The evolution of CT imaging in metabolic bone disease assessment

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ABSTRACT

Computed tomography (CT) is becoming increasingly important in the field of osteoporosis, both in terms of dedicated applications and for opportunistic screening. The latter is a hot topic likely to change osteoporosis risk stratification and management to an unprecedented degree; it is also arguably one of the key areas for the use of Artificial Intelligence (AI) in medicine. Quantitative CT (QCT) is currently undergoing a revival, with technological improvements allowing reduced radiation exposure and offering significant advantages over traditional techniques like Dual-energy X-ray Absorptiometry (DXA). Moreover, innovative modalities such as high-resolution peripheral QCT (HR-pQCT) and, to a lesser extent, cone beam CT (CBCT) are emerging and becoming more available in clinical practice for osteoporosis imaging, especially in specific scenarios. Furthermore, Dual-Energy CT (DECT) and Photon-Counting CT (PCCT) are becoming more popular in radiology departments and represent promising options for the detection of osteoporosis. This brief narrative review explores the world of CT applied to metabolic bone diseases, focusing in particular on its use for opportunistic diagnosis and screening, an attractive application that has been emerging in recent years.

KEYWORDS

Opportunistic screening, bone frailty assessment, osteoporosis, quantitative computed tomography (QCT), artificial intelligence (AI).

Introduction

Osteoporosis is a significant and widespread public health issue, costing the Italian national health system more than 10 billion euros per year according to a 2025 ISS press release [1]. It is defined as a systemic skeletal disorder characterized by a gradual reduction in bone mass and microarchitectural deterioration of bone tissue, resulting in decreased mechanical strength and increased susceptibility to fracture [2]. Osteoporosis can be primary (postmenopausal or senile), but also secondary, when caused by underlying conditions like diabetes mellitus, chronic kidney disease (CKD), thyroid and parathyroid disorders, gastrointestinal disorders, malnutrition, or the use of drugs that induce bone loss [3,4]. The clinical significance of osteoporosis is related to the onset of fractures, which are in turn linked to high morbidity and mortality, especially in the setting of an aging population [5].

As osteoporosis remains silent until a fracture occurs, screening and preventive strategies are suboptimal. In this context, imaging can play a significant role in detecting the disease before it becomes clinically manifest. It is now evident that the concept of bone frailty cannot be fully described based on areal bone density measured by DXA alone. Consequently, attention has shifted toward advanced imaging techniques capable of evaluating bone density in a volumetric yet non-invasive manner, providing insight into bone microarchitecture. These novel instruments, now being rapidly disseminated, are discussed in this short review.

Article history
Received 11 Apr 2025 – Accepted 8 Jul 2025

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DXA

DXA is the current reference standard for assessing bone mineral density (BMD) in the general population, usually at the lumbar spine and femur (Figure 1). However, despite its availability, precision, and low radiation dose, it may fall short in terms of its ability to characterize bone fragility in complex settings or populations. For example, bone quality is recognized as a major determinant of fracture risk in osteoporosis—a risk that may be underestimated by an assessment based on bone densitometry alone [6]. In the general population, a substantial number of fragility fractures occur in individuals with normal or osteopenic BMD. In a study of 616 postmenopausal women, only 26.9% of fractures occurred in patients with BMD in the osteoporotic range (versus 16.6% in the normal range and 56.5% in the osteopenic range) [7]. This demonstrates that bone fragility depends not only on bone density, but also on structural and material properties of bone that are not captured by a standard DXA scan, including trabecular microarchitecture,

elasticity, and collagen matrix composition [8]. However, it is important to mention that application of an additional approach, known as Trabecular Bone Score (TBS), to DXA images of the lumbar spine can provide surrogate information on trabecular microstructure based on gray-level texture analysis [9]. TBS values are independent of BMD and have been shown to predict bone fractures independently of Fracture Risk Assessment Tool (FRAX) results [10]. As a result of sound evidence on its role in osteoporosis, TBS was included in the 2023 update of the Adult Official Positions of the International Society of Clinical Densitometry (ISCD) [11]. A further limitation of DXA is related to its two-dimensionality, which renders measurement dependent on body size and makes it susceptible to inaccuracies in the presence of spine osteoarthritis, vertebral fractures, and superimposed aortic calcifications [12].

QCT and opportunistic screening

Quantitative Computed Tomography (QCT) is a dedicated modality for measuring volumetric BMD (vBMD) at axial sites, and it has been undergoing a revival in recent years. A standard acquisition is performed at the lumbar spine, with either a single-slice (L1-L3) or a volumetric (L1-L2) technique, or at the hip, with either a volumetric or a projectional technique. It may be especially useful in patients with comorbidities or anatomical alterations that undermine the accuracy of DXA, such as individuals with abnormally small or large body size, advanced degenerative spine disease, significant obesity (BMI > 35), or undergoing pharmacologic therapies that require more sensitive monitoring. QCT makes it possible to evaluate the trabecular compartment directly (Figure 2), providing some insight into bone microarchitecture [13,14]. Conventional QCT requires the presence of a calibration phantom to be scanned simultaneously with the patient; phantoms contain materials with X-ray attenuation characteristics similar to those of bone at a set of known densities, enabling conversion of Hounsfield Units (HU) to actual BMD values via regression curves [15]. Moreover, CT can readily identify unsuspected compression fractures, which establish the diagnosis of osteoporosis even when DXA T-scores are normal [16].

Aside from standard QCT, scientific interest is now turning toward the opportunistic use of CT to identify individuals with osteoporosis or at high risk of fracture, as the technique may allow screening for bone fragility with no additional time, costs, or radiation exposure [16]. Although the QCT standard approach is based on synchronous calibration with a phantom, it is not suitable for routine clinical scans.

Therefore, asynchronous and phantomless methods have been proposed. The former approach entails periodic scanning of the phantom separately from the patient, in order to build corresponding calibration curves; a key requisite is stability of the scanner [17]. The latter instead exploits known attenuation values of specific tissues, referred to as internal calibration materials, to derive vBMD [18] via a scanner-specific calibration curve, which enables conversion of HU to vBMD. Unfortunately, this method is still not sufficiently robust, presenting notable limitations related to scanner factors, heterogeneity in the composition of reference tissues, and the influence of contrast media [19]. A recent scoping review, which identified 26 relevant published studies, showed that phantomless BMD estimation approaches based on CT are a feasible way to detect osteoporosis, but that further studies are needed to improve the consistency of results [20].

Figure 1 Examples of DXA images at the lumbar spine and left hip, with T-score in the osteoporosis range at the lumbar spine (- 3.0) and the normal range at the femoral neck (- 0.7).

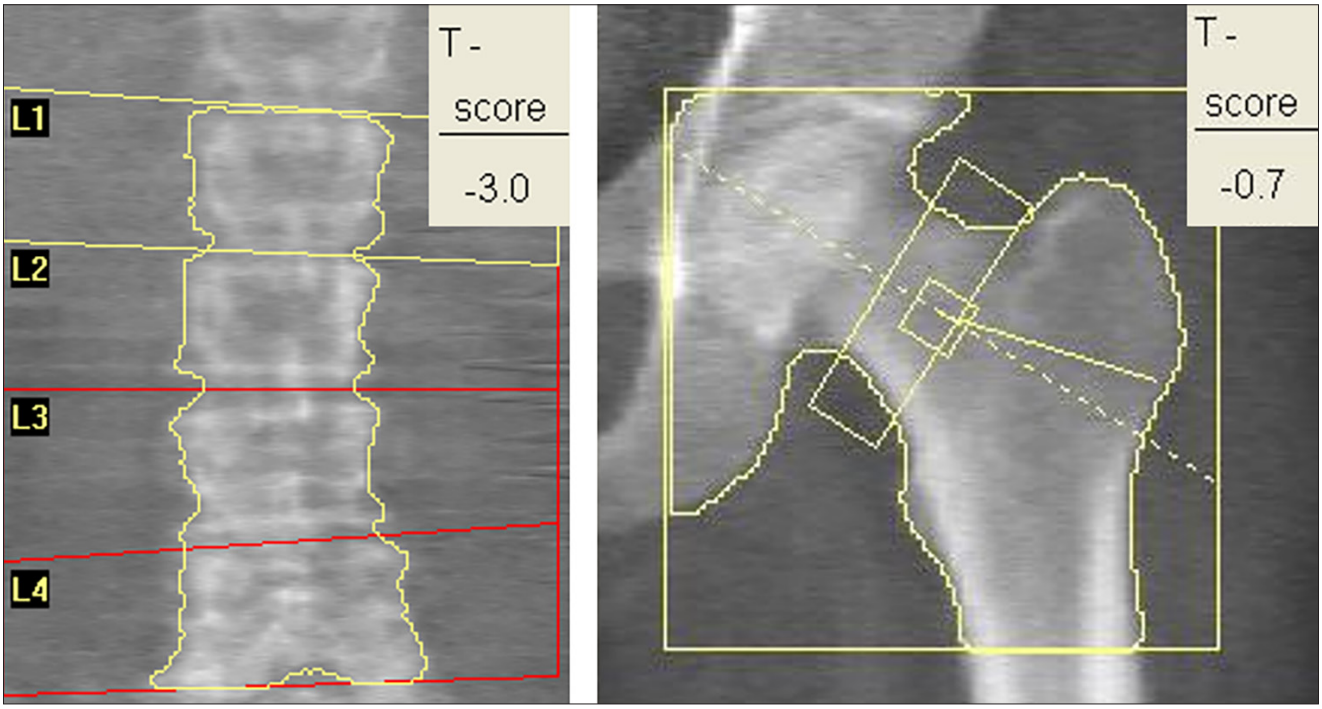
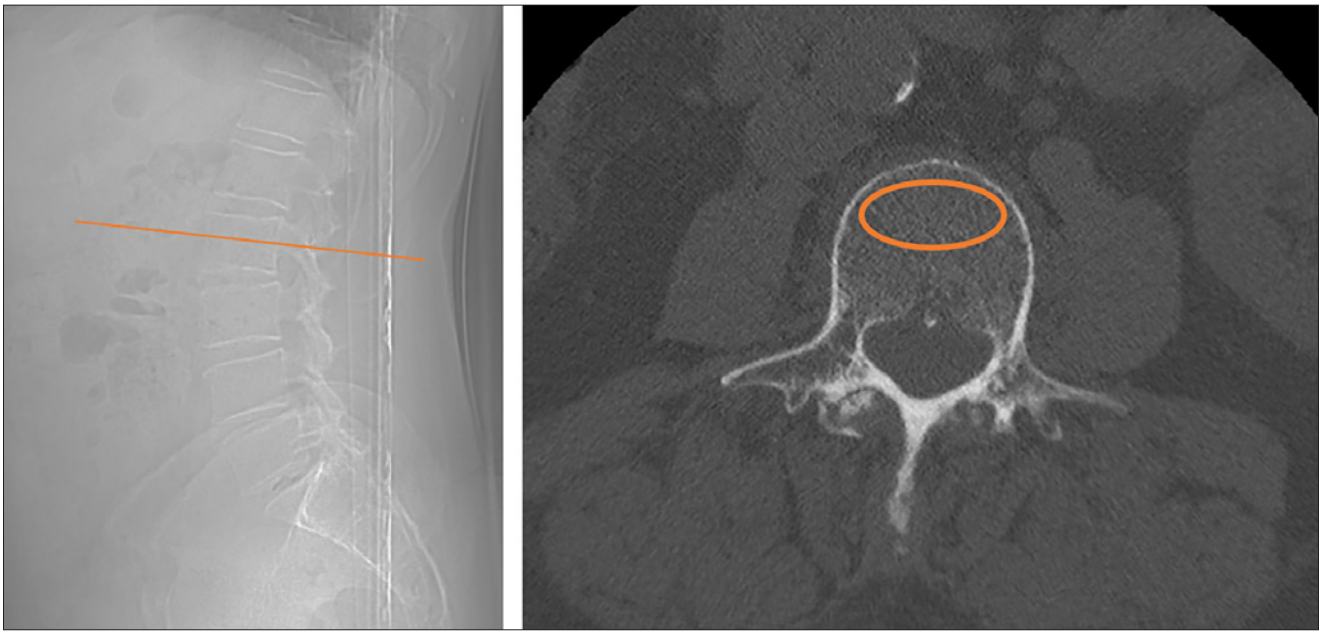


Figure 2 Example of axial QCT acquisition at the lumbar spine, where volumetric acquisition is generally performed at L1-L2. In this case, the L2 vertebral body was selected based on the lateral topograph and the ROI was placed in trabecular bone, avoiding the cortex and the vascular plexus.



In the setting of opportunistic and phantomless QCT, AI may be a game changer, assisting in the analysis of complex imaging data and automating tasks such as image segmentation and pattern recognition in osteoporosis [21]. Deep learning (DL), especially via convolutional neural network (CNN) algorithms, could reduce the manual burden for radiologists and improve fracture risk prediction [22].

Fang *et al*. recently investigated a deep CNN model to predict the BMD of the lumbar vertebrae (L1-L4) from routine CT scans, demonstrating high correlation ($r > 0.98$) with QCT taken as reference [23]. Wu *et al*. instead developed a DL model based on low-dose chest CT scans with segmentation of T1-L2 vertebral bodies, which was tested on three different CT scanners, yielding high sensitivity and specificity for the screening of osteopenia and osteoporosis [24]. These findings highlight the substantial potential of AI in the field of metabolic bone diseases, which could translate into reduced need for dedicated scans and hence decreased healthcare costs and radiation exposure for patients.

HR-pQCT

Originally developed for *in vivo* assessment of bone microarchitecture at the distal tibia and distal radius (Figure 3) in osteoporosis, HR-pQCT is an innovative X-ray-based three-dimensional technique that combines low dose (3–5 μSv of effective dose per scan) with high resolution (61–82 μm) [25]. It provides data on volumetric BMD as well as on bone structure and quality, in both the trabecular (e.g., orientation, spacing, number and thickness of trabeculae) and the cortical compartments (e.g., thickness and porosity). These features may offer insight into the pathophysiological mechanisms underlying skeletal fragility and improve fracture risk stratification and prediction in primary and secondary osteoporosis; moreover, HR-pQCT could have several other potential applications [26].

Several studies, both in post-menopausal females and in males, have correlated HR-pQCT parameters with fractures. They include the OFELY [27], MrOS [28], CaMos [29], and STRAMBO [30] studies. A landmark study carried out by the Bone Microarchitecture International Consortium (BoMIC), involving a large international cohort of 7254 patients (66% women and 34% men), demonstrated that some HR-pQCT parameters could predict incident fractures independently of femoral neck areal BMD (aBMD) measured by DXA, and also of fracture risk estimates obtained using the FRAX algorithm [31]. Two recent systematic reviews and meta-analyses confirmed the ability of HR-pQCT parameters to predict fractures [32,33]. Beyond standard indices, a recent study suggested that HR-pQCT could further improve our understanding of bone fragility by evaluating bone phenotypes and heterogeneous microarchitectural defects leading to the formation of void spaces [34].

HR-pQCT may be particularly suitable for the assessment of secondary osteoporosis, linked to CKD for example, where bone microstructure may be deteriorated regardless of BMD measured by DXA [35]; in this context, the technique could complement bone biopsy in identifying the type of renal osteodystrophy [36]. Available evidence also suggests that HR-pQCT is feasible in patients with osteogenesis imperfecta and other rare skeletal diseases [25,37].

Additionally, HR-pQCT appears to be a promising tool for refining assessment of responses to anti-osteoporotic drug treatments [38], given its unique capacity to simultaneously assess bone microstructure and volumetric density, in both the cortical and the trabecular compartments. Of note, the identification of patients presenting severe microstructural deterioration despite moderately decreased DXA-BMD could have important implications for therapeutic decisions [26,39].

Despite its valuable potential, there are still some obstacles to more widespread use of HR-pQCT. First, the number

of machines installed worldwide is limited (approximately 100 as of mid-2022) and they are largely found at research centers [25]. Furthermore, these machines are quite expensive and their cost-effectiveness is still insufficiently determined. Moreover, there is a need for standardized image acquisition and data analysis protocols to facilitate research and the adoption of HR-pQCT in clinical practice. Guidelines addressing this subject were recently published by a joint working group of the International Osteoporosis Foundation, American Society of Bone and Mineral Research, and European Calcified Tissue Society [40]. Furthermore, there is still a paucity of validated normative datasets on HR-pQCT parameters, which would be crucial to identify pathological alterations in bone density and microarchitecture across different ages and ethnicities, in both males and females [25].

CBCT

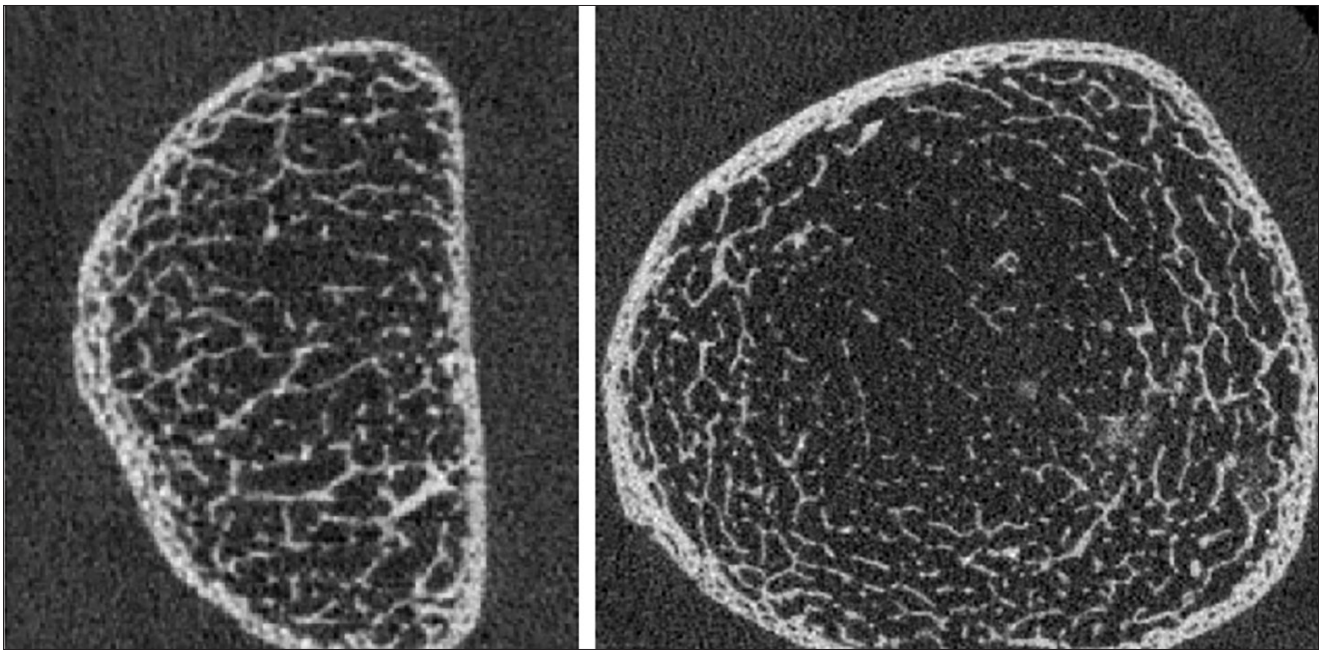
A very similar technology to HR-pQCT is CBCT. Initially used for dental imaging, it employs a cone-shaped X-ray beam falling on a flat panel detector, rather than a fan-shaped beam as in conventional CT. This technique is increasingly being applied to the musculoskeletal system thanks to its reduced radiation dose and ability to generate images that characterize bone microarchitecture with excellent resolution [41]. CBCT systems tend to be smaller and less expensive than HR-pQCT ones, and offer the additional benefit of shorter acquisition times, but they do not usually provide a calibrated BMD output [26], although there have been some attempts to quantify trabecular bone parameters [42].

A recent systematic review of 10 studies assessed the capacity of CBCT to accurately detect low BMD in post-menopausal women, reporting good sensitivity and specificity for the diagnosis of osteoporosis [43]. However, further research is needed, especially considering some known limitations of the system, such as its increased susceptibility to beam-hardening artifacts and radiation-scattering effects caused by the conical geometry of the beam, as well as the absence of standardized calibration phantoms [44]. These factors can cause inconsistency in the measurement of HU across different scanners or even within the same machine [45]. Nevertheless, recent advances in CBCT technology, including improved calibration methods and image reconstruction algorithms, are tackling these issues with the aim of improving reliability [46].

DECT and PCCT

DECT and PCCT are emerging technologies that offer substantial advantages for the imaging of metabolic bone diseases. DECT employs two photon spectra at different energy levels, yielding spectral information based on separate absorption measurements and enabling the generation of material decomposition images [47]. DECT was proposed for the assessment of trabecular BMD in vertebrae some decades ago, and phantomless approaches have also been described [48]. DECT is able to detect changes in bone marrow composition, to which a standard QCT evaluation is insensitive. Interestingly, a phantom study demonstrated that DECT may be more accurate than QCT in measuring BMD [49]. Moreover, a recent study evaluated the performance of a phantomless DECT algorithm based on material decomposition in determining BMD at the lumbar spine. Compared with traditional HU measurements, it showed superior diagnostic accuracy for osteoporosis, with DXA used as the reference standard [50]. Furthermore, retrospective assessment of BMD with DECT was shown to predict the two-year occurrence of fragility fractures in at-risk patients with excellent sensitivity and specificity (approximately 85% and 89%, respectively) [51].

Figure 3 HR-pQCT images at the distal radius (a) and distal tibia (b) in an adolescent with osteogenesis imperfecta.



PCCT has been only very recently introduced into clinical practice, and it is likely to have a major impact in the field of musculoskeletal radiology due to its ability to quantify and discriminate the energy of individual photons interacting with detectors; this will mean improved spatial resolution, inherent multienergy spectral imaging capabilities, and more efficient control of radiation dose [52]. PCCT can provide a detailed evaluation of the microstructure of cortical and trabecular bone, generating quantitative and qualitative information, with initial studies reporting outcomes comparable to those of micro-CT [53]. Moreover, from an opportunistic screening perspective, BMD determination using PCCT localizer radiographs reconstructed at different energy thresholds has been investigated, on the basis of a principle similar to that of DXA [54]. A very recent prospective study in 51 subjects suggested that aBMD values and corresponding T-scores derived from PCCT localizer spectral images could serve as an opportunistic tool to screen for osteoporosis, as demonstrated by a Lin concordance correlation coefficient = 0.90 between T-scores and DXA [55].

Although these techniques appear to be very promising, further research is needed to define their role in the field of osteoporosis, focusing particularly on their validation for diagnostic purposes and potential inclusion in clinical practice guidelines.

Conclusion

Computed tomography, in the form of both traditional and emerging technologies, such as QCT, HR-pQCT, CBCT, DECT, and PCCT, has a key role to play in the characterization of osteoporosis and bone fragility. Each of these modalities has peculiar features, and could complement a standard DXA evaluation. Moreover, CT offers the significant advantage of enabling opportunistic screening for low BMD, which could improve patient outcomes through earlier detection of osteoporosis and thus prevention of fractures. While challenges remain—such as the need for greater standardization of procedures and harmonization of data, as well as for more solid evidence on cost-effectiveness— ongoing research combined with technological advances and computational progress will undoubtedly lead to improved assessment of bone density and quality, even using opportunistic approaches. This will pave the way for new diagnostic scenarios in the world of metabolic bone diseases.

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Conflict of Interest Statement: *The authors have no conflicts of interest to declare.*