Bone-composition imaging using coherent-scatter computed tomography: Assessing bone health beyond bone mineral density

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Quantitative analysis of bone composition is necessary for the accurate diagnosis and monitoring of metabolic bone diseases. Accurate assessment of the bone mineralization state is the first requirement for a comprehensive analysis. In diagnostic imaging, x-ray coherent scatter depends upon the molecular structure of tissues. Coherent-scatter computed tomography (CSCT) exploits this feature to identify tissue types in composite biological specimens. We have used CSCT to map the distributions of tissues relevant to bone disease (fat, soft tissue, collagen, and mineral) within bone-tissue phantoms and an excised cadaveric bone sample. Using a purpose-built scanner, we have measured hydroxyapatite (bone mineral) concentrations based on coherent-scatter patterns from a series of samples with varying hydroxyapatite content. The measured scatter intensity is proportional to mineral density in true g/cm³. Repeated measurements of the hydroxyapatite concentration in each sample were within, at most, 2% of each other, revealing an excellent precision in determining hydroxyapatite concentration. All measurements were also found to be accurate to within 3% of the known values. Phantoms simulating normal, over-, and under-mineralized bone were created by mixing known masses of pure collagen and hydroxyapatite. An analysis of the composite scatter patterns gave the density of each material. For each composite, the densities were within 2% of the known values. Collagen and hydroxyapatite concentrations were also examined in a bone-mimicking phantom, incorporating other bone constituents (fat, soft tissue). Tomographic maps of the coherent-scatter properties of each specimen were reconstructed, from which material-specific images were generated. Each tissue was clearly distinguished and the collagen-mineral ratio determined from this phantom was also within 2% of the known value. Existing bone analysis techniques cannot determine the collagen-mineral ratio in intact specimens. Finally, to demonstrate the in situ potential of this technique, the mineralization state of an excised normal cadaveric radius was examined. The average collagen-mineral ratio of the cortical bone derived from material-specific images of the radius was 0.53±0.04, which is in agreement with the expected value of 0.55 for healthy bones. © 2006 American Association of Physicists in Medicine.

Key words: coherent scatter, computed tomography, tissue composition, mineralization, bone mineral density (BMD), metabolic bone disease

I. INTRODUCTION

Bones are comprised of hydroxyapatite (bone mineral (BM)) crystals embedded in a collagenous matrix.¹ The association of BM and collagen in this structural arrangement provides bones with the strength and rigidity needed for mechanical skeletal functions. BM also acts as the body’s calcium and phosphorous mineral reservoir. Metabolic bone disorders form a group of diseases that affect either bone structure, as in osteoporosis, or mineral metabolism, as in osteomalacia.² These effects are not independent. Thus, as an intrinsic link between structure and function, bone mineral density (BMD) is an important metric of skeletal health.³ Several radiographic techniques have been developed to measure BMD in vivo, including dual-energy x-ray absorptiometry (DXA) and quantitative computed tomography (QCT). These techniques are routinely used to diagnose and monitor osteoporosis.³⁵

Despite their clinical utility, BMD measurements suffer two major limitations. First, bulk mineral content alone does not fully describe bone strength. Fracture risk is also influenced by bone structure (both gross bone size and trabecular microarchitecture) and the mineralization state of the osteoid
New, nondestructive techniques are being developed to provide insight into bone structure. Quantitative ultrasound (QUS) has the ability to deduce a bone’s mechanical properties through its architecture-, elasticity-, and BMD-dependent measurements. Alternatively, high-resolution computed tomography (CT) and magnetic resonance imaging (MRI) can provide structural information about the trabecular network throughout the bone marrow region in images acquired with an in-plane resolution of 150 μm or less.

Despite recent advances in imaging technology, histomorphometry or ashing of biopsy samples remains the standard for assessing the structure and mineralization state of bone. In histomorphometry, a biopsy specimen is preserved in 70% ethanol, then dehydrated, and defatted by processing through a series of ethanol and acetone washes. The specimen is then embedded in partially polymerized methyl methacrylate, microtomed into sections 4 to 5 μm thick, and mounted on slides. Following appropriate staining, specimens are examined using light or fluorescence microscopy. Histomorphometric analysis can report trabecular bone volume, trabecular number, osteoblast, or osteoclast surface (the percentage of the bone’s surface occupied by bone cells), mineralization lag time (the time between the creation of the osteoid surface and its mineralization), osteoid surface, and osteoid seam thickness. The last three characteristics are used to assess a bone’s mineralization state. A gross measure of the osteoid-to-mineral ratio can be obtained by ashing dry bone samples and comparing the residual mineral mass to the mass of the original sample. Unfortunately, histomorphometry requires a highly experienced operator to prevent the accruing excessive artifacts caused by bone dust from microtoming or crushing of the specimen during handling. It also remains unsuitable for in situ investigations due to the requirement for excised bone samples in analysis. Currently, no clinical, nondestructive method has been devised to assess the osteoid-to-mineral ratio or map its distribution.

As well as providing incomplete fracture risk information, the utility of BMD measurements is equally limited due to the impossibility of making these measurements in isolation. Matrix collagen, surrounding soft tissue, and fat, and haemopoetic tissue in the marrow canal all confound BMD measurements. Existing x-ray techniques are effective when the collagen-hydroxyapatite ratio within the bone tissue remains constant, as is assumed for osteoporosis. There is, however, evidence that mineralization ratios change naturally with age, or with disease progression and treatment in osteoporosis. Mineral-collagen imbalances are also a hallmark of other metabolic bone diseases, such as osteomalacia. These changes can lead to erroneous BMD measurements. Normal bone consists of 58% hydroxyapatite, 32% collagen, and 10% water by mass, with a density of 1.92 g/cm³. Thus, the normal collagen and hydroxyapatite concentrations are 0.61 and 1.11 g/cm³, respectively, while the collagen-hydroxyapatite ratio is 0.55. In osteomalacia, bone consists of only 49% hydroxyapatite, 32% collagen, and 19% water, with a corresponding decrease in density to 1.72 g/cm³. The concentrations of collagen and mineral in this disease state are 0.55 and 0.84 g/cm³, with a ratio of 0.65. Thus, any technique aspiring to distinguish between normal and osteomalacic bone must be sensitive to a 24% (0.27 g/cm³) decrease in hydroxyapatite concentration or an 18% increase in the collagen-hydroxyapatite ratio. As such, a technique that provides quantitative material-specific images showing the distribution of bone mineral content independent of all other tissues present may be an important tool for understanding the disease processes in bone. Coherent-scatter computed tomography (CSCT) is being developed to provide information of this nature.

X-ray coherent scatter is sensitive to the molecular structure of different tissue types, or scatterers. Measurements of coherent-scatter properties in bone samples can therefore provide a basis for analyzing bone composition. CSCT applies imaging principles to crystallographic techniques that have been used for nearly a century in the analysis of material composition. First demonstrated by Harding et al., coherent-scatter imaging is based on the low-angle (< ~ 10°) coherent scatter from a sample. The angular distribution of this scatter is described by the differential coherent-scatter cross section per atom:}

\[
\frac{d\sigma_{coh}}{d\Omega}(\theta) = \frac{r_e^2}{2} \left(1 + \cos^2 \theta \right) F(x, Z)^2,
\]

where \( r_e \) is the classical electron radius, \( x = (1/\lambda)\sin(\theta/2) \) is the momentum transfer argument, and \( F(x, Z) \) is the coherent-scatter form factor. This is equal to the Fourier transform of the electron charge distribution and is, therefore, a characteristic of the material. In general, different tissue types are organized in regions with dimensions much greater than x-ray wavelengths, resulting in no interference between x rays scattered from different tissues within a composite. Therefore, the cross section of a composite material is simply a linear sum of the cross sections of its components, weighted by their concentrations. The composition of a conglomerate can often be determined from an analysis of measured coherent scatter. Thus far, all coherent scatter-based bone analysis techniques have been aimed at providing a more accurate measurement of BMD than attenuation-based clinical techniques. Coherent-scatter signals can, however, provide more tissue-specific information. To date, the simultaneous measurement of collagen and hydroxyapatite in intact specimens has not been explored.

In this study we demonstrate that the coherent-scatter signatures from bone constituents (hydroxyapatite, collagen, water (soft tissue), and fat) exhibit characteristic features. Accordingly, they are used to identify tissue composition and to produce material-specific maps of tissue concentrations, in true g/cm³, in both bone-mimicking phantoms and in intact bone specimens. We also present an evaluation of quantitative coherent-scatter analysis, focusing on the determination of hydroxyapatite and collagen concentrations. The precision and accuracy with which hydroxyapatite concentration can be measured were assessed in hydroxyapatite-embedded acrylic phantoms. Varying proportions of collagen and hydroxyapatite were subsequently mixed to explore mineraliza-
tion ratio measurements in a phantom. The potential of this technique to determine collagen-hydroxyapatite ratios throughout tomographic slices of more complicated samples (bone-mimicking phantom and excised cadaveric radius) was evaluated from their associated material-specific images.

II. MATERIALS AND METHODS

In this section, we describe the techniques required to provide an assessment of bone composition via CSCT and also outline the steps required to demonstrate the technique’s precision and accuracy in quantifying components relevant to bone disease. Descriptions of the instrumentation, as well as the data processing techniques used to create material-specific tomographic images from a series of scatter patterns are first presented to provide a foundation for subsequent bone composition analyses. With these standards established, we then describe the simultaneous mapping of all four bone components via CSCT in a bone-tissue phantom and an excised cadaveric bone sample. To validate the quantitative composition information provided within these maps, we assess the accuracy and precision of the coherent-scatter analysis technique through measurements of hydroxyapatite and collagen, mixed in known concentrations, within phantoms. These results will indicate whether or not coherent scatter-based measurements can detect changes in bone composition with the sensitivity required to usefully identify bone disease states. Finally, we extract the ratio of collagen to hydroxyapatite from CSCT material-specific images of the bone phantom and cadaveric bone sample analyzed initially. The ability to assess this ratio and its distribution allows us to describe bone structure as well as the state of mineralization of its collagen matrix, thus providing a good indicator of bone integrity.

A. Instrumentation

CSCT has been implemented using the diagnostic x-ray image intensifier- (XRII-) based system illustrated in Fig. 1. This scanner has been presented in detail previously.37,38 As described by Westmore et al.,37 the output of a diagnostic x-ray source (tungsten anode, 70 kVp, 0.6 mm focal spot) is filtered by 0.30 g/cm² gadolinium to reduce the spectral width [from 27% root-mean-square (rms) width to 14% rms width], thereby improving the angular resolution of the measured coherent-scatter patterns. Filtration reduces the x-ray intensity to 17% and produces a beam with a mean energy of 43 keV. A 1 mm² square pencil beam is produced using a triple-aperture, parallel-plate collimator. This arrangement minimizes the likelihood that scatter arising from collimator elements will reach the detector.

Samples are mounted on a translate-rotate stage situated in front of the collimator (source-object distance=25 cm, object-detector distance=30 cm33). Data are collected either as projection measurements, with a stationary specimen, or as a first-generation CT dataset. The transmitted primary beam is blocked by a 5 mm thick lead disk (Fig. 1), while the coherent scatter is detected by the 31 cm diameter XRII (Thales Electron Devices Model TH9432QXH304VR, France) coupled to a charge-coupled device (CCD) camera (640×480, 0.03 cm pixels, Cohu, Poway) with a frame capture rate of 30 frames per s. CT data are collected either from short, stationary exposures between translation steps, or while the specimen is translated continuously during a 2 to 5 s exposure. As in first generation CT, the specimen is rotated between each translation dataset. In the case of continuous translation, each frame collected is a projection measurement of the coherent-scatter pattern for the corresponding translation position, analogous to the transmitted x-ray signal collected at each translation-rotation position in first-generation CT. Specimen translation and video acquisition are synchronous with an external video signal generator. Each frame is collected with a translation step-size of 0.5 mm. The specimen position for each video field is known with an accuracy of 0.03 mm.38 Collecting images while the specimen is moving can introduce motion blur of 1/30 s. This is not detrimental to the coherent-scatter-based images presented here, as they do not inherently contain high spatial frequencies. This modification of first generation CT was introduced to reduce acquisition time.

Three silicon photodiodes are mounted in the beam line to monitor tube fluctuations, transmitted x-ray intensity and temporal lag in the XRII phosphors (M0, M1, M2, Fig. 1).38 Due to the low quantum efficiency of Si in the x-ray energy range, the first two diodes use a scintillating screen [Kodak Lanex Fine (Gd₂O₂S)] to convert the x-ray photons into visible light. Diodes were selected to have a maximum sensitivity to the output photon wavelength (λ=545 nm). Additionally, lead glass is mounted between the screen and diode to offer protection against radiation damage.
B. Imaging low-angle scatter

The data collected with the XRII consist of scatter patterns, which are images representative of the coherent-scatter cross section. The reconstruction of tomographic images from these patterns was first presented by Harding et al.\textsuperscript{27} and has been refined by our group.\textsuperscript{38,39} The process is briefly described here. In a tomographic acquisition, scatter patterns from a specimen are acquired at a series of translation steps for each of the angular views spanning \(180^\circ\).\textsuperscript{38} The patterns are corrected for self-attenuation within the object (using M1, Fig. 1) and for temporal lag in the XRII phosphors (using M2, Fig. 1).\textsuperscript{38}

Most polycrystalline and amorphous materials produce scatter patterns consisting of concentric rings of varying intensity.\textsuperscript{28} These patterns provide measures of coherent-scatter intensity, integrated along the beam path through the object. Information is extracted from each of the patterns acquired over \(180^\circ\) by segmenting them into a series of 100 concentric annuli (width=0.6 mm) and integrating the signal within each. The integrated data are then normalized to both the solid angle subtended by the annulus at the object and the number of transmitted photons for that beam path (to correct for self-attenuation).\textsuperscript{38,39} This can be expressed as\textsuperscript{38} (Eq. 2)

\[
\frac{N_i}{N_{ij} \Delta \Omega_i} = \int n_0(l) \cdot \frac{d \sigma_{\text{col}}[l,x(\theta_j)]}{d \Omega} dl = \int \gamma[l,x(\theta_j)] dl, \quad (2)
\]

where \(N_i\) is the integrated number of photons scattered into the \(i\)th annulus, \(N_{ij}\) is the number of transmitted photons for the \(j\)th ray path (for each of \(j\) rays we obtain a scatter pattern that is segmented into \(i\) annuli), \(\Delta \Omega_i\) is the solid angle subtended by the annulus, \(l\) is the position along the path through the object, \(n_0(l)\) is the volumetric number density of scattering centers at \(l (\text{cm}^{-3})\), \(d \sigma_{\text{col}}[l,x(\theta_j)]/d \Omega\) is the differential coherent-scatter cross section per scattering center per solid angle, and \(x(\theta)\) is the momentum transfer argument for scatter angle \(\theta\). The quantity \(\gamma[l,x(\theta_j)]\) is defined as the differential linear coherent-scatter coefficient per unit solid angle (cm\(^{-1}\) sr\(^{-1}\)).\textsuperscript{38,39} Processing a scatter pattern in this fashion yields a curve displaying the variation with an angle of measured scatter intensity (Fig. 2). From Eq. (2), this intensity is proportional to the number of scattering centers, \(n_0(l)\), interrogated by the beam, while the shape of the curve is defined by the differential coherent-scatter cross section. For any particular ray path, \(j\), \(n_0(l)\) is a constant. Thus, the curves determined by analyzing the scatter patterns, as described above, are proportional to the differential coherent-scatter cross section and are referred to as cross sections in this paper for the sake of brevity and consistency with the literature.\textsuperscript{37–39}

The line integral of \(\gamma[l,x(\theta_j)]\), described in Eq. (2), is analogous to the line integral of the linear attenuation coefficient in conventional CT. Thus, by measuring \(N_i/N_{ij} \Delta \Omega_i\), we can reconstruct \(\gamma[l,x(\theta_j)]\).\textsuperscript{38,39} Since each acquired pattern is segmented into symmetric annuli, indexed by the subscript \(i\), an image will be reconstructed for each annulus, with the \(i\)th image corresponding to the signal detected in the \(i\)th annulus of patterns in each reconstructed pixel. Thus, in a single acquisition, a complete CT dataset is collected for each scatter angle. Tomographic images of \(\gamma[l,x(\theta_j)]\), displaying the scatter intensity at each scatter angle throughout an object (CSCT images),\textsuperscript{38,39} are then reconstructed onto a grid with 0.5 mm \(\times\) 0.5 mm pixels using filtered backprojection.\textsuperscript{41} The measured transmitted primary intensity is reconstructed to map the radiographic density of the object.

C. Material-specific image generation

CSCT images are used to determine the tissue composition in each voxel. Material calibration for this study was accomplished using samples of chemically pure collagen, fat, hydroxyapatite, water (soft tissue), and poly(methyl methacrylate) (PMMA) of known density (Table I). The fat sample was a solid, rendered beef fat. The type I collagen source was a purified, flaked bovine Achilles tendon and the hydroxyapatite was a microcrystalline powder (Sigma-Aldrich Co., St. Louis, MO). A solid block of PMMA and a sample of water formed the final basis samples.

The collagen, hydroxyapatite, fat, and water samples were all placed in thin walled acrylic tubes with an outer diameter and length of 1 cm. The ends of the sample holders were sealed with acetate sheets (thickness=75 \(\mu\)m). The specimens were all placed coaxial to the beam so that the scatter contribution from the container would be entirely due to the acetate end walls. Measurements taken with an empty tube

<table>
<thead>
<tr>
<th>Material</th>
<th>PMMA</th>
<th>Collagen</th>
<th>Hydroxyapatite</th>
<th>Fat</th>
<th>Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>g/cm(^3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basis density</td>
<td>1.18</td>
<td>0.348±0.0008</td>
<td>0.407±0.009</td>
<td>0.92±0.01</td>
<td>1.00</td>
</tr>
<tr>
<td>True density</td>
<td>1.18</td>
<td>1.3</td>
<td>~3.1</td>
<td>0.91</td>
<td>1.00</td>
</tr>
</tbody>
</table>
and decomposed into linear combinations of the pure material basis functions using a non-negative least squares (NNLS) algorithm. The resulting fit parameters give the proportion, \( m_k \), of each basis material present in each voxel as a fraction of the densities of the pure material samples:

\[ m_k = \frac{\rho_k}{\rho_k^*}, \]

where \( \rho_k \) is the mass density of material \( k \) in the pixel under consideration and \( \rho_k^* \) is the mass density of basis sample \( k \). This is determined by minimizing

\[ \chi^2 = \sum_i \left( \sum_k m_k \gamma_i^k[x(\theta_i)] - \gamma_i[I(x, \theta_i)] \right)^2, \]

over all scatter angles, \( i \), and materials, \( k \).

The fit parameters, \( m_k \), for each pixel are assigned to the corresponding pixel in each of \( k \) images. The individual images are then scaled by the appropriate basis-sample density. Thus, an independent map of the density, in g/cm\(^3\), of each component is constructed. Contrast in these material-specific images depends solely on the mass concentration of each particular material.

This material analysis can also be performed on scatter patterns acquired in the same manner as the basis functions, that is, from a single beam path through the object of interest. The unknown cross section is extracted as described, and the material fitting is performed on that cross section. This mode of measurement is analogous to projection measurements in conventional radiography. This provides an opportunity to extract gross measures of bone composition without performing a CT scan.

D. Material-specific images of bone tissue

1. Bone-mimicking phantom

The generation of material-specific images of bone components was first tested in a phantom where the spatial distribution, and concentration, of each tissue type was known. For CSCT, bone mimics must have the same molecular structure as the real tissue, not simply the same radiographic density. A bone-mimicking phantom for CSCT was created by embedding pure type I collagen, hydroxyapatite, fat and water (soft-tissue) in a 2 cm diameter cylinder of PMMA. Four 0.6 cm diameter cylinders were drilled into the PMMA phantom. Water, fat, hydroxyapatite, and collagen were then each placed in one of the cylinders formed in the phantom. Thus, each material is simultaneously present in an axial slice through the phantom and isolated from all other phantom materials. To prevent evaporation or leaking, each cylinder was plugged with PMMA. These plugs had the added benefit of providing pressure on the microcrystalline hydroxyapatite and flaked collagen, allowing us to achieve higher densities than in our basis samples. The collagen density was determined to be 0.74±0.01 g/cm\(^3\), while that of hydroxyapatite was 0.60±0.01 g/cm\(^3\). The densities of fat, water, and
PMMA were the same as Table I. As this phantom was designed for a tomographic study, nonuniformities in the distribution were not an issue.

For each of 64 angular views, covering a 180° CT dataset (angle increment = 2.8°), the phantom was continuously translated during a 2.1 s exposure (70 kVp, 100 mA, 0.033 s per ray, 0.3 g/cm² Gd filtration). Diffraction patterns were acquired at 64 positions during each 3.2 cm translation. CSCT images were reconstructed and material-specific images generated. Grey levels in material-specific images are concentrations, given by the fit parameters, $m_k$ [Eq. (4)], determined from NNLS analysis, scaled by the density of each pure material basis function:

$$C_k = m_k \cdot \rho'_k$$

(6)

where $C_k$ is the concentration of material $k$, $m_k$ is the fit parameter, and $\rho'_k$ is the density of the $k$th basis material. Maximum and mean density values were determined from these images. Mean values and standard deviations were determined from a 6 × 6 pixel region of interest (ROI) placed in the centre of each material distribution.

2. Cadaveric radius

As a demonstration of the potential for in situ material-specific analysis, tissue-specific maps of an excised segment of human radius (female, 56 years, 1.2 cm in width, no known bone disease). The sample had been stripped of soft tissue, dehydrated and frozen, but was otherwise unprocessed. As for the bone-mimicking phantom, scatter patterns from the human radius were acquired using a translate-rotate geometry (first-generation CT). For each of 64 angular views, 64 scatter patterns (angle increment = 2.8°, translation field of view (FOV) = 3.2 cm) were acquired during specimen translation. The acquisition technique was 70 kVp, 300 mA, 0.033 s per CT ray. An attenuation map was reconstructed, along with a series of CSCT images. Hydroxyapatite-, collagen-, fat-, and water-specific distributions were then generated.

E. Measurements of scatter patterns from projections

1. Precision and accuracy: Hydroxyapatite concentrations

The measurement of BMD is the primary clinical means of in vivo skeletal analysis. BMD, however, is a measure of physical density of bone tissue. It is not possible to distinguish between a loss of whole bone and a reduction in bone mineral based on BMD values. Accurate measures of true hydroxyapatite concentrations can, however, reveal mineral deficiencies. The precision and accuracy of coherent-scatter-based hydroxyapatite concentration measurements were evaluated using nine rods containing hydroxyapatite embedded in acrylic (CIRS Inc.). The rods varied in hydroxyapatite concentration from 0.0 to 0.400 in 0.05 g/cm³ steps. Due to the fact that microcrystalline hydroxyapatite powder is difficult to mix uniformly with acrylic, even at relatively low concentrations, it was not possible to create phantoms with greater concentrations. It should be noted that all samples of hydroxyapatite described in previous sections were not mixed with acrylic, allowing us to achieve densities greater than 0.400 g/cm³ in the bone-material phantom.

Each rod was exposed 5 times for 4 s each at 70 kVp, 320 mA (0.3 g/cm² Gd filtration), which, with the acquisition frame rate of 30 frames/s, resulted in 120 diffraction patterns from each exposure. These low-angle scatter patterns were corrected for intensifier lag and self-attenuation and then averaged. Material-specific analysis was applied to the resulting cross sections. Averages and standard deviations for each set of five exposures were determined for each rod.

2. Precision and accuracy: Collagen-hydroxyapatite ratios

A more complete picture of the relationship between bone mineral and its matrix can be derived from measures of collagen and hydroxyapatite simultaneously. Four phantoms mimicking the collagen-hydroxyapatite ratios of normal, severely under-mineralized, over-mineralized, and osteomalacic bone were created by placing known quantities of collagen (flaked bovine Achilles tendon, Sigma Chemicals) and hydroxyapatite (powder, Aldrich Chemical) into acrylic tubes with thin end windows. The samples were placed with the tube’s axis parallel to the beam axis to avoid generating any scatter in the acrylic. Each sample was interrogated 5 times (4 s, 70 kVp, 320 mA, 0.3 g/cm² Gd filtration). Material analysis was performed using basis functions from collagen and hydroxyapatite.

F. Collagen-hydroxyapatite ratios in material-specific images

1. Phantom study

The possibility of extracting accurate ratio values from tomographic images was first investigated in the bone-mimicking phantom with known concentrations of collagen and hydroxyapatite. As described, material-specific images of the bone-mimicking phantom were generated from CSCT images acquired with a computed average in-slice dose of 7 mSv, and mean density values for each phantom component were determined. The result for collagen was divided by that for hydroxyapatite to determine the collagen:hydroxyapatite ratio for the phantom.

2. Cadaveric radius

This sample consisted of cortical bone surrounding a region of fatty marrow, without any trabeculae crossing the marrow space. With a pixel size of 0.5 mm, the bone was, at most, four to five pixels in width. This made it impossible to examine a single representative ROI. Instead, ten 2 × 2-pixel ROIs were chosen from throughout the cortical bone region in both the collagen- and hydroxyapatite-specific images. The mean and standard error in the mean of the collagen:hydroxyapatite ratio was determined for each ROI to assess the performance of this technique for a biological specimen.
III. RESULTS

A. Bone-material scatter characteristics

Scatter patterns from hydroxyapatite (BM), collagen, fat, and water (soft tissue) are shown in Fig. 4. Each displays axial symmetry, characteristic of amorphous (fat, water, and collagen) and polycrystalline (hydroxyapatite) materials. The patterns are distinctive, particularly hydroxyapatite with its series of sharp rings. The bone pattern, acquired from a sample containing marrow fat and surrounded by soft tissue, shows features of each constituent tissue, as expected. The dark circle in the center of each image is the shadow cast by the beam stop. The coherent-scatter cross sections derived from each pure-material scatter pattern are displayed in Fig. 5, where the amplitude of the curves reflects the relative scattering strength, per gram, of each material. The shape of each cross section is, again, distinctive. Collagen and fat do, however, have somewhat similar cross-sections, although fat is a stronger scatterer per gram, and its cross section has a much sharper peak.

B. Tissue-specific concentration maps

1. Bone-mimicking phantom

Discriminating and quantifying tissues of interest in bone imaging was first tested on the CSCT bone-mimicking phantom. Material-specific images of the phantom are displayed in Fig. 6. The different tissue types are all distinct. The density bars in this figure represent the corresponding densities for the displayed grey-level window. The maximum densities resulting from this analysis are all within 3% of the known densities. The maxima, however, represent only one or two pixels per image. Average values from 6×6-pixel ROIs within each region are within 2% of the known densities in g/cm³, except for collagen, which is within 4% (Fig. 7). As seen in Fig. 5 and noted in the previous section, collagen has the smallest cross section for coherent scatter of all the bone tissue components considered here. This means that for equivalent amounts of collagen and hydroxyapatite, or any of the other materials, fewer photons will undergo coherent scatter in the collagen. Thus, for a given x-ray exposure, the counting statistics for coherently scattered photons arising from collagen will be poorer than for any of the other tissues. This leads us to expect a larger standard deviation for collagen (Fig. 7) than the other materials.
2. Cadaveric radius

An excised section of healthy human radius was imaged using CSCT. The resulting material-specific images of the collagen, hydroxyapatite, fat, and water distributions are seen in Fig. 8 along with the conventional (attenuation) CT. Each tissue type exhibits the expected spatial distribution. The hydroxyapatite and collagen are found in the cortical region. A comparison of the two distributions shows the expected relative distribution of bone mineral and its matrix. Some collagen was also identified in the marrow space. Fat is contained within the marrow canal. These images are intended solely to demonstrate the feasibility of this technique in an intact biological specimen. Consequently, an absolute concentration analysis has not been performed for this specimen. Further studies will be performed to confirm the in situ accuracy.

C. Quantitative assessment of projection measurements
1. Precision and accuracy: Hydroxyapatite concentration

The accuracy of coherent-scatter based investigation of hydroxyapatite concentrations is illustrated in Fig. 9. The values determined for each of five trials at each concentration were averaged and plotted against the nominal concentration with error bars contained within the plot symbols. The data are plotted with an ideal result of unity slope and zero intercept. Linear regression analysis resulted in the line \( y = 1.02x - 0.002 \), with \( R^2 = 0.999 \). The root-mean-squared (rms) error for this dataset was 0.005 g/cm\(^3\). Measurement precision ranged from 0.7% to 2%, with an absolute standard deviation of 0.002 or 0.003 g/cm\(^3\). Measured hydroxyapatite concentrations were within 2% of the nominal values for all samples except at 0.400 g/cm\(^3\). The manufacturers of the phantom materials could not, however, guarantee the accuracy of the higher concentration samples, as mixing hydroxyapatite into a binding matrix at these concentrations is extremely difficult. Given the accuracy of the remainder of the dataset, it is likely that the true concentration of that sample is greater than 0.400 g/cm\(^3\).

2. Precision and accuracy: Collagen–hydroxyapatite ratios

After ensuring that quantities of hydroxyapatite alone could be measured accurately, mixtures of the materials comprising bone tissue were examined. The assessment of collagen-hydroxyapatite ratios was first tested with phantoms consisting of known masses of collagen and hydroxyapatite measured with a digital scale. Simple division determined the ratios. The results are displayed in Fig. 10.

Ratios measured by material-specific coherent-scatter analysis are plotted versus the known ratios and compared to the expected straight line through the origin with a slope of one. Error bars, representing the standard deviation of the five measurements for each sample, are contained within the plot symbols. The linear least squares fit result for these data is \( y = 0.98x + 0.003 \), with an \( R^2 \) value of 1.00. A circle and a square indicate samples approximating the ratio found in normal and osteomalacic bone, respectively. These are clearly distinguished from one another. Each phantom was measured with an accuracy of 1.8% or less and a precision (for each set of repeated measurements) of 3%–4%. The rms error for the measured ratios was 0.026.
D. Quantitative assessment of tomographic image-based measurements

The accuracy and precision of coherent-scatter based measurements of hydroxyapatite concentrations and collagen-mineral ratios have been demonstrated. The technique was next applied to tomographic data.

1. Bone-mimicking phantom

The ratio of collagen to hydroxyapatite in the phantom was calculated from the densities of these materials obtained from the material specific analysis. The collagen density was determined to be 0.7±0.1 g/cm³ and that of hydroxyapatite was found to be 0.60±0.03 g/cm³, both of which are in agreement with the known densities (Fig. 7). As described previously, the collagen measurement is expected to have a larger standard deviation than hydroxyapatite due to the lower signal-to-noise ratio (SNR) for scatter arising from collagen, for a given x-ray exposure. The difference in scattering strengths per gram between collagen and hydroxyapatite is large enough (Fig. 5) that, even though collagen has a larger density in this phantom, fewer photons are coherently scattered in the collagen. From the individual densities, the collagen-hydroxyapatite ratio is determined to be 1.2±0.1, while the known collagen-hydroxyapatite ratio is 1.23±0.01. The uncertainties in the ratios were determined by adding the individual errors in quadrature.

2. Cadaveric result

A human radius with no known bone disease was analyzed to demonstrate the application of this technique to biological specimens. These preliminary results are meant solely to illustrate the viability of coherent-scatter-based analysis and provide the motivation for further research. The means and standard errors in the mean from the ratio of each 2×2-pixel ROI were determined (Fig. 11). The average ratio from the ten ROIs was 0.53±0.04, which is in agreement with expectations (0.55) for healthy human bone. This provides a strong indication of the potential for coherent-scatter-based bone analysis.

IV. DISCUSSION

Current radiographic densitometry procedures rely on the assumption that the composition of bone tissue (its mineral and collagen content) is unaltered by disease. The bone mineralization state is, however, known to change in several diseases (e.g., osteomalacia and osteogenesis imperfecta), as well as during normal growth and aging. Therefore, there is a need for further, more detailed, information in order to investigate the nature of bone tissue in these cases. Moreover, in conventional densitometry, fat and collagen can cause errors in the assessment of BMD. The presence of fat in the trabecular space leads to underestimates of BMD, while the collagen content can cause overestimates. Thus, a technique that does not rely on assumptions regarding the composition of bone may also improve standard BMD assessments.

Coherent-scatter properties are determined by structure at the atomic level and CSCT is the only radiographic technique where physical tissue density and image contrast are de-coupled. CSCT contrast is based on information acquired from photons that have interacted with the specimen, whereas x-ray transmission techniques rely on the surviving fraction of photons to infer knowledge about the specimen. CSCT thus provides direct information about the composition of intact tissue samples. Hence, in coherent-scatter measurements, hydroxyapatite is measured independently and is not influenced by the fat or collagen content. Guttmann and Goodsitt have, in fact, suggested the use of scatter data to ameliorate the detrimental effects of fat on QCT results. We describe a method for examining the composition of tissue samples based on measures of the coherent-scatter cross section.

CSCT is likely restricted to the analysis of relatively small objects (10–15 cm diameter, ~3 half-value layers) to limit the degrading effect of multiple-scatter events in the object. This makes CSCT appropriate for the study of the phalanges, calcaneus, distal radius, or tibia, similar to other peripheral BMD analysis techniques. This technique can be applied in either a projection or a tomographic mode. In the latter, material-specific images are generated, providing the concentration (g/cm³) of each tissue type at each point in the tomogram. In this study, we have shown that coherent-scatter-based analysis can provide tissue-specific information regarding bone composition. A study of bone components has been made to assess the quantitative potential of this technique.

The feasibility and accuracy of the method has been validated using bone-mimicking phantoms. These results clearly show that individual components of bone tissue can be identified (Fig. 6) and that measures of the coherent-scatter cross section result in accurate determinations of both hydroxya-
The collagen-mineral ratio in a cadaveric radius was also assessed from a tomographic image. The ratios measured from this specimen were in agreement with the expected value. This measurement has not been independently confirmed. The images and data from the radius are included in this work solely as a proof-of-concept demonstration. The accuracy of measurements from bone specimens is the subject of ongoing work in our lab.

Evidence from experiments performed during the development of this technique indicates that the correct identification of collagen may depend on SNR. Of all the bone components, collagen is the weakest scatterer per gram (Fig. 5) and, thus, has the lowest SNR for a given number of scatterers and x-ray exposure technique. The collagen cross section for coherent scatter is also grossly similar to that of fat, and this can potentially lead to the misidentification of collagen as fat. This is illustrated in Fig. 6, where ~3% of the collagen pixels were misidentified as fat and ~6% were identified as a composite of collagen and fat. This is obviously undesirable, particularly in the trabecular region, where no a priori knowledge regarding the fat and collagen distributions can be had. An important component of future developments of this technique for bone analysis will be to elucidate the minimum SNR required to adequately separate fat and collagen. Meanwhile, efforts are on going to enhance the SNR in collagen measurements. SNR in CSCT images depends directly on the differential linear coherent-scatter coefficient, the number of projection angles, the reconstructed pixel size, the size of the beam, the incident fluence, and the quantum efficiency of the detector used. Increasing either the pixel size or the size of the beam will decrease our resolution and are not, therefore, desirable. SNR can be improved without degrading resolution by better defining the measured scatter patterns (increasing angular resolution of the measured differential linear coherent-scatter coefficient), acquiring more projections during the CT scan, or increasing the incident fluence. SNR can also be improved by using a detector with higher quantum efficiency.

Improving the angular resolution of measured coherent-scatter cross sections is an area of active interest in our group. The cross section for coherent scatter depends on the energy of the incident beam [Eq. (1)]. Therefore, coherent-scatter patterns acquired with polyenergetic diagnostic x-ray sources are blurred by the spectrum of the incident beam. Reducing the spectral width will increase angular resolution and, thus, offer one means of improving material discrimination by increasing SNR. Preliminary calculations suggest that a graphite Bragg monochromator can, in principle, be used to improve angular resolution from the current 14% root-mean-square (rms) to approximately 3.9%. This could be accomplished without a loss of intensity relative to the highly filtered beam presently used. An alternative approach would be to use synchrotron radiation. This would improve material discrimination, but would also limit accessibility. CSCT, as described here, reflects a balance between angular resolution and the ease of access.

Increasing the incident x-ray fluence or the number of projections acquired results in an increase in the delivered dose. While this is not an issue for a benchtop scanner used to investigate in vitro samples, it should be considered before development for clinical use. In the images of the human radius (acquired at 70 kVp, 300 mA, and 0.033 s per ray path), where a gadolinium filter reduces beam intensity to 17%, the in-slice average dose is calculated to be 20 mSv. This is the equivalent dose, that is, the absorbed dose weighted for the radiation quality (for x rays, Q=1). In order to assess the risk due to radiation, we must convert this to an effective dose, which takes into account the radiation sensitivity of the exposed tissues. To calculate this we used the parameters stated above and hypothesized that CSCT is applied to the distal tibia (one potential anatomic site compatible with CSCT size restrictions) with a 2 mm slice thickness. The effective dose was calculated to be 4.4 μSv using the method described by Braun.

This is higher than the peripheral-QCT dose of 0.72 μSv quoted by Braun, but the CSCT dose should also be compared to an anterioposterior spine exam using two-dimensional (2-D) DXA that delivers an effective dose of 8.4 μSv to the patient or to a typical QCT effective dose of 300 μSv. Furthermore, all patient doses in densitometry are at the low end of the dose range encountered in diagnostic radiology. For example, a multislice CT scan of the lumbar spine results in an effective dose of 7.2 mSv, which is almost three orders of magnitude larger than the projected dose for CSCT. This indicates that we can increase the dose in CSCT, if necessary, and still be within the range of current clinical practice. A full dose-sensitivity study will be necessary to determine the optimum dose parameters for accurate coherent-scatter-based bone analysis.

V. CONCLUSIONS

Tomographic densitometry techniques are superior to projection techniques, such as DXA, as they provide true volumetric densities (g/cm³) and allow the separation of compact bone from the more metabolically active trabecular bone. QCT has these advantages but is limited in the number of tissue components that can be simultaneously examined. In dual-energy QCT, it is possible to investigate only three tissue types: fat, soft tissue, and bone tissue. Thus, information regarding the mineralization state of the bone’s collagen matrix cannot be derived from QCT. While CSCT with a 1 mm² beam size may not be able to determine the mineralization state of individual trabeculae, it can investigate the cortical and trabecular regions separately to provide bulk measurements of hydroxyapatite and collagen content and thus provides information currently not available by other nondestructive radiographic methods.

The technique presented here for determining hydroxyapatite and collagen concentrations by measuring coherent-scatter signals from tissue specimens has been shown to be
accurate (<5%) and precise (<4%) in phantom studies. These measurements can be made in either a projection or CT mode. The results demonstrate that the information content of coherently scattered x-rays is sufficient to discriminate and quantify the two major tissue components of bone. The precision and accuracy of the phantom results show that coherent-scatter imaging can discern osteomalacic bone, for which hydroxyapatite concentrations are reduced by 24% and collagen-mineral ratios are increased by 18% in comparison to healthy bone. CSCT measurements from a human radius sample, while slightly less precise than phantom measurements, provide evidentiary support that coherent-scatter based characterizations can extend the breadth of information available for diagnosis over current clinical techniques. CSCT is used to produce tomographic, quantitative, material-specific maps of tissue composition, which provide a means for nondestructively examining BM and collagen independently and without interference from surrounding tissue. Thus, CSCT may be an important and unique tool for understanding metabolic bone disease processes as well as normal bone growth and aging.

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M. S. Westmore, A. Fenster, and I. A. Cunningham, “Angular-dependent coherent scatter measured with a diagnostic x-ray image intensifier-based...


