Internal Medicine Faculty Publications   Internal Medicine

4-23-2021

Bone Quality in CKD Patients: Current Concepts and Future Directions – Part I

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Bone Quality in CKD Patients: Current Concepts and Future Directions – Part I

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Abstract

Background: There is ample evidence that patients with CKD have an increased risk of osteoporotic fractures. Bone fragility is not only influenced by low bone volume and mass but also by poor microarchitecture and tissue quality. More emphasis has been given to the quantitative rather than qualitative assessment of bone health, both in general population and CKD patients. Although bone mineral density (BMD) is a very useful clinical tool in assessing bone strength, it may underestimate the fracture risk in CKD patients. Serum and urinary bone biomarkers have been found to be reflective of bone activities and predictive of fractures independently of BMD in CKD patients. Bone quality and fracture risk in CKD patients can be better assessed by utilizing new technologies such as trabecular bone score and high-resolution imaging studies. Additionally, invasive assessments such as bone histology and micro-indentation are useful counterparts in the evaluation of bone quality. *Summary:* A precise diagnosis of the underlying skeletal abnormalities in CKD patients is crucial to prevent further bone loss and fractures. We must consider bone quantity and quality abnormalities for management of CKD patients. Here in this part I, we are focusing on advances in bone quality diagnostics that are expected to help in proper understanding of the bone health in CKD patients. ***Key Messages:*** Assessment of bone quality and quantity in CKD patients is essential. Both noninvasive and invasive techniques for the assessment of bone quality are available.
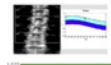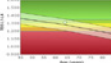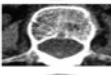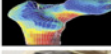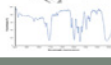
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Published by S. Karger AG, Basel

Introduction

CKD affects 8–10% of the population [1]. The fracture risk in CKD patients increases with worsening kidney function, suggesting specific CKD-related causes. Bone disease is a major complication of CKD and is a manifestation of CKD-mineral bone disorder. Renal osteodystrophy (ROD) is an alteration of bone morphology in patients with CKD and is a measure of the skeletal compo-

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	PROS	CONS
PTH & bone turnover markers	• Noninvasive • Aids in prediction of bone turnover	• Because of renal clearance, osteocalcin, P1NP and CTX has limited use in CKD
BMD- DEXA	• Widely available and noninvasive • Low radiation exposure & used in FRAX • Correlates with cortical porosity in CKD	• Unable to assess type of ROD • Assess areal density only • Cannot distinguish cortical from trabecular bone
Trabecular bone score	• Noninvasive, Independent fracture predictor • Can be applied retrospectively to DEXA • No extra radiation, time and expense	• Cannot detect type of ROD • Image noise degrades resolution • Variability among various software's
Quantitative ultrasound	• Non invasive with no radiation exposure • Portable • Correlates with BMD-DEXA	• Only at distal extremity sites • Inter-observer variability • Lack of fracture predictability data in CKD
QCT	• 3D volumetric assessment of spine and femur • Not affected by extra skeletal calcification	• High radiation exposure • Expensive and cannot detect type of ROD
HRpQCT	• Assesses microarchitecture noninvasively • Good cortical and trabecular differentiation • Correlates with bone histopathology	• Expensive and not widely available • Investigational tool only • Only distal extremity site (tibia and radius)
HR-MRI	• Non-ionizing • Can image central bones (hip)	• Expensive • Not widely available
Finite element analysis (FEA)	• Improves bone quality assessment by CT and MRI • Aids CT and MRI in evaluating mechanical properties & fracture prediction	• Lack of standardization • Various loading conditions can affect the estimation of strength
Reference point indentation	• Good in-vivo measure of bone stiffness & quality • Correlates well with fracture risk • Correlates with BMD and TBS in CKD	• Invasive and can cause local complications • Does not represent whole bone strength • Does not detect type of ROD
Bone biopsy	• Gold standard as it directly assesses bone turnover, mineralization and volume • Assess bone marrow, can detect heavy metals and micro-cracks	• Invasive and cannot detect whole bone strength • Not widely available and needs expertise
FTIR & nano-indentation	• Provides data on bone material properties • Adds additional information about bone quality	• Limited availability and needs bone tissue • Only provides relative measures of mineral/matrix etc

Fig. 1. The pros and cons of each method of bone quality assessment in CKD patients.

nent of the systemic disorder of CKD-mineral bone disorder, which is quantifiable by histomorphometry [2].

Because of the ease of use and widespread availability of dual-energy X-ray absorptiometry (DEXA), operationally the World Health Organization (WHO) defined osteoporosis as a reduction in bone mineral density (BMD) t scores of ≥2.5 standard deviations from the mean value in young adults [3]. This definition is now routinely used worldwide in clinical practice for the diagnosis of osteoporosis. Fractures may also occur, however, with low-energy trauma in non-osteoporotic patients, as classified based on their BMD t scores [4–6]. In 2000, the NIH defined osteoporosis as "a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture." Bone strength reflects the integration of 2 main components: bone quantity and bone quality [7].

Thus, bone quantity (assessed by DEXA to give 2-dimensional areal BMD or with quantified 3-dimensional quantitative computed tomography [QCT] for volume) is only one component. Bone quality is a second major component and includes bone remodeling abnormalities, collagen cross-linking, and mineralization properties. Remodeling abnormalities are generally evaluated with bone biopsy and dynamic histomorphometry (tetracycline labeling), and such abnormalities are nearly universal in patients with CKD [8].

WHO developed a Fracture Risk Assessment Tool (FRAX) in the general population [9]. The addition of BMD to the FRAX score improves the prediction of fracture risk; however, bone quality is not included in this tool. There is an option to say yes or no to secondary osteoporosis; however, this does not include CKD. It might be useful to add bone quality measurement in the general population and the CKD as a secondary cause of osteoporosis to improve fracture risk prediction.

Bone quality can be evaluated by studying bone volume, microarchitecture, material properties, and microdamage. All these factors can be assessed at macro, micro, and nano hierarchical levels by various diagnostic modalities [10]. Of the spectrum of methods available to assess bone quality from several different perspectives, we describe the clinically relevant ones. The pros and cons of each method of bone quality assessment in CKD patients are included in Figure 1.

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PTH and Bone Turnover Markers

Bone turnover markers (BTMs) give an idea of the bone resorption and bone formation rate. They provide an integrated dynamic assessment of skeletal metabolism and facilitate ROD management [11]. Bone formation markers including bone-specific alkaline phosphatase (BSAP), osteocalcin, and procollagen type-1 N-terminal propeptide (P1NP) are markers of osteoblast function. Bone resorption markers such as tartrate-resistant acid phosphatase 5b (Trap-5b) and C-terminal telopeptides of type I collagen (CTX) are markers of osteoclast function. BSAP and Trap-5b are not cleared by the kidneys, hence used in CKD patients. On the other hand, osteocalcin, P1NP monomer, and CTX are cleared by the kidneys, and their usefulness in CKD patients remains unclear. Serum intact PTH (iPTH) and BSAP are the most commonly used turnover markers to discriminate renal bone disease. In dialysis patients, Sprague et al. [12] reported that iPTH and whole PTH (wPTH) level of <2 times the upper limit of normal had a sensitivity of 65 and 74% and a specificity of 67 and 57%, respectively, for low-turnover bone disease (LTBD). iPTH and wPTH of >9 times the upper limit of normal showed a sensitivity of 37 and 31% and a specificity of 86 and 88%, respectively, for high-turnover bone disease (HTBD) [12]. Monier-Faugere et al. [13] studied PTH-(1–84)/-(7–84) ratio. They found that a ratio of >1 had 100% sensitivity for HTBD, and a ratio of <1 had 100% sensitivity for LTBD. Ureña et al. [14] demonstrated that BSAP >20 and <20 ng/mL has 100% sensitivity and specificity for HTBD and LTBD, respectively, in hemodialysis (HD) patients.

BTMs also assist in bone loss and fracture risk prediction in CKD patients. In a cross-sectional study, Nickolas et al. reported that osteocalcin, P1NP, and Trap-5b discriminated fracture status in pre-dialysis CKD patients independent of BMD. They also noted a strong relationship between iPTH and BTMs, trabecular volumetric BMD, and microarchitecture compared to cortical volumetric BMD or thickness. They explained this by the effect of hyperparathyroidism preferentially on the metabolically active trabecular bone [15]. However, the same group, in a more recent longitudinal study of CKD patients (including dialysis), showed that hyperparathyroidism and high BTMs were associated with decreased cortical density and thickness but not with trabecular changes [16].

Laowalert et al. [17] in a recent study found that serum iPTH >484.5 or TRAP-5b >1.9 pg/mL has 92% sensitivity and 50% specificity for prediction of HTBD in Asian HD patients. The sensitivity goes down to 58% but the specificity goes up to 100% when they combined both. Limori et al. [18] found that iPTH levels of <150 or >300 pg/mL along with higher BSAP levels (>19.9 μg/L) were associated with a higher fracture risk in ESRD. Perrin et al. [19] reported that iPTH levels ≥130 pg/mL at 3 months post-transplantation predicted incident fractures in kidney transplant recipients.

In our laboratory, we previously studied FGF23 as a potential bone marker in adult dialysis patients. FGF23 correlated well with mineralization parameters. Patients with very high FGF23 levels had normal mineralization lag time [20]. Activin A is considered a regulator of bone turnover and is one of the markers of increased osteoclast activity [21]. Our group previously reported that serum activin A is one of the first biomarkers that goes up in ROD and correlates well with bone turnover [22].

Sclerostin levels increase with CKD progression, and its serum levels are associated with cardiovascular events [23, 24]. Osteocytes are the main source of sclerostin, though kidney, liver, and vascular wall can secrete it too [25]. Mare et al. [26] reported a negative correlation between skeletal and circulating sclerostin levels with histomorphometric measures of bone turnover. Cejka et al. [27] previously described a promising role of serum sclerostin level in addition to iPTH in the diagnosis of HTBD in dialysis patients. Furthermore, Malluche et al. [28] found that baseline serum sclerostin and Trap-5b levels predicted bone loss. Circulating sclerostin is dialyzable, so timing of blood draw is crucial while interpreting the results in dialysis patients [29]. Furthermore, in patients undergoing peritoneal dialysis, sclerostin is present in very high concentrations in the peritoneal fluid [30]. Thus, the utility of serum sclerostin as a BTM in CKD, especially in HD and peritoneal dialysis patients, is yet to be determined.

DEXA Scans: BMD and Trabecular Bone Score

It is challenging to diagnose osteopenia based on plain radiographs. Conventional X-ray films are insensitive to the changes in BMD. Patient might lose up to 50% of bone mass before it can be detected on a lumbar radiography [31]. Moreover, it is a subjective rather than objective tool with a significant interobserver variabilities. The agreement between the readers for the diagnosis of osteopenia based on X-ray was achieved only in 43% of all radiographs [32].

Although it is widely available and a good test for bone quantity, DEXA areal BMD does not detect the type of ROD in CKD patients and cannot evaluate bone quality. Other limitations of DEXA scans include the confounding effects of surrounding soft tissue, bone artifacts caused by osteoarthritis, degenerated disks, vertebral compression fractures, and aortic calcification, which are not uncommon in CKD patients. However, femoral BMD is correlated with cortical porosity histomorphologically in dialysis patients [33]. Because DEXA is a 2-dimensional technique, it also cannot be used to measure true volumetric BMD (vBMD) and bone size or to separate trabecular from cortical bone. Thus, a large bone will yield a higher areal BMD than a small bone, although the vBMD would be the same.

Fractures occur in 30–50% of people with normal BMD. This might be due to lack of capturing of poor bone quality by DEXA scans. Trabecular bone score (TBS) captures vertebral trabecular texture from the lumbar DEXA images [34]. It is a noninvasive tool to assess bone microarchitecture. TBS does not add any extra time, cost, or radiation exposure to the DEXA scans. The TBS software can be applied retrospectively to BMD images to better assess the bone quality and thus the fracture risk. TBS software has been modified over the past few years. TBS-v1 algorithm was the initial software utilized to assess bone quality, which was developed after studies on females with average body habitus. The reference values could not correlate well in male population or people with a BMI of <15 or >35. TBS-v2 algorithm was developed to counter the shortcomings of the previous TBS version, and it has improved the fracture prediction [35].

Certain conditions like CKD, diabetes, obesity, and long-term glucocorticoid use have increased fracture risk despite normal BMD. All these conditions affect bone quality, particularly trabecular microarchitecture. TBS can be extremely helpful in predicting fracture risk and assessment of bone quality in these circumstances [36–38]. TBS is usually low in patients with CKD including dialysis patients [39]. TBS correlated better with incidence of fracture in pre-dialysis CKD, dialysis patients, and kidney transplant recipients, as compared to BMD [40, 41]. In a multivariate analysis in ESRD patients by Ramalho et al. [42], TBS was correlated with trabecular bone volume and trabecular width histopathologically. However, Holloway-Kew et al. [43] found that TBS and BMD did not correlate with prior history of fractures in CKD patients compared to micro-indentation parameters.

Perez-Saez et al. [44] reported that despite a persistent decline in the BMD, TBS and bone quality stayed normal up to 10 years after kidney transplantation. Furthermore, Silva et al. [40] previously reported that TBS can be used as a tool to assess the response to different therapeutic interventions. They demonstrated a maximal TBS improvement with teriparatide followed by denosumab and tamoxifen, then bisphosphonates in older women.

Quantitative Ultrasound

Quantitative ultrasound (QUS) machines employ waves with lower frequencies compared to the conventional soft tissue US. The studied skeletal sites are the distal metaphysis of the phalanx, the calcaneus, the radius, and the tibia. All these sites are predominantly cortical bone, except the calcaneus, which is mainly composed of trabecular bone [45].

As QUS waves propagate through the bone, their velocity reflects the material properties of the bone such as its density, architecture, and elasticity. The degree of attenuation of the wave amplitude, measured by broadband ultrasound attenuation, is influenced by trabecular separation and other structural characteristics of trabecular bone. Several other more complex wave parameters such as shape (number of peaks), bone transmission time, and amplitude-dependent speed of sound (SOS) have been developed, and these have been correlated with several bone properties measured by micro-CT [46].

In the 1990s, studies on QUS showed that SOS measured in bones such as tibia inversely correlated with dialysis vintage and iPTH levels [47]. Similarly, in a study employing phalangeal QUS in HD patients, amplitude-dependent SOS was significantly lower compared to control groups, and it was negatively correlated with iPTH levels [48]. Furthermore, HD patients had reduced calcaneal broadband ultrasound attenuation and SOS scores compared to controls, and there was a significant association between calcaneal QUS parameters and DEXA scans [49]. QUS measures have been correlated with DEXA at both phalanges and calcaneus [50, 51]. In osteoporotic patients, QUS measurements have been used to monitor the effects of treatment with alendronate, raloxifene, and teriparatide [45]. Ten-year fracture risk probabilities have been calculated using QUS measures in osteoporotic patients [52]. However, the predictive value for CKD patients has not been studied, and it is an interesting potential topic for future research. It might also have an application in monitoring of therapy in ROD.

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Quantitative Computed Tomography

QCT is an in vivo diagnostic modality that can be applied to the axial or appendicular skeleton, where large body segments such as hip or spine are imaged to measure vBMD. One of the main advantages of QCT, particularly in CKD patients, is that it is not confounded by the presence of extra-osseous calcium, which can be a problem with DEXA scans. It also better identifies bone loss over time compared to DEXA in HD patients [53]. The disadvantages of this method include high radiation exposure and cost and it does not assess the type of ROD.

High-Resolution Peripheral Quantitative Computed Tomography

High-resolution peripheral quantitative computed tomography (HRpQCT) is another tool that employs narrower slice width and field of view compared to QCT and maximizes spatial resolution using image reconstruction algorithms. It is a good tool to assess bone microarchitecture (cortical porosity and trabecular connectivity) and vBMD at distal extremity sites such as distal radius and tibia. It provides more detailed information about bone microstructure than QCT, which does not detect trabecular thickness or cortical porosity [10]. Measurement of bone microarchitecture by HRpQCT in addition to BMD can explain the variance in bone strength. Studies using HRpQCT have demonstrated a preferential loss of cortical bone in CKD patients [16]. In CKD stages 2–4, before the onset of secondary hyperparathyroidism (SHPT), impairment of trabecular bone is noted with HRpQCT, and this could explain the increased risk of fractures in early CKD. As CKD progresses and SHPT ensues, with increased turnover, bone loss assessed by HRpQCT is predominantly cortical and is highly associated with fractures in weight-bearing and non-weight-bearing sites [16, 54]. Measures of bone microarchitecture obtained by HRpQCT have been validated against bone micro-CT [55]. Nickolas et al. [15] in a cross-sectional study in pre-dialysis patients demonstrated that several HRpQCT measures of microarchitecture were significantly lower in patients with fractures. In CKD patients with HTBD and osteoporosis, there is cancellization of endocortical bone. This cancellization can confound cortical measurements obtained by HRpQCT and can lead to errors in quantifying changes in trabecular and cortical morphology [56].

High-Resolution Magnetic Resonance Imaging or Micro-Magnetic Resonance Imaging

High-resolution magnetic resonance imaging (HR-MRI) or micro-MRI is a noninvasive and nonionizing method for the quantification of bone microarchitecture. Whereas HRpQCT is limited to places like ankle and wrist, HR-MRI can measure other sites like the proximal femur. In a small cross-sectional study in patients with ROD, MRI indices of trabecular network integrity correlated with histomorphometric trabecular bone volume, separation, and thickness. HR-MRI parameters also correlated with trabecular separation measured by micro-CT and turnover indices [57]. Parameters of bone microarchitecture obtained by both HR-MRI and HRpQCT have been correlated with bone strength using finite element analysis (FEA) [58, 59].

Finite Element Analysis

FEA is a computational method that provides information on bone quality, microarchitecture, fracture risk, and mechanical properties. It can be generated through QCT, HRpQCT, or MRI data. CT-based FEA improved assessment of bone strength compared to DXA or QCT but is not standardized, and variability in loading conditions can affect the strength estimates [60, 61]. MRI-based FEA improved diagnosis precision, predicted fracture, and was useful for monitoring bone loss and response to treatment [61]. HRpQCT-based FEA cortical thickness and volume correlated with BTMs, while cortical porosity correlated with PTH in a cross-sectional study in ESRD patients [62]. MRI-based micro-FEA mechanical parameters significantly decreased 6 months after kidney transplantation, but structural parameters did not change significantly by using micro-MRI only [59].

Reference Point Indentation

Reference point indentation (RPI) is a less invasive measure of bone material strength (BMS) compared to bone biopsy. The RPI instrument performs bone indentation testing by inserting a probe assembly through skin and subcutaneous tissues directly onto the surface of the bone after displacing the overlying periosteum in a very small area. Microscopic fractures are then induced on the surface of the bone, and bone mechanical properties at tissue level are measured. Local infection and edema may

preclude the use of these methods. People on anticoagulants need special attention to hemostasis [63]. Osteoprobe is a newer version of RPI that measures bone material properties by evaluating the BMS index without displacing the periosteum or using a reference probe [64, 65]. Patients with atypical femoral fractures have significant abnormalities in BMS measurements using the RPI methods despite having normal DEXA-BMD scores [66].

Bone Biopsy and Histopathology

Bone biopsies are performed at the anterior iliac crest after double tetracycline labeling [67]. For diagnostic purposes, pathologists perform a qualitative comprehensive assessment of the bone specimens [67, 68]. In addition, for research purposes, quantitative histomorphometric analysis of bone sections may be used. Furthermore, bone quality and mechanical properties can be evaluated using various methods such as Fourier transform infrared (FTIR) spectroscopy, FEA, and nano-, micro- and macro-indentation [69, 70].

In 2006, the Kidney Disease: Improving Global Outcomes (KDIGO) introduced the notion that bone histological abnormalities in patients with CKD should be characterized by bone turnover, mineralization, and volume [71]. Bone turnover is classified as low, normal, or high. Mineralization is characterized as normal or abnormal, and volume as low, normal, or high. The "abnormal" mineralization may include defective or precipitous diffuse mineralization as in woven osteoid [72]. This classification should help the clinicians to focus on correcting the bone abnormalities observed in their patients and direct appropriate therapies.

In patients with CKD stages 2–5 before dialysis, various abnormalities have been described ranging from mild increase in bone turnover resulting from moderate SHPT, with or without mineralization defect [73–75], to various degrees of LTBD [76]. In an ongoing study, we found that the majority of adult patients with CKD stages 2–5 predialysis have low or low-normal bone turnover without mineralization defect. When patients reach ESRD, the bone abnormalities usually intensify. The spectrum of ROD histological features is very wide and has evolved over time. Traditionally, the various forms of ROD encompass predominant SHPT, adynamic bone disease, low turnover osteomalacia, and mixed uremic osteodystrophy. Predominant SHPT bone disease is characterized by HTBD with increased formation and resorption surfaces. Osteoid volume and surface are high with numerous irregular osteoblasts and osteocytes. In some areas, osteoid and mineralized bone lose their normal lamellar structure and become irregularly "woven." The resorption surfaces are high and resorption lacunae are deep with abundant multinucleated large osteoclasts. In addition, formation and resorption surfaces may be covered by peritrabecular fibrosis, which can extend deeply into the bone marrow. Under fluorescent light, the extent of tetracycline double labeling is high and may show diffuse uptake in woven osteoid. The cancellous bone volume/tissue volume may be low, high, or normal, whereas cortical bone exhibits a high degree of porosity.

At the other end of the spectrum, patients may present with adynamic bone disease, where bone turnover is very low with paucity of bone formation sites and osteoblasts. Osteoid volume and surface are low with thin osteoid seams. Osteoid and bone are mostly lamellar but may show some remnants of woven structure from previous overactivity. Similarly, bone resorption surfaces may vary from low to slightly elevated. Under fluorescent microscopy, the mineralizing surfaces are mainly low with few thin passive single labels. Cancellous bone volume and cortical thickness are usually low.

Low-turnover osteomalacia in CKD patients is characterized by a severe mineralization defect with very high volume and surface of osteoid and wide osteoid seams. There is a paucity of osteoblasts. Resorption surfaces and osteoclasts may be seen on the few bone surfaces not covered with osteoid. The tetracycline uptake is minimal and consists of few thin single labels. This usually happens in patients with aluminum toxicity, where aluminum can be seen at the mineralization front. The cancellous bone volume and cortical thickness and porosity may vary from low to elevated.

Mixed ROD represents a combination of various degrees of SHPT along with signs of mineralization defect (osteomalacia). Bone volume and cortical thickness may vary.

The spectrum of bone diseases has evolved over the years [77]. In the early 1980s, there was a predominance of mixed ROD and low turnover osteomalacia (in the most severe cases) due to aluminum intoxication in ESRD patients. With prevention of aluminum toxicity in the subsequent years, the main histological forms of ROD consisted of various degrees of SHPT bone diseases. In the mid-1980s, the frequency of "aplastic" [78] or adynamic [79] bone disease increased significantly. Moreover, there are differences in the prevalence of the various histological forms of ROD between black and white patients with CKD. Black patients are less prone to develop LTBD and low bone volume [72, 73, 80–82].

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In post-kidney transplant patients, several factors influence bone diseases such as pre-existing ROD, immunosuppressive therapy, and suboptimal kidney function. One of the prominent effects of renal transplantation is bone loss [83] with low bone volume/tissue volume and decrease in bone turnover [84–86]. Focal or generalized mineralization defects are also not uncommon [85].

Bone histomorphometry is mainly used for research [87, 88]. The parameters that characterize bone turnover include bone formation rate/bone surface and activation frequency as well as number of osteoblasts and osteoclasts. Bone formation rate/bone surface relates exclusively to the level of bone formation, whereas activation frequency includes also parameters of bone resorption and quiescent periods and indicates the frequency at which the bone is completely renewed. Defective mineralization is defined as osteoid thickness >20 μm and mineralization lag lime >100 days. Volume encompasses cancellous bone volume/tissue volume, trabecular thickness, and separation as well as cortical thickness and porosity. Normal values vary by age, gender [89, 90], and race.

FTIR Spectroscopy

FTIR provides another way to measure bone quality on bone biopsy specimens. The chemical bonds between the components of bone matrix and mineralized bone, like all chemical bonds, undergo vibrations. The parameters of FTIR spectroscopy pertinent to bone material properties that are measured include (a) mineral to matrix ratio, (b) mineral maturity/degree of crystallization, (c) collagen cross-linking ratio (the relative proportion of mature to immature collagen), and (d) carbonate/phosphate ratio [91].

Malluche et al. [92] previously reported that mineral to matrix ratio is lower in dialysis patients with HTBD. This finding on FTIR in patients with HTBD correlated with lower hardness, as measured by nano-indentation techniques. There is shortened duration of remodeling cycle in HTBD, and this can lead to diminished duration of mineralization. This interferes with bone quality and leads to decreased bone stiffness [92]. In LTBD dialysis patients, there was no reduction in mineral to matrix ratio compared to normal controls. Hardness measured by nano-mechanical properties in this group was not decreased. However, the microstructural properties of bone, as measured by histomorphometry, such as trabecular volume and thickness were noted to be lower [92].

When combined with histological evaluation of the bone, FTIR can add valuable information on the bone material properties. As another example, changes in collagen cross-link ratio strongly suggest that factors other than bone turnover may be playing a role in the clinically manifested fragility. FTIR technique is not widely available, and it needs human tissue from a bone biopsy. FTIR can only measure relative quantities of minerals and matrix and the varying cross-link types and no absolute quantitation can be provided.

Micro-Computed Tomography

Micro-computed tomography is an ex vivo technique used to image small (millimeter-sized) bone samples using high amounts of radiation and can provide high-resolution 3D bone microstructural data [10]. It is not a clinically available technique but is considered the gold standard for measurement of bone structure against which other in vivo modalities are usually compared [57]. Sharma et al. [93] reported that micro-computed tomography was able to detect the deterioration of cortical microarchitecture in CKD patients. Of note, their cohort of patients did not have trabecular abnormalities.

Conclusion

CKD-induced bone quality and quantity abnormalities are complex disorders that confer high morbidity and mortality in the CKD population. Proper diagnosis of the actual underlying skeletal problems helps to prevent future bone loss and fractures. Once the diagnosis of ROD has been established, knowing the bone quality and turnover abnormality could help predict the fracture risk.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

Funding Sources

Author Contributions

All authors contributed equally in reviewing the literature and writing the manuscript.

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