau, and patellar fractures, occur in osteoporotic patients, aged > 50 years, as a result of low-energy trauma.[43] Unsatisfactory outcomes are common following surgery in elderly patients with osteoporosis due to loss of fixation, post-traumatic arthritis, malunion, and nonunion. Appropriate forms of treatment include conservative management, internal fixation, or arthroplasty and the availability of suitable implants including locking fixation systems, bone grafts, cements, or prostheses are required for managing these fractures.[44-46] The use of parameters based on the radiographic appearances of the knee might allow easy evaluation of bone quality before treatment. Two such parameters with different natures were proposed and evaluated in our study, a numerical value (CBTavg) and a ratio (DFCI). Previously, only one type of parameter was used in most studies, either a numerical value or an index.[11,13,15-21] We found that the radiographic parameters of the distal femur, CBTavg and DFCI, correlated well with BMD and the T-score. Thus, these parameters could be used for identifying both osteoporosis and osteopenia. Although the CBTavg was more accurate than DFCI in the diagnosis of both, DFCI had better ICCs than CBTavg, as it is a ratio and could be measured using a relatively simple formula regardless of the magnification of radiographic images or the size of the bone.

In addition, radiographs are routinely undertaken in symptomatic patients with arthritis of the knee, which is common in the elderly.[47] Different views are not required and the measurements are based only on the AP view of the knee, without the lateral view, which may have varying degrees of rotation.

In order to eliminate the selection bias, the study was designed as a prospective study and the patients were screened to represent the general population without age limitation. DXA scans and radiographs were prospectively collected and examined simultaneously. We found a weak correlation between age and bone quality. Thus, analysis was not stratified according to age.

This study has limitations. It involved healthy Chinese patients, and the results are not generalizable to all races. Furthermore, the local BMD from the knee using DXA or a specific qCT was not obtained as a control, because we thought that these might be influenced by many factors, including the choosing of regions of interest, the measurement scope, and the regional soft tissue.

In conclusion, we propose two new radiographic parameters, the CBTavg and DFCI, from the distal femur, which may be used to predict osteoporosis and osteopenia reliably. They are simple and effective screening tools. The DFCI, which is a ratio, might be more user-friendly in clinical practice because of the simpler calculation with fewer influential factors.

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Funding Statement
- No funding received.

Acknowledgements
- We thank W. W. Yao of the radiological department for screening the radiographs and assigned Kellgren-Lawrence grades, and thank Y. Wang of the osteoporosis department for leading her team to conduct the DXA scan.

- Q-F. He and H. Sun contributed equally to this work.

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- Q-F. He: Designing and conducting the study, Collecting and analyzing the data, Drafting the manuscript.
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- L-Y. Shu: Collecting the data, Drafting the manuscript.
- Y. Zhu: Analyzing the data, Drafting the manuscript.
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- Y. Zhan: Analyzing the data, Drafting the manuscript.
- C-F. Luo: Designing and conducting the study, Drafting the manuscript.

Conflict of Interest Statement
- No conflicts of interest