Title
Characterization of trabecular bone structure from radiographs using fractal analysis

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Publication Date
1995

Characterization of Trabecular Bone Structure from Radiographs Using Fractal Analysis

by

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THESIS

Submitted in partial satisfaction of the requirements for the degree of

MASTER OF SCIENCE

in

Oral Biology

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA

San Francisco

[redacted]

Date University Librarian

Degree Conferred: . . . .

To the love of my life, **Leila**

Thanks for all the support.

Acknowledgement

I wish to extend my deepest gratitude to my dear mentors: Dr. Sharmila Majumdar, Dr. Arnold Kahn, and Dr. Donald Curtis, whose direction and assistance were invaluable to the completion of this thesis. In particular, I am indebted to Dr. Majumdar for familiarizing me with the technical aspects of fractal analysis. I thank Dr. Kahn for the opprtunities he provided for me to participate in various scientific meetings to present my findings. I appreciate Dr. Curtis for his helpful suggestions on dental related facets of this investigation.

I also gratefully acknowledge the following individuals for their generous assistance with various aspects of this project:

- Dr. Harry Genant
- Dr. Clark Izu
- Dennis Meany
- Alice Giese

Characterization of Trabecular Bone Structure from Radiographs Using Fractal Analysis

Paul Massood Khosrovi

ABSTRACT

With the steadily increasing number of adults seeking orthodontic treatment, it has become increasingly important to recognize and assess those factors, almost unique to this population, that may affect treatment. One such factor is bone quality; a term meant to include both bone density and micro-architecture. Bone quality is currently evaluated by bone densitometry methods such as quantitative computed tomography (QCT), and dual energy x-ray absorptiometry (DXA); techniques which are not readily available to the dental community, thereby, creating the need for the development of other approaches. In recent years, it has been shown that a new form of geometry, namely fractal analysis, is capable of describing complex structures, such as bone micro-architecture, in mathematical terms. The procedure yields a number, called the fractal dimension, that not only describes the structure but can also be used to relate the geometry to other properties of the structure. It has been previously reported that the fractal dimension derived from bone biopsies positively correlates with bone porosity, i.e., the degree of osteoporosis, as assessed by quantitative histological analysis. In this study, we propose (i) to develop a methodology to perform fractal analysis on hand-wrist and dental radiographs and (ii) to confirm what preliminary studies already suggest, viz., that fractal analysis of radiographs is an effective and readily applicable tool for (a) characterizing bone geometry, (b) detecting differences in bone quality between normal subjects and subjects affected by systemic bone disorders such as osteoporosis and/or more localized conditions such as oral bone loss, and (c) monitoring changes in bone quality over time. With this technique available, the dental and medical practitioners will be in a position to make an accurate assessment of bone quality both before initiating treatment and, equally importantly, during the course of therapy.

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I. BACKGROUND & INTRODUCTION

Orthodontic treatment for adults has been the fastest growing area in orthodontics in recent years. Since the 1960s, there has been a dramatic increase in the number of adults receiving adjunctive and comprehensive orthodontic treatment (1). Although no precise data are available, informal practice surveys indicate that the number of adults seeking orthodontic treatment in the United States has increased nearly fivefold in recent years. Adults represented approximately 5% of all orthodontic patients before 1970, but were estimated to be 20-25% in the 1980s (2). Orthodontic treatment for adults brings with it a set of concerns that rarely exist with younger patients. These include: 1) their heightened susceptibility to bone loss due to periodontal disease or residual ridge resorption in areas of missing teeth and the possibility that such deterioration in the periodontium is one reason for seeking treatment in the first place, and 2) the presence of other age related systemic diseases particularly in older patients which might adversely affect tooth movement.

One such age related systemic disease, which like periodontal disease is considered a "silent disease" (i.e., progresses to advanced stages without symptoms obvious to the patient), is osteoporosis. Osteoporosis is characterized by low bone mass and micro-architectural deterioration of the bone, which leads to decreased bone strength and increased risk of fracture (3). Given the aging population of the United States, osteoporosis has become a major public health problem. Each year in the U.S., more than 1.4 million fractures in persons over 45 years are attributed to osteoporosis (4). The cost associated with the treatment of hip fractures alone exceeds $7 billion (5). Approximately 10 million women (predominantly post-menopausal) are at risk for osteoporosis and are prime candidates for fracture (6). Many peri-menopausal and post-menopausal women visit their dentists regularly and may even be candidates for adjunctive if not comprehensive orthodontic treatment. Dental professionals can increase their patients' knowledge and awareness about osteoporosis and risk factors. They should also know prevention techniques and types of treatment for both oral and systemic bone loss, and refer the patient to her internist or gynecologist for final diagnosis and treatment when systemic bone loss is suspected. In addition to humane and ethical considerations, accurate assessment of the status of the skeletal system is essential for economic and health policy reasons.

Bone loss in the oral cavity can result from a number of systemic diseases including: Papillon Lefevre syndrome, Down syndrome, HIV infection, diabetes, and osteoporosis. More frequently, however, oral bone loss is associated with periodontitis and residual ridge resorption (7). Although the links between periodontitis or residual ridge resorption and age related systemic osteoporosis are not clear, a growing body of evidence suggests that older women are at risk for both osteoporosis and oral bone loss (8). As with osteoporosis, the prevalence of periodontitis increases with age. The 1985 National Survey of Oral Health in U.S. Employed Adults and Seniors measured attachment level, which generally correlates with loss of bone. The percentage of sites with attachment loss increases with age (9). In a recent study, post-menopausal osteoporosis has been shown to contribute to periodontal attachment loss in the form of gingival recession (10).

Osteoporosis and oral bone loss are both characterized by the loss of bone mass and density and microstructural deterioration, however, as shown in Table 1, other than increasing age and smoking, they do not share much similarity with respect to their initiating factors (7). Generalized bone loss from systemic osteoporosis may render the jaws susceptible to accelerated alveolar bone resorption. Similarly, systemic osteoporosis also may cause an increased rate of bone loss around the teeth or in the edentulous ridge (11, 12). It has also been shown that a strong correlation exists between dental and total bone mass in female subjects (13). It has been suggested that post-menopausal women with osteoporosis retain less bone following tooth loss (14). In one report, women with severe post-menopausal osteoporosis were three times as likely as controls to experience edentulism (15).

PERIODONTITIS	SYSTEMIC OSTEOPOROSIS	RESIDUAL RIDGE RESORPTION
Increasing age	Increasing age	Increasing age
Smoking	Smoking	Tooth loss
Medications (e.g., long term steroids)	Medications (e.g., Steroids)	Ridge anatomy
Systemic bone Loss (e.g., osteoporosis)	Menopause	Denture fit & mechanics (postulated)
Pathogenic Bacterial plaque	Inadequate CA intake	Systemic factors
Host-response abnormalities (i.e., immune dysfunction)	Alcohol/coffee consumption	
Diabetes	Leanness	
	Genetic factors	

Table 1: Risk factors for oral and systemic bone loss (16, 17, 18, 19)

Recent research has focused on developing techniques that permit the accurate, quantitative assessment of the human skeleton so that osteoporosis and other osseous anomalies may be detected, monitored and the risk of fracture ascertained. The skeleton is composed of about 80% cortical ("dense") bone and 20% trabecular ("spongy") bone. Spongy bone has a calculated remodeling (turnover) rate approximately eight times that of cortical bone because of its high surface to volume ratio and its greater sensitivity to metabolic perturbation (20, 21). Thus, trabecular bone is a prime target for detecting early bone loss and monitoring the response to therapeutic interventions. This emphasis on trabecular bone is further justified by clinical and epidemiological interventions showing that osteoporotic fractures occur initially in the vertebral bodies and distal radius, sites that are composed predominantly of trabecular bone.

Among the techniques currently used to estimate bone density and to predict the risk of fracture resulting from osteoporosis are quantitative computed tomography (QCT) (22, 23), single photon absorptiometry (24), and dual energy x-ray absorptiometry (DXA) (25, 26). However, bone density alone does not seem to be able to predict the likelihood of fractures, because bone strength, which ultimately dictates resistance to fracture, is a biomechanical property that depends upon a number of factors other than bone density (27, 28, 29, 30). These factors include, the distribution of mineral content of bone in three dimensions, the connectivity of bone trabeculae, trabecular spacing, microstructural characteristics, and, finally, loading of the skeleton. Fractal geometry (31) holds great promise as a technique to define the structural variations in trabecular bone including such features as connectivity, trabecular volume, and trabecular spacing.

Age and sex linked losses in trabecular bone density and structural connectivity have been documented (32, 33, 34) and related to the loss of bone strength (33). Thus, it is not surprising that recent efforts have been directed towards understanding trabecular structure in addition to assessing bone density. Cody et al. have shown that the spatial distribution of bone mineral density within a vertebral body affects the mechanical properties and different regions appear important to the strength of the vertebral body at various spinal levels (30). Other techniques such as analysis of high resolution images obtained using radiographs (35), feature extraction and texture analysis, and development of finite element models (36, 37, 38) to stimulate bone structure have been proposed. The use of fractal geometry and measurement of fractal dimension of bone radiographs is one such technique that has recently been explored. Investigators have measured the fractal dimension of trabecular bone from radiographic images of the wrist (39) and the jaw (40, 41) in order to characterize osteoporosis related changes. Van der Stelt et al. (39) have found that the fractal dimension does not correlate with bone mineral density, while Doyle et al. (41) and Ruttiman et al. (40, 42) have shown differences in fractal dimension of trabecular bone in the maxilla between pre- and post-menopausal women. Lynch et al. have used the fractal signature to assess osteoarthritic changes in the knee joint using radiographic images (43), while the fractal dimension of the trabecular pattern has also been determined (44).

i. Fractal Analysis

Fractal geometry was popularized by Mendelbrot (31) and is a generalization of Euclidean geometry where a new length-area-volume relationship is defined. Typically, Euclidean geometry describes only smooth objects such as cubes, spheres, etc. adequately. Using concepts of fractal geometry, more complex surfaces that possess self similarity, i.e., that appear similar over a range of scales, may be defined. The self similarity of such structures is not neccessarily resolved visually, but is self-similarity as described by the statistical features of the structure. Associated with every fractal object is a characteristic dimension, called the fractal dimension (FD), which generally increases as the complexity of the structure increases (Figure 1).

FRACTAL ANALYSIS

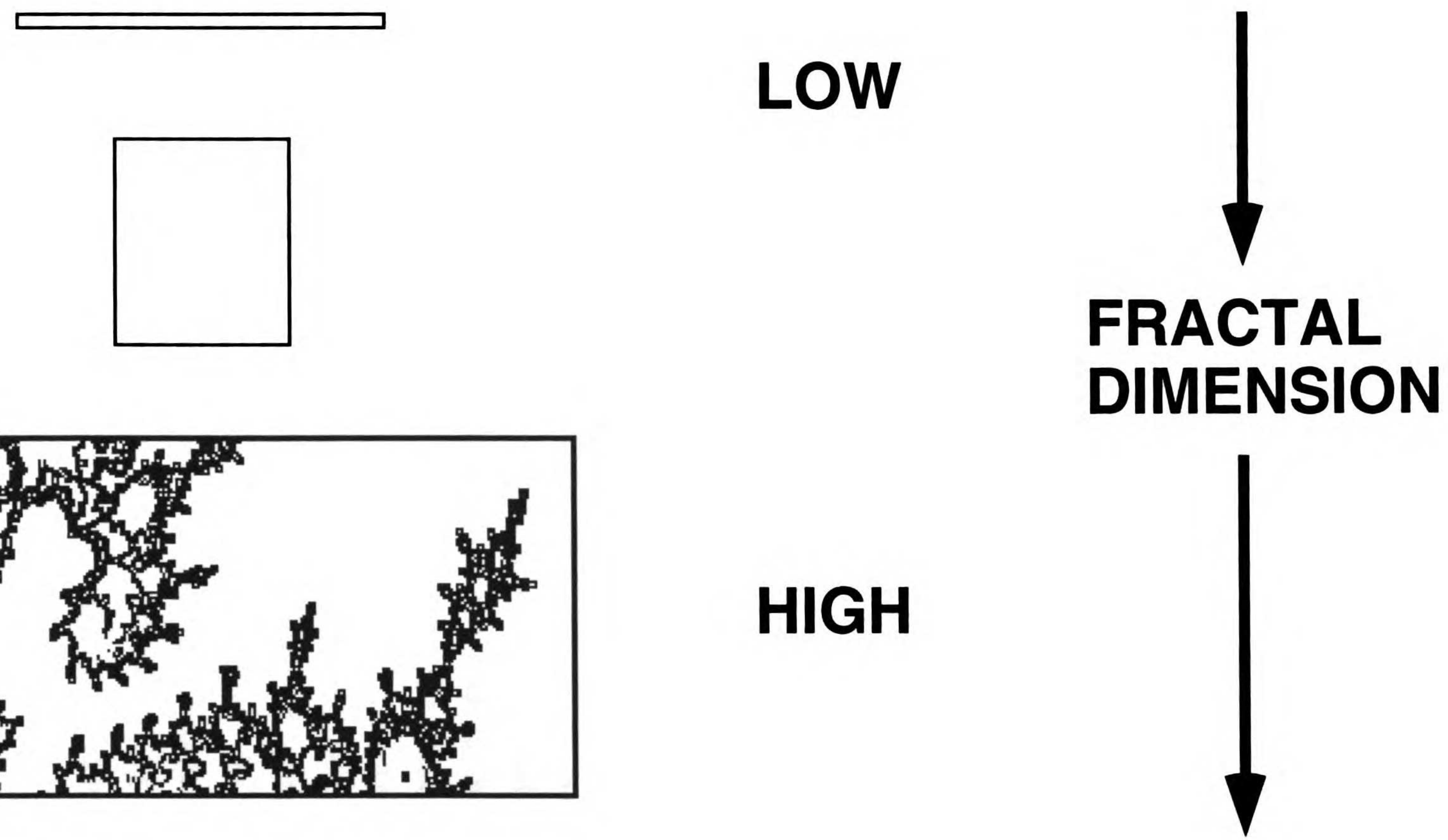


Figure 1

These techniques have been applied to the field of geology and land formation to describe the sedimentation and formation of rocks, fracture propagation, the analysis of porous materials, and the methods have also found use in the biological sciences. The complex trabecular network of bone, where apart from the thickness of the trabeculae, spatial architecture, connectivity, and porosity play a role in defining biomechanical strength, lends itself very aptly to fractal analysis.

As noted above, it is only mathematically constructed fractal structures which possess self-similarity (at least statistically) over all scales. However, most biological fractals are scale limited in that the fractal characteristics can be only described over a finite range of scales. In addition, there is usually a definite preferred orientation and hence anisotropy to biological structures. For such structures, instead of one fractal characteristic or property over all scales, it is possible to describe a range of fractal dimensions, which may be dependent on the direction over which the characteristics are calculated. Such objects are self-affine and the concepts of fractal analysis may be extended to study such objects. Thus, although trabecular bone is not a true self-similar mathematical fractal e.g., a single trabeculum does not have the same appearance visually or even statistically as a network of trabeculae, the complexity of trabecular architecture and radiographic patterns, makes the techniques of fractal analysis relevant and applicable to the analysis of trabecular bone. The analysis techniques and the measured dimension or characteristics may however, depend on the imaging modality and the resolution of the images of trabecular architecture. The advantage of fractal geometry based analysis techniques are that they may be potentially extended to quantify radiographic patterns of trabeculae.

One of the primary considerations in using fractal techniques in quantitative image analysis is the applicability of the specific technique used to calculate the fractal dimension. There are two main classes of fractal analysis techniques, a deterministic technique where the geometrical structure itself is resolved and analyzed, and a second technique which uses statistical modeling of the pattern of trabecular bone, for example as seen in radiographic projections. The method used in this study (the Power spectrum of the Fourier transform) will be discussed in the next section. Some of the other basic methods of fractal analysis include the box-counting, the surface area, and the semi-variance techniques. The description of these techniques is beyond the scope of this thesis.

From this information, it is clear that fractal analysis is a relatively new field with investigators using differing approaches that produce varying results. Clearly, depending on the theoretical formulation, the fractal dimension may vary numerically, and some techniques may be more relevant to the analysis of radiographic patterns of trabecular bone than others.

ii. Review of the Literature on Fractal Analysis of Bone

Although fractal analysis of trabecular structure is relatively new, each of the above mentioned methods has been used in the analysis of trabecular bone structure from radiographs. Buckland-Wright et. al (45) used fractal geometry to analyze radiographs of the lumbar spine. In comparing two groups of post-menopausal women, one with high bone mineral density (BMD) and one with lower BMD, they detected an increase in the fractal dimension of the vertebral structures in the low BMD group. They attributed this finding to "the increased perforations that are seen with the onset of osteoporosis, which results in an increase in cross connectivity due to broken connections". The authors recognized that their study was not conclusive and that further studies were required to derive the precise relationship between the fractal measures and the structural organization of trabecular bone. Calgiurli et. al. have recently presented an analysis of lumbar spine radiographs (46). Fractal dimension of radiographs was calculated using the surface-area technique. They showed using this technique, that there appears to be a promising discrimination between subjects with and subjects without fractures. However, given the standard quality of lumbar radiographs, there is very little texture apparent in the lumbar vertebrae they have analyzed, and with the overlap between soft tissue folds, ribs, and other intruding structures, the interpretation of this data is difficult.

Ruttiman et al. (42) have assessed the fractal characteristics of the dentoalveolar bone from the maxillary periapical dental radiographs in two groups of 6 patients each (pre- and post-menopausal). They have shown that the fractal dimension, calculated using the power spectrum of the Fourier transform technique, shows age related differences ($p<0.008$) between the groups and is higher in the post-menopausal group. The conclusion of their study is that fractal dimension measured from radiographs reflects changes in trabecular bone structure that occur with the onset of post-menopausal osteoporosis. However, in this study, the dental history of the patients, such as tooth loss, periodontal status and other factors that affect the quality of dentoalveolar bone were not known. In a related in-vitro study (42), these investigators reported that the radiographic fractal dimension of mandibular alveolar bone, measured using the power spectrum of the Fourier transform, increased after acid induced demineralization, which in a way simulated loss of bone density due to a disease process such as osteoporosis. They also demonstrated that there were regional variations associated with the fractal dimension and that there was an increase in fractal dimension as the region of analysis moved posteriorly along the mandible. Importantly, variations in angulation projection were found not to have a significant effect on the fractal dimension.

In contrast to Ruttiman et al.'s in-vitro findings, Southard et al. showed the opposite trend in fractal dimension as a result of acid-induced demineralization (47). Five specimens of human maxillary alveolar bone were progressively decalcified and the percentage calcium lost at different stages were quantified. Based on inspection of densitometric plots, they concluded that the radiographic alveolar bone signal becomes less, not more, complex during bone loss and that fractal dimension of maxillary alveolar bone decreases during simulated osteoporosis. It is important to note, however, that Southard et. al have used specimens from the human maxilla in their study as opposed to the mandible as in Ruttiman et. al's investigation.

In a limited study in six animals, Samarabandu et al. (48) compared the power spectrum of the Fourier transform method and a morphological surface area based technique for measuring the fractal dimension of trabecular pattern from radiographs of rat femur. Each rat had one limb immobilized, the assumption being that with immobilization, there was a decrease in trabecular bone density and changes in trabecular structure. In the case of surface-area based analysis, the authors found that the fractal dimension of trabecular bone pattern from x-ray images was greater in the normal limb compared to the immobilized limb in 3 out of 4 cases. The Fourier spectral technique yielded a higher fractal dimension in the trabecular pattern of the immobilized limb compared to the normal limb in 4 out of 6 cases.

Berry et. al (49) utilized fractal analysis based on the Fourier transform technique to see whether different regimens of diet and exercise could alter the trabecular structure of bone in rats. It was hypothesized that a dairy source of calcium alone and or in combination with weight bearing exercise would promote a greater increase in bone density when compared to a diet of calcium citrate malate alone and or in combination with lack of exercise. Fractal dimensions obtained by scanning the tibia of these rats revealed the greatest amount of trabecular structure in dairy calcium exercising rats, and the least in the non-exercising group fed calcium citrate malate diet, and the difference in fractal dimension between the two groups was statistically significant ($p<0.5$).

Table 2 is a summary of the changes in fractal dimension measured from radiographs with assumed changes in trabecular structure. A careful look at this table reveals that, while trabecular structure may aptly be described and quantified using fractal analysis techniques, studies to date using radiographic analysis have been incomplete, contradictory in trend, and unsubstantiated with biomechanics, histomorphometry, or other objective measures of trabecular structure. The techniques of fractal analysis used, e.g., the Fourier transform method, surface area technique, etc., have vastly different theoretical formulations and need not yield the same results. Some techniques may be more appropriate for the analysis of trabecular patterns and yield results that better predict biomechanics and bone architecture.

Author	Fractal Dim. (Technique)	Bone Density / Structure	Type of Study
Buckland-Wright(45)	Increases (vertical direction) (Surface area based)	Decreases (Lumbar Spine)	Post-menopausal, Low BMD and high BMD group
Calgiurli(46)	Decreases (Surface area)	Decreases (Lumbar Spine)	Fracture vs. Non-fracture
Ruttiman(42)	Increases (Fourier Transform)	Decreases (n=6) (Maxillary Alveolar Bone)	Pre and Post-menopausal
Samarabandu(48)	Increases (Fourier Transform) Decreases (Surface area based)	Decreases (n=6) (Rat Femur) Decreases (n=6) (Rat Femur)	Immobilization

Table 2: Summary of the current work in fractal analysis of radiographs

In a recent investigation, Chen et al. have attempted to identify some of the methodological differences and technical difficulties in fractal analysis of trabecular patterns from projection radiographs which might be responsible for some of these contradictory trends (50). In an environment that is devoid of image noise, fractal dimension is expected to increase with increasing complexity of an imaged structure, a fact that has been confirmed with a different approach to fractal analysis, viz., cross sectional computed tomography (51). Chen et al. believe that the reason why certain investigators find the opposite trends in fractal dimension is image noise, which may include the noise associated with quantum, film-screen system, and film digitization. Image noise (white or nonwhite) has a high complexity or non-self-similarity (highest fractal dimension). Superimposition of the bone structure acts to mask the complexity of the underlying noise, thus reducing, not increasing the estimated fractal dimension in the image by the introduction of structural order. Chen et al. also reported on the effect of size of the region of interest in the scanned image and data windowing on fractal dimension. They found that reducing the size of the region of interest without reducing resolution has the effect of larger dependence of computed fractal dimension on the higher frequencies in the power spectrum. Therefore, fractal dimension in non-corrected regions will decrease as the size of the region of interest decreases. Finally, as a word of caution, they emphasize that characterization of image and digitizer noise, which can be largely assessed and partially corrected for in sequential measurements over time, will be essential to the successful use of fractal analysis in longitudinal clinical studies.

Recently, Benhamou et. al (52) undertook fractal analysis of radiographs based on a Fractional Brownian Motion model and, in a preliminary study were able to separate osteoporotic cases from normal cases. In addition they found that Fractal analysis of bone radiographic images may be distorted by variations linked to the radiographic process or by the random noise associated with the digitization process. Loussot et. al (53) demonstrated that random noise of digitization has an important influence on the results of fractal analysis based on Fractional Brownian Motion model. However, this influence may be reduced by accumulating the images to obtain an averaged image before analysis. It is important to note that, what is meant by digitization noise in this study differs from what Chen et. al (50) refer to as digitizer noise; however, the details on this difference are beyond the scope of this thesis.

The above information suggests that the use of fractal geometry holds promise as a technique to define the structural variations in trabecular bone, which may have potential value in assessing bone architecture and diagnosis of conditions that degrade the quality of osseous structures.

II. AIMS & OBJECTIVES

The overall objective of this study was to devise a non-invasive, readily available technique that can be used to accurately assess changes in bone quality (as determined by the geometry of trabecular bone) in large numbers of individuals at relatively low cost. To this end, we proposed (i) to fully develop the methodology necessary to perform fractal analysis on dental and other types of skeletal radiographs and (ii) to confirm what preliminary studies already suggested, viz. that fractal analysis of radiographs is an effective and readily applicable tool for (a) characterizing trabecular bone geometry, (b) detecting changes in bone quality due to osseous degrading conditions such as osteoporosis, periodontitis and residual bone resorption, and (c) monitoring changes in bone quality over time. With this tool in hand, dental and medical practitioners should be in a better position to make an accurate assessment of bone quality both before initiating treatment and, equally importantly, during the course of therapy.

III. GENERAL RATIONALE & METHODOLOGY

This retrospective study was conducted in two phases. In the first phase, wrist radiographs from osteoporotic and normal subjects were digitized and the fractal dimension of the trabecular pattern determined. These samples were drawn from a group of patients who had already had single photon absorptiometry analysis of the wrist and had also been assessed relative to their skeletal health status and site specific bone density. The fractal dimension, derived from the wrist, was compared to bone density analysis and tests of significance used to determine agreement (or lack there of) between the fractal dimension and bone density. These determinations were, in turn, used to establish whether and with what precision the fractal dimension of radiographs may distinguish between normal and osteoporotic subjects. Furthermore, regional variations across and along the wrist, as well as between the two wrists, and their effects on the fractal dimension were determined.

With the knowledge gained from the first phase of the study, the software and the methodology were adapted for the analysis of dental periapical radiographs in the second phase of the study. There are several advantages in choosing periapical radiographs for fractal analysis. Periapical radiographs are fairly inexpensive, involve low exposure to ionizing radiation, and offer high image resolution as a result of direct film exposure (i.e., no screens are used). They are taken routinely, and therefore offer the potential to monitor and objectively measure changes in bone quality over time in a quantitative manner.

It became obvious that prior to investing time and effort in applying the technique prospectively, more knowledge and experience needed to be gained from the analysis of retrospective dental radiographs. Thus, the second phase was intended as an intermediate step in testing the ability of fractal analysis to detect differences in trabecular bone structure obtained from existing periapical radiographs. To this end, in the second phase of the study, retrospective periapicals from two groups of dental patients separated based on the existing extent of oral bone loss were subjected to fractal analysis. A cross sectional comparison between the healthy and periodontally compromised subjects was made to determine whether this technique may differentiate between the two groups. To assess the viability of this technique as a monitoring tool for disease progression, a longitudinal evaluation of patients whose oral bone status had deteriorated over time was also undertaken. In addition, a comparative evaluation of alveolar bone before and after extraction of teeth was made to assess the capability of our fractal analysis to detect treatment induced changes in the trabecular bone structure. Finally, similar to the wrist films, the effect of regional variations along the mandible and between the two jaws was evaluated.

With this groundwork completed, the basis will have been established for undertaking a much larger prospective study. This phase will involve the taking and fractal analysis of dental films, using an already standardized set of criteria, from individuals of known osteoporotic or periodontally compromised status and either performing cross sectional comparative studies with the normal subjects or monitoring changes in their bone quality over time.

IV. PHASE 1

FRACTAL ANALYSIS OF WRIST RADIOGRAPHS

i. OBJECTIVES

The objectives of this phase were:

- To perform fractal analysis on high quality wrist radiographs of two clearly separated populations: normal and osteoporotic.

- To determine if fractal dimension can differentiate between the normal and osteoporotic subjects.

- To determine variations in fractal dimension in different regions of the wrist.

ii. MATERIALS & METHODS

High quality industrial grade wrist films (Kodak, XOMAT-XTL 2, 50 KVP, 50 mA, 1s) from 2 well separated populations were used in this study. One group included 10 pre-menopausal normal subjects (41.6 + 1.8 years of age). The other group consisted of 10 post-menopausal osteoporotic subjects (65.7 + 8.3 years of age) with vertebral fractures and substantially different spinal bone density measurements compared with the normal group (88.2 + 15.4 gm/cc vs. 139.9 + 21.4 gm/cc). The radiographs were digitized by scanning the image at 85 micron resolution (XRS 6XS Omni Media Scanner, Macintosh interface, 8 bit gray scale, 0.01-2.8 optical density). A region of interest (ROI) 2-3 cm below the growth plate was selected in the digitally scanned wrist image and the Fourier transform of this region of interest was then determined (Sun Sparc Workstation using IDL (Research Systems Inc.)). The two dimensional power spectrum of the Fourier transform of this region of interest was then calculated (Figure 2).

The Fourier transform technique to calculate fractal dimension relies on the fact that the pattern to be analyzed is similar to a gaussian noise or a stochastic process. This technique has been applied to the analysis of radiographs and the assessment of trabecular bone structure (42, 48). The Fourier transform measures how frequently a structure changes and from histomorphometry images it has been shown that the power spectrum is related to the mean intercept length measure. In this technique, a two dimensional Fourier Transform, F(u,v), is taken of the two dimensional region of interest within the trabecular bone in an x-ray image. The two dimensional power spectrum of the Fourier Transform is calculated as:

$$S^2(uv) = |F(u,v)\ F^*(u,v)|$$

Where $F^*(u,v)$ is the complex conjugate of the Fourier Transform. S(u,v) will be converted into the polar coordinate system and will be averaged for all angular distributions for a given spatial frequency f. The averaged power spectrum is related to the fractal dimension as:

$$S(f)\ \alpha\ f^{-D}$$

Essentially, the Fourier transform measures the rate at which textural variations occur; rapid changes in texture are reflected as high frequency components in the power spectrum. Figure 3 illustrates representative regions of interest and their corresponding power spectra from the normal and osteoporotic groups. Note that the power spectrum of the normal subjects contains a larger cluster of high frequency components centered around the origin.

The two dimensional power spectrum of each region of interest is quantified by averaging over all angles at a given distance from the origin. This decomposed the two dimensional data set into a one dimensional graph with the x-axis showing the radial frequency offset from the origin and the y-axis the average power at that spacial frequency. Fractal dimension is then obtained by calculating the slope of the linear portion of the logarithmic plot of the power spectrum vs. spacial frequency (log S(f) vs. log (f)) and applying the formula:

$$D_{fft} = 7 - |slope|/2$$

Using this technique, the fractal dimension falls in the range of 2-3 (Figure 4). The data is then analyzed statistically using the t-test (Statview, Kaleidograph) and the Receiver Operating Characteristic (ROC) analysis (LABROC1).

To assess the effect of regional variations on the fractal dimension, the following tests are performed on a subset of patients. The selected regions of interest are divided equally into two subregions. This is done to compare whether there are any differences between the fractal dimension obtained from the medial or lateral side of the same wrist. In each subject, regions of interest from the right and left wrists are selected and their fractal dimensions compared. Finally, the effect of regional variations on the fractal dimension along the wrist is determined by selecting regions of interest further away from the articular surface.

FOURIER TRANSFORM TECHNIQUE

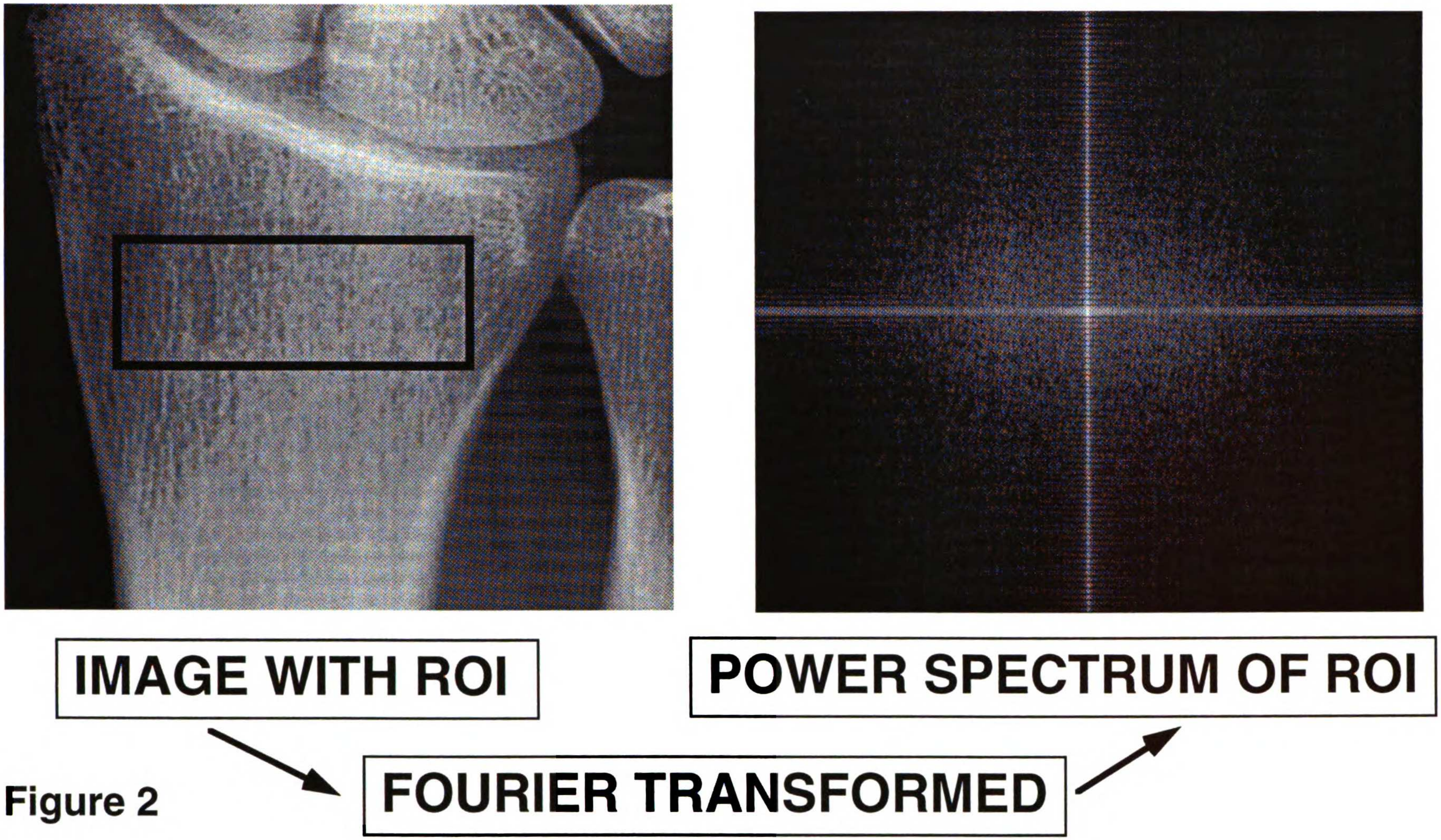


Figure 2

Figure 3 **ROI & POWER SPECTRUM**

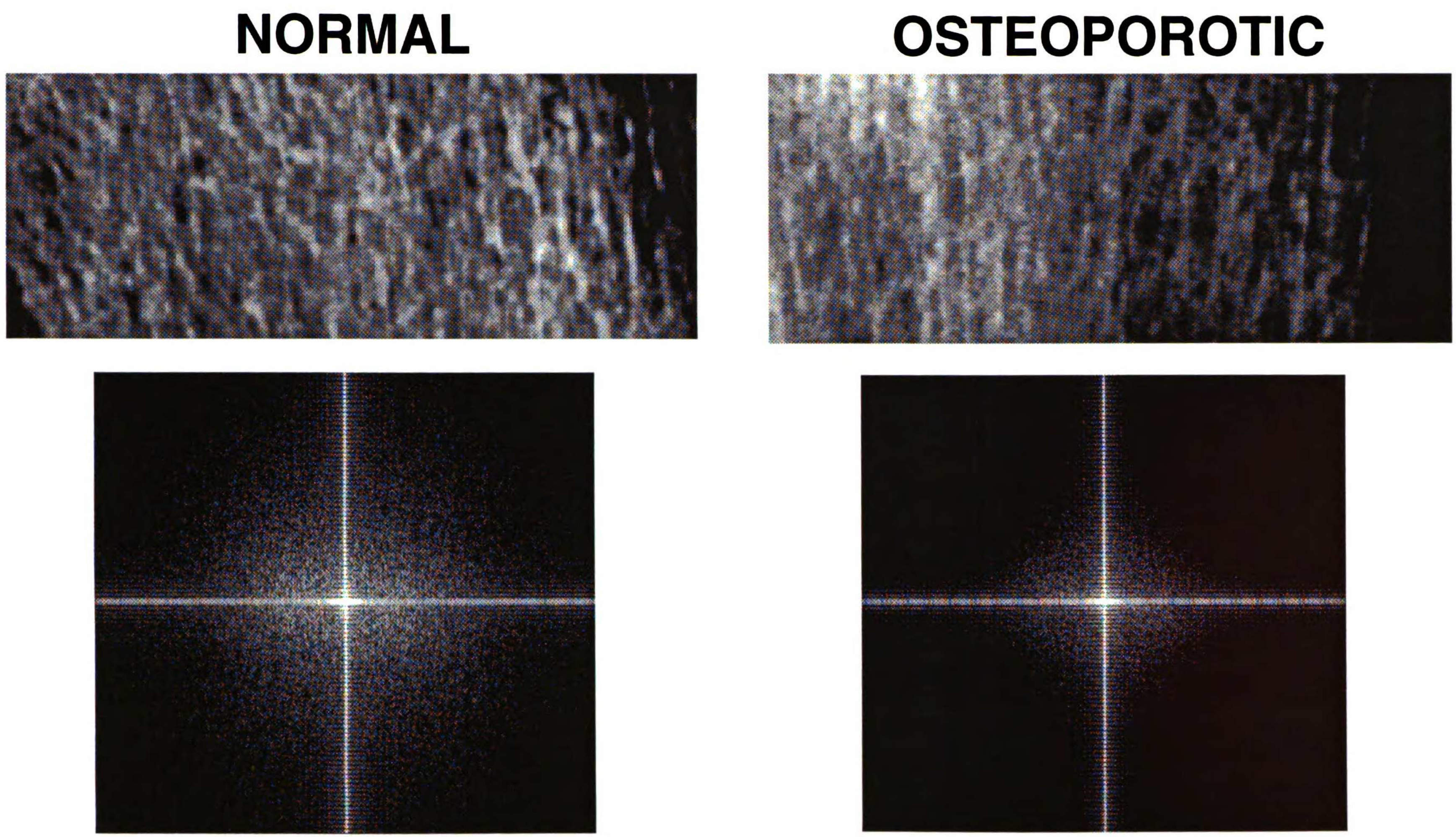
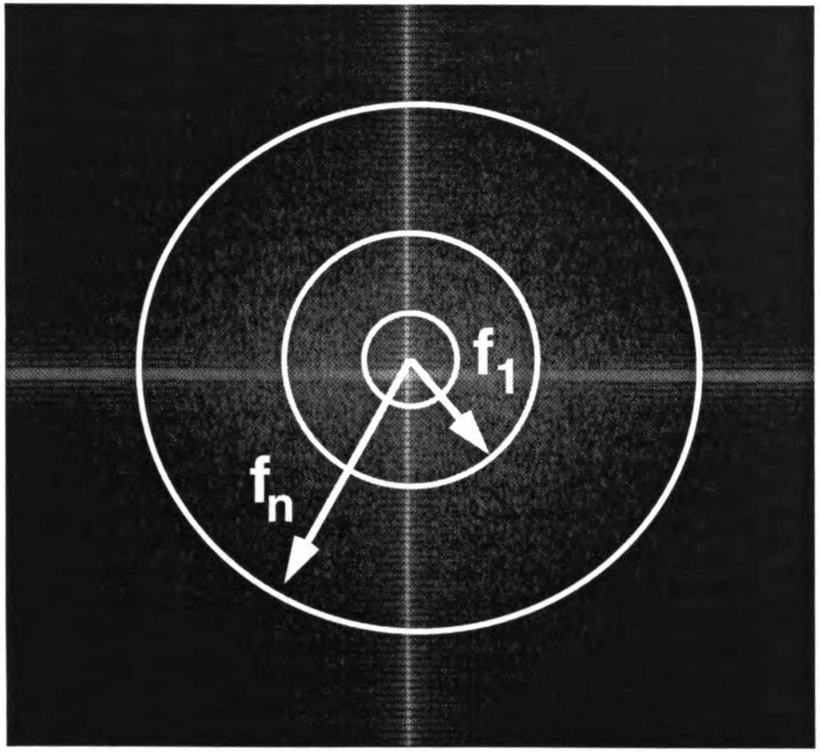
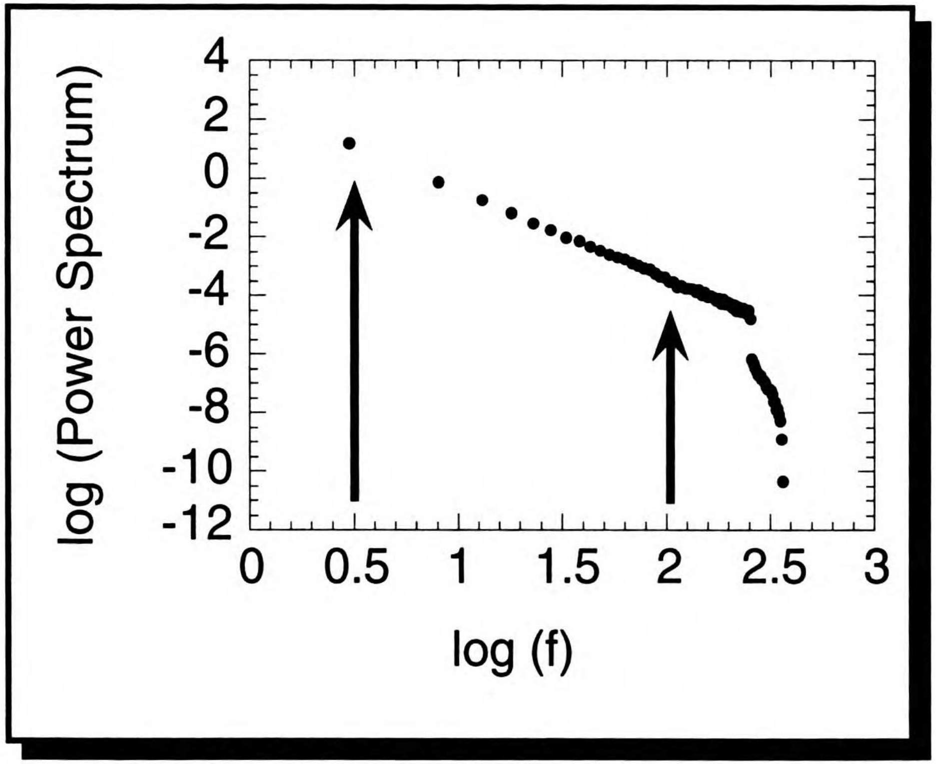


Figure 4

FRACTAL DIMENSION





ANGLE AVERAGED POWER SPECTRUM

$$D = \frac{7 - |\text{slope}|}{2}$$

Range 2-3

iii. RESULTS

As shown in Figure 5, using the fractal technique described above, there is a statistically significant difference ($p<0.004$) between the osteoporotic and normal subjects (the plot on the left). Therefore the technique is able to discriminate between the two groups. Figure 5 also shows a parallel analysis on the same subjects using QCT to determine spinal bone density (middle plot). The fractal dimension plot on the left compares favorably with the information provided by QCT. However, the P value is somewhat better in the QCT cases ($p<0.0001$). The plot on the right depicts the age profile of the osteoporotic and non-osteoporotic subjects used in the study. Note that the two groups are widely separated on the basis of age.

When fractal dimension of the wrist vs. QCT of the spine (Figure 6, left plot) is plotted, there appears to be a trend, suggestive of a positive association between the two techniques such that a subject with a high QCT measurement generally presents with a higher FD. On the other hand, no association is found between fractal dimension and age in the two populations used in this study (Figure 6, right plot). However, Age adjusted and QCT adjusted tests of significance using logistic regression analysis suggest that age and QCT are not statistically significant in determining the fractal dimension ($p<0.9$ and $p<0.7$ respectively).

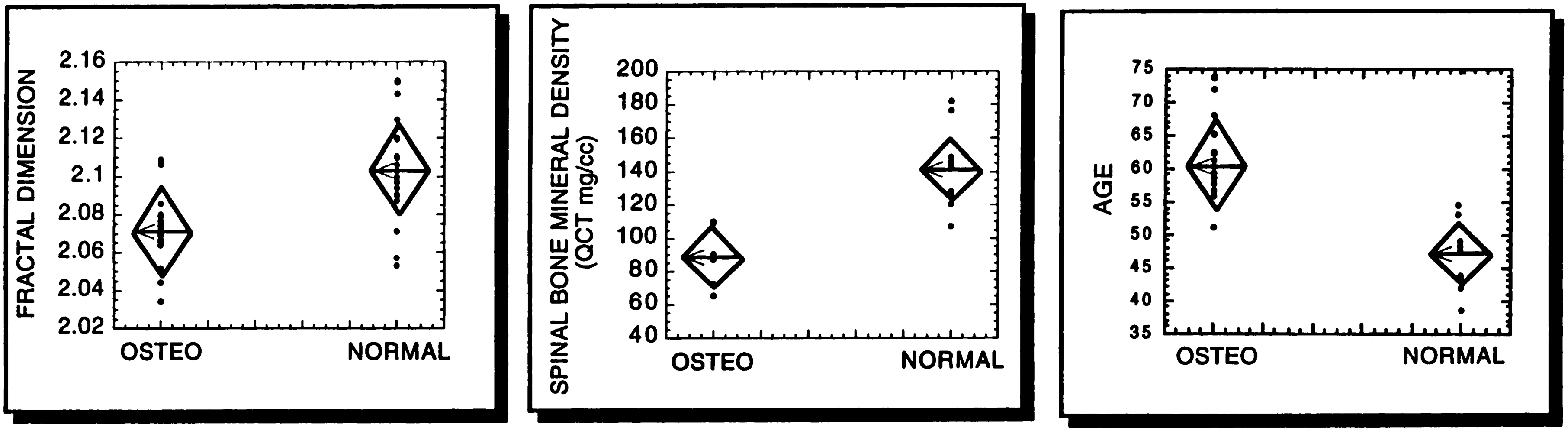
ROC analysis is done to estimate the power of the two techniques in fracture discrimination (Figure 7). Given the biased selection of osteoporotic and normal subjects with substantially different QCT's, the area under the ROC curve is 97% for the spinal bone density measurements as compared with that of fractal analysis of the wrist which is 84%. This indicates that although not as powerful as QCT which is more site specific, fractal analysis shows promise for fracture discrimination based on trabecular bone structure.

To begin to assess the reproducibility of our technique, the effect of regional variations in the skeleton on fractal dimension was evaluated in a subset of subjects. Figure 8 illustrates a comparison between the medial and lateral sides of the original region of interest. The plot on the right shows percent differences in fractal dimension between these two subregions in each subject. The results suggest no discernible trends in fractal dimension as subregions are selected mediolaterally within the same region of interest, and the difference between medial and lateral subregions is not significant.

The left and right wrists of the same subject are compared in Figure 9, and the plot on the right shows the percent difference in fractal dimension between the left and right wrist of a given subject. Once again the data suggests no discernible trend and there is no significant difference in fractal dimension between the left or the right wrist of any particular subject.

Figure 10 shows fractal dimension as a function of distance from the articular surface. The plot on the right illustrates the difference between the top and bottom regions of interest. In contrast to the previous findings, fractal dimension decreases as the region of interest moves away from the joint line as shown by the positive peaks in the plot. Moreover, the difference between the two regions of interest is statistically significant ($p<0.05$).

Figure 5 **NORMAL - OSTEOPOROTIC**



	Probability, p
D	0.0042
QCT	0.0001
Age	0.0001

FD vs. QCT & vs. AGE

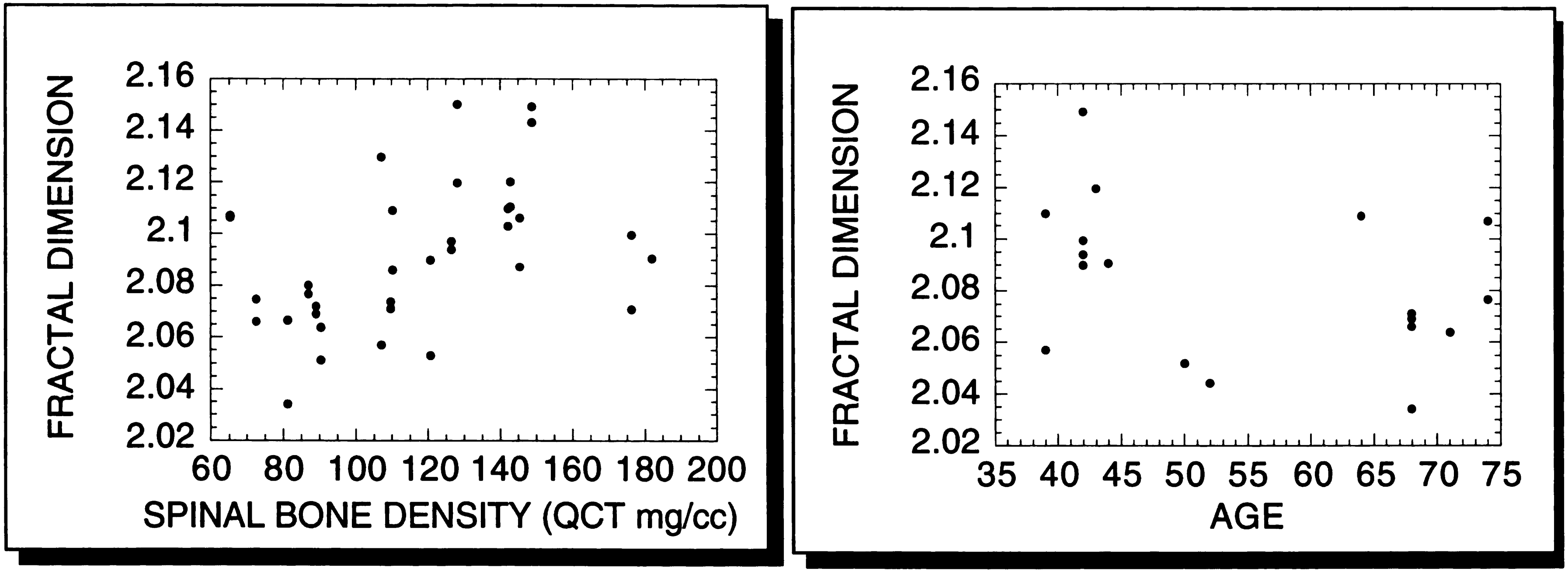


Figure 6

ROC ANALYSIS

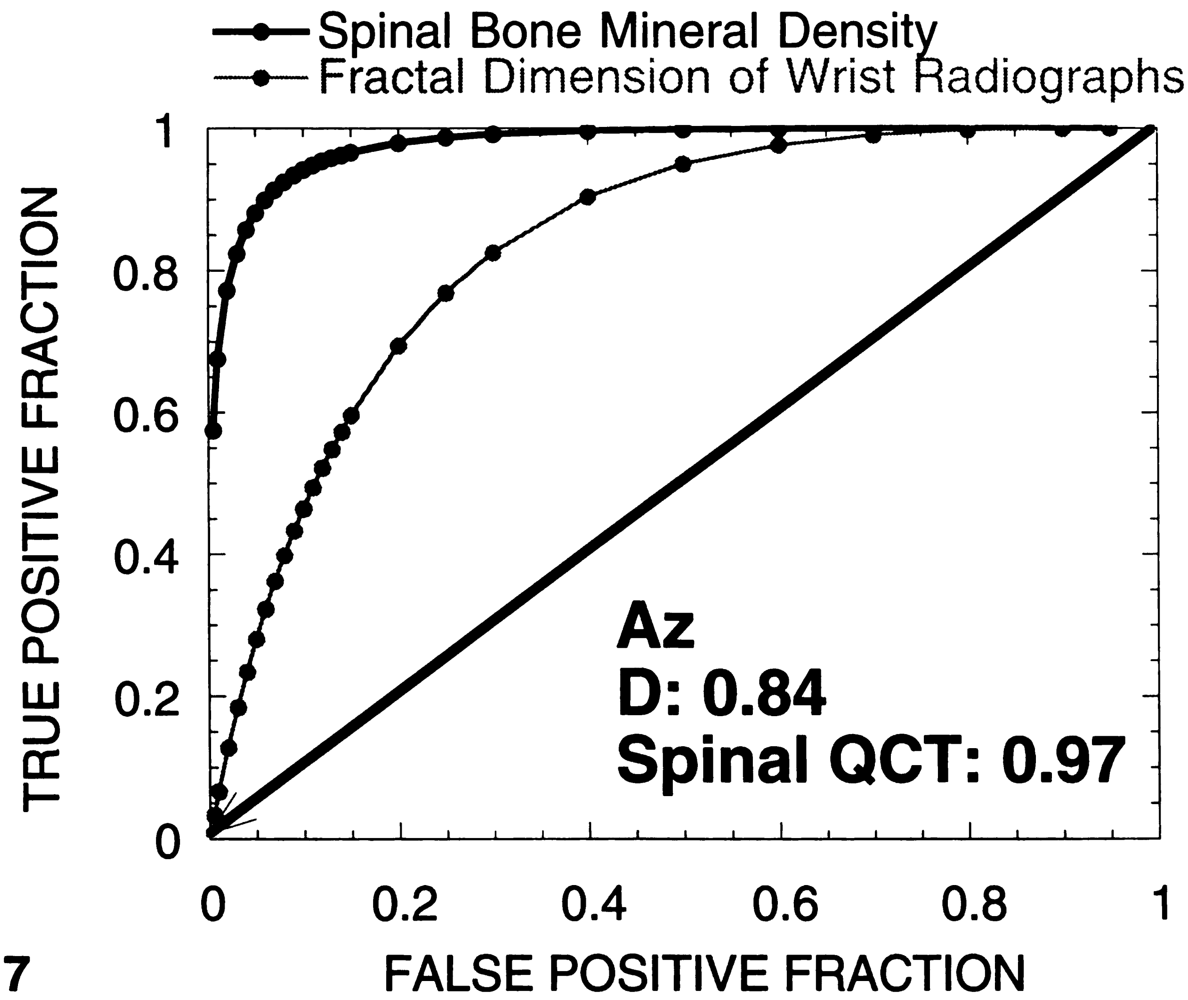
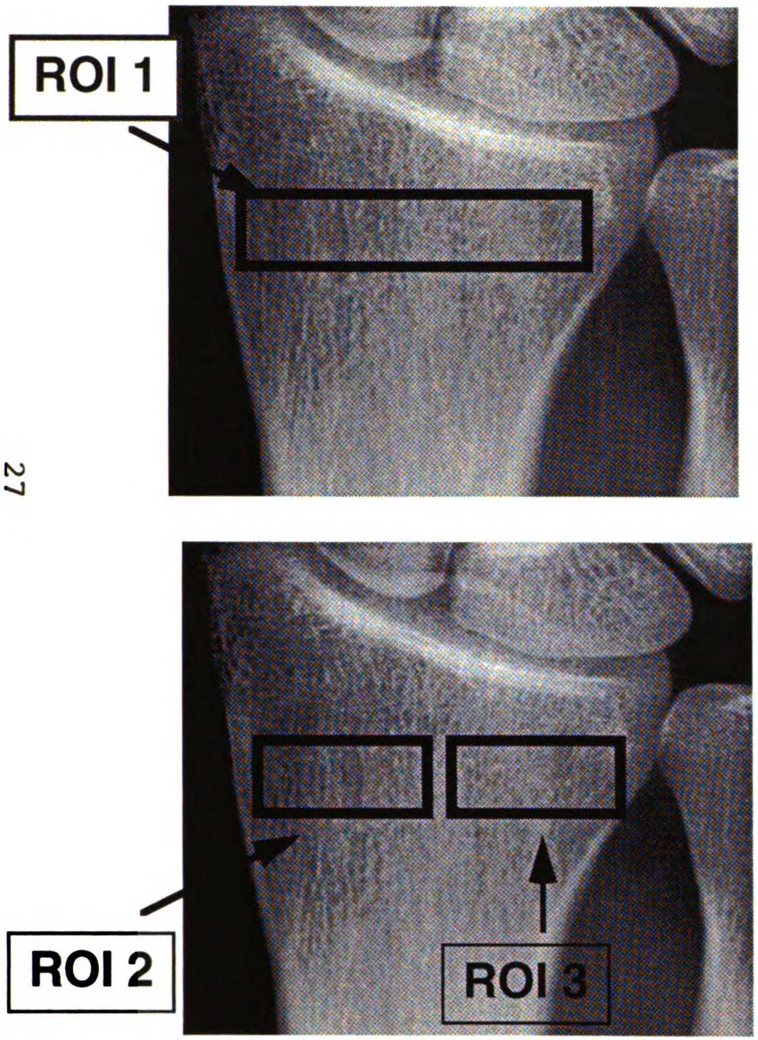
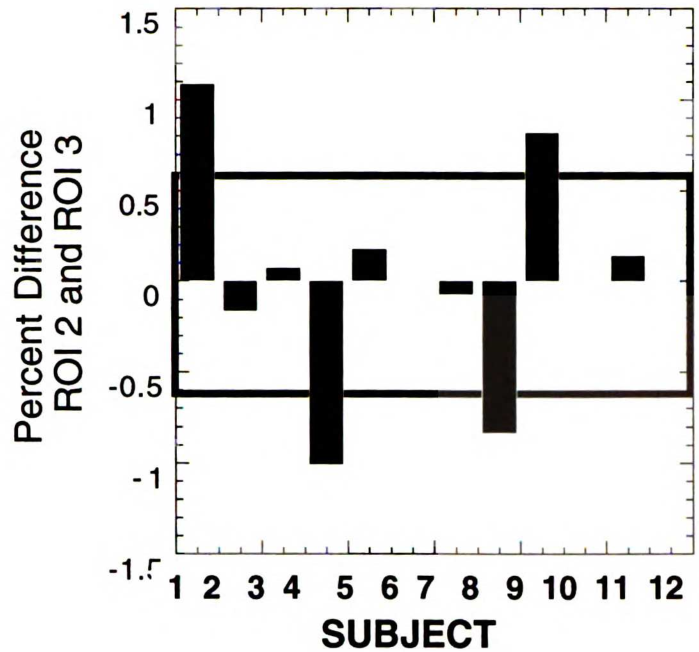


Figure 7

Figure 8

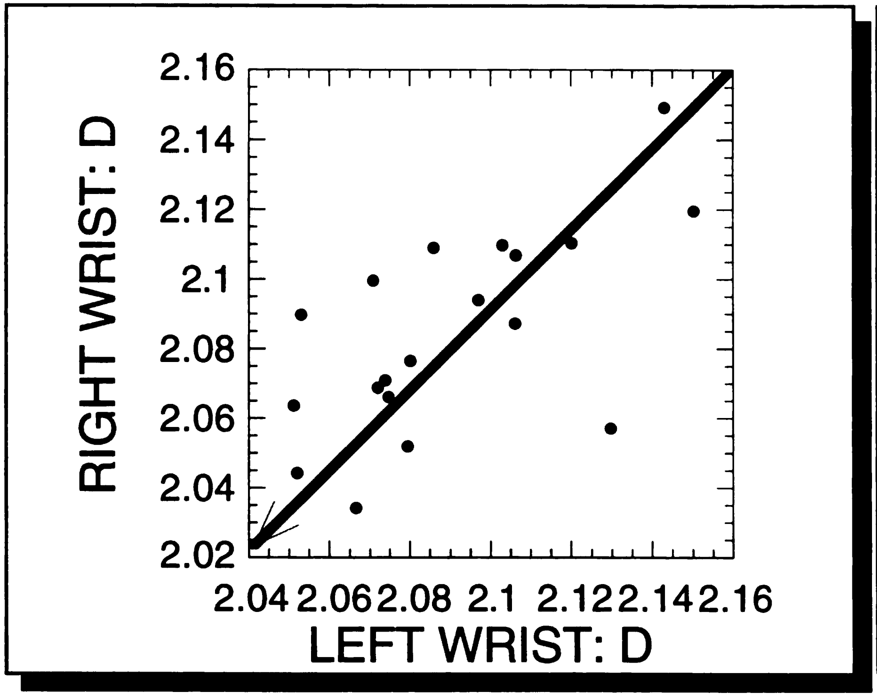
VARIATION OF D WITH ROI

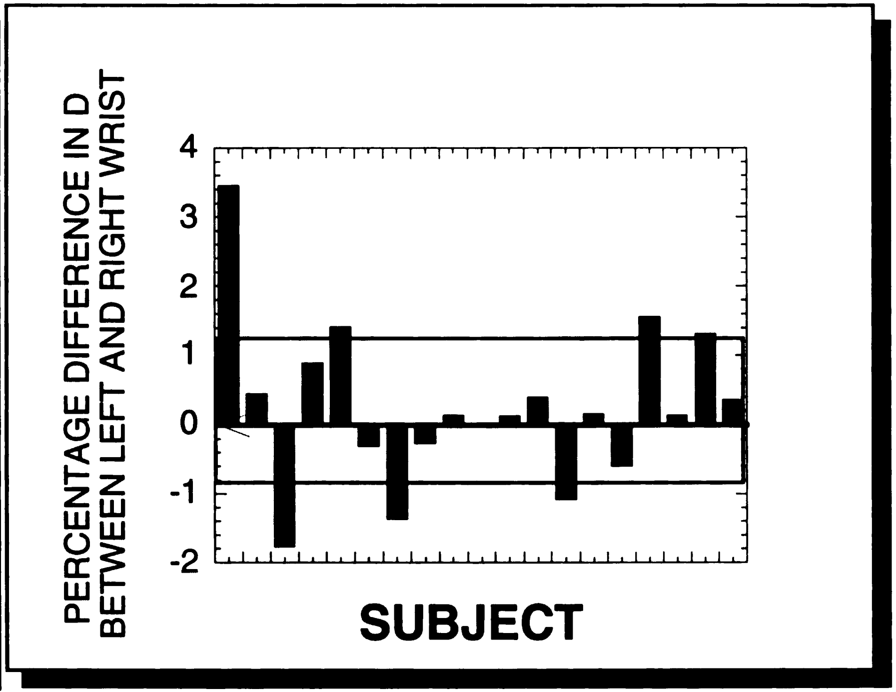




Mean Difference between ROI 2 and ROI 3 = 0.02%
SD = 0.6 %

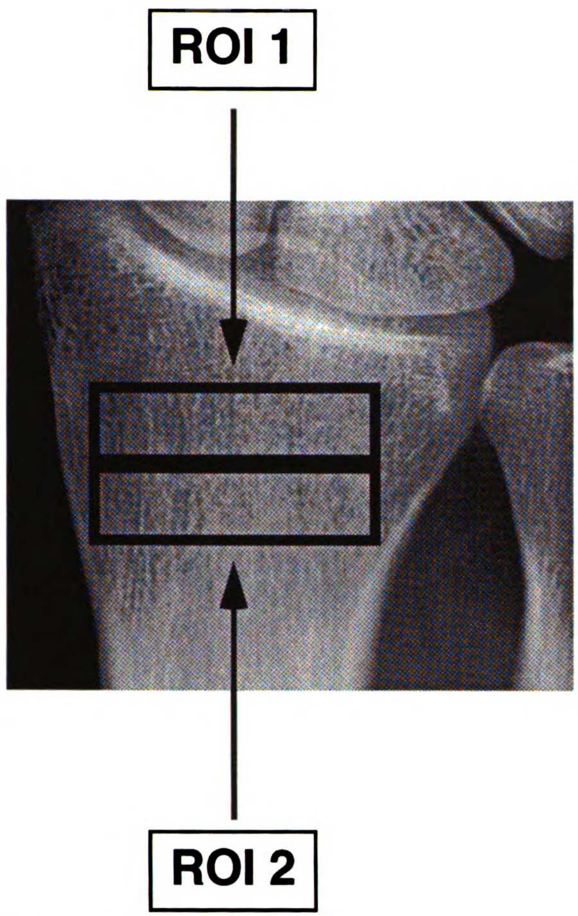
Figure 9 LEFT WRIST - RIGHT WRIST





Mean Difference between Left and Right Wrist = .26%
SD = 1.2 %

ROI ALONG THE RADIAL SHAFT



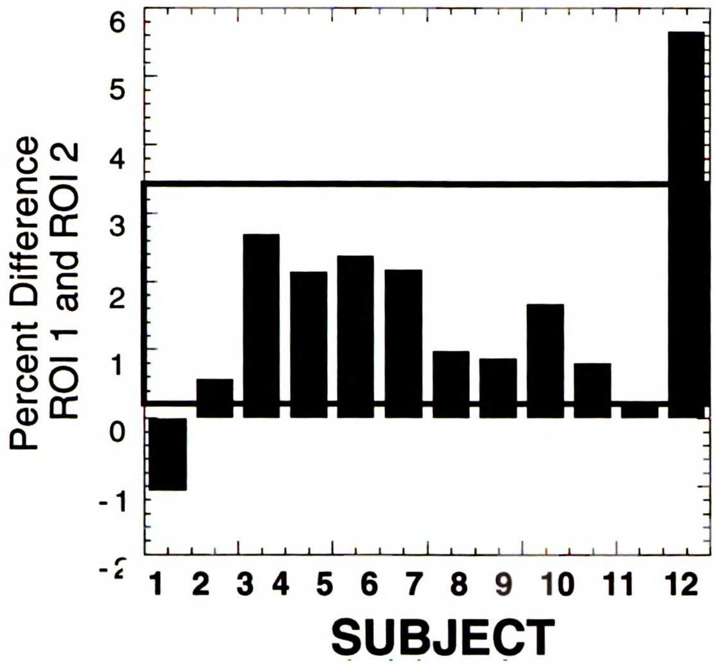


Figure 10

Mean Difference between ROI 1 and ROI 2 = 1.6 %
SD = 1.7 %

V. PHASE 2

FRACTAL ANALYSIS OF DENTAL PERIAPICAL RADIOGRAPHS

i. OBJECTIVES

The objectives of the second phase of this study were:

• To perform fractal analysis on high quality periapical radiographs of two clearly separated populations: healthy and periodontally compromised.

• To determine variations in fractal dimension in different regions of the mouth.

• To determine if there are differences in fractal dimension between the healthy and periodontally compromised subjects.

• To determine if fractal analysis may be used to monitor disease progression or treatment induced changes over time.

ii. MATERIALS & METHODS

High quality E speed periapical radiographs from 2 well separated populations of dental patients at the University of California, San Francisco dental clinic were used in this study. One group included 15 subjects in excellent periodontal health with no bleeding on probing, pocket depth <3 mm and no radiographic evidence of bone loss. The other group consisted of 15 periodontally compromised subjects with a pocket depth > 5 mm and radiographic evidence of bone loss. Periodontal status in this study was determined based on clinical examination and radiographic findings. The term periodontally compromised in this study mainly refers to those individuals who had experienced a significant amount of radiographically apparent bone loss (>3 mm below the CEJ) and makes no inference as to what has been the underlying etiology for the bone loss, and whether or not the disease process was active at the time the radiographs were taken. The two groups were not matched for age, sex, or presence of any systemic diseases. Periapicals used in this study were from the lower incisor region and upper and lower premolar/molar regions.

Generally speaking, from the standpoint of minimizing angulation error, bitewing radiographs may be superior to the periapical radiographs, because bitewing radiographs are taken with the beam entering fairly parallel to the occlusal plane. However, periapicals are much better suited for revealing the trabecular structure of bone. Bitewings show mainly teeth and very little bone is captured. Ruttiman et al. (42) studied the effect of projection angulation on the fractal dimension obtained in vitro and found that a 5^{o} deviation of the beam source mesially or distally had no significant effect on the fractal dimension. Therefore, despite the fact that periapicals may be subjected to more variations in projection angulation, such variations should have little effect on the fractal dimension.

The methodology and instrumentation used in the second phase of the study were the same as those of the first phase. The periapical radiographs were digitized by scanning the image using an 8 bit scanner at 85 micron resolution. A 128 x 128 pixel region of interest in the alveolar bone just below the roots (avoiding any root structure) was selected in the digitally scanned image and the Fourier transform of the region of interest determined. The two dimensional power spectrum of this region of interest was then calculated (Figure 11). The power spectrum of each region of interest was quantified by averaging over all angles at a given distance from the origin. This decomposed the two dimensional data into a one dimensional graph with the x-axis showing the radial frequency offset from the origin and the y-axis the average power at that spacial frequency. Fractal dimension was then obtained using the approach previously described. The data were then statistically analyzed using the t-test (primer of Biostatistics).

To compare the fractal dimension of the healthy vs. the periodontally compromised subjects, regions of interest were taken from the lower incisor periapical radiographs and the fractal dimension was obtained using the above technique. To begin to assess the reproducibility of the technique, the effect of regional variations on fractal dimension was also studied in a subset of healthy and compromised subjects. This included intra-arch variations in the region of interest from the incisor region of the mandible to that of the premolar/molar area (18 patients). In addition, inter-arch variations in the region of interest were evaluated by comparing the premolar/molar region of the mandible with that of the maxilla (11 patients).

Finally, to assess the ability of this fractal technique to monitor changes in bone quality longitudinally, the analysis was also applied in seven subjects whose periodontal status had deteriorated over time and for whom serial radiographs ranging from a minimum of 3 to a maximum of 10 years were available. Furthermore, treatment induced changes in alveolar bone were also evaluated by comparing pre and post-extraction changes in fractal dimension in eight patients who had experienced extraction of teeth.

FOURIER TRANSFORM TECHNIQUE

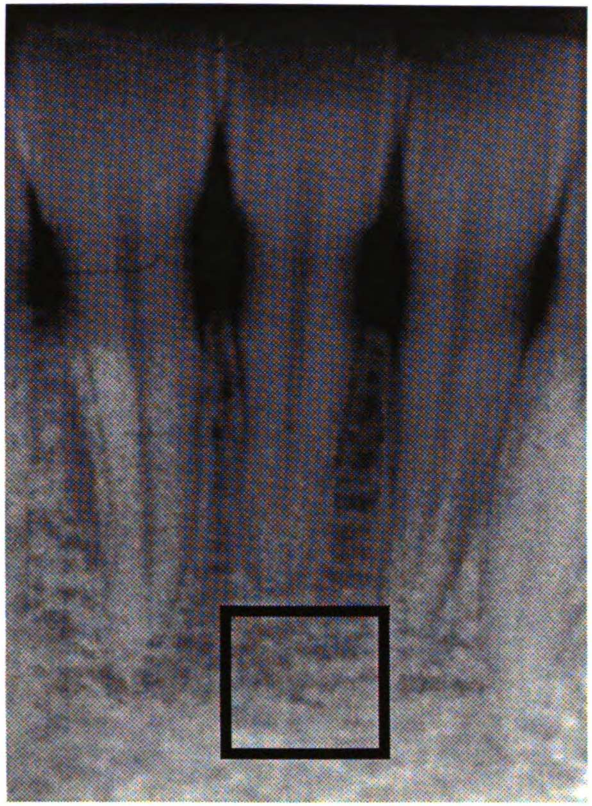
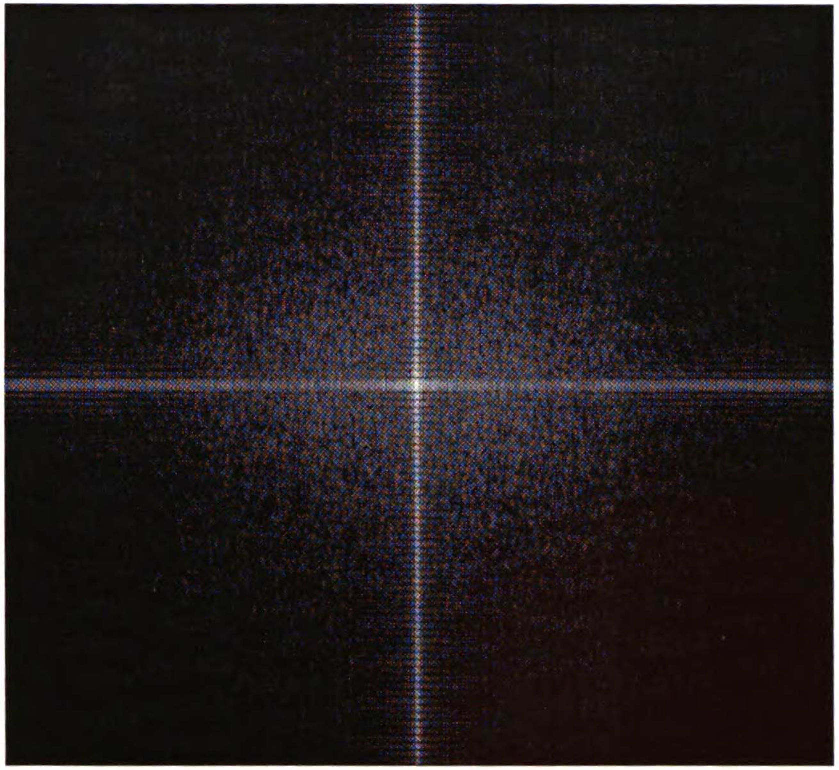


IMAGE WITH ROI



POWER SPECTRUM OF ROI

FOURIER TRANSFORMED

Figure 11

iii. RESULTS

The results of this study indicate that using the fractal technique just described, there is a statistically significant difference ($p<0.001$) between the healthy and periodontally compromised subjects. Therefore the technique is able to discriminate between the two groups (Figure 12). The periodontally compromised patients on average demonstrated a smaller fractal dimension as compared with the healthy group.

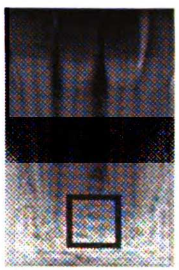
Figure 13 illustrates a comparison between regions of interest taken from the anterior and the posterior regions of the mandible in 18 healthy and periodontally compromised subjects. The plot on the right depicts the difference in fractal dimension between selected regions of interest from the anterior and posterior regions in a given subject. There appears to be a trend suggesting that the fractal dimension increases as the region of interest moves posteriorly along the mandible as seen by the negative peaks in the plot. This difference is statistically significant ($p<0.05$).

Figure 14 illustrates a comparison between regions of interest taken from the posterior region of the maxilla and the posterior region of the mandible. The plot on the right shows the difference in fractal dimension between selected regions of interest from the maxilla and the mandible in a given subject. The fractal dimension is higher in the maxilla than it is in the mandible as seen by the positive peaks in the plot. This difference is statistically significant ($p<0.05$).

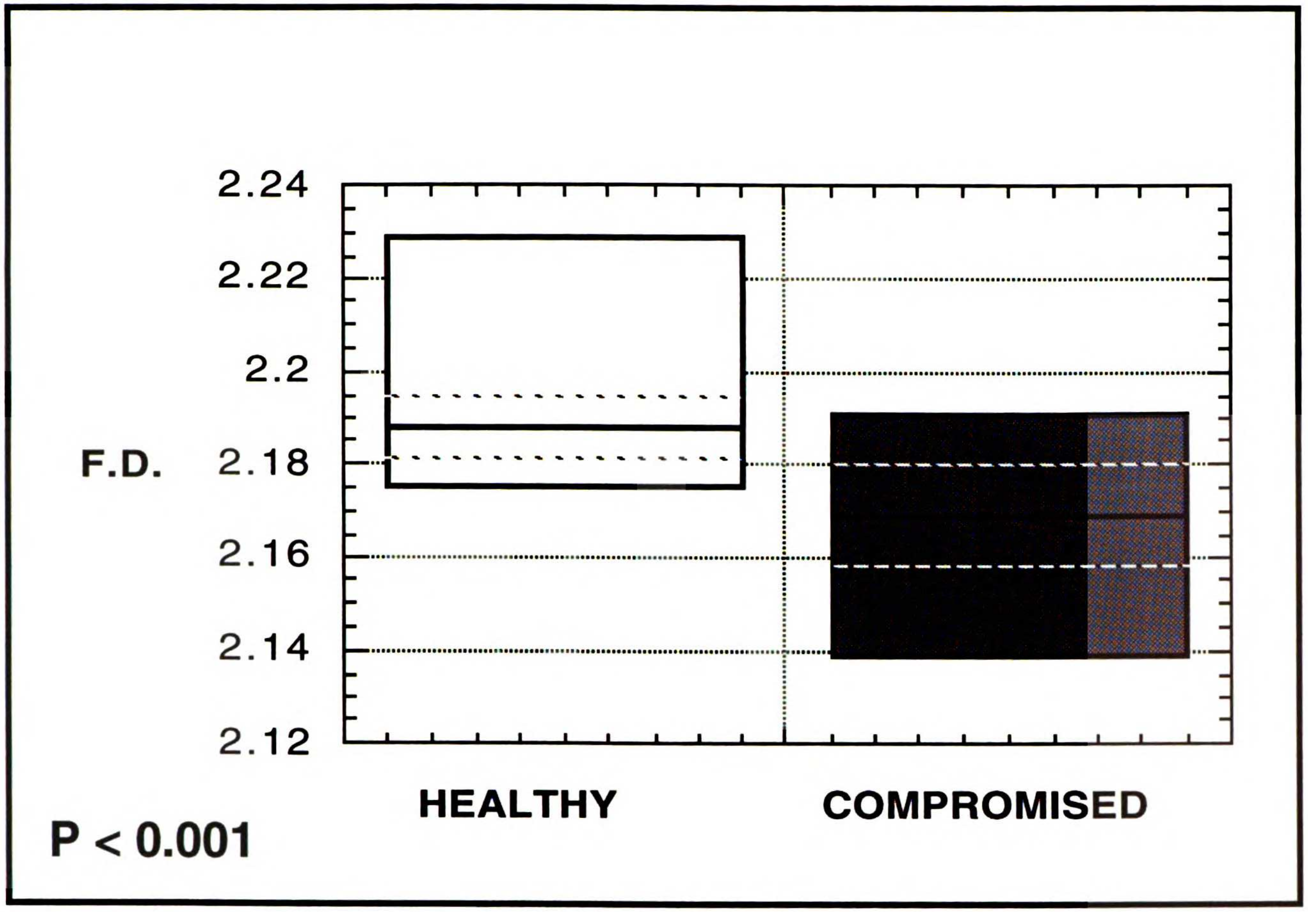
To assess longitudinal changes in bone quality, the analysis was applied in seven subjects whose periodontal status had deteriorated over time and for whom serial radiographs ranging over a period of 3 years minimum to 10 years maximum were available (Figure 15). The plot on the right illustrates the difference in fractal dimension between the region of interest from the more recent periapical as compared with the original baseline value in a given subject. Note that as the disease progresses there is a decrease in fractal dimension. This decrease in fractal dimension is statistically significant ($p<0.05$).

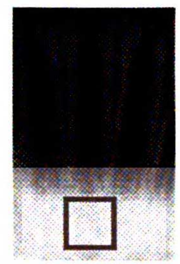
Finally, radiographs of subjects who had their teeth extracted were analyzed and their fractal dimensions determined (Figure 16). The plot on the right shows the difference in fractal dimension between post and pre-extraction regions of interest. Note that fractal dimension decreases in regions where teeth were lost and that this decrease in fractal dimension is statistically significant ($p<0.05$) .

HEALTHY VS. COMPROMISED



m = 2.19
S.D.= 0.012



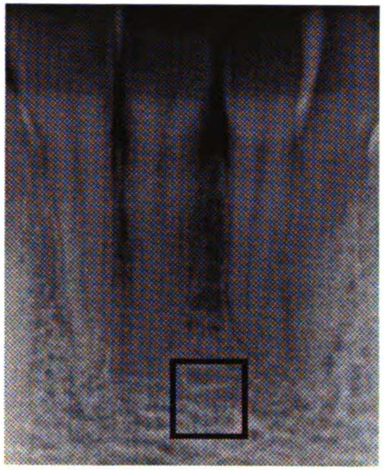


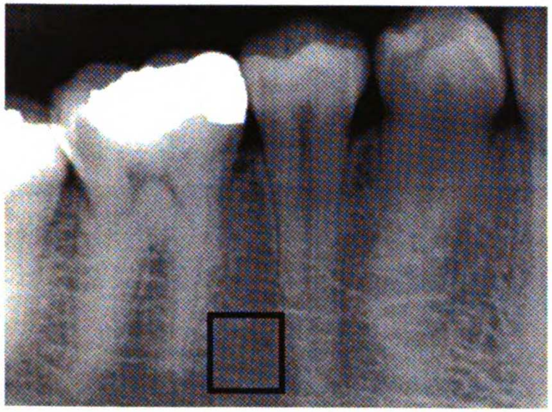
m = 2.17
S.D.= 0.014

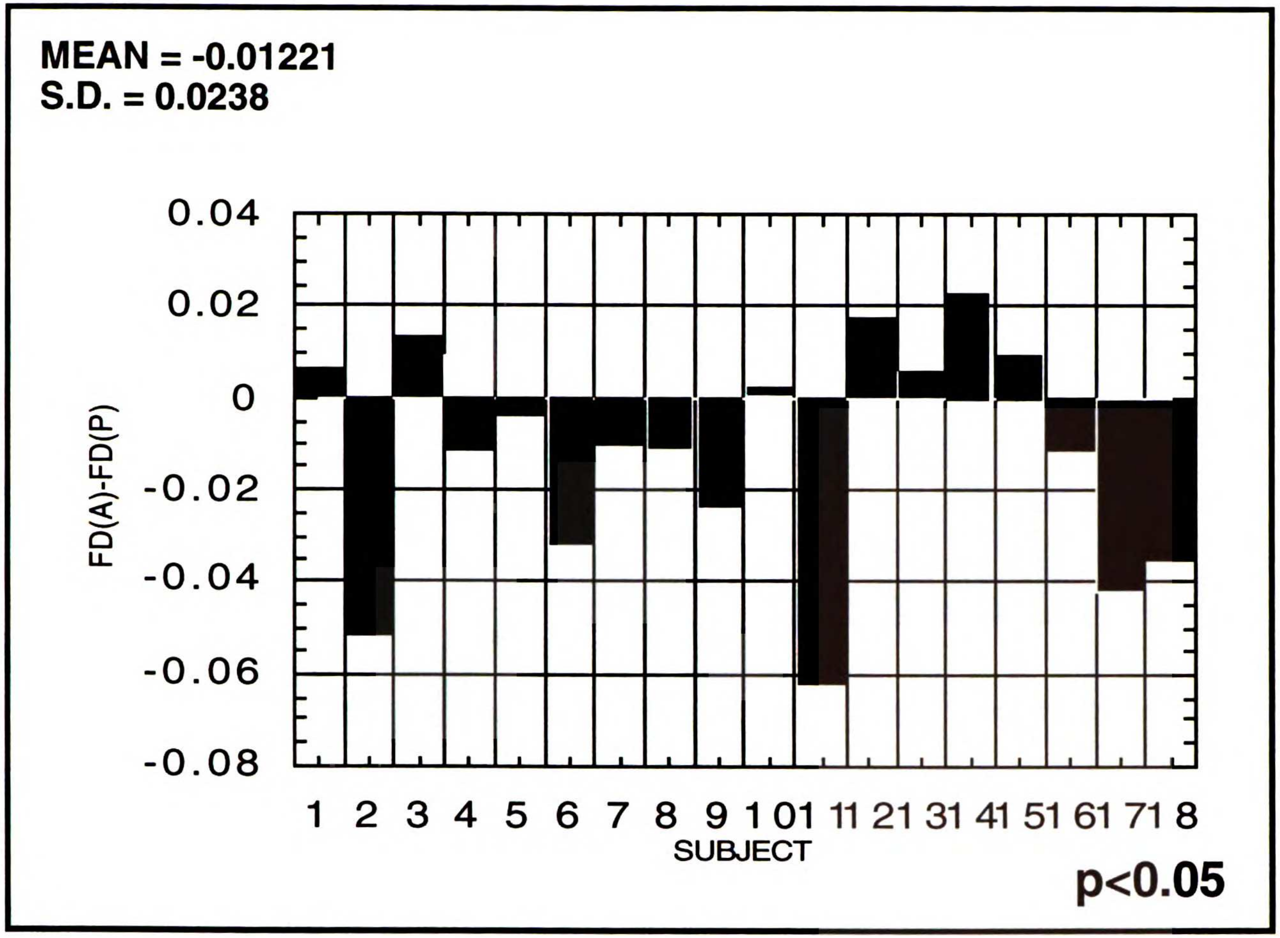
Figure 12

Figure 13

ANTERIOR vs. POSTERIOR







MAXILLA vs. MANDIBLE

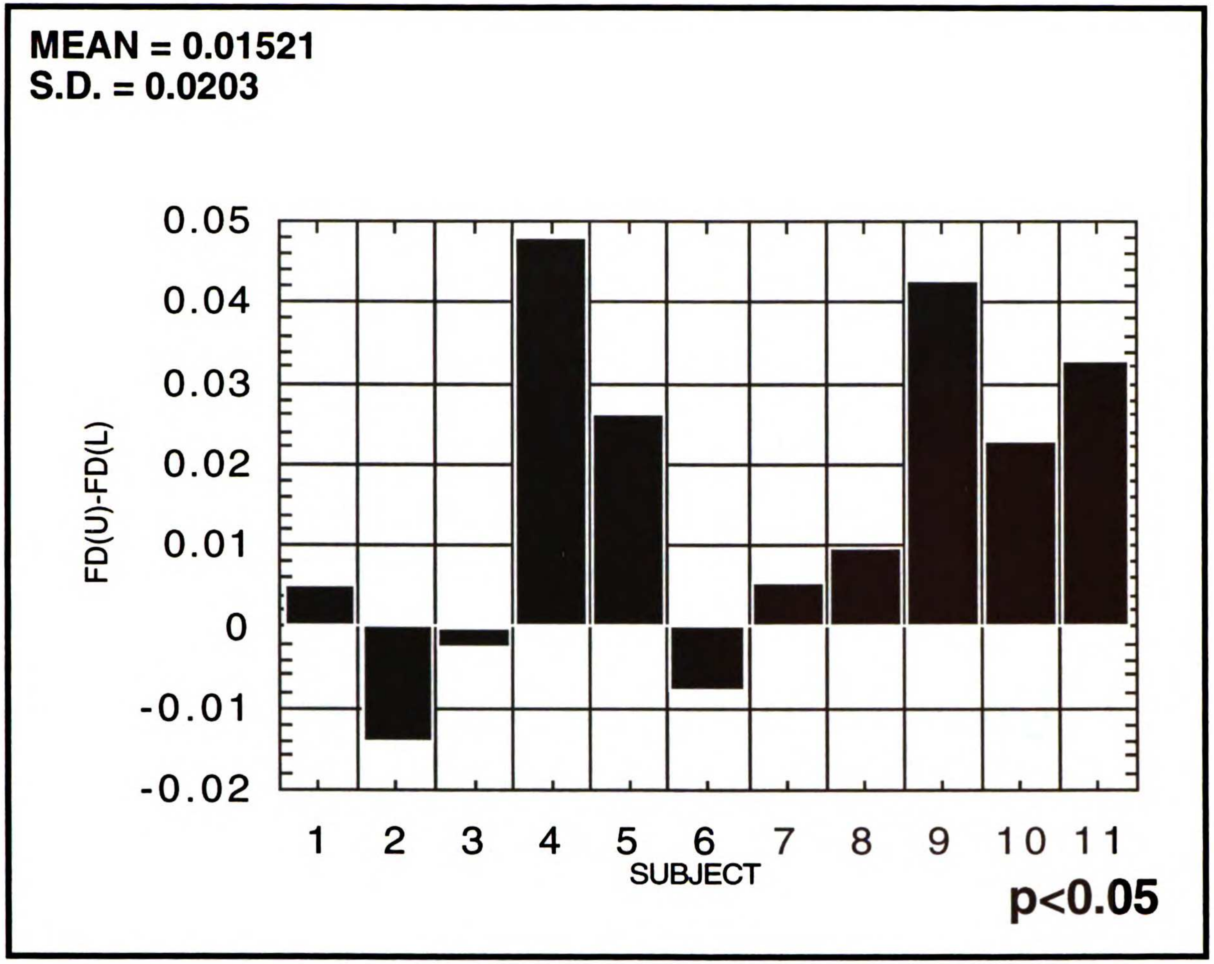
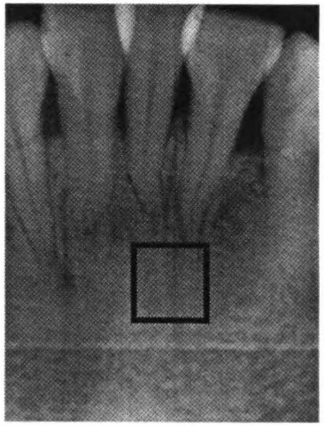
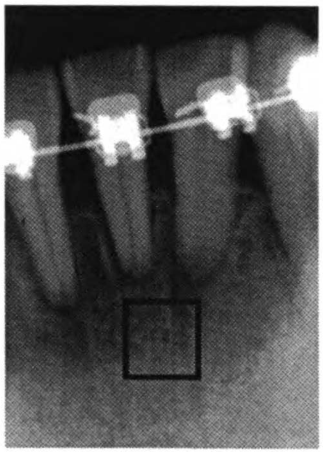


Figure 14

LONGITUDINAL CHANGE IN F.D.





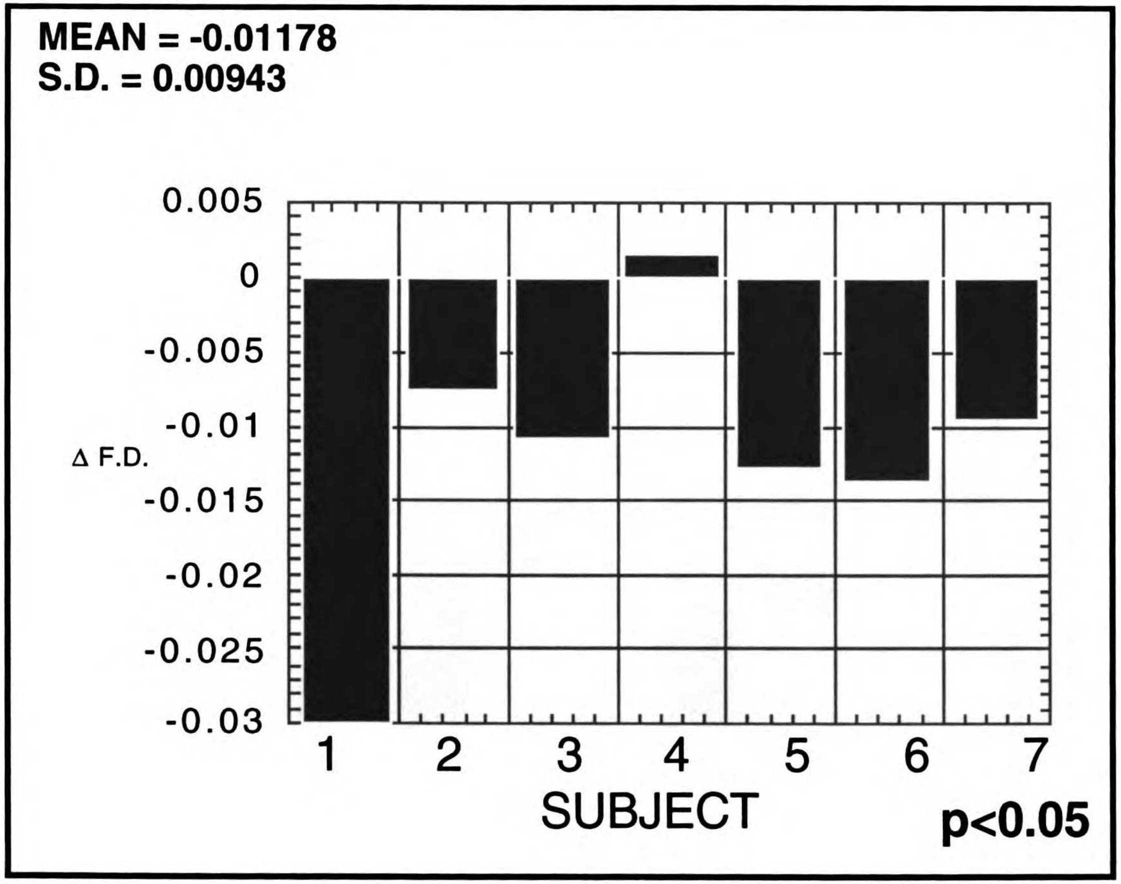
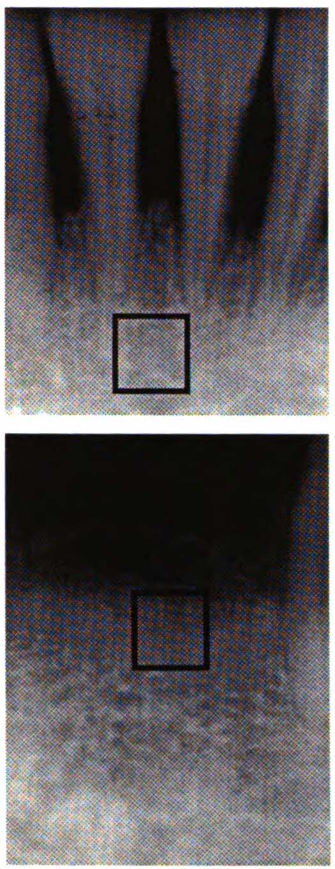


Figure 15

POST EXTRACTION CHANGES IN F.D.



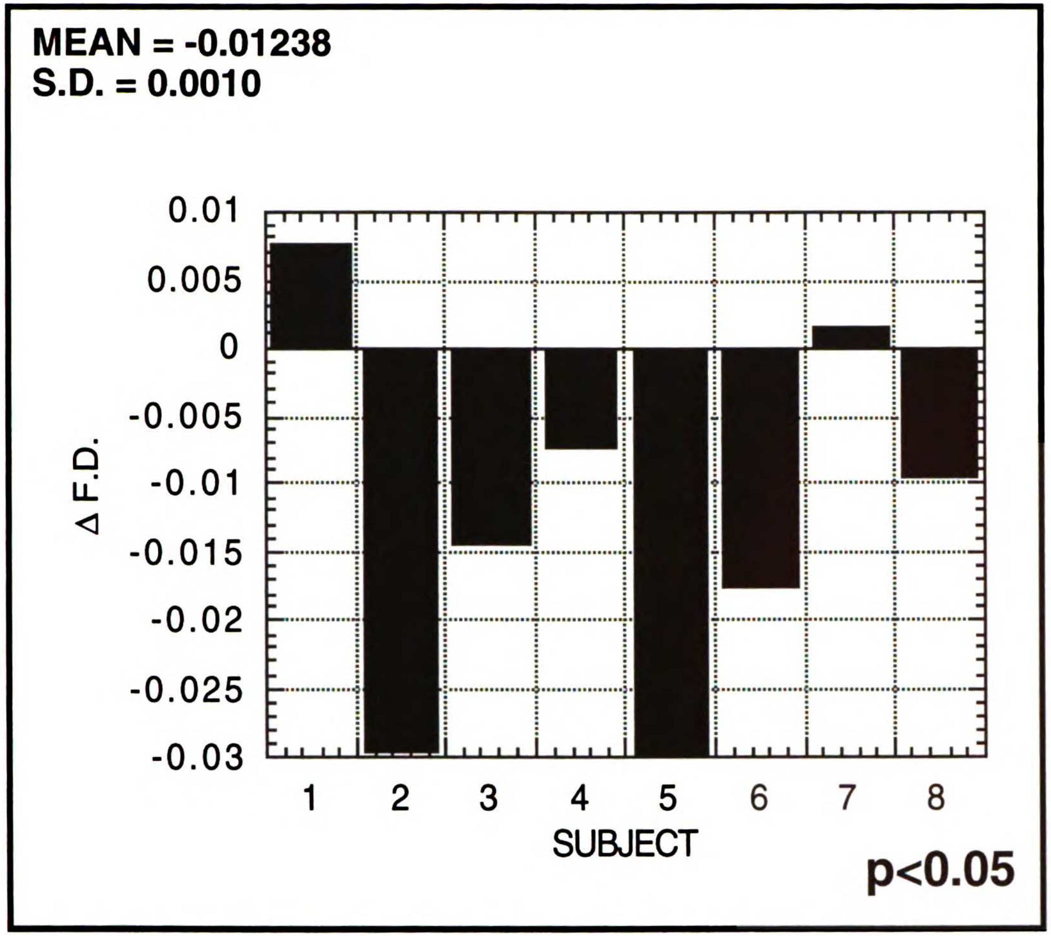


Figure 16

VI. DISCUSSION

The first phase of the study applied the fractal technique developed in this investigation to two clearly distinct groups of patients based on their skeletal status. The two groups were not only different in terms of chronological age (i.e., pre-menopausal vs. post-menopausal), but also in terms of their history of osseous pathology. The normal group presented with significantly higher spinal bone density measurements compared with the osteoporotic group, which in addition to lower QCT values, also had experienced vertebral fractures.

A statistically significant difference in fractal dimension was observed between the osteoporotic and non-osteoporotic groups (Figure 5). Osteoporotic subjects, on average, presented with a smaller fractal dimension compared with that of the normal subjects. This is not in agreement with the findings reported by several investigators (42,45,48). However, as Table 2 illustrates, there is no consensus on the relationship between bone density or architecture and fractal dimension. However, recent publications (47,49) are attempting to explain why some studies have reported an increase in fractal dimension with loss of bone density, which seems to be at odds with the theoretical definition of fractal dimension. As mentioned in the Introduction, fractal dimension generally increases with an increase in complexity of structures. With disease, the trabecular network of bone within a selected region of interest is disturbed and the region appears more diffuse and sparse. Therefore, a region of interest taken from a healthy site should appear more complex than that of a diseased site because the intact trabecular pattern of healthy bone results in greater complexity. This notion agrees with our findings from the first phase of the study. Fractal dimensions obtained from regions of interest taken from normal subjects were higher in value as compared with those obtained from the osteoporotic subjects.

Comparison of spinal bone mineral density, as measured by QCT, with fractal dimension (a standard method to differentiate between the normal and osteoporotic subjects) is also shown in Figure 5. The data in Figure 6 also suggests that there appears to be a modest correlation between the two techniques. In addition, a statistical comparison between these two techniques using Receiver Operating Characteristic (ROC) analysis to estimate the power of fracture prediction is illustrated in Figure 7. Note that spinal bone density as measured by QCT, is more powerful in discriminating between the two groups ($p<0.0001$ vs. $p<0.0042$). This, however, should not be surprising because the osteoporotic subjects in this study had previously experienced vertebral fracture, and spinal bone mineral density is much more site specific (relative to pathology) than fractal dimension of the wrist radiographs. On the other hand, it is likely that osteoporosis affects skeleton even in areas remote from the site of fracture and therefore it is encouraging to see that a non-invasive method such as fractal analysis of wrist images may be sensitive enough to differentiate between normal and osteoporotic patients.

The effect of regional variations on fractal dimension depends on whether the sites examined are side by side (i.e., medio-lateral) or proximal and distal relative to the joint surface. The absence of difference in fractal dimension between the medial and lateral subregions suggests that the fractal dimension does not change as long as the region of interest stays at the same level with respect to the joint line. A similar lack of difference was also found when comparing the right and the left wrists of a given subject as long as regions of interests from both wrists were at about the same distance from their corresponding joint line. In contrast, the fractal dimension decreased as the region of interest was moved proximally along the radial shaft i.e., further away from the joint line. This is consistent with the fact that there is less textural variation due to a progressively decreasing amount of trabecular bone as the region of interest moves proximally along the radial shaft. This loss in trabecular bone is paralleled by an increase in cortical bone.

In the second phase of the study, the protocol implemented in phase I, was adapted to the fractal analysis of dental periapical radiographs. Periapicals of two clearly separated population of dental patients were evaluated based on the degree of their oral bone loss probably associated with either current or past periodontitis or residual ridge resorption or osteoporosis. However, for the purpose of this study, the reason for oral bone loss is immaterial. Any of these factors alone or in combination could have contributed to the bone loss. Fractal analysis does not provide information on the etiology of the observed change in the bone quality, it only highlights textural variations that arise when bone quality degrades as a result of various disease processes.

Comparison of healthy vs. the periodontally compromised patients, was based on the fractal analysis of lower incisor periapical radiographs. In other words, all patients who fell in the category of periodontally compromised, had experienced bone loss in the lower incisor region. The reason for choosing this region of the dental arch for comparative analysis was because it contains ample amount of dentoalveolar bone and lacks other interfering anatomical structures. In their study of fractal dimension from peridental alveolar bone, Ruttiman et al. (42) chose periapicals from the maxillary premolar-molar region. This region is where periodontal disease is most prevalent. However, because of the presence of the maxillary sinus which is almost always evident in these periapicals and the rather small amount of visible interradicular dentoalveolar bone, it is difficult to select a reliable region of interest which would be devoid of such impositions. Similarly, the lower premolar/molar region presents with the problem of long molar roots and the presence of the mandibular canal which is difficult to avoid in selecting the region of interest.

As shown in Figure 12, fractal analysis was successful in discriminating between healthy and periodontally compromised subjects. The latter group of subjects demonstrated a lower fractal dimension compared with the former. This finding is consistent with the results in the first phase of our study, where osteoporotic subjects demonstrated a lower fractal dimension when compared with normal. Therefore, we conclude that using the fractal technique, as applied in this study, diminution in bone quality results in a decrease in fractal dimension.

The effect of regional variations on fractal dimension was assessed on both an intra- and inter-arch bases. As illustrated in Figure 13, as the site of analysis was moved posteriorly along the mandible, the fractal dimension increased. This result is consistent with Ruttiman et al.'s (42) in-vitro findings, which showed the fractal dimension to be higher in the posterior region of the mandible as compared with the anterior. Furthermore, when posterior region of the maxilla was compared with the posterior region of the mandible, the fractal dimension was found to be higher in the maxilla (Figure 14). Histologically speaking, there is a greater content of cortical bone in the mandible than the maxilla which is composed mainly of trabecular bone. The higher fractal dimension in the maxilla is therefore due to its greater content of trabecular bone and hence larger textural variations. It is also possible that because of the proximity to highly cortical structures, such as the genial tubercle and menton, the composition of bone in the lower incisor area is richer in cortical bone (i.e., has less trabecular bone). This might explain why the fractal dimension in this region is lower in comparison with the posterior region of the mandible.

The notion that a diminution in bone quality causes a decrease in fractal dimension is further supported when longitudinal disease progression and treatment induced changes are evaluated using fractal analysis. Figure 15 illustrates subjects whose oral bone status had deteriorated over time. Note that as oral bone loss continues, there appears to be a decrease in fractal dimension which is once again due to a decrease in complexity of the osseous texture; probably the result of a disruption in the trabecular bone network. The same explanation holds true in the case of patients who had their teeth extracted due to disease or the initiation of orthodontic treatment. As Figure 16 illustrates, the post-extraction decrease in fractal dimension suggests that the residual ridge has experienced structural weakening due to loss of trabecular bone subsequent to tooth loss. In the case of patients who have lost a tooth and the extraction site is left untreated, the residual ridge resorption and a corresponding decrease in fractal dimension is expected to continue. In patients whose extraction space will be closed orthodontically, one would expect the bone to reorganize and the extraction site to restrengthen structurally. Whether or not the fractal dimension of bone in the region of interest after space closure will be lower or higher than the same region prior to tooth extraction requires further investigation.

It is important to recognize the several limitations associated with the present study that require refinement before any future work is undertaken. The sample sizes have been relatively small, and the two groups were vastly separated in terms of their QCT status in the first phase of the study and their oral bone status in the second phase of the study. In most cases, a diminution in bone quality was radiographically visible in the compromised group. For a new diagnostic modality to have clinical value, it should offer advantages over existing clinical tools and, in this instance, should certainly detect changes in bone quality that are not easily observed on visual inspection. Therefore, fractal analysis needs to be performed on more borderline cases and in groups that are not so vastly different at the time of analysis.

In addition to the above, the two groups in the second phase were not matched for age, sex, or presence of other systemic diseases or medications which might have affected bone quality. Thus, it is important in future studies to eliminate complicating variables, and to better assess the correlation between disease and age as determined by fractal dimension. As mentioned previously, there are several fractal techniques that are available but only one technique i.e., the power spectrum technique, was applied in this study. Whether this technique is superior for this type of analysis, or whether other fractal techniques would yield the same or better results requires further investigation. Because the present data are retrospective, there was no opportunity for standardization on image acquisition including: projection angulation, KVP and exposure settings. Finally, inherent digitization factors and noise associated with the analysis need to be better understood and further refined. Currently, some of these issues are being investigated.

VII. CONCLUSIONS

From the first phase of the study, the following may be concluded:

• In a small, well separated group of subjects, normal and osteoporotic, establishment of the fractal dimension based upon radiographs of trabecular bone structure discriminates between the two groups.

• Fractal dimension of trabecular bone does not vary significantly between the left and right wrist or the medial and lateral sides of the wrist at the same level with respect to the joint line.

• Fractal dimension of trabecular bone is higher closer to the joint line than further away from the joint line (i.e., proximally along the radial shaft).

From the second phase of the study, the following is concluded:

• In a small, well separated group of subjects, healthy and periodontally compromised, establishment of the fractal dimension based upon radiographs of trabecular bone structure showed a difference between the two groups.

• Fractal dimension of trabecular bone varies significantly between the anterior and posterior regions of the jaw.

• Fractal dimension of trabecular bone varies significantly between the two jaws, and is higher in the maxilla than in the mandible.

• Changes in trabecular structure, due to the progression of disease or the treatment induced, may be detected by applying fractal analysis.

VIII. FUTURE OUTLOOK

In light of what has already been discussed in this thesis, it is clear that in order for fractal analysis to be adopted as a diagnostic modality, it should demonstrate its merit in long term prospective clinical studies. To this end, wrist and dental radiographs need to be analyzed prospectively under a standardized set of conditions which attempt to minimize error in data collection.

The recent surge of interest in identifying links between systemic and local factors associated with oral bone loss, is a strong justification for future fractal studies. One such study may be a comparative fractal analysis of periapicals of normal and osteoporotic subjects, whose wrist radiographs had been analyzed in this study, in order to determine 1) whether periapicals may be used to differentiate between the two groups and 2) whether osteoporotic patients, on average, experience more oral bone loss.

The impact of technical variations on the fractal dimension requires a great deal of investigation. As mentioned previously, these include (1) image acquisition factors such as projection angulation, KVP and exposure settings, (2) differences between radiographs using different imaging systems, (3) digitization factors such as inherent noise, and (4) the need for post-digitization processing and filtering for image enhancement. From the standpoint of reproducibility and reliability of the technique, intra and inter-operator selection of the region of interests from the radiographs, and its effect on the fractal dimension needs to be explored.

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