MICROFOCAL TECHNIQUES IN QUANTITATIVE RADIOGRAPHY: MEASUREMENT OF CANCELLOUS BONE ORGANIZATION

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SUMMARY
Microfocal radiography records, with unusually good resolution, the detailed structural organization of cancellous bone. A textural imaging method, fractal signature analysis (FSA), was used to quantify the horizontal and vertical trabecular organization recorded within microangiographic images of the spine of post-menopausal women and the tibia in osteoarthritic knees, and the analysis of variance method was applied to the wrist and hand of rheumatoid patients. Changes in trabecular structure were found to correlate with (i) body weight, age and bone mineral density in the lumbar spine of post-menopausal women; (ii) the degree of cartilage loss and age in the tibia of patients with knee OA; and (iii) analysis of variance quantified the extent of 'normal', osteopaenic and eroded bone in rheumatoid joints. Quantitation of cancellous bone organization can add significantly to our understanding of disease processes and effect of therapy in diseased joints.

KEY WORDS: Cancellous bone, Fractal signature analysis, Microfocal radiography, Osteoarthritis, Osteoporosis, Rheumatoid arthritis.

QUANTITATIVE MICROFOCAL RADIOGRAPHY
Microfocal X-ray tubes are characterized by a micron-sized X-ray source in which the object being examined is placed close to the X-ray tube and the film is positioned 1.5–2 m away, resulting in magnification (macroangiograms) of the image with high spatial resolution [1, 2]. For accurate and reproducible measurements of the features recorded in macroangiograms, standardized procedures are employed to define the precise anatomical position of the joint for radiography [3–6]; to correct for the effect of radiographic magnification [3–6]; to define precisely the anatomical boundaries used for measurements of features [3–6]; and to determine the reproducibility of the measurement from an assessment of the coefficient of variation for repeat measures and test–retest procedures [6–12].

Quantitative microfocal radiographic examination of arthritic patients allows measurement of the extent [13, 14] and progression [15] of disease in the rheumatoid hand from changes in erosion size. Assessment of the effects of therapy in patients with early rheumatoid arthritis, treated with Myocrisin, showed not only a halt in erosion area progression, but, importantly, erosion repair [10]. In patients with knee OA, quantifying the extent and progression of the radiographic features revealed that bony features, osteophytosis and subchondral sclerosis, preceded the onset of cartilage loss measured as joint space narrowing [11]. Precise methods for measuring joint space width permitted the detection of the effects of non-steroidal anti-inflammatory therapy on cartilage in knee OA [16].

CANCELLOUS BONE
A major advantage of microfocal radiography is its ability to record, with unusually good resolution, the fine detail of cancellous bone. The difference between compact and cancellous bone is that the latter has a greater surface area to volume ratio available to cellular activity and greater tissue vascularity. Due to the rapid rate of trabecular bone turnover [17], its response to unloading, increased blood flow and synovitis [18], cancellous bone is more sensitive to changes to physiological and biomechanical environment than compact bone.

QUANTIFYING CANCELLOUS BONE ORGANIZATION
We report the results of a new method for quantifying the trabecular organization using a recently developed method of fractal signature analysis (FSA) [19, 20]. Fractal analysis measures the degree of 'roughness' of an image of those structures, and also quantifies the change in 'roughness' with alterations in spatial scale [21]. Self-similar images (looking the same at all magnifications) [22] are said to be 'fractal' and have associated with them a fractal dimension, which is between 2 and 3 for a surface [21]. When the pattern of a structure has altered at a particular size or sizes so as to be no longer self-similar, the 'fractal signature' of its image quantifies the alteration in the fractal dimension of the structure, and the size(s) at which those changes have occurred [19, 20]. The fractal dimension, and similarly the fractal signature, has no units since it is calculated from the ratio of two areas [21]. The fractal dimension of cancellous bone assesses the composite nature of the tissue, which is determined principally by trabecular number, spacing and cross-connectivity [23], features which are here referred to as trabecular structures. FSA provides more information than the mean fractal dimension employed by previous investigators [20, 21] which only quantifies the overall

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appearance of cancellous bone, whereas FSA measures separately the fractal dimension of the horizontal and vertical trabecular structures within the cancellous bone [19, 20] and quantifies how the fractal dimension varies with the size of the structures.

**CANCELLOUS BONE CHANGES IN THE SPINE OF POST-MENOPAUSAL WOMEN**

The trabecular organization in the lumbar spine of post-menopausal women was obtained using FSA, and its relationship to vertebral bone mineral density (BMD), patient's age, weight and body mass index determined [24].

BMD measurements, obtained by dual-energy X-ray absorptiometry (DXA) using the Hologic QDA-1000, and X4 macroradiographs, were taken of the lumbar spine (L1-L4) from 47 early post-menopausal (3-36 months) women (mean age 54.1 ± 3.2 yr). Patients were divided into two groups on the basis of their BMD: those with low BMD (mean 0.86 ± 0.17 g/cm², n = 19) and high BMD (mean 1.06 ± 0.12 g/cm², n = 28).

The results showed that (i) patient weight and body mass index correlated with the fractal signature values for thick vertical trabecular structures ranging in size from 0.5 to 1.0 mm (P < 0.005-0.05); (ii) age correlated with fractal signature values for fine horizontal structures (size range 0.1-0.25 mm) (P < 0.005-0.05); BMD correlated with fractal signature values for fine vertical structures (size range 0.1-0.4 mm) (P < 0.005-0.05) [24]. The low BMD patients also had a significantly raised fractal signature for fine vertical structures (size range 0.18-0.84 mm) when compared to the patients with high BMD (P < 0.003-0.04) [24] (Fig. 1).

The correlation of FSA for thick vertical trabecular structures with weight confirms the expected association between the thicker weight-bearing trabeculae and load transmission. The correlation between age and FSA for fine trabecular structures indicates that FSA quantifies age-related changes, which include a reduction in the number of horizontal trabeculae [25].

FSA of the fine vertical trabecular structures correlated with reduced BMD and appears to correspond to early stages of axial bone loss in post-menopausal women. In this process, focal perforation of coarse vertical trabecular plates progresses into a lattice of bars and rods [25]. These changes would result in an increase in the number and cross-connectivity of fine trabecular structures and an increase in the 'roughness' in the radiographic appearance of the cancellous bone organization, leading to higher fractal signature values [24].

**CANCELLOUS BONE CHANGES IN KNEE OSTEOARTHRITIS**

FSA was used to quantify tibial cancellous bone changes in osteoarthritic knees with minimal and definite joint space narrowing (JSN) compared to knees without arthritis [26].

Thirty-three patients with knee OA (9 male, 24 female, mean age 65.5 ± 10.2 yr) were selected on the basis of clinical and radiographic evidence of OA. X5 macroradiographs were taken of both knees in the standing semi-flexed and weight-bearing tunnel views [11]. Macroradiographs of the knees of 14 non-OA subjects (mean age 37.0 ± 10.6 yr) were also taken. Joint space width (JSW) was measured in the medial and lateral compartments using a computerized technique [12]. A box analysis was set up based on Ahlback's criteria [27], and OA knees were grouped on their minimum JSW in the medial compartment, into those with early OA (JSW > 3 mm) and those with definite OA (JSW < 3 mm) in either or both views. Fractal signatures for horizontal and vertical trabecular structures (size range 0.06-1.20 mm) were calculated for the central region of subchondral cancellous bone in each tibial compartment of all knees. The differences in the fractal signatures between groups of knees were examined for significance using multivariate analysis of variance (MANOVA) with repeated measures.

All OA knees had medial compartment disease. FSA of the trabecular structure of the medial diseased compartment of the tibia was significantly different from the lateral side.
TABLE I

Using mean image variance, regions of "normal", osteopcaenic and eroded bone were found to be statistically significantly different between each of the categories as shown in (A); the ability of this image texture measure to identify correctly the different categories of bone is shown in (B).

(A) Mean image variance vs class of cancellous bone

<table>
<thead>
<tr>
<th>Bone type</th>
<th>Variance of intensity</th>
<th>Significance between groups vs normal bone</th>
<th>Significance between groups vs eroded bone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>16.13 (10.68)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Eroded</td>
<td>6.68 (4.48)</td>
<td>P &lt; 0.00001</td>
<td>-</td>
</tr>
<tr>
<td>Osteopaenic</td>
<td>9.60 (7.70)</td>
<td>P &lt; 0.00001</td>
<td>P &lt; 0.0053</td>
</tr>
</tbody>
</table>

(B) Image texture as a classifier of cancellous bone

<table>
<thead>
<tr>
<th>Actual bone group</th>
<th>Predicted bone group (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>Normal</td>
<td>61.3</td>
</tr>
<tr>
<td>Osteopaenic</td>
<td>21.0</td>
</tr>
<tr>
<td>Eroded</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*Values are mean (x.d.).

| Wilcoxon matched pairs test. |

(P < 0.003) from that in the non-arthritic joints: changes indicated that horizontal trabeculae structures (size range 0.36–0.66 mm) increased in thickness significantly in knees with early OA (joint space > 3 mm) (P < 0.001) and that vertical trabecular structures (size ~0.77 mm) increased in knees with marked JSN (joint space < 3 mm) in both views and showed a significant increase in those knees with definite JSN in the tunnel view only (P < 0.001). In the lateral compartment of the tibia, FSA did not show a difference between any of the categories. With increasing age of all subjects, FSA showed a significant increase in the number of fine horizontal and vertical trabecular structures (size range 0.18–0.30 mm) (P < 0.005–0.02). No correlation was found between the subjects' body weight and changes in the subarticular cancellous bone organization.

In the medial diseased compartment of the tibia in OA knees, the horizontal trabeculae increased in thickness in early OA and vertical trabecular connectivity increased in knees with more advanced disease [26]. With increasing age of the subject, a rise in the number of fine trabecula structures occurred in the proximal end of the tibia.

CANCELLOUS BONE CHANGES IN RHEUMATOID HANDS

Two types of bony change are recorded radiographically in rheumatoid arthritis: erosions and juxta-articular osteopaenia. Current methods of assessment use changes in the numbers of the first, and tend to neglect the second. An image texture analysis method [28] was used to quantify differences in the cancellous bone between region of 'normal', eroded and osteopaenic bone.

This textural method is based upon fact that an image with rapid and repetitive changes in intensity (fine texture) appears different to one with slower changes (coarse texture). Thus, the intensity of a fine-textured image will vary more than a coarse-textured image in any unit area, given that both images have the same mean intensity. As a result, measures of statistical spread such as variance will have higher values for fine-textured images [28]. Such measurements can be made in different directions, and will have markedly different values for cancellous bone with different structural appearance.

X5 macroradiographs were taken of the hands of 10 rheumatoid patients. A total of 62 images of metacarpophalangeal, proximal and distal interphalangeal joints were assessed. The variance of intensity was measured for regions of 'normal', osteopaenic and eroded bone (Table I). A grid was imposed upon each X-ray image. The images within each square of the grid, or sub-images, were individually analysed and the values used to produce a map of the different types of bone: 'normal', osteopaenic and eroded (Fig. 2).

Significant differences in image texture were found between the three types of bone (Table I) recorded in the macroradiographs. The significantly lower variances for osteopaenic and eroded bone, compared to 'normal', are attributable to the loss of trabeculae, resulting in a more homogeneous image (Table IA). The progressive changes that occur in the osteopaenic bone represent the continuous nature of the inflammatory process, resulting in an overlap at both the 'normal' and eroded extremes in the values for osteopaenic bone (Table IB). Simple texture measures show promise in automatically quantifying the extent of both erosions and osteopaenic bone.

DISCUSSION

The methods for clinically examining cancellous bone in vivo do not directly measure the detailed structure at the lumbar spine, knee joint and wrist. DXA examines mineral content, but does not quantify structure.
method for quantifying cancellous bone structure, erosion number or size. Recently, validation of FSA as a recorded in macroradiographs, has come from detailed disease progression and therapeutic response than either to id patients, providing a far more sensitive measure of articular cartilage loss; and (iii) the hands of rheuma-

tibia of patients with knee OA, providing an insight into the relationship between subchondral bone changes and in predicting patients at risk of spinal fracture; (ii) the relationship of BMD and bone structure and their role women, leading to a better understanding of the quantify cancellous bone organization in macro-

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radiographs can be scored for changes in trabecular architecture [33], but this technique is insensitive for quantifying subtle changes in bone structure. Whereas image analysis techniques of FSA and variance quantify cancellous bone organization in macro-

radiographs of (i) the lumbar spine of post-menopausal women, leading to a better understanding of the relationship of BMD and bone structure and their role in predicting patients at risk of spinal fracture; (ii) the tibia of patients with knee OA, providing an insight into the relationship between subchondral bone changes and articular cartilage loss; and (iii) the hands of rheumatoid patients, providing a far more sensitive measure of disease progression and therapeutic response than either erosion number or size. Recently, validation of FSA as a method for quantifying cancellous bone structure, recorded in macroradiographs, has come from detailed studies of post-mortem tissue, demonstrating the capacity of this technique to quantify those trabecular features directly related to its strength, i.e. anisotropy and connectivity [34].

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Quantitative computed tomography (QCT) measures bone mineral and gross trabecular structure, but has a resolution limitation of ~0.5 mm, and trabecular structures, particularly in the spine, are at sizes below this value [29]. MRI can indirectly detect changes in trabeculae from magnetic susceptibility artefacts and alterations in the parameter $T_2^*$ [30], but fine trabecular detail is lost since resolution is limited to ~0.5 mm. Interpretation of these images is difficult and involves the use of artefacts to examine changes occurring at very fine resolution, which are not seen even in special high-resolution scans [31]. The particular pulse sequences used cause variations in the apparent size and structure of the trabecular network [32]. Standard radiographs can be scored for changes in trabecular architecture [33], but this technique is insensitive for quantifying subtle changes in bone structure. Whereas image analysis techniques of FSA and variance quantify cancellous bone organization in macroradiographs of (i) the lumbar spine of post-menopausal women, leading to a better understanding of the relationship of BMD and bone structure and their role in predicting patients at risk of spinal fracture; (ii) the tibia of patients with knee OA, providing an insight into the relationship between subchondral bone changes and articular cartilage loss; and (iii) the hands of rheumatoid patients, providing a far more sensitive measure of disease progression and therapeutic response than either erosion number or size. Recently, validation of FSA as a method for quantifying cancellous bone structure, recorded in macroradiographs, has come from detailed studies of post-mortem tissue, demonstrating the capacity of this technique to quantify those trabecular features directly related to its strength, i.e. anisotropy and connectivity [34].

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Fig. 2.—(Top) Part of a macroradiograph of the wrist showing a large erosion at the distal end of the radius (radiographic magnification ×5, reproduced at ×2.1). (Bottom) Processed image of the same macroradiograph showing the different types of bone obtained from the ratio of the variances in the x and y directions within each square of the grid or sub-image. Normal bone is bright and osteopaenic and eroded bone light to dark grey.


