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Invited Review / Davetli Derleme

The role of quantitative computed tomography and magnetic resonance imaging in diagnosis and follow-up of osteoporosis: A review

Kantitatif bilgisayarlı tomografi ve manyetik rezonans görüntülemenin osteoporoz tanı ve takibindeki rolü: Bir derleme

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ABSTRACT

Use of quantitative computed tomography (QCT) in bone mineral density (BMD) measurement dates earlier than dual-energy X-ray absorptiometry (DXA). However, when World Health Organization defined osteoporosis based on T score values, all BMD measurement methods except DXA lost popularity. Fear of radiation is another factor that reduced the popularity of QCT. Quantitative computed tomography evaluates trabecular, and cortical bone separately. Bone mineral density is measured volumetrically and bone is analyzed in three dimensions. Quantitative computed tomography's not being affected by arthrosic changes and vascular calcifications is a considerable advantage. It can be used in vertebra, femur, and peripheral skeleton. Radiation dose in peripheral application is negligible. Magnetic resonance imaging (MRI), even though not used in diagnosis of osteoporosis routinely, is a valuable tool in differential diagnosis as well as in research investigating the microstructure of the bone. Recently, bone strength can also be evaluated with QCT and MRI. In this review, we emphasize the role of QCT and MRI in diagnosis and follow-up of osteoporosis.

Keywords: Magnetic resonance imaging; osteoporosis; quantitative computed tomography.

ÖZ

Kantitatif bilgisayarlı tomografinin (QCT) kemik mineral yoğunluğunu (KMY) ölçmek amacıyla kullanımı tarihsel olarak çift-enerjili X-ray absorbsiyometri yönteminden (DXA) eskilere dayanır. Bununla birlikte, Dünya Sağlık Örgütü'nün, osteoporozu DXA ile ölçülen T skoruna göre tanımlamasıyla, DXA dışındaki tüm KMY ölçüm yöntemleri geri plana itilmiştir. QCT'nin rağbetini azaltan bir diğer faktör radyasyon korkusudur. Kantitatif bilgisayarlı tomografi trabeküler ve kortikal kemiği ayrı ayrı değerlendirebilir. Kemik mineral yoğunluğu hacimsel olarak ölçülür ve kemik üç boyutlu olarak analiz edilir. Kantitatif bilgisayarlı tomografinin artrozik değişimler ve vasküler kalsifikasyonlardan etkilenmemesi önemli bir avantajıdır. Vertebra, femur ve periferik iskelette kullanılabilir. Periferik uygulamalarda radyasyon dozu yok denecek kadar azdır. Manyetik rezonans görüntüleme (MRG), osteoporoz tanısı için rutinde kullanılmasa da gerek ayırıcı tanıda ve gerekse kemiğin mikroyapısını değerlendiren araştırmalarda oldukça değerli bir gereçtir. Son zamanlarda, kemik gücü QCT ve MRG ile de değerlendirilebilmektedir. Bu derlemede; osteoporoz tanı ve takibinde QCT ve MRG'nin rolünden bahsedilecektir.

Anahtar sözcükler: Manyetik rezonans görüntüleme; osteoporoz; kantitatif bilgisayarlı tomografi.

Bone tissue is a woven matrix of organic and inorganic materials. Type 1 collagen and cells form the organic matrix, hydroxyapatite crystals are the most important building block of the inorganic matrix. Two major compartments of human bone are cortical and trabecular bones. Cortical bone constitutes approximately 80% of an adult human skeleton mass. It constitutes mainly the shaft of long bones. It also surrounds trabecular bone. Cortical bone, which is stiffer and shows less cavitation, resists load better than trabecular bone. Trabecular bone, which is centrally located and spongy in structure, is eight times more metabolically active. Cortical and trabecular bone ratios differ in various bone types. For example, the ratio of trabecular bone is higher in vertebrae, but femurs are rich in cortical bone.[1]

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The structure of bones are remodeled continuously throughout a person's life. While the remodeling balance favors bone formation in young individuals, formation-destruction is in equilibrium during middle age. In the elderly, remodeling cycle shifts to destruction.

Advancing age and processes affecting bone remodeling cycles do not affect cortical and trabecular bone, which have different structures and features.[2,3] For this reason, analyzing cortical and trabecular bones separately enables better understanding of the pathological process in metabolic diseases of bone including osteoporosis.

The elderly population is increasing in the world. The aging process reveals itself in many tissues and organs. The most important changes occur in bone tissue in the process of osteoporosis. Osteoporosis arising from either aging or other causes is a disease defined by a loss of bone strength and an increased risk of fracture caused by a decrease in bone mass and the deterioration of microstructure features.[2] Even though the definition includes changes in the microstructure of the bone in addition to loss of bone mass, clinical diagnosis is based mostly on the loss of bone mass. The decrease in bone strength and the increased risk of fracture are mostly diagnosed by looking at the patient's clinical background and family history. Dual energy X-ray absorptiometry (DXA) which is the most frequently used method in the diagnosis of osteoporosis cannot supply all the necessary clinical answers even though it is considered the gold standard. Almost half of the patients with low-energy osteoporotic fractures have osteopenic values in DXA. Mass identified by DXA reflects approximately 70% of bone strength. In this manner it becomes clear that DXA is not a sufficient evaluation method in the diagnosis as well as follow-up care for osteoporosis. In the follow-up studies of certain medications; a decrease in fracture risk is not correlated with BMD values identified by DXA. In fact, it has been reported in clinical follow-up studies that fracture risk is lowered due to medication even without changes in DXA. In addition, there are many situations in which DXA use is limited, such as with metabolic bone diseases, severe obesity and childhood osteoporosis.[4-10]

In summary, the insufficiencies of DXA in identifying parameters mentioned in the definition of osteoporosis such as "microstructure feature changes and decrease in bone strength" have created the need to evaluate bone both qualitatively and quantitatively by using different non-invasive methods. Therefore, quantitative computed tomography (QCT) has regained its value in diagnosis and treatment of osteoporosis, and as a result the use of magnetic resonance imaging (MRI) in evaluating bone structure has become more common.

QUANTITATIVE COMPUTED TOMOGRAPHY

The use of QCT in bone density measurement dates back further than DXA. Quantitative CT, which has been used since the late 1970's, lost popularity due to the higher radiation exposure compared to DXA. On the other hand, even though the radiation dose might seem high when compared to DXA, it is almost 1/10 of that in routine CT scans. This fact should be kept in mind. Even X-ray scans, which are used frequently in daily practice, might give out higher radiation than QCT. Radiation doses are shown in μSv in Table 1.[11] As it can be seen here; even though abdominal tomographic scans give out almost three times higher radiation compared to three dimensional (3D) QCT, clinicians use them in their routine practice, ignoring this fact. Another example can be given for X-rays. If an osteoporotic fracture is evaluated by X-ray, the patient is exposed to a radiation dose comparable to QCT. For this reason; in terms of clinical necessities, when QCT use is considered in osteoporosis evaluation and follow-up; "fear of radiation dose levels" should be considered with up to date facts. Furthermore, when the World Health Organization (WHO) defined osteoporosis based on T score values, all BMD measurement methods except DXA lost popularity.[5]

Table 1. Examples of effective radiation doses of various evaluation methods

Evaluation method	Effective dosage (μSv)
DXA for adults (vertebra and femur)	5-20
2D QCT (lateral scanogram and 3 sections)	60-90
3D MD QCT (vertebra, L1-L2, one section)	1500
3D MD QCT (femur, one section)	2500-3000
3D MD QCT (radius, one section)	<10
HR-pQCT	<3
Posteroanterior chest X-ray	20
Abdominal CT (adult)	8000-10.000
Lumbar anterior-posterior X-ray	700
Lumbar lateral X-ray	300
8-10 hours of air travel	60
Background radiation (daily)	7-10

DXA: Dual energy X-ray absorptiometry; QCT: Quantitative computed tomography; 2D: Two dimensional; 3D: Three dimensional; MD: Multidetector; HR-pQCT: High-resolution peripheral quantitative computed tomography; CT: Computed tomography.

Dual energy X-ray absorptiometry evaluates areal bone density, and thus, cannot accurately reflect bone strength or fracture risk.[6-10] Dual energy X-ray absorptiometry does not offer separate evaluation of cortical and trabecular bone BMD. Quantitative CT is the only method that can measure volumetric BMD value in terms of gr/cm3 separately in both trabecular and cortical bone since it has the advantage of axial imaging. It is possible to take measurements in vertebra, femur and peripheral skeleton.[3,12,13]

Quantitative CT can be implemented in any CT system. It simply requires a special software and calibration phantom. Calibration phantoms are apparatuses comprised of substances similar to bone mineral structure. Different calibration phantoms are used in different devices. For this reason measurements done with different devices cannot be compared. Technically, a water or gel filled pad is placed between the phantom and the area to be evaluated. Measurements are done with the phantom placed below. Calibration phantoms convert values measured by CT systems as Hounsfield units (HU) into BMD (mg hydroxyapatite/mL).[6,14]

Volumetric QCT measurements are usually done in the lumbar region (L1-3) of the spine. 8-10 mm thick slices of the chosen vertebrae are scanned using a low dose energy technique with a lateral scanogram. The region of interest (ROI) is marked in the axial plan. Since ROI is chosen manually, it allows for the evaluation of trabecular and cortical bone areas as well as the exclusion of fractured vertebra and arthrosic changes. Similar to DXA; results obtained from the patient are compared with young adults and other people from the same age group. T and Z scores are identified.[13]

In an analysis of a femur which has a more complex anatomical structure than a vertebra, the scanned region extends from 1-2 cm above the femur head to a few centimeters below the lesser trochanter. The volume to be evaluated is selected in scanned slices (VOI= Volume of interest). It allows geometric measurement. Thus, both BMD and structural analysis can be done.[15,16]

Peripheral QCT (pQCT) is most commonly used in the evaluation of the distal radius and tibia. Measurements are usually taken on the non-dominant extremity. Radiation doses are low (1-2 micro Sv) and workup time is short. Osteoporosis cannot be diagnosed by pQCT. However, once the patient is diagnosed, it can be used for treatment follow-up. Recently, it has been used widely by researchers. Many studies report that pQCT measurements are comparable to BMD results measured by DXA.[17,18] The most important limitation of pQCT is the difficulty in measuring the same area during therapy/disease follow-up appointments. This is especially an issue if the patient is a growing child.[19] The American College of Radiology (ACR) defined normal, osteopenic and osteoporotic values for volumetric QCT based on the density of hydroxyapatite in g/cm^3 (Table 2).[20]

The most important fact a clinician needs to know about osteoporosis is that the WHO based the definition of osteoporosis on a -2.5 T score in DXA. As such, "values obtained using other techniques should not be evaluated according to the same cut-off value." As QCT analyze trabecular areas separately, bone loss due to aging occurs earlier. If -2.5 T values measured by QCT are interpreted as osteoporosis, many young adults would be misdiagnosed as osteoporotic. However, a -2.5 T score of DXA equals an average -3.4 T score (min: -3.1 max: -3.8) of QCT. This reflects approximately 80 mg mineral density in cm^3.[12,21]

Advantages of QCT over DXA

- It can measure BMD of trabecular and cortical bone separately.
- Compared to areal density of DXA (mg/cm^2), QCT can provide volumetric density data.
- Measurements are affected by tissue on vertebra and proximal femur in DXA. However, QCT is not affected by degenerative changes in spine or vascular calcifications.
- Quantitative CT is superior to DXA in BMD measurements in obese patients.
- It provides volumetric measurement advantage in children.

Table 2. Values defined by American College of Radiology for bone mineral density measured by quantitative computed tomography

QCT trabecular vertebra BMD values	Equivalent of WHO osteoporosis definition
>120 mgr/cm^3	Normal
120-80 mgr/cm^3	Osteopenic
<80 mgr/cm^3	Osteoporotic

QCT: Quantitative computed tomography; BMD: Bone mineral density; WHO: World Health Organization.

- Quantitative CT is superior to DXA in metabolic bone diseases.
- When these advantages are considered, Table 3 summarizes under which clinical conditions and on what grounds QCT is favored over DXA,[11,22-25]

Disadvantages of QCT over DXA[11,26]

- Most important disadvantage of QCT is higher radiation exposure compared to DXA (0.06 mSv versus 3 mSv). This especially limits its use in young women.
- T scores acquired with QCT can't be used in the diagnosis of osteopenia and osteoporosis. Presently, DXA is accepted as the leading method in clinical decision making. Even if DXA is not feasible, the Social Security Institution refuses to pay for QCT tests in osteoporosis treatment.
- Special software for CT systems and educated personnel are required for evaluating volumetric bone with QCT.
- It takes a little longer to report results with QCT compared to DXA.
- Because both the abdominal and pelvic regions are included in the area of assessment, overlooking any visceral organ pathology might cause legal problems. For example there might be enlarged lymph nodes in the para-aortic or inguinal region and if it is not reported in the analysis of QCT, a lymphoma diagnosis might get overlooked.
- Evaluating osteoporosis with QCT is more expensive compared to DXA.

In brief, many reports show that when measurements of vertebra and femur in QCT and DXA are compared BMDs of DXA and QCT are highly correlated; T scores of QCT are 15-20% lower; when corrected T scores are similar, and even though results of QCT and DXA correlate in cases with and without vertebra fracture, correlation is higher in cases with fractures.[27-29]

In a study that compared QCT and DXA in post-menopausal women; 140 women with an average age of 63 are compared.[30] Mineral density levels lower than 80 mg/cm^3 in QCT was categorized as osteoporosis. Accordingly osteoporosis was identified in 24% of the patients in the lumbar DXA while lumbar QCT classified 65% of cases as osteoporosis. This indicates a very dramatic difference. The authors reported that there were 41 cases that were diagnosed as osteoporotic by QCT and non-osteoporotic by DXA and, seven of these cases (17.1%) had single or multiple fractures. They reported that all of these 41 cases had vertebral arthrosis.

A study that compared the contralateral hips of 50 women with osteoporotic hip fractures using QCT and DXA included similarly aged women without fractures as a control group. In the results of the research; cortical thickness and volumetric BMD as measured by QCT compared to areal BMD measured with DXA was more valuable in the estimation of hip fracture.[31]

High resolution QCT techniques

Quantitative CT can also evaluate the skeletal structure of the spine, femur and appendicular skeleton in high resolution. Spatial resolution of these techniques is between 0.25-0.3 mm^2 when 0.6 mm slices are used. Considering that trabecula diameter has an average of 0.02-0.2 mm; even if they cannot completely reflect the trabecular structure, they might identify some microstructure features. They have been reported to have a correlation with micro CT.[4]

The multi-detector CT radiation dose is high in spine and femur (3000 micro SV). This radiation dose is much lower and negligible in peripheral analysis (HR-pQCT),[11]

High resolution-pQCT has been identified as the most important innovation in the evaluation of bone

Table 3. Clinical conditions in which quantitative computed tomography is superior to dual energy X-ray absorptiometry

Clinical indications for QCT	Reason
Very small or very big built individuals	Unlike projectional measurement in DXA volumetric measurement is not affected by the size of the body
Severe degenerative spine diseases (degenerative disk disease, facet arthropathy, DISH	Only trabecular bone in corpus vertebrae can be measured. Osteophytes affect measurement minimally.
Severely obese patients	DXA cannot remove impact of soft tissue completely
Conditions requiring high sensitivity to follow-up changes in metabolic bone	Trabecular bone is more active metabolically

QCT: Quantitative computed tomography; DXA: Dual energy X-ray absorptiometry; DISH: Diffuse idiopathic skeletal hyperostosis.

architecture in the last 10 years. The spatial resolution is provides is better than MD-spinal QCT, MRI and other pQCT devices. The radiation dose of 500-1000 is lower than abdominal CT and it takes approximately three minutes for each scan. A disadvantage is that it is a method limited to the peripheral skeleton. Cortical bone density, cortical thickness, cortical porosity, trabecular bone density, bone volume fraction (bone volume/trabecular volume), number of trabeculae, trabecular thickness and trabecular separation can be evaluated with HR-pQCT. Especially trabecular thinning and the decrease in trabecular connections can be identified in osteoporotic cases. High resolution-pQCT is used in many drug efficacy studies for this reason. Changes in the parameters before and after therapy have been reported.[1,32-36] Also HR-pQCT is reported to be correlated with micro CT, which is accepted as the gold standard in treatment follow-up studies.[37]

Cortical porosity which is the most important parameter evaluated with HR-QCT techniques, expresses the number and the width of pores in the cortical bone. The average cortical porosity in the femur neck is 5-13%. This ratio increases with aging or as the osteoporosis process advances. Both the diameter and the number of pores increase. This leads to the thinning and weakening of the cortex. Many studies report a correlation between the increase in cortical porosity and femur neck fractures. Also, cortical porosity is considered to be the most important indicator of bone quality.[2]

Women who use and do not use drugs that effect bone turnover were prospectively evaluated in a study that follows microstructure changes with HR-pQCT. In cases where bone turnover effecting-drugs were not used; trabecular separation and the increase in heterogeneity were identified along with decrease in total bone density and trabecular amount. In HRT users; decreases in the cortical area, total bone density, cortical content and thickness were reported along with an increase in the trabecular area. In women who use bisphosphonate, increases in bone volume fraction and trabecular density were reported. It was especially more apparent in the inner trabecular area. It has been reported that cortical and trabecular area changes in distal radius were reciprocally related.[38]

In a study that evaluated the correlation of HR-pQCT with DXA in the peripheral skeleton; distal radius measurements were obtained from 161 post-menopausal women. Researchers reported that QCT was correlated with DXA and it provided a significant advantage while evaluating cortical and trabecular bone microstructure in addition to its high accuracy and high level of precision.[39]

The low radiation dose of HR-pQCT allows identification of bone in healthy individuals. Chevalley et al.[40] used HR-pQCT to evaluate the distal radius of healthy post-menopausal women. They evaluated the bone microstructure in women with and without a history of fracture. As a result of their study in which they found significant differences between both T scores and cortical bone structures, they reported that 1 lower standard deviation in cortical thickness was related with a three times increase in fracture risk. They also pointed out that fractures in the pre-menopausal period might be an indicator for post-menopausal osteoporosis.

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging, a ground-breaking method which has the advantage of zero radiation exposure, is used in the diagnosis and follow-up of many diseases. It provides an opportunity to analyze trabecular and cortical bone separately. Bone vitality can be evaluated with a functional MRI. The higher the Tesla power of the MRI, the more successful it is in displaying bone structure. It has high reproducibility and variability in serial measurements is reported as 2-4%.[3] Comparative research is only possible for MRI measurements using the same Tesla power and the same area.

Mineralized tissue itself does not cause signals in MRI. This is actually a disadvantage because trabeculae are seen as signal voids in high intensity fatty bone marrow. Quantitative analysis can be done in T_1-weighted, T_2 fat-suppression weighted and diffusion weighted MRI sequences.[3]

An increase in bone marrow fat tissue in a MRI is associated with a BMD decrease in DXA. This is also supported since the osteoporotic process accompanies a fatty change in bone marrow.[41]

High resolution-MRI is mostly used in the peripheral skeleton (distal radius, distal tibia, and calcaneus). Scanning in these areas can be done with small coils. Gadolinium enhancement of fatty bone marrow and trabeculae can be seen. It even allows for the taking of a virtual biopsy.[42,43] Microstructural analysis via a virtual biopsy shows noticeable differences in individuals with fractured and non-fractured bones.

The high accuracy rates of data acquired by MRI in bone evaluation, and the fact that it is non-invasive make MRI an attractive option while performing drug studies.[44,45]

There are many differences between spinal osteoporotic fractured and non-fractured individuals in peripheral HR-MRIs. Trabeculae thickness and continuity are significantly different between fractured and non-fractured cases.[3] Recently, it is possible to analyze trabeculae in the femur with over 3T HR-MRI.[4]

Vertebral fracture risk is primarily associated with trabecular bone structure whereas; cortical bone geometry, thickness and porosity are important indicators for hip fractures. It is known that the thinnest cortical bone region in the femur neck is valuable to identify hip fracture risk. The value of MRI in evaluating cortical bone needs to be investigated.[4]

In a study that investigated whether the bone marrow fat ratio as identified by MRI correlated with DXA, 3T MRI evaluations were made. Two radiologists analyzed 58 post-menopausal women who were included in the study. This study reported that the bone marrow fat ratio measured by 3T MRI correlated with BMD measured by DXA. Also, MRI was reported to have a low inter-observer bias ratio and high reproducibility.[46]

In another animal study (sheep tibia), MRI was reported to correlate with micro CT. In this study morphometric analysis of trabecula was done using 3T MRI. This study also reported high levels of reproducibility and accuracy rate.[47] Another study that analyzed the wrists of four healthy individuals using 7 Tesla MRI reported that MRI was efficient in evaluating the distal radius trabecular microstructure.[48]

FINITE ELEMENT ANALYSIS: BONE STRENGTH AND FLEXIBILITY

The "Finite element analysis" (FEA) method can be acknowledged as the most important technological advancement in non-invasive analysis of bone. Quantitative CT and MRI also provided major innovations. The FEA method based on data from QCT and MRI, which is useful for assessing bone strength, fracture risk and therapeutic effects on osteoporosis. Finite element analysis is a computer-based program that can reflect complex geometry and heterogeneous density distributions of bone into colors and simulate stress and strain of objects under mechanical load. The purpose of the measurements of bone strength is to predict possible fracture risk in the bone under stress. FEA can also be used in evaluation of the response to drug therapy.[4,6,49,50]

In conclusion, in addition to the advantage of volumetric evaluation of bone mass and separate analysis of cortical and trabecular bone, QCT can be preferred to DXA in metabolic bone diseases, children and obese patients. Also calcifications that cause artifacts in DXA do not alter measurement results in QCT. One must keep in mind that T scores of QCT are not equivalent to T scores of DXA, so they must be adjusted accordingly. Especially HR-QCT stands out in evaluation of bone structure and is used in many drug studies. The radiation dose is negligible especially in peripheral analysis. Although MRI enables the analysis of bone structure, it cannot be used routinely in the diagnosis of osteoporosis. The FEA method that permits the evaluation of bone strength using both QCT and MRI looks promising to help answer many questions.

Osteoporosis is a clinical situation with many mysteries. We believe that in search of answers for understanding bone, QCT and MRI will contribute substantially.

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