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REVIEW

The use of bone mineral density measured by dual energy X-ray absorptiometry (DXA) and peripheral quantitative computed microtomography in chronic kidney disease

Martin Jannot[1] · Fabrice Mac-Way[2] · Vanessa Lapierre[1] · Marie-Helene Lafage-Proust[1]

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Abstract Chronic kidney disease (CKD) is a risk factor for fractures. The current evaluation of fracture risk is based upon the combination of various clinical factors and quantitative imaging of bone. X-ray-based tools were developed to evaluate bone status and predict fracture risk. Dual energy X-ray absorptiometry (DXA) is available worldwide. Longitudinal studies showed that low areal Bone Mineral Density (BMD) measured by DXA predicts fractures in the CKD population as it does in non uremic populations, with good specificity and moderate sensitivity. Peripheral quantitative computed tomography (pQCT) and high resolution pQCT are research tools which measure volumetric BMD at the tibia and radius. They are able to discriminate between the cortical and trabecular envelopes which are differentially affected by renal osteodystrophy. In CKD, a rapid thinning and increased porosity at the cortex is observed which is associated with increased the risk for fracture.

Keywords DXA · pQCT · HRpQCT · Fractures · Chronic kidney disease · Bone

Introduction

Patients with chronic kidney diseases (CKD) stages 3a–5d have higher risk for fractures than the general population, worldwide [1–5]. In addition, incident hip fractures are associated with substantial worsening of morbidity and mortality in dialyzed patients [6–8]. However, there is little consensus on the methods for evaluating bone status in CKD patients. To date, no large clinical trials specifically targeting CKD patients for testing the efficacy of treatments currently used for osteoporosis have been performed. Thus, we need to develop and validate diagnosis and treatment strategies for better management of bone fragility in this population. The current evaluation of fracture risk is based on a combination of various clinical factors plus quantitative imaging based on X-Ray attenuation by bone. As it passes through bone, the X-ray beam loses part of its energy, due to photon absorption (removal from the beam) and scattering (change of direction). The amount of attenuation depends on the intensity of the incident X-ray beam and the physical properties of bone (including the amount of minerals and the size of the bone). This allows to image bone and, eventually, after calibration, to deduce quantitative parameters such as bone mineral density (BMD).

Determinants of bone strength

Fractures occur when the load in a region of a bone exceeds the ultimate strength of that bone. The risk of fracture increases with falls and trauma in combination with a decrease in bone strength (illustrated in Fig. 1) [9]. Bone strength results from bone loss (i.e. reduced bone quantity) and/or reduced bone quality [10]. Bone quantity (i.e. bone mass) ensues, in adults, from the bone remodeling balance, which is determined by a number of elements including genomic, hormonal, nutritional and mechanical factors. Bone loss occurs when bone is more resorbed than formed. The level of bone remodeling (turnover) is defined by the

✉ Marie-Helene Lafage-Proust
lafagemh@univ-st-etienne.fr

[1] INSERM 1059, SAINBIOSE, Université de Lyon, CHU 42023-42055, Saint-Etienne Cedex 2, France

[2] Centre de Recherche du CHU de Québec, Hôpital Hôtel-Dieu de Québec, Division of Nephrology and Endocrinology, Laval University, 0877, 10 McMahon, Québec City, Québec G1R 2J6, Canada

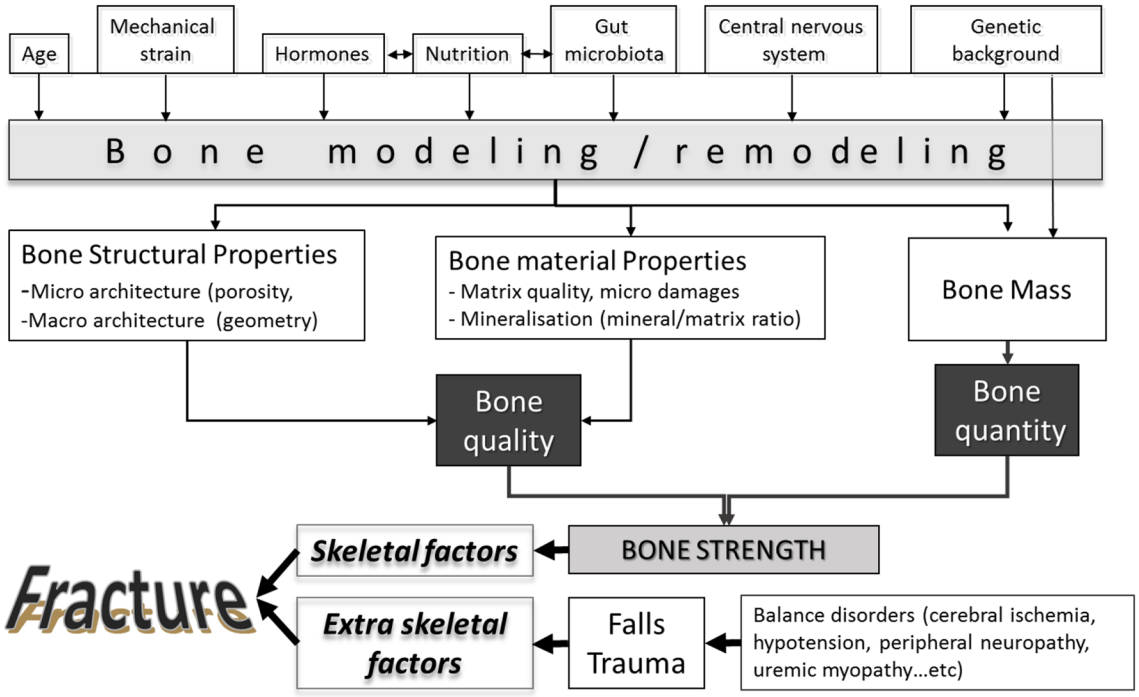

Fig. 1 Schematic illustration of determinants of fracture

'activation frequency' which represents the birth rate of bone remodeling units. Bone quality depends on both bone material and structural properties [11]. Structural parameters correspond to bone micro- and macro-architecture (i.e. geometry and topology), while material properties depend on the quality of bone mineral and matrix. Microarchitecture (e.g. cortical porosity, trabecular number/thickness and spatial distribution) impacts bone strength at both cortical and trabecular levels. Bone mass and some of the structural properties can be evaluated using X-ray based tools. In addition, macro- and micro-architecture parameters, combined or not with mineral density data, are used for modeling biomechanical properties of bone. The spatial distribution of cortical bone is computed via several parameters, which allow to predict cortical bone strength. For instance, the cross-sectional moment of inertia reflects the distribution of the bone mass around a neutral or central axis of the bone and the buckling ratio is the ratio of the outer radius to the cortical thickness [12]. Other engineering methods such as finite element analysis (FEA) allow to test virtual mechanical stress on bones to evaluate bone strength.

Deterioration of bone strength in CKD

CKD affects both structural and material properties of bone [13]. Bone primary and secondary mineralization are substantially impaired by renal insufficiency which leads to a decrease in material properties. Indeed, primary mineralization slows down or even ceases when osteomalacia or uremic mixed lesions occur while secondary mineralization (which takes place after primary mineralization, once the new bone osteons have been formed) can be increased in adynamic osteopathy or decreased in osteitis fibrosa.

Evaluation of bone fragility

The main characteristics of the quantitative X-ray-based devices are summarized in Table 1.

Standard X-rays and morphological evaluation of bone for fracture detection

Standard skeletal X-rays are useful morphological tools to detect fractures or fissures. This evaluation is guided by clinical symptoms and thorough physical examination. Indeed, while some fractures such as hip fractures are obvious on standard X-ray, others such as tarsal, metatarsal or rib fissures can remain difficult to assess and necessitate further evaluations, including technetium bone scans coupled to computerized tomography or magnetic resonance imaging (MRI) (Fig. 2). As for vertebral fractures, it is well known that they are underdiagnosed [14] and that spine fractures observed on lateral chest X-rays are often overlooked or not reported [15]. Osteopenia (i.e. reduction in bone density on

Table 1 Main characteristics of X-ray based tools used for assessment of bone status

	IN VIVO				EX VIVO	
	DXA	QCT	pQCT	HR-pQCT	Micro-CT Nano-CT	Biopsy
Resolution µm	3000	3000–1000	500	80–100	10 −1 µm and <1 µm	5–10 µm
Bone mineral density	Areal BMD g/cm^2	←	Cortical and trabecular volumetric BMD g/cm^3		→	–
Information provided by the device	Trabecular bone score (TBS)	←3D cortical macro architecture→		3D cortical macro-architecture cortical porosity trabecular µ architecture	3D cortical porosity trabecular µ architecture	2D micro architecture
Bone site	Hip spine	Hip spine	Tibia radius	Tibia radius	Any bone small samples	Iliac crest

DXA dual energy X-ray absorptiometry, *QCT* quantitative computed tomography, *pQCT* peripheral QCT, *HR-pQCT* high resolution pQCT, *BMD* bone mineral density, *µ* micro

radiographs) can be found on plain X-rays; however, this sign is observed when more than 30–40% of bone has been lost. In CKD, thin cortices or endocortical resorption can be detected, indicating more or less the severity of renal osteodystrophy. It is worth noting that standard X-ray is not sufficient to confirm or exclude the diagnosis of osteoporosis.

High-resolution X-ray images can be used to analyze bone texture, a surrogate of trabecular microarchitecture, via fractal analysis methods. The combination of this technique with BMD measurements has been shown to better predict fractures in osteoporotic women than BMD alone [16]. However, this technique is not widely available and there are no data on CKD patients.

Dual energy X-ray absorptiometry

Bone mineral density

DXA measures areal bone mineral density (g/cm^2) at the hip (neck and total regions), the spine (L1/L2 to L5) and the radius (ultradistal, distal and proximal regions). The results are expressed as a T-score, i.e. the number of standard deviations above or below the mean BMD measured in sex-matched 25-year-old healthy subjects (i.e. at the end of peak bone mass acquisition). Densitometric osteoporosis is defined by a T-score lower than −2.5. Spine BMD may be overestimated due to vertebral osteoarthritis or aorta calcifications. Areal BMD is influenced by body size, which is a major limitation for its use in pediatric CKD populations. Epidemiological studies have clearly identified low BMD as a fair predictor of osteoporotic fractures. However, in a non-uremic population, up 40–50% of patients with osteoporotic vertebral fractures have BMD values higher than −2.5 [17], indicating that factors other than BMD must be taken into account when evaluating the fracture risk [18]. For instance, a prevalent fracture is unequivocally a risk for future fracture. Indeed, patients with fractures are at higher risk for future osteoporotic fractures of the spine, wrist and hip compared to patients with similar BMD with no fractures [19] and prior vertebral fractures are a better predictor of future fracture than low BMD alone [20].

Vertebral fracture assessment (VFA)

Two-thirds of patients with vertebral fractures (VF) are asymptomatic; therefore, these fractures are often ignored while it is essential, as seen above, to identify previous vertebral fractures. Lateral imaging of the spine using fan-beam methodology (which eliminates parallax errors in viewing the vertebral body, compared to routine spine X-ray) can be performed on the same device as DXA BMD measurement. These images are then analyzed by the VFA software which allows to identify prevalent vertebral fractures. However, the automatic fracture detection provided by the VFA software needs to be checked by a trained physician [21].

Trabecular bone score (TBS)

TBS is derived from an algorithm that analyzes the spatial organization of pixel intensity, which in turn corresponds to the differences in the X-ray absorption power of an osteoporotic bone versus a normal trabecular pattern [22]. TBS is not a direct measurement of bone microarchitecture but it is related to bone microarchitecture parameters.

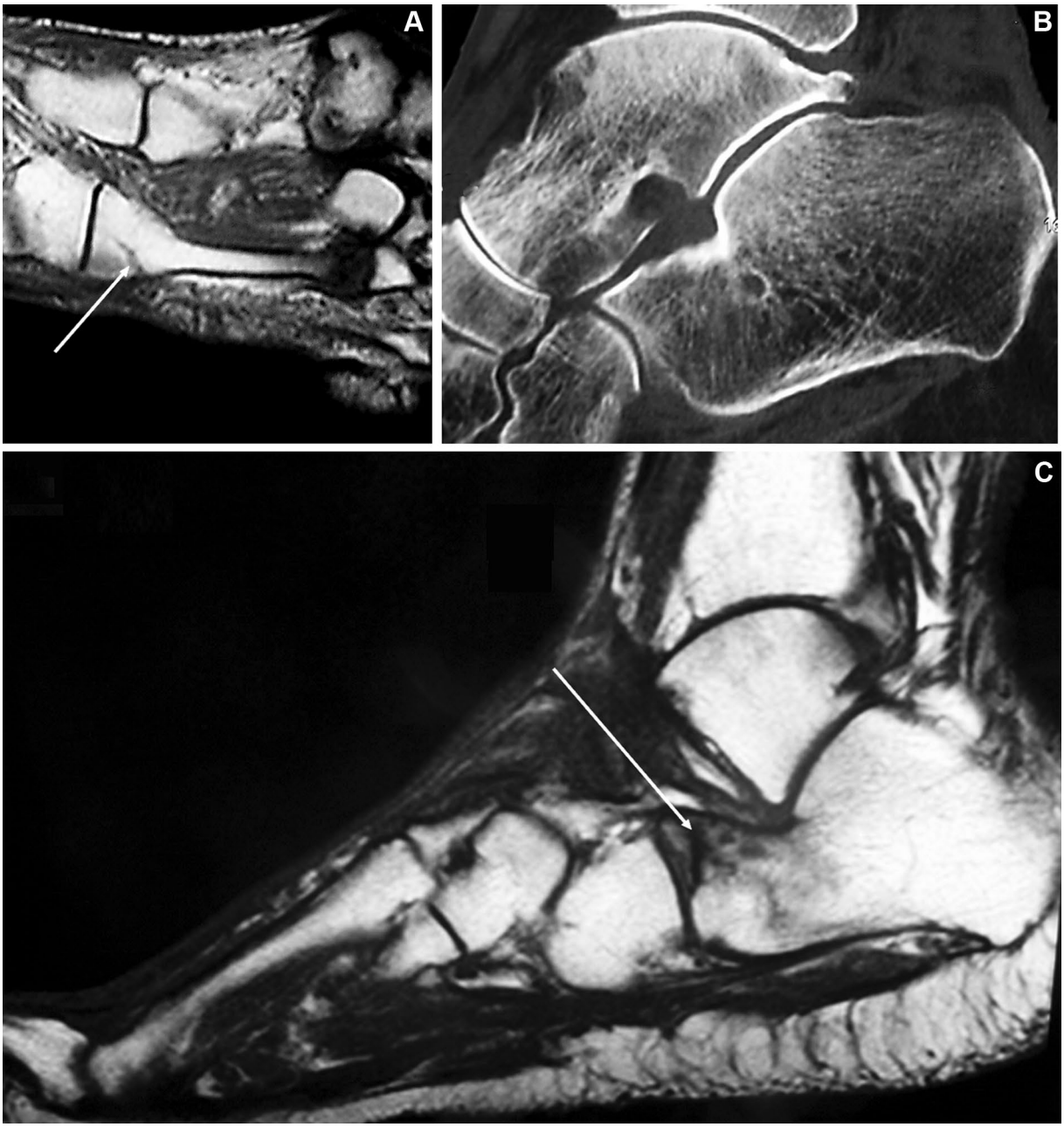

Fig. 2 a, b MRI T1-weighted imaging of the foot in a CKD-5D 75-year-old patient referred for "subacute arthritis of the foot". *Arrows* fracture localized at the proximal metaphysis of the first metatarsal bone (**a**) and anterior part of the calcaneus (**b**). **c** Standard X ray: The calcaneus fracture is barely visible

Neck geometry and hip structural analysis

Due to a better understanding of bone biomechanics and of the role of geometry in bone strength, a number of techniques has been derived from DXA hip measurements such as hip structural analysis (HSA). The major limitations of these approaches are mainly due to the bi-dimensional nature of DXA measurements. HSA parameters correlate with BMD. Whether they provide additional information independent of BMD and improve fracture prediction is still a matter of controversy [23].

FRAX for evaluating fracture risk at the individual level

We have seen above that BMD measurement is a fair but not perfect predictor of fractures in the general population, in which 1/3 of fractures occur in patients with BMD higher than −2.5 [24]. The FRAX tool combines BMD

measurement at the femoral neck and clinical risk factors for fracture such as weight, height, prevalent fracture, family history of hip fracture, and steroid use, but it does not take falls into account. This software, a World Health Organization (WHO) initiative, calculates the 10-year probability of hip fracture and major osteoporotic fractures at the individual level. Major osteoporotic fractures include hip, vertebral, wrist and humeral fractures.

DXA in CKD

At the radius, both cortical and trabecular measurements may be affected by the fistula in CKD-5d patients. Bone mineral content is not influenced by hemodialysis sessions [25]. BMD measured by DXA integrates bone quality and quantity properties but BMD does not provide any information on the underlying renal osteodystrophy. BMD measurement by DXA was not recommended by the 2009 Kidney Disease Improving Global Outcomes (KDIGO) guidelines, but only cross-sectional studies comparing BMD in CKD patients with and without a prevalent fracture were available at this time [26]. In 2015, a meta-analysis gathering data from 13 studies including 1782 patients at stages CKD 3–5d showed that BMD was significantly lower at the femoral neck, lumbar spine, the 1/3 and ultradistal radius in patients with fractures compared to those without, regardless of dialysis status [27]. These data, together with longitudinal studies, led the KDIGO working group to revise the guidelines [28] and recommend, in 2017 [29], BMD measurements in CKD patients.

In the Health, Aging and Body Composition Study, 2754 participants (70–79 years of age at enrolment), including 587 CKD patients (21%) were measured at baseline and followed for 11 years [30]. The CKD population consisted of 83% CKD stage 3a and 13% CKD 3b. The adjusted fracture hazard ratio (HR) for each standard deviation (SD) of lower femoral neck BMD was 2.69 [95% confidence interval (CI) 0.99–3.77] in CKD and 2.15 (1.80–2.57) in the non-uremic population. For hip fractures only, the adjusted femoral neck BMD hazard ratio was 5.82 (3.27–10.35) in CKD and 3.08 (2.29–4.14) in the non-uremic subjects. Thus, lower femoral neck BMD was associated with greater fracture risk regardless of renal function.

A second prospective cohort of 131 predialysis patients (mean age 62 years) was measured with DXA BMD at the total hip, lumbar spine, and ultradistal and 1/3 radius at baseline and after 2 years [31]. Most of the patients had type 2 diabetes. They included, at baseline, 34% CKD stage 2, 40% CKD stage 4 and 26% CKD stage 5. Low BMD at all sites and a greater annualized % decrease in BMD predicted fracture. Multivariate models showed that the odds ratio (OR) of fracture was 1.75 (1.30–2.20) for each SD of lower total hip BMD. Interestingly, in this study, HRpQCT was not better at predicting fracture than BMD measured by DXA.

Finally, a Japanese study measured 485 hemodialyzed (HD) patients (mean age 60 years) at baseline and 40 months later. Forty-six fractures occurred during the follow-up period. The adjusted fracture HR was 0.65 (0.47–0.90) for each SD of higher femoral neck BMD ($p = 0.009$). Receiver operating characteristic (ROC) analyses stratified according to parathyroid hormone (PTH) below or above the median value of 204 pg/ml (21.6 pmol/l), showed that the area under the curve (AUC) for femoral neck BMD was 0.72 in the lower stratum and 0.51 in the higher stratum [32].

Thus, while BMD measurement by DXA predicts fractures in CKD patients with bone and mineral disorders, a number of issues remain to be discussed. The community of nephrologists must be aware that BMD measurement by DXA has high specificity and moderate sensitivity. In addition, the FRAX software does not take into account CKD as an independent risk for fracture. Thus, it is likely that the FRAX score calculation underestimates fracture risk in this population. The follow-up rate needs to be outlined, knowing that the International Society for Clinical Densitometry recommends calculating "the least significant change" (LSC), i.e. the least amount of BMD change between two measurements that can be considered significant at the individual level, for a 95% confidence level (=precision error × 2.77). Precision characterizes the reproducibility of the measurement and depends on the operator, the DXA device and the population. Thus, it should be checked whether the LSC generally used in non-uremic populations (0.030 g/cm^2 at the hip) is similar in CKD patients. The type of CKD patients who will benefit from DXA measurement remain to be defined, knowing that the current drugs for osteoporosis treatment are not recommended in CKD 4–5 patients. Finally, the reimbursement of this test in the CKD population needs to be addressed by Health Authorities in each country.

As for the techniques derived from DXA measurements such as TBS, scant data are available and it is difficult to draw conclusions about their utility in routine practice. In addition, aorta calcifications may alter TBS calculation in the CKD population. In a cohort of 1426 participants (aged ≥40 years, mean age 67 years) including 199 patients with glomerular filtration rate (GFR) below 60 ml/min/1.73 m^2 (72.4% CKD stage 3a, 25.1% CKD stage 3b, and 2.5% CKD stage 4) lower lumbar spine TBS was independently associated with a higher fracture risk in adults with reduced kidney function [33]. In a smaller population of 53 CKD-5d patients, analyzed at the time of kidney transplantation, spinal X-ray detected prevalent asymptomatic fractures in 26% of patients. TBS was 8% lower in CKD patients than in controls; however, TBS was similar in CKD patients with or without fractures [34].

Quantitative computed tomography

Central quantitative computerized tomography

This technique, which uses standard computerized tomography, provides volumetric BMD (g/cm^3), after calibration with a phantom, as well as macro-geometry parameters at the level of the hip and the spine, the bone sites prone to osteoporotic fractures. It is not influenced by osteoarthritis and its measurements of bone geometry are true 3D parameters, while DXA-derived evaluation is an extrapolation from 2D parameters [35]. Its drawbacks are the higher radiation doses and greater costs for routine diagnosis.

Peripheral quantitative computed tomography

In addition to volumetric BMD, macro- and micro-architecture parameters can be evaluated with an accuracy that depends on the spatial resolution of the device (Table 1). Interestingly, while DXA use is limited in children with CKD due to the confounding effect of smaller body size and opposing PTH effects on the trabecular and cortical envelopes, peripheral quantitative computed tomography does not suffer from these limitations [36]. Peripheral as well as high resolution QCT are not used in routine practice due to the lack of device availability.

Peripheral QCT (pQCT)

pQCT analyses the trabecular and cortical compartments separately at the tibia and radius (resolution 400–500 µm). Recently, clinical cone beam computed tomography improved this technique and its resolution (220 µm). It allows to measure large portions of distal bones with fair spatial resolution and limited irradiation [37]. In a cross-sectional study of 52 CKD 5d patients, including 27 patients with fractures, pQCT analysis showed that a decrease in cortical density, area and thickness was associated with fractures—with the OR varying from 3 to 16—while DXA BMD was not [38].

High-resolution peripheral QCT (HR-pQCT)

HR-pQCT measures volumetric BMD at the distal tibia and radius. Acquisition time is 15 min per site. This device also provides information on trabecular and cortical microarchitecture parameters such as trabecular thickness, number and distribution and cortical porosity (Fig. 3a–c). The XtremeCT II (Scanco®, Brüttisellen, Switzerland) has an 82 µm spatial resolution. Longitudinal follow-up is possible due to specific software. This technique allows to compare two images of the same bone slice and enables to describe where formation and resorption took place during the observation period [39].

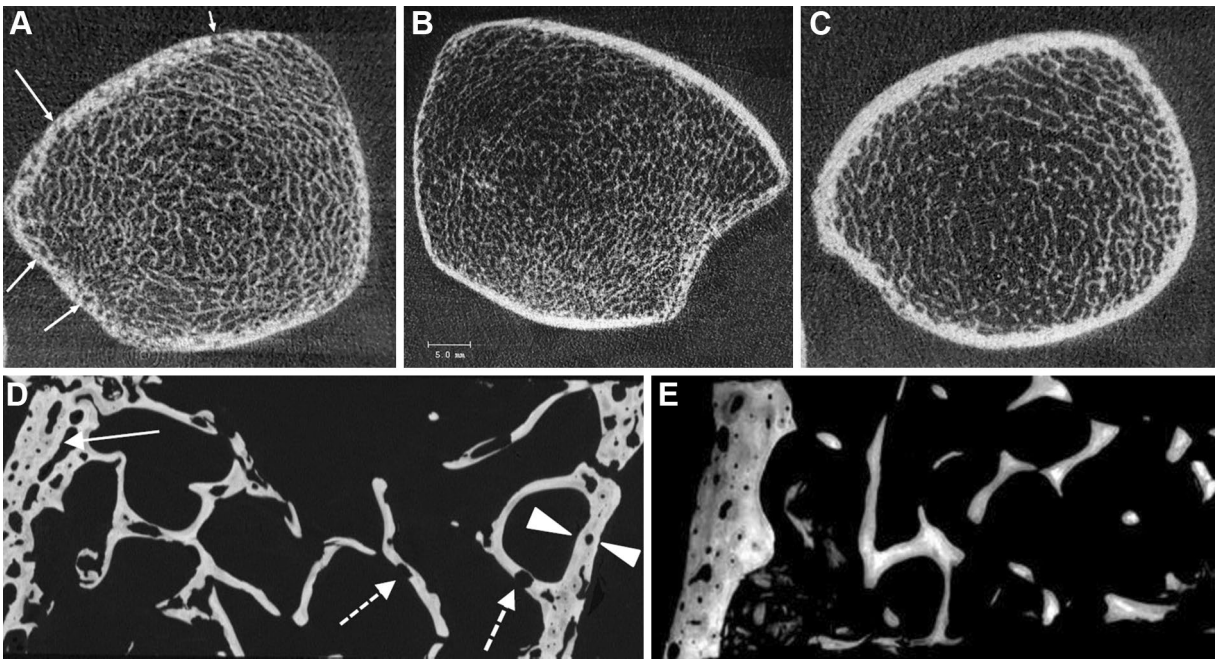

Fig. 3 **a–c** HRpQCT images of tibia (**a, c**) and radius (**b**) in a CKD patient **a, b** with increased cortical porosity at the radius level compared to healthy control (**c**). **d**, **e** Synchrotron radiation computerized tomography images of iliac crest bone biopsies from a CKD-5d (**d**) and non-uremic osteoporotic patient (**e**). Note in **a** and **d** the increase in cortical porosity (*arrow*) and in **d** the deep erosion lacunae (*dotted arrow*), the thin cortices (*arrow heads*) and the increase in cortical porosity at the endocortical surface (*arrows*)

HR-pQCT analysis helps us to better understand the mechanisms of bone loss in CKD [40]. Nickolas at al, studied 53 CKD patients (including ten hemodialysis patients) with HR-pQCT and DXA at baseline and after 1.5 years [41]. They found a significant decrease in DXA BMD at the total hip and ultradistal radius. Cortical area, density, and thickness at the distal radius were reduced significantly while cortical porosity increased. Most interestingly, time-averaged levels of PTH and bone turnover markers predicted cortical deterioration. Thus, for the first time, the relationship between the severity of secondary hyperparathyroidism and cortical bone loss was evidenced, thanks to these longitudinal data. The same team demonstrated the persistent bone loss at the peripheral skeleton despite corticosteroid withdrawal in kidney transplant patients [42]. Thus, cortical porosity and cortical thickness are critically affected by CKD [43]. Cortical architecture depends mostly on modeling levels at the periosteal surface and remodeling at the endosteal surface and within the cortex. The endocortical (inner) third of cortices is the most active surface, where trabecular bone is formed at the expense of the cortex, a process highly deleterious for bone strength (Fig. 2a, b). Recent studies confirmed that cortical porosity is highly heterogeneous and demonstrated that thorough analysis of this heterogeneity, using HR-pQCT, would improve our knowledge of how cortical bone can deteriorate rather quickly [44] in the osteoporotic process associated with CKD [43]. Finally, HR-pCQT has been used to analyze the complex relationships between bone structure and vascular calcifications in the general population [45] and in CKD [46].

Very high-resolution QCT, nano-CT and synchrotron radiation CT

It is possible, for research purposes, to analyze *ex vivo* bone biopsies at higher resolutions (10 µm to 10 nm) using nano quantitative CT or synchrotron radiation CT [47] (Fig. 3d, e). Synchrotron radiation provides a high-energy monochromatic X-ray beam, which yields high-quality images. These approaches allow to examine micro and nano structures of bone including collagen and mineral properties such as the degree of mineralization of bone (DMB), a strong determinant of bone strength [48] as well as osteocytes lacunae and their canaliculi network [49] (Fig. 3).

Magnetic resonance imaging (MRI)

MRI can distinguish microarchitecture deterioration in patients with various metabolic bone diseases, compared to controls, as shown by a number of cross-sectional studies with small sample sizes (summarized in [50]). In the trabecular compartment, MRI images the marrow content since bone signal is hypointense. The voxel sizes range from 130 to 250 µm with a slice thickness of 400–1500 µm (for a scan time of 10–15 min). Bone can be analyzed at any site, including spine and hip, and there is no patient irradiation. Using high to ultrahigh field scanners (3-7T) and specific sequences may improve image and quantification accuracy. Fifty CKD patients were analyzed with 1.5T MRI early and 6 months after kidney transplantation. All patients received glucocorticoids. While vertebral BMD decreased by 3% during follow-up, trabecular microarchitecture parameters did not change significantly. In contrast, FEA analyses of bone strength such as cortical and trabecular stiffness and failure strength were significantly reduced overtime [51]. Recently, ultrashort echo time MRI has made it possible to analyze cortical bone. This technique is based on the measurement of concentrations of bone water (BW) at two levels (bound to collagen and within the porosities). Techawiboonwong et al. reported that CKD patients with renal osteodystrophy had higher BW than premenopausal and postmenopausal controls (by 135 and 43%, respectively) while no difference in volumetric BMD between CKD patients and controls was observed. Taken together, these preliminary data suggest that MRI could yield additional information beyond BMD, to better assess bone fragility [52].

Conclusions

Fractures have become an increasing concern in the CKD population. HRpQCT remains the research tool that helps us to better understand the mechanisms of increased bone fragility. DXA BMD is available worldwide and is a fair predictor of fractures with a good specificity but insufficient sensitivity. Now, DXA measurements are recommended for assessment of bone status in the CKD population—however a number of questions remains regarding the modalities of these measurements and the therapeutic strategies to implement when high risk for fracture is detected in patients with late-stage CKD.

Compliance with ethical standards

Conflict of interest The author(s) declare that they have no competing interests.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

References

1. Alem AM, Sherrard DJ, Gillen DL, Weiss NS, Beresford SA, Heckbert SR, Wong C, Stehman-Breen C (2000) Increased risk of hip fracture among patients with end-stage renal disease. Kidney Int 58(1):396–399

2. Maravic M, Ostertag A, Torres PU, Cohen-Solal M (2014) Incidence and risk factors for hip fractures in dialysis patients. Osteoporos Int 25(1):159–165
3. Beaubrun AC, Kilpatrick RD, Freburger JK, Bradbury BD, Wang L, Brookhart MA (2013) Temporal trends in fracture rates and postdischarge outcomes among hemodialysis patients. J Am Soc Nephrol 24(9):1461–1469
4. Lin ZZ, Wang JJ, Chung CR, Huang PC, Su BA, Cheng KC, Chio CC, Chien CC (2014) Epidemiology and mortality of hip fracture among patients on dialysis: Taiwan National Cohort Study. Bone 64:235–239
5. Nickolas TL, McMahon DJ, Shane E (2006) Relationship between moderate to severe kidney disease and hip fracture in the United States. J Am Soc Nephrol 17(11):3223–3232
6. Ball AM, Gillen DL, Sherrard D, Weiss NS, Emerson SS, Seliger SL, Kestenbaum BR, Stehman-Breen C (2002) Risk of hip fracture among dialysis and renal transplant recipients. JAMA 288(23):3014–3018
7. Mittalhenkle A, Gillen DL, Stehman-Breen CO (2004) Increased risk of mortality associated with hip fracture in the dialysis population. Am J Kidney Dis 44(4):672–679
8. Tentori F, McCullough K, Kilpatrick RD, Bradbury BD, Robinson BM, Kerr PG, Pisoni RL (2014) High rates of death and hospitalization follow bone fracture among hemodialysis patients. Kidney Int 85(1):166–167
9. Keaveny TM, Bouxsein ML (2008) Theoretical implications of the biomechanical fracture threshold. J Bone Miner Res 23(10):1541–1547
10. Seeman E (2008) Bone quality: the material and structural basis of bone strength. J Bone Miner Metab 26:1–8
11. Currey JD (1979) Mechanical properties of bone tissues with greatly differing functions. J Biomech 12(4):313–319
12. Van Der Linden JC, Verhaar JA (2001) Weinans H A three-dimensional simulation of age-related remodeling in trabecular bone. J Bone Miner Res 16(4):688–696
13. Nickolas TL, Stein E, Cohen A, Thomas V, Staron RB, McMahon DJ, Leonard MB, Shane E (2010) Bone mass and microarchitecture in CKD patients with fracture. J Am Soc Nephrol 21(8):1371–1380
14. Delmas PD, Van de Langerijt L, Watts NB et al (2005) Underdiagnosis of vertebral fractures is a worldwide problem: the IMPACT study. J Bone Miner Res 20:557–563
15. Kim N, Rowe BH, Raymond G, Jen H, Colman I, Jackson SA, Siminoski KG, Chahal AM, Folk D (2004) Majumdar SR Underreporting of vertebral fractures on routine chest radiography. AJR Am J Roentgenol 182(2):297–300
16. Lespessailles E, Gadois C, Kousignian I, Neveu JP, Fardellone P, Kolta S, Roux C, Do-Huu JP, Benhamou CL (2008) Clinical interest of bone texture analysis in osteoporosis: a case control multicenter study. Osteoporos Int 19(7):1019–1028
17. Wainwright SA, Marshall LM, Ensrud KE, Cauley JA, Black DM, Hillier TA, Hochberg MC, Vogt MT, Orwoll ES (2005) Hip fracture in women without osteoporosis. Study of Osteoporotic Fractures Research Group. J Clin Endocrinol Metab 90(5):2787–2793
18. Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, Cauley J, Black D, Vogt TM (1995 23) Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. N Engl J Med 332(12):767–773
19. Sornay-Rendu E, Munoz F, Garnero P, Duboeuf F, Delmas PD (2005) Identification of osteopenic women at high risk of fracture: the OFELY study. J Bone Miner Res 20(10):1813–1819
20. Ross PD, Davis JW, Epstein RS, Wasnich RD (1991) Pre-existing fractures and bone mass predict vertebral fracture incidence in women. Ann Intern Med 114(11):919–923
21. Lee JH, Lee YK, Oh SH, Ahn J, Lee YE, Pyo JH, Choi YY5, Kim D, Bae SC, Sung YK, Kim DY (2016) A systematic review of diagnostic accuracy of vertebral fracture assessment (VFA) in postmenopausal women and elderly men. Osteoporos Int 27(5):1691–1699
22. Hans D, Barthe N, Boutroy S, Pothuaud L, Winzenrieth R, Krieg MA (2011) Correlations between trabecular bone score, measured using antero-posterior dual-energy X-ray absorptiometry acquisition, and 3-dimensional parameters of bone microarchitecture: an experimental study on human cadaver vertebrae. J Clin Densitom 14(3):302–312
23. Bredbenner TL, Mason RL, Havill LM, Orwoll ES, Nicolella DP (2014) Osteoporotic Fractures in Men (MrOS) Study. Fracture risk predictions based on statistical shape and density modeling of the proximal femur. J Bone Miner Res 29(9):2090–2100
24. Schuit SC, van der Klift M, Weel AE, de Laet CE, Burger H, Seeman E, Hofman A, Uitterlinden AG, van Leeuwen JP, Pols HA (2004) Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study. Bone 34(1):195–202
25. Georgiou E, Virvidakis K, Douskas G, Lambrinoudaki I, Voudiklari S, Katsoudas S, Mountokalakis T, Proukakis C (1997) Body composition changes in chronic hemodialysis patients before and after hemodialysis as assessed by dual-energy X-ray absorptiometry. Metabolism 46(9):1059–1062
26. Jamal SA, Hayden JA, Beyene J (2007 May) Low bone mineral density and fractures in long-term hemodialysis patients: a meta-analysis. Am J Kidney Dis 49(5):674–681
27. Bucur RC, Panjwani DD, Turner L, Rader T, West SL, Jamal SA (2015) Low bone mineral density and fractures in stages 3–5 CKD: an updated systematic review and meta-analysis. Osteoporos Int 26(2):449–458
28. Ketteler M, Elder G, Evenepoel P, Ix JH, Jamal SA, Lafage-Proust MH, Shroff R, Thadhani R, Tonelli M, Kasiske B, Wheeler DC, Leonard MB (2015) Revisiting KDIGO clinical practice guideline on chronic kidney disease-mineral and bone disorder: a commentary from a kidney disease: improving global outcomes controversies conference. Kidney Int 87(3):502–528
29. Ketteler M, Block GA, Evenepoel P, Fukagawa M, Herzog CA, McCann L, Moe SM, Shroff R, Tonelli MA, Toussaint ND, Vervloet MG, Leonard MB (2017) Executive summary of the 2017 KDIGO chronic kidney disease-mineral and bone disorder (CKD-MBD) guideline update: what's changed and why it matters. Kidney Int 92(1):26–36
30. Yenchek RH, Ix JH, Shlipak MG, Bauer DC, Rianon NJ, Kritchevsky SB, Harris TB, Newman AB, Cauley JA, Fried LF (2012) Bone mineral density and fracture risk in older individuals with CKD. Health, aging, and body composition study. Clin J Am Soc Nephrol 7(7):1130–1136
31. West SL, Lok CE, Langsetmo L, Cheung AM, Szabo E, Pearce D, Fusaro M, Wald R, Weinstein J, Jamal SA (2015) Bone mineral density predicts fractures in chronic kidney disease. J Bone Miner Res 30(5):913–919
32. Limori S, Mori Y, Akita W, Kuyama T, Takada S, Asai T, Kuwahara M, Sasaki S, Tsukamoto Y (2012) Diagnostic usefulness of bone mineral density and biochemical markers of bone turnover in predicting fracture in CKD stage 5D patients—a single-center cohort study. Nephrol Dial Transplant 27(1):345–351
33. Naylor KL, Jerilynn P, Garg AX, Berger C, Langsetmo L, Adachi JD, Goltzman D, Kovacs CS, Josse RG, Leslie WD (2016) Trabecular bone score and incident fragility fracture risk in adults with reduced kidney function. CJASN 11:2032–2040
34. Pérez-Sáez MJ, Herrera S, Prieto-Alhambra D, Vilaplana L, Nogués X, Vera M, Redondo-Pachón D, Mir M, Güerri R, Crespo M, Díez-Pérez A, Pascual J (2017) Bone density, microarchitecture, and material strength in chronic kidney disease patients at the time of kidney transplantation. Osteoporos Int 11 **(Epub ahead of print)**

35. Clotet J, Martelli Y, Di Gregorio S, Del Río Barquero LM, Humbert LJ (2017) Clin Densitom. Structural parameters of the proximal femur by 3-dimensional dual-energy X-ray absorptiometry software: comparison with quantitative computed tomography. **(Epub ahead of print)**
36. Denburg MR, Tsampalieros AK, de Boer IH, Shults J, Kalkwarf HJ, Zemel BS, Foerster D, Stokes D, Leonard MB (2013) Mineral metabolism and cortical volumetric bone mineral density in childhood chronic kidney disease. J Clin Endocrinol Metab 98(5):1930–1938
37. de Charry C, Boutroy S, Ellouz R, Duboeuf F, Chapurlat R, Follet H, Pialat JB (2016) Clinical cone beam computed tomography compared to high-resolution peripheral computed tomography in the assessment of distal radius bone. Osteoporos Int 27(10):3073–3082
38. Jamal SA, Gilbert J, Gordon C, Bauer DC (2006) Cortical pQCT measures are associated with fractures in dialysis patients. J Bone Miner Res 21(4):543–548
39. Schulte FA, Lambers FM, Kuhn G, Müller R (2011) In vivo micro-computed tomography allows direct three-dimensional quantification of both bone formation and bone resorption parameters using time-lapsed imaging. Bone 48(3):433–442
40. Pelletier S, Vilayphiou N, Boutroy S, Bacchetta J, Sornay-Rendu E, Szulc P, Arkouche W, Guebre-Egziabher F, Fouque D, Chapurlat R (2012) Bone microarchitecture is more severely affected in patients on hemodialysis than in those receiving peritoneal dialysis. Kidney Int 82(5):581–588
41. Nickolas TL, Stein EM, Dworakowski E, Nishiyama KK, Komandah-Kosseh M, Zhang CA, McMahon DJ, Liu XS, Boutroy S, Cremers S, Shane E (2013) Rapid cortical bone loss in patients with chronic kidney disease. J Bone Miner Res 28(8):1811–1820
42. Iyer SP, Nikkel LE, Nishiyama KK, Dworakowski E, Cremers S, Zhang C, McMahon DJ, Boutroy S, Liu XS, Ratner LE, Cohen DJ, Guo XE, Shane E, Nickolas TL (2014) Kidney transplantation with early corticosteroid withdrawal: paradoxical effects at the central and peripheral skeleton. J Am Soc Nephrol 25(6):1331–1341
43. Nishiyama KK, Pauchard Y, Nikkel LE, Iyer S, Zhang C, McMahon DJ, Cohen D, Boyd SK, Shane E, Nickolas TL (2015) Longitudinal HR-pQCT and image registration detects endocortical bone loss in kidney transplantation patients. J Bone Miner Res 30(3):554–561
44. Zebaze R, Ghasem-Zadeh A, Mbala A, Seeman E (2013) A new method of segmentation of compact-appearing, transitional and trabecular compartments and quantification of cortical porosity from high resolution peripheral quantitative computed tomographic images. Bone 54(1):8–20
45. Chow JT, Khosla S, Melton LJ 3rd, Atkinson EJ, Camp JJ, Kearns AE (2008) Abdominal aortic calcification, BMD, and bone microstructure: a population-based study. J Bone Miner Res 23(10):1601–1612
46. Pelletier S, Confavreux CB, Haesebaert J, Guebre-Egziabher F, Bacchetta J, Carlier MC, Chardon L, Laville M, Chapurlat R, London GM, Lafage-Proust MH, Fouque D (2015) Serum sclerostin: the missing link in the bone-vessel cross-talk in hemodialysis patients? Osteoporosis Int 26(8):2165–2174
47. Nuzzo S, Lafage-Proust MH, Martin-Badosa E, Boivin G, Thomas T, Alexandre C, Peyrin F (2002) Synchrotron radiation microtomography allows the analysis of three-dimensional microarchitecture and degree of mineralization of human iliac crest biopsy specimens: effects of etidronate treatment. J Bone Miner Res 17(8):1372–1382
48. Bala Y, Depalle B, Douillard T, Meille S, Clément P, Follet H, Chevalier J, Boivin G (2011) Respective roles of organic and mineral components of human cortical bone matrix in micromechanical behavior: an instrumented indentation study. J Mech Behav Biomed Mater 4(7):1473–1482
49. Hesse B, Varga P, Langer M, Pacureanu A, Schrof S, Männicke N, Suhonen H, Maurer P, Cloetens P, Peyrin F, Raum K (2015) Canalicular network morphology is the major determinant of the spatial distribution of mass density in human bone tissue: evidence by means of synchrotron radiation phase-contrast nano-CT. J Bone Miner Res 30(2):346–356
50. Chang G, Boone S, Martel D, Rajapakse CS, Hallyburton RS, Valko M, Honig S, Regatte RR (2017) J Magn MRI assessment of bone structure and microarchitecture. Reson Imaging. **(Epub ahead of print)**
51. Rajapakse CS, Leonard MB, Bhagat YA, Sun W, Magland JF, Wehrli FW (2012) Micro-MR imaging-based computational biomechanics demonstrates reduction in cortical and trabecular bone strength after renal transplantation. Radiology 262:921–931
52. Techawiboonwong A, Song HK, Leonard MB, Wehrli FW (2008) Cortical bone water: in vivo quantification with ultrashort echo-time MR imaging. Radiology 248:824–833