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Evaluating bone quality in patients with chronic kidney disease

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Abstract

Bone of normal quality and quantity can successfully endure physiologically imposed mechanical loads. Chronic kidney disease–mineral and bone disorder (CKD–MBD) adversely affects bone quality through alterations in bone turnover and mineralization, whereas bone quantity is affected through changes in bone volume. Changes in bone quality can be associated with altered bone material, structure, or microdamage, which can result in an elevated rate of fracture in patients with CKD–MBD. Fractures cannot always be explained by reduced bone quantity and, therefore, bone quality should be assessed with a variety of techniques from the macro-organ level to the nanoscale level. In this Review, we demonstrate the importance of evaluating bone from multiple perspectives and hierarchical levels to understand CKD–MBD-related abnormalities in bone quality. Understanding the relationships between variations in material, structure, microdamage, and mechanical properties of bone in patients with CKD–MBD should aid in the development of new modalities to prevent, or treat, these abnormalities.

Introduction

Bone is a composite material that consists of mineral and matrix. When these two different materials are combined, the aggregate mechanical properties are remarkably different from either constituent alone. The chemical composition, relative amounts, and distribution of mineral and matrix govern the shape-independent mechanical properties of bone. The anatomical arrangement of this mineral–matrix composite, and the organization by

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cancellous and cortical compartments determine bone stiffness (the ability to avoid excess whole-bone deformation during physiological loading) and load-bearing capacity (the ability to avoid fracture in response to physiologically imposed forces, or ‘loads’). In addition, bone cells confer the ability to change the shape of bone in response to alterations in physiological loading and repair bone microdamage—an important factor involved in bone quality because small (micron sized) cracks induced by normal loading can coalesce and ultimately become clinical fractures.

Bone quality is the term currently used to describe the ability of bone to successfully perform its mechanical load-bearing functions that are essential for loco motion and major-organ protection. Two slightly different definitions are found for the term ‘bone quality’ in the literature. One definition includes all characteristics that influence the load-bearing capacity of bone, that is, bone size, shape and material properties.^{1,2} The second definition includes only the characteristics that influence load-bearing capacity independently of bone quantity (mass).^{3,4} In this Review, we adopt the former definition and consider bone quality to be influenced by all characteristics that enable bone to resist excess deformation and avoid fracture in response to physiologically applied loads.

Bone quality can be affected by a variety of diseases including chronic kidney disease—mineral and bone disorder (CKD–MBD)—a deleterious condition that develops early during reduction of glomerular filtration rate (GFR).^{5–7} Bone histological abnormalities that accompany CKD–MBD, referred to as renal osteodystrophy, affect many aspects of bone quality on all hierarchical levels, and have been the subject of considerable study.^{8–11} The abnormalities associated with renal osteodystrophy include changes in bone turnover, mineralization and volume,^{7,12,13} which contribute to the elevated rate of fractures in patients with CKD–MBD. For example, patients aged 50 years with CKD, who are not on dialysis and whose GFR is <45 ml/min/1.73m², have twice the risk of hip fracture compared with healthy individuals.¹⁴ Additionally, patients on dialysis with stage 5 CKD have a 4.4-fold higher risk of hip fracture than that of the general population.¹⁵ These fractures cannot be explained solely by declines in bone quantity (mass)^{16,17} and, therefore, other factors encompassed by the term bone quality, must be considered. Little attention, however, has been devoted to assessing bone quality in patients with CKD to date.

Factors that determine bone quality include those that affect bone volume, structure, material properties, and microdamage (Figure 1). These factors can be considered on a variety of hierarchical levels—from macro to micro to nano (Figure 1). Clinically relevant changes in the macroscopic mechanical properties of bone, ultimately manifested as a change in fracture susceptibility, can be attributable to disease-related structural and chemical changes at more than one hierarchical level. A spectrum of methods is, therefore, needed to measure bone quality owing to this multidimensional nature of bone quality.

This Review focuses on bone quality. We describe the methods used to assess bone quality and outline the clinical relevance and importance of evaluating bone quality in patients with CKD–MBD. We discuss the study of bone quality at the various organizational levels and the variety of techniques that are used to evaluate relevant bone quality parameters in patients with CKD–MBD on one or more of these hierarchical levels (Figure 1).

Material properties of bone

The material aspects of bone quality are evaluated by considering the composition and properties of inorganic bone mineral and organic bone matrix. Bone mineral influences the ability of bone to withstand compressive loading.¹⁸ Similarly, bone matrix provides tensile and shear load-bearing capabilities.¹⁸ Mineral and matrix are separate and distinct, and are proportioned such that bone, on a shape-independent basis, has optimal mechanical properties.¹⁸ The techniques used to assess alterations in bone quality owing to changes in bone mineral or matrix are described in the following sections.

Material evaluation at the macroscale

Gravimetric analyses—This *ex vivo* method of quantifying the mineral fraction of bone involves complete incineration of the bone sample. The material quantity is compared before and after combustion to assess the ash (mineral) content.^{19,20} This method is simple but primitive, time-consuming, and has largely been replaced by newer, nondestructive techniques to evaluate mineral quantity.

Dual-energy X-ray absorptiometry—Dual-energy X-ray absorptiometry (DXA) is a radiographic technique that passes X-ray beams of two different energy levels through several filters and through the bone (*in vivo* or *ex vivo*) to determine bone density. Differences in the observed radiographic densities are then evaluated on the basis of differential transmitted beam intensities analysed with an algorithm and calibrated with a standard of known radiographic density. The result is a calculated value for bone mineral density (BMD) that correlates with the ash content.²⁰ The resulting bone density data are compared with known populations from which assessments are made regarding overall density and, albeit less accurately, fracture risk.

DXA is the most widely used noninvasive technique for measuring bone mineral content and evaluating bone mass. The KDIGO (Kidney Disease: Improving Global Outcomes) guidelines recommend DXA measurements for the assessment of fracture risk in patients with stage 1 through to early stage 3 CKD.⁷ A reduction in bone mass is linked to an increase in fracture risk, but no independent effect of CKD has been demonstrated.²¹ The usefulness of spine BMD for predicting cancellous bone volume (determined by histology) was found to be limited, most probably because of interference from soft tissue calcifications. By contrast, femoral BMD is correlated with cortical porosity in iliac crest bone samples from patients on dialysis with stage 5 CKD.²² DXA, although widely used, has limitations. For example, the measurement of ‘areal’ density is not true ‘volumetric’ density. DXA is unable to account for bone shape, an important factor in predicting fracture risk (especially for traumatic mechanical loading modes).²³ Moreover, DXA is also confounded by factors attributable to patients of differing size, collapsed vertebrae, and mineral deposited in tissue overlying bone that DXA misinterprets as bone.²² Quantitative computed tomography (QCT) can be more accurately employed to quantify BMD, as discussed later.

Quantitative ultrasonography—The use of ultrasonography has been explored for the assessment of bone quality in patients with CKD. This noninvasive technique is easy to use

and radiation-free. Prospective studies in large groups of patients and comparisons with bone markers, bone histology, and other bone-quality measures are needed to assess the role of quantitative ultrasonography for the clinical management of renal osteodystrophy.

Material evaluation at the microscale

Fourier transform infrared spectroscopy—Fourier transform infrared (FTIR) spectroscopy provides material-relevant information on the basis of the interaction and absorption of infrared (IR) light with particular chemical bonds characteristic of the composition of bone mineral and matrix (Figure 2). Such *ex vivo* measurements occur on the submicron scale and provide important information about the material composition and structure of bone samples.^{24–28} Commonly reported parameters measured by FTIR include the mineral-to-matrix ratio (relative mineralization), carbonate-to-phosphate ratio (crystal purity), crystallinity (crystal size and perfection), and collagen crosslinking ratio (the relative proportion of mature to immature collagen crosslinks). Except for the need for thin (<5 μm) specimens that allow IR light transmission, FTIR is non destructive and requires only small amounts of material with little preparation other than dehydration, but can measure only relative (not absolute) quantities of mineral, matrix and varying crosslink types.

Raman spectroscopy—Raman spectroscopy involves *ex vivo* sample irradiation with a monochromatic light source and detection of the scattered rays. Raman spectroscopy allows the use of wet samples of bone and requires little preparation (no sectioning required), offers greater spatial spectral resolution than FTIR, and can measure chemical bonds that are more difficult to detect with FTIR. Raman spectroscopy is, thus, complementary to FTIR and can also be used to measure the carbonate-to-phosphate ratio, crystallinity, and mineral-to-matrix ratio.²⁹ Raman spectroscopy has not been widely employed and, therefore, a small comparative database exists.

Quantitative backscatter electron imaging—Quantitative backscatter electron imaging (qBEI) is an analytical electron microscopy-based technique that detects electrons reflected by elastic scattering. The intensity of these reflected electrons is strongly related to the atomic number of the sample and, therefore, these backscattered electrons are useful for providing information about the distribution of different elements in the sample and the relative bone mineralization.³⁰ qBEI permits areal mapping of relative mineralization, but requires extensive *ex vivo* sample preparation (dehydration and electrically-conductive sputter-coating) before electron microscopy examination.

Material evaluation at the nanoscale

High-performance liquid chromatography—Liquid chromatography is a mass transfer process that involves the selective adsorption of components for material analyses. High-performance liquid chromatography (HPLC) uses high-pressure pumps to pass a pressurized liquid containing a dissolved *ex vivo* bone sample mixture through a column packed with small (2–50 μm) sorbent particles. The size and chemistry of these particles selectively adsorb various compounds according to chemical bond type and these characteristics can be used to isolate sample components. Component separation occurs due

to the varying degrees of chemical interaction of the sample components with the sorbent particles. In contrast to FTIR, which allows measurement of the ratio of one type of mature to immature collagen crosslinks, HPLC measures the absolute amounts of several different types of collagen crosslinks.³¹

Energy-dispersive X-ray spectroscopy—Energy-dispersive X-ray spectroscopy (EDAX) is used, in conjunction with scanning electron microscopy to determine the elemental composition of a sample of interest. The area of interest is irradiated with high-intensity X-rays—particular elements contained in the region emit radiation characteristic of their composition. EDAX examination of *ex vivo* bone mineral and matrix is advantageously employed for foreign element identification. Bone-quality abnormalities attributable to individual elements, such as aluminium, can thus be readily identified. Sample preparation for EDAX examination requires specimen dehydration and metal coating.

Biochemical bone markers—The enzymes and proteins released by the processes of bone formation or bone resorption, that is, bone markers, are ‘measures of measures’. They are not universally recognized for assessing bone material, and are thus not discussed in this Review.

Structural properties of bone

Bone quality depends not only on the chemistry of bone mineral and matrix but also on the structural arrangement and orientation of these materials. Thus, bone structure must be quantified on all hierarchical levels in a manner analogous to that conducted for bone material (Figure 1). Important bone quality structural parameters include the length, periosteal and endosteal cortical diameters, femoral neck angle, cortical thickness and cortical porosity. These parameters are important for determining the load-bearing competence of bone. Similarly, measures of trabecular length, thickness, connectivity and orientation are among the important parameters that quantify the structural aspects of cancellous bone. These parameters are measured by mineralized bone histology, QCT, peripheral QCT, high-resolution (HR) peripheral QCT (HR-pQCT), micro-CT, MRI, or HR-MRI. Note that some parameters, such as bone volume, cortical thickness and porosity, and trabecular thickness and connectivity, provide information on both bone quantity and bone quality.

Structural evaluation at the macroscale

Bidimensional texture analysis—Bidimensional texture analysis is an emerging *in vivo* technique that provides information concerning trabecular bone microarchitecture founded upon new methods for analysing bone radiographic data. Fractal analysis of trabecular bone is conducted on radiographs of the calcaneus, tibia or radius with a 2D HR X-ray device. Signal-processing techniques are used to extract bone-structure information. The results obtained from this technique indicate that bone connectivity and porosity are correlated,³² although this novel technique awaits further study.

QCT and pQCT—QCT is an *in vivo* imaging modality that uses a computer-based analysis of multiple radiographic images to create planar representations of biological structures.

Subsequent digital geometry processing can be used to produce 3D images of these biological structures. QCT can be applied centrally or peripherally. Central QCT is typically applied to large body segments, such as the hip or spine, to measure the BMD of these bones. QCT, however, exposes considerable volumes of tissue to large radiation dosages. QCT-derived BMD measurement techniques allow determination of true volumetric BMD (not areal as obtained from DXA), and is not confounded by the presence of extra-osseous calcium. QCT can measure BMD of trabecular and cortical bone independently in the hip, but not in the spine. Disadvantages of QCT include high radiation levels, high instrumentation expense and, necessarily high per use costs, the inability to measure thin vertebral cortices, and low device availability. pQCT is an application of QCT used for evaluating BMD in distal appendicular body regions, such as the arms or legs.

HR-pQCT and micro-CT—HR-pQCT is similar to standard QCT techniques although the spatial resolution is maximized by use of a narrow slice width, minimal field of view, and high spatial resolution image reconstruction algorithms. HR-pQCT can be used to measure BMD in the distal extremities and can also provide more detailed information about bone microstructure than regular QCT. A limitation of HR-pQCT, however, is that only the distal extremities, specifically the radius and tibia, can be evaluated.³³ HR-pQCT has a resolution of 82 μm , which is at the limit of detection for trabecular thickness, and it can also detect large cortical pores. HR-pQCT evaluates cortical and trabecular compartments separately, measures microarchitectural parameters that correlate with bone strength, and uses reduced radiation doses compared to pQCT.^{34,35} Micro-CT is used to image small (at the millimetre level) bone samples *ex vivo*. Micro-CT requires high radiation doses, but provides spatially detailed (nominally 5–15 μm) 3D bone microstructural data.³⁶

MRI: regular and HR—MRI and HR-MRI are *in vivo* techniques that employ NMR to image atomic nuclei in the constituent materials of bone. No ionizing radiation is used. HR-MRI is obtained by use of modified equipment (dual versus single radio frequency coils) and procedures (reduced field-of-view and slice thickness, increased number of acquisitions and scan time) to obtain images with enhanced resolution.^{37,38} These techniques can produce 3D images from which conventional structural parameters can be obtained.³⁹ Such HR-MRI images of bone structures have been referred to as a ‘virtual bone biopsy’⁴⁰ and they enable estimations of the load-bearing capacity of bone to be made on the basis of finite element analyses. Investigators in a few studies have used ³¹P MRI to measure bone mineral *in vivo*.^{41,42} Additionally, another study indicated that MRI provides information about ‘bone water’, which is related to porosity (a structural parameter).⁴³

Structural evaluation at the microscale

Bone histology and histomorphometry—Bone histology and histomorphometry are the gold standard for quantifying bone structure on the microscale in patients with CKD–MBD.⁴⁴ This invasive technique requires procurement of a bone sample, typically via iliac crest bone biopsy. Bone samples are then processed by use of conventional sample mounting, sectioning, staining, light microscopy, and computer-based image analyses to allow quantification of bone architecture, turnover, and mineralization. A variety of key architectural parameters are generated including bone volume, trabecular thickness,

trabecular separation, trabecular number, cortical thickness, cortical porosity, and collagen texture. Important bone turnover parameters are activation frequency, bone formation rate, and osteoblast and osteoclast surface and number. Bone mineralization parameters include osteoid thickness, osteoid maturation time, and mineralization lag time. Previously noted microstructural parameters can provide a trained observer with an approximate qualitative 'impression' of the load-bearing mechanical competence of cancellous bone, but rigorous quantitative analyses require additional imaging (typically micro-CT) with subsequent computer-based modelling and finite element analyses. Bone samples obtained from patients with CKD indicate that vertebral bone density, as assessed by QCT, correlates with histomorphometrically assessed trabecular bone volume, thickness, number, and separation.⁴⁵ This correlation notwithstanding, micro-CT was found to be less effective than bone histomorphometry for differentiating renal osteodystrophy from normal bone.⁴⁶ Similarly, correlations were found between histologically measured cortical width and cortical thickness as measured by HR-pQCT (but only in the tibia and not the non-dominant forearm of patients with osteoporosis or hypoparathyroidism).⁴⁷

Structural evaluation at the nanoscale

Electron microscopy—Electron microscopy has been used in both scanning and transmission modes to determine the structure of *ex vivo* bone mineral and matrix. In addition, high resolution transmission electron microscopy (HR-TEM) has been used to study the shape and orientation of apatite crystals in mouse bones.⁴⁸ This technique might have an application in human bone to evaluate the distribution and orientation of mineral crystals and their relationship with bone matrix.

X-ray crystallographic techniques—Determination of nanoscale mineral and matrix structure, arrangement, or orientation requires examination by use of wavelengths from the X-ray portion of the electromagnetic spectrum. These techniques irradiate *ex vivo* bone samples with X-rays and the reflected or scattered radiation provides information that can be used to quantify collagen fibre and mineral crystal arrangement and orientation. X-ray crystallographic (diffraction) techniques are useful for determining atomic and molecular crystal structure, whereas X-ray scattering techniques, for example small angle-X-ray scattering, wide-angle X-ray scattering, and synchrotron X-ray scattering, are useful for measuring mineral crystal orientation and estimating mineral strain during sample deformation.^{49–51}

Microdamage of bone

Normal physiological loading produces bone microdamage (Figure 1). The term 'microdamage' includes both microcracks and diffuse damage.⁵² Microcracks are a partial determinant of bone quality because their initiation, growth, and coalescence can lead to clinically relevant macroscopic fractures. Parameters used to quantify bone microdamage include microcrack length, microcrack density, and extent of diffuse damage. Typically, microdamage of the bone is measured by *ex vivo* histological techniques,⁵³ although micro-CT and scanning electron microscopy are also used.^{54,55} All of these techniques are

invasive, and without saturated lead-staining and synchrotron-based CT bone imaging,^{56,57} cannot assess crack density in three dimensions.

Mechanical properties of bone

Destructive mechanical testing to failure is the gold standard for quantifying the mechanical properties of bone, and thereby evaluating bone quality. All destructive mechanical tests use specialized equipment to apply controlled mechanical forces of increasing amplitude at a user-adjustable rate to a bone sample that is mechanically fixed to the testing equipment. Load cells measure the forces applied to the sample and one or more specialized transducers measure force-related changes in one or more sample dimensions. All destructive mechanical tests require invasive procurement of a bone sample, either whole organ or a small portion that is subsequently machined to a square, rectangular or cylindrical shape of known dimensions.

Stress and strain are important parameters needed to evaluate the shape-independent mechanical response of bone to applied forces (Figure 3). When an external force (or forces) is applied to a material, internal forces are generated by the material to enable it to endure this force without failure. Stress is the parameter that quantifies the magnitude and direction of the internal forces exerted by neighbouring particles of a continuous material that resist the externally applied force. Stress is defined as the applied force normalized by the area of application (units of Pascals). Forces can also act simultaneously in more than one dimension and can induce normal and shear stresses. Strain is the parameter that quantifies the material shape change owing to the applied force. On a one-dimensional basis, strain is defined as change in length per unit length (dimensionless). Strains can also simultaneously occur in more than one dimension, and in directions parallel (normal strains) and perpendicular (shear strains) to the applied force. Stress and strain are defined here in one dimension for simplicity, although both are generally multiplanar, multidirectional, and are properly described by the use of tensors.

Mechanical testing performed on machined samples enables the shape-independent material properties of bone to be quantified (Figure 3a). Important mechanical testing parameters obtained from machined bone sample testing include Young's modulus, strength, yield point, strain at failure, and toughness. Young's modulus quantifies the shape-independent ability of the material to resist deformation, and is calculated by dividing stress by strain in the 'early' (typically linear) elastic region of the stress–strain curve. Strength refers to the ability of a material to withstand an applied stress and not fail. More precise specification of strength definitions requires information regarding the type of applied stress, such as compressive, tensile, or shear.

Mechanical testing performed on whole bone samples simultaneously quantifies the collective ability of bone material, shape and mass to resist deformation and endure loads (Figure 3b). Important mechanical parameters obtained from whole bone testing to fracture include stiffness, maximum load to fracture, and energy to fracture. Stiffness refers to the ability to avoid excess whole bone deformation during physiological loading and is given by the slope of the load–deformation curve, similar to the manner in which Young's modulus is

given by the slope of the stress–strain curve. The energy to fracture (clinical fracture) is quantified by the area under the curve as shown in Figure 3b.

Mechanical evaluation on the macroscale

Controlled forces have been applied to whole or macroscale machined bone samples obtained from humans and animals in a variety of directions to produce compressive, tensile, torsional, or shear loading. The variety of load amplitudes and directions applied to such samples attempts to imitate the activities of daily living as well as occasional overloads. Most mechanical testing studies apply a single, steadily increasing load until fracture occurs owing to large force amplitude. Much less frequent are repetitive-load studies in which forces are cyclically applied (typically according to a sinusoidal waveform) until fracture occurs. Load amplitudes for repetitive-loading tests are usually near physiological force amplitude levels. Monotonically applied single-load-to-fracture tests are easier, quicker, and simpler to interpret, and so they are more common than repetitive-loading tests. Other specialized mechanical tests, including fracture toughness and notch sensitivity, have also been employed, albeit uncommonly.

Major limitations of mechanical testing include the invasiveness of specimen procurement, and test-necessitated specimen destruction. Thus, mechanical testing is generally limited to bones from animals, cadavers, or small specimens obtained from surgical procedures. Other limitations include the need for both large sample numbers and large sample dimensions, inconvenience of reproducing tests at *in vivo* temperatures, and maintaining bone in a state of full physiological hydration.

Mechanical evaluation on the microscale

The development of ‘reference point indentation’ instrumentation, techniques, and the availability of a reference comparative database offers a new approach to the minimally invasive *in vivo* quantification of the indentation depth increase (related to Young's modulus) of living bone from humans.⁵⁸ Nanoindentation testing permits measurement of the Young's modulus of bone on a microscale. This test involves use of low-level controlled indentation of a specialized hard-pointed tip (typically pyramidal, 50 nm on edge) into a prepared bone sample with a spatial accuracy of approximately 1 μm (Figure 4). Bone hardness can also be calculated from nanoindentation.^{59,60} The high spatial resolution of nanoindentation, coupled with precise microscope-guided indenter tip placement, allows quantification of spatially dependent modulus variations reflective of particular micro-anatomical features or spatially varying bone material properties. Freedom from instrument vibration and an isothermal environment are essential given the low-force amplitudes and high-spatial precision of this technique.

Mechanical evaluation: theoretical analyses

Some mechanical parameters of bone can also be assessed theoretically. This technique begins by obtaining HR 3D images of bone microstructure by use of micro-CT, micro-MRI, or pQCT imaging. A mathematical 3D ‘mesh’ is applied to divide these complex microstructural images into many simple structures that, when taken together, accurately represent the bone structure (Figure 5). Subsequent to the representation of the bone

structure of interest by this mesh, a virtual stress is mathematically applied, and the virtual strains that result are calculated on the basis of the solution of established equations derived from the underlying physics. Such calculations are typically performed by use of commercially available finite element analysis (FEA) software. FEA is a computational tool pioneered in the aerospace industry seven decades ago and is now well established in conventional engineering disciplines. Historically, this technique was performed on small excised bone samples, although noninvasive methods that use pQCT or micro-MRI to obtain the images are now being investigated. Limitations of this method include the inherent assumptions made regarding the material behaviour of the sample under analysis, which include a spatially uniform Young's modulus and often, but not exclusively, linear elasticity.

Bone quality abnormalities in CKD

CKD-MBD affects bone quality on many hierarchical levels as demonstrated by the study of human bone from patients with CKD-MBD, and rodent models of kidney dysfunction. The results of these rodent studies are difficult to reconcile with patient studies because the rodent skeleton differs substantially from the human skeleton. Specifically, rodent skeletons lack Haversian systems and grow throughout life, which contrasts with human bone microanatomy and growth plate fusing. After adolescence in humans, internal bone remodelling replaces bone modelling activity. Owing to these fundamental differences between rodent and human bone, and the resulting differences in bone quality, subsequent discussion will focus on human studies.

CKD and the material properties of bone

The alterations in bone turnover that accompany CKD are associated with several bone material abnormalities. Specifically, high bone turnover is associated with a low mineral-to-matrix ratio²⁴ and low carbonate-to-phosphate ratio.⁶¹ An abnormal mineral-to-matrix ratio is linked with reduced toughness.¹⁸ Also, a variety of abnormalities in collagen crosslinking of bone matrix are observed in these patients. Specifically, advanced glycation end products (AGEs) are greater, and mature enzymatic crosslinks are lower, in patients on dialysis with stage 5 CKD with high turnover than in healthy individuals.³¹ Abnormalities in matrix collagen crosslinking were associated with low-energy atraumatic fractures in premenopausal women.^{62,63} Pentosidine, an AGE, correlates negatively with bone formation rate and mineral apposition rate.³¹ Similarly to the case of high bone turnover, low bone turnover in patients with CKD is also associated with a reduced carbonate-to-phosphate ratio.²⁴ The material property relevance of the altered carbonate-to-phosphate ratio awaits further study.

CKD and the structure of bone

Women on dialysis with stage 5 CKD have lower radial and tibial cortical density, higher radial cortical porosity, lower tibial cortical thickness, fewer trabeculae, and greater trabecular separation compared with healthy women.⁶⁴ Men in the same study displayed only a lower radial cortical density compared with healthy individuals.⁶⁴ The distal radii of women on dialysis with stage 5 CKD also had a lower cortical and trabecular density, and lower trabecular bone volume (as determined by HR-pQCT) compared to healthy

women.^{64,65} The cortical thickness of bone was lower in men with stage 2–4 CKD compared with healthy control individuals. An impairment of trabecular microarchitecture has also been observed in both men and women with CKD when compared to healthy individuals.⁶⁶ The resistance of long bones, having nearly circular cross sections, to deformation in bending and torsion is sensitive (fourth power) to changes in radius. Loss of trabecular connectivity results in a dramatic reduction in the force required to cause buckling and failure in compression.⁶⁷ Given the known differences in cortical bone size and cancellous architecture, these findings underscore the need for sex-specific approaches to studying bone quality in CKD–MBD. Broadband ultrasound attenuation and the speed of sound are also altered in patients with CKD.^{68,69} Measurements obtained by quantitative ultrasonography also correlate with measurements obtained by BMD measured in the hips of patients with CKD.⁷⁰

Quantitative HR-MRI at the tibial midshaft was used to demonstrate that the cortical bone cross-sectional area (expressed as percentage of total bone area), and the mean cortical thickness, is lower in male patients on dialysis with stage 5 CKD than in age, sex and BMI-matched control individuals.⁷¹ Ultrashort echo-time MRI was used to measure bone water at the tibial midshaft in six patients with stage 5 CKD on dialysis, five healthy premenopausal women, and five healthy postmenopausal women. The results were compared with BMD at the same site using QCT, and were compared with BMD of the lumbar spine and hip using DXA. Patients on dialysis with stage 5 CKD had higher bone water than healthy individuals, whereas BMD was lower in the patients with stage 5 CKD on dialysis than in healthy individuals (but with smaller between-group differences). The majority of bone water is located in the pores of cortical bone and the measurement of bone water might, therefore, serve as a surrogate measure of cortical porosity.⁴³ The results from these studies confirm the findings from large-scale histological studies that show an increased cortical porosity in patients with high turnover renal osteodystrophy.¹²

Histologically, CKD is characterized by alterations in bone volume (either decreased or increased) secondary to changes in bone turnover (either low or high).^{9,12} Specifically, high bone turnover in white patients with CKD is associated with increased cortical porosity, higher trabecular thickness, and abnormal collagen texture (woven versus lamellar osteoid and bone) compared to healthy volunteers.⁹ Data from a study of 630 bone biopsy samples obtained from African-American and white patients on dialysis with stage 5 CKD, indicated that low bone turnover is found mainly in white individuals, and is associated with low cancellous bone volume, thin trabeculae, and reduced cortical thickness.¹² High bone turnover was more prevalent in African-American patients on dialysis with stage 5 CKD than in white patients on dialysis with stage 5 CKD. Furthermore, African-American patients with stage 5 CKD had a mostly high cancellous bone volume and normal cortical thickness, but high cortical porosity.¹² These findings underscore the need for tailored approaches to studying bone quality and CKD–MBD in patients of varying ethnicities.

CKD and bone microdamage

No definitive data are available on the relationship between CKD–MBD and bone microdamage, although consideration of bone biology, material, and structure does indicate

that a relationship could exist. Specifically, bone maintains its mechanical integrity if the rate of microdamage repair equals, or exceeds, the rate of microdamage generation. If the rate of microdamage generation exceeds the rate of microdamage repair, bone cracks might accumulate, coalesce into macroscopic cracks, and ultimately become clinical fractures. The rate of microdamage generation might be increased owing to greater bone deformation caused by CKD-related high bone turnover and resulting reduced material modulus, thinner cortices, or reduced trabecular connectivity. Bone cracks will accumulate if the rate of microdamage formation remains unchanged, but the rate of microdamage repair is reduced owing to a CKD-related reduction in bone turnover. In addition, low bone turnover accompanying CKD can mimic the low bone turnover observed as a consequence of normal ageing, and the attendant compromises in microdamage repair, load-bearing capacity, and fracture risk.^{72,73} Thus, patients with CKD and with either high or low bone turnover could have increased bone micro damage and an accompanying elevated propensity for fracture, albeit from different mechanisms.

CKD and mechanical properties of bone

White female patients on dialysis with stage 5 CKD and high bone turnover have reduced nanoindentation-derived Young's modulus.²⁴ Reduced modulus signals decreased bone quality attributable to a lessening of the ability of bone to resist deformation. This effect could have adverse consequences for microdamage generation and fracture susceptibility. Reduced modulus accompanying high turnover could be attributable to an inadequate time available to reach full mineralization and achieve normal strain resistance.

CKD and bone fracture

Predialysis patients with CKD and with fractures have a lower BMD (as determined by DXA), thinner cortices, and lower trabecular bone volume (as determined by HR-pQCT) compared with predialysis patients with CKD without fractures.^{33,74} The observed structural changes in bone provide a logical explanation for the high rate of fractures in patients with CKD. Cortical and trabecular microarchitecture, (determined by HR-pQCT), was found to be superior to bone mass (determined by DXA), for discriminating patients on dialysis with stage 5 CKD and fractures from those patients who did not have fractures.⁷⁵ A different conclusion (that bone mass and bone structure independently determined by DXA and HR-pQCT, respectively, are able to discriminate fracture status) was reached in another study, however, where DXA and HR-pQCT were compared for the discrimination of fracture status in patients with CKD stages 3–5.⁷⁶

Conclusions

CKD affects many aspects of bone quality on all hierarchical levels, thus underscoring the importance of evaluating bone quality to understand CKD–MBD and its histological manifestations, such as renal osteodystrophy. The various abnormalities in material, structure, and micro damage described in this Review can contribute synergistically or antagonistically to changes in bone quality.

Nonroutinely used diagnostic methods, including invasive methods such as iliac crest bone biopsy, and noninvasive methods such as pQCT and micro-MRI, are needed for a comprehensive analysis of bone-quality abnormalities that accompany CKD–MBD. The study of bone quality should be integrated into the clinical workup and management of patients with CKD–MBD to enhance our understanding of the onset of bone quality abnormalities with reduction of kidney function, and the expected changes in response to disease progression, comorbidities, and therapeutic interventions.

Available therapeutic interventions that influence bone turnover, mineralization, or volume that can ameliorate the detrimental effects of CKD–MBD on bone quality include vitamin D-receptor agonists, calcimimetics, phosphate binders, and osteoporosis drugs, including selective oestrogen-receptor modulators, antiresorbers, and anabolic agents. Medications that have an anti anabolic effect or an inhibitory effect on mineralization, such as corticosteroids and cytochrome p450 inducers, can negatively affect bone quality and should be used with caution. Further studies on CKD–MBD and bone quality will facilitate the development of new therapeutics for this unresolved clinical problem.

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Key points

- Chronic kidney disease–mineral and bone disorder (CKD–MBD) is accompanied by histological bone changes (encompassing abnormalities in bone turnover, mineralization, and volume) called renal osteodystrophy
- Loss of bone quantity (mass) can increase fracture susceptibility, but loss of mass alone is insufficient to explain the increased occurrence of fractures, suggesting bone quality is also involved
- Bone quality, the ability to perform the mechanical functions needed, can be evaluated on various levels to quantify the structural, material, and microdamage parameters influencing the load-bearing capabilities of bone
- Abnormalities in bone structure, materials, and microdamage are associated with reduced bone-quality metrics; notably, abnormal bone modulus, strength, and toughness and can be observed in patients with CKD–MBD
- Current therapies address changes in bone turnover, mineralization, and volume; consideration should also be given to reversal of abnormalities known to influence the load-bearing capabilities of bone

Review criteria

The PubMed database was searched up to 1 August 2013 using the following search terms: “CKD”, “bone quality”, “chronic kidney disease”, “fractures”, “bone mineral density”, “end-stage renal disease”, “nanoindentation”, “FTIR”, “Raman”, “bone histology”, “pQCT”, “QCT”, “HR-MRI”, “MRI”, and “micro-CT”. All full-text, English language publications were evaluated for their relevance for inclusion in the Review. Publications from the reference lists of cited articles were also reviewed to identify additional relevant articles.

		Scale	Material properties		Structural properties and microdamage		Mechanical properties	
			Parameter	Methods	Parameter	Methods	Parameter	Methods
a	Macro		Ash content	Gravimetric analyses				
			Bone mineral density	DXA	Shape	X-ray QCT	Stiffness	Mechanical testing
			Speed of sound	QCT	Size	pQCT	Strength	FEA
				QUS	Anatomical dimensions	HR-pQCT MRI	Toughness	
b	Bone specimen					Micro-CT HR-MRI	Endurance	Fatigue testing
		~3cm–3mm						
c	Micro		Mineralization	Histology	Collagen texture	Histology	Stiffness	Microindentation
			Crystal purity	FTIR			Strength	FEA
			Crystal size	Raman	Cortical thickness and porosity	Histology		
			Crystal perfection		Trabecular thickness and connectivity	QCT		
d			Relative mineralization			pQCT		
			Collagen crosslinking ratio			HR-pQCT		
			Mineral density distribution	Backscatter electron imaging		Micro-CT	Modulus	Nanoindentation
						HR-MRI		
		~100µm						
		~75µm						
		~1µm						
e	Nano		Collagen crosslinking type	HPLC	Crystal shape, placement	Electron microscopy	NA	NA
			Elemental analysis	EDAX	Collagen spacing	X-ray imaging		
		~90nm						

Figure 1.

Illustration of the hierarchical methods and parameters used to assess bone quality. Scales of bone quality assessments from **a** | the macro-organ level, **b** | the bone specimen level consisting of cortical and trabecular bone, **c** | the micro-level showing cortical (left, viewed under polarized light and red filter) and trabecular (right, viewed using bright field light microscopy) components, both stained with modified Masson-Goldner trichrome stain, **d** | microdamage in trabecular bone (identified by arrows) stained with basic fuchsin, and **e** | the nanoscale-level of mineral crystals in the triple helix of covalently crosslinked collagen fibres (illustrated schematically). Abbreviations: DXA, dual-energy X ray absorptiometry; EDAX, energy-dispersive X-ray spectroscopy; FEA, finite element analysis; FTIR, Fourier transform infrared spectroscopy; HPLC, high-performance liquid chromatography; HR, high resolution; NA, not available; pQCT, peripheral QCT; QCT, quantitative computed tomography; QUS, quantitative ultrasonography.

Figure 2.

Fourier transform infrared spectra from bone biopsy samples from patients with stage 5D chronic kidney disease with low, normal, and high turnover. The spectra were analysed using the carbonate peak (carbonate substitution into hydroxyapatite) between 850 cm^{-1} and 900 cm^{-1} , phosphate peak (mineral) between 900 cm^{-1} and 1,200 cm^{-1} , and amide I peak (matrix) between 1,590 cm^{-1} and 1,720 cm^{-1} . Permission obtained from the American Society of Nephrology © Malluche H. H. *et al. J. Am. Soc. Nephrol.* 23, 525–532 (2012).

Figure 3.

Idealized stress–strain and load–deformation curves defining important mechanical performance metrics. **a** | In high turnover renal osteodystrophy, Young's modulus will decrease commensurate with decreases in mineralization. In low turnover renal osteodystrophy, an increase in Young's modulus is expected with increases in mineralization. **b** | In high turnover renal osteodystrophy, overall stiffness will be the net result of decreases in stiffness associated with decreases in mineralization and increased stiffness associated with altered structural parameters, that is, an increase in cortical thickness, trabecular thickness and trabecular connectivity. In low turnover renal osteodystrophy, overall stiffness will be the net result of increases in stiffness related to higher mineralization and decreases in stiffness related to decreases in structural parameters, that is, a decrease in cortical thickness, trabecular thickness, trabecular connectivity, and increased microdamage.

Figure 4.

Load and unload cycle for nanoindentation of bone from patients on dialysis with stage 5 chronic kidney disease with low, normal, and high turnover. Nanoindentation was performed by applying a maximum load of 10 mN at which a 10 s hold time was placed to ensure elastic unloading. The specimens were then unloaded to 90% of maximum load and held there for 25 s to correct for thermal drift. Permission obtained from the American Society of Nephrology © Malluche H. H. *et al. J. Am. Soc. Nephrol.* 23, 525–532 (2012).

Figure 5.

3D images of an iliac crest bone sample. **a** | Representative 3D image obtained by micro-CT imaging of cancellous segment of iliac crest bone sample. **b** | Finite element modelling of the image in part a and a 1% strain in the longitudinal direction to produce the stresses shown colorimetrically (blue equates to the least stress, yellow/green equates to more stress).