Quantitative CT to assess bone mineral density as a diagnostic tool for osteoporosis and related fractures

Osteoporosis: a common disease in the elderly

Osteoporosis is the most common metabolic bone disorder. It is defined as “a skeletal disease, characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture” [1]. Bone is a highly metabolic tissue, incorporating multiple functions such as stabilization of the body, protection of the inner organs and calcium storage. It constantly remodels. In young individuals, bone formation exceeds bone resorption, until the peak bone mass is reached around the age of 30-35 years. In the elderly, with decreasing levels of estrogen and testosterone, bone resorption exceeds bone formation; thus, bone mass in any older individual is determined by peak bone mass and amount of bone loss [2].

As a disease of the elderly, the prevalence of osteoporosis will increase as the population ages. Already, every third postmenopausal woman and every fifth man older than 50, suffers from osteoporosis [3]. Sustained fractures compromise the quality of life and shorten life expectancy [4, 5].

Osteoporosis has become a major public health threat for an estimated 44 million Americans. In the U.S. today, 10 million individuals are estimated to already have the disease and almost 34 million more are estimated to have low bone mass, placing them at increased risk for osteoporosis [6]. Fractures of the spine are the most common complications (Figure 1), while hip fractures are attended by the highest morbidity. Treatment costs in Europe are expected to increase up to 75 billion Euro by 2050 [7].

Assessing osteoporosis: from the beginning to QCT

As preventive therapies become increasingly available, there is a huge clinical demand to extend the assessment of osteoporosis to a larger population and, at the same time, to have access to reliable diagnostic methods.

Figure 1. Sagittal reformatting of the lumbar spine in a healthy patient and a patient with osteoporosis

Figure 1a. Healthy patient.

Figure 1b. Osteoporosis with a non-traumatic fracture of T12.

Figure 1c. Follow-up scan (same patient as Figure 1b). There is a new fracture of L3. There are also aortic calcifications that would artificially increase DXA-based bone mineral density (BMD) measurements.
Osteoporosis is assessed by measurement of the bone mineral density (BMD) in absolute terms (mg/cc) and by comparison with a known standard, typically the T-score, which is the number of standard deviations above or below the mean for a healthy 30 year old adult of the same sex and ethnicity as the patient, or the Z-score, which is the number of standard deviations above or below the norm for a person of the patient’s age, sex, weight, and ethnic origin.

The early methods of quantification included measurement of cortical morphometry, usually of the second metacarpal, as well as photon absorptiometry using radionuclide sources [8, 9]. Due to the long scan time of about 15 minutes per site, photon absorptiometry was replaced by the planar method Dual-Energy X-ray Absorptiometry (DXA) in the 1980s. Using this technique, spatial resolution improved and a short scan time of less than one minute was achieved [10].

In the previous decade, computed tomography (CT) had been introduced, initially for scans of the head in 1973 [11]. A few years later, whole-body scanners were available and were soon being used for quantitative analysis of the skeletal bone mineral density BMD [12].

Due to lower radiation dose and cost, DXA remained the predominant screening tool. However, in recent years, the use of quantitative CT (QCT) has increased [13] with the advent of new developments in CT technique and the recognition of its following advantages over DXA:

- Ability to separate cortical and trabecular bone
- Provides true volumetric density in units of mg/cc
- No errors due to spinal degenerative changes or aortic calcification
- Information on bone morphometry.

Technical aspects

Contrary to the planar method DXA and X-ray examinations, CT uses X-rays from multiple angles to generate reconstructed 3D-image datasets of the scanned object, based on its X-ray absorption. Volumes with materials of large atomic number and material density present with higher X-ray attenuation and appear brighter in CT images. The X-ray attenuation is expressed as CT numbers, measured in Hounsfield units (HU).

All clinical whole-body CT scanners are calibrated with respect to water at 0 HU. Cortical bone exhibits high CT numbers of more than 1000 HU. Converting the Hounsfield numbers to bone mineral density requires a reference material with known attenuation properties. Some systems use external phantoms that are scanned together with the patient.

Phantom-less QCT

The Extended Brilliance Workspace (Philips Healthcare, Cleveland, OH, USA) employs a phantom-less QCT method, combining the inherent advantages of QCT with ease of use and a wider range of application. Because no phantom is used and no special preparation is required, phantom-less QCT can be applied to thoracic and abdominal studies not primarily intended for BMD assessment, and can even be applied retrospectively to previously acquired image data.

Phantom-less QCT relies on the patient’s paraspinal muscle and subcutaneous fat as calibration references and assigns the mode to the resulting peak of the best-fit Gaussian function for each component, instead of merely adopting an average CT number (Figure 2). A clinical cross-sectional study of vertebral BMD with this system yielded highly reproducible results [14].

The phantom-less method offers several advantages. The reference regions of interest (ROIs) are in direct proximity to the vertebral bodies, thus avoiding beam hardening and scatter effects caused by an external phantom. The method also opens the possibility to increase the utility of abdominal and thoracic CT scans. For example, it can be used in conjunction with virtual colonoscopy [15] or cardiac scans [16], also retrospectively, to obtain an ancillary BMD assessment.
Initially, QCT BMD was determined in 2D-slices, placed centrally in three lumbar vertebrae, usually L1-L3. With the recent advent of multi-detector CT technology, 3D image stacks can be acquired within a sub-second acquisition time, and 3D BMD analysis can be performed relatively easily. Other main advantages of 3D-BMD analysis are the better reproducibility due to a more stable and matched placement of the ROIs, reduced partial volume effects and reduced motion artifacts. This is particularly important in the case of follow-up examinations.

The monitoring time interval (MTI), which is the minimum time over which a significant change in BMD can be expected, is highly dependent on reproducibility and bone turnover [9, 17, 18]. Phantom-based 2D single slice QCT has an associated reproducibility error of -3% [19]. With an average bone loss of 2.6% per year in trabecular bone of the spine, a significant change can be determined in a follow-up exam about 3.1 years later. The better reproducibility of phantom-based 3D-QCT of -1.8% [20] decreases the MTI to about 2 years.

For comparison, in spinal DXA with a reproducibility error of 1% and an average bone loss of 0.8% per year, the MTI is about 3.5 years. This demonstrates the advantage of selectively measuring the trabecular bone compartment, due to the more rapid bone turnover. In a study [21] devoted to the clinical evaluation of the Philips phantom-less method, the measured precision was 4.0%. A negligible bias (systematic shift of absolute values) with respect to phantom-less QCT BMD was observed. The consecutive MTI is about 4.2 years, just slightly higher than that of phantom-based 2D single slice QCT and DXA.

In QCT, the density of trabecular bone is the essential variable measured. In contrast, the cortical bone of the vertebrae is not thick enough to be measured with reasonable accuracy; for good results in the case of a CT voxel size of 0.4 mm, the cortical thickness would have to be more than 2.5 mm [22].

Radiation dose in QCT is significantly higher than that in DXA (0.001-0.006 mSv), but is still considerably lower than that of other X-ray based examinations for osteoporosis, such as radiographs of the spine (0.7-2.0 mSv), or the annual natural background radiation (~2.5 mSv).

The radiation exposure in QCT is highly dependent on the protocol. It can be estimated to be about 0.09 - 0.15 mSv in the case of single slice QCT (L1-L3) and about 1 mSv in the case of a 3D QCT of the lumbar spine (L2-L3, 8 cm scan range) [13]. A significant reduction in radiation dose is possible using modern MDCT systems with wide detector systems [23]. In the case of the Philips Brilliance iCT, with a 8 cm wide detector, using the axial scan mode, our investigations show that the radiation dose can be limited to about 0.35 mSv for a scan range of 7.5 cm using at 80 kV and 120 mAs. This is sufficient to cover two vertebrae (unpublished data).

Accuracy errors are still substantial in QCT. Averaging effects of water, fat, collagen and hydroxyapatite in trabecular bone can be responsible for an error of 5-15%, as compared with the true mineral content [13]. This error can be reduced using dual-energy CT [24]. While this was not clinically feasible with older systems, due to the long scan times, higher radiation dose and lower reproducibility, the method has come back into the focus of current research as the former limitations have been partly resolved.

**Comparison with DXA**

DXA is currently the most widely used method for bone mineral assessment in order to establish a diagnosis of osteoporosis, as well as for treatment monitoring. Clinicians and researchers favor DXA because scanners are readily available and relatively inexpensive. The radiation dose is negligible and the T-score scale, defined by the WHO specifically for DXA, provides a standardized classification. However, BMD - as a single surrogate for bone integrity - cannot sufficiently quantify fracture risk or a decrease in bone strength.

More than 60% of elderly women who have sustained a non-traumatic fracture would not be classified as osteoporotic by WHO criteria [25]. A meta-analysis of placebo-controlled clinical trials of antiresorptive therapies showed that therapeutic effect on BMD is unrelated to fracture reduction efficacy [26]. Thus, the WHO now favors the calculation of a 10-year-fracture risk, based on clinical risk factors in addition to BMD measurements [27]. This fracture risk should be used to initiate appropriate treatment, while BMD measurements are needed for treatment monitoring. This will become more important in the near future with new, powerful, but expensive drugs becoming available [28, 29].

In addition to the reproducibility errors affecting the monitoring time interval, DXA results are also dependent on patient size. Aortic calcifications and degenerative changes can lead...
First, calibration of the CT system needs to be performed regularly, to avoid drift of the CT numbers. Secondly, the most important part of the scanning procedure is the proper selection of suitable vertebrae. In the case of follow-up examinations, previous studies have to be reviewed and the same vertebrae and ROIs (position and size) should be selected for scanning. In the phantom-less method, the CT numbers of the muscle and fat ROIs should be as close as possible to the respective values in the preceding measurements [21].

While in single-slice QCT usually three vertebrae were scanned, in volumetric QCT two to overestimates of spinal DXA BMD, especially in the elderly (Figures 3 and 5). Finally, from the economic point of view, the provision of an extra room, costs for maintenance and dedicated staff for DXA is often not justifiable, especially when CT is available in almost every radiological facility.

Considering clinical utility, the vast number of abdominal and thoracic CT scans being performed daily all over the world in patients who are at potential risk of osteoporosis, means that routine assessment of BMD could be performed in these patients using the phantom-less method, with no additional radiation dose and just a small amount of additional effort [21].

In children, the indication for QCT scans has to be thoroughly checked. Only Z-scores, i.e. comparison with age-matched controls, should be used. Overall, DXA seems to be the preferable method in children, as radiation dose is substantially lower, while disadvantages such as degenerative changes are not applicable in children, there are larger reference databases available for DXA [30].

\section*{Skills needed to obtain meaningful results by QCT}

QCT is fast and easy to perform. However, good reproducibility – which is the major quality criterion – demands well-trained and motivated staff.

Figure 4. The lateral scout view image is used to plan the acquisition of the volumetric QCT scan. Regions with fractures and degenerative changes should be avoided, visible osteoporotic fractures should be described in the report.
• Normal BMD > 120 mg/cc
• Osteopenia < 120 mg/cc
• Osteoporosis < 80 mg/cc
• Very high fracture risk < 50 mg/cc.

The Z-score and T-score provided by the manufacturer should be mentioned but should be accompanied by a warning that they are not comparable to DXA-based results [32]. The spinal density is measured by an oval or a “pac-man”-shaped vertebral ROI (Figure 5, left). By visual inspection one should check that the CT numbers obtained in Fig. 2 reflect a reasonable representation of the dominant gaussian (bell-shaped) contribution. The results of the phantom-less BMD analysis associated with the ROI histograms from Figure 2 are displayed on the right in Figure 5.

Based on the lateral scout view, osteoporotic spine fractures should be reported. They can be classified in mild (vertebral height reduction between 20% and 25%), substantial (25% - 40%) and severe ( > 40%), according to the spinal fracture index (SFI), first described by Genant et al. [33].

Finally, changes observed in follow-up scans should be reported and the significance of these changes should be stated. The least significant change (LSC) is related to the previously discussed MTI and the reproducibility (measured as coefficient of variation, CV) of the QCT system used: LSC ~ 2.8 CV.

In the case of 2D single slice QCT, the LSC is about 8.5%; in the case of the 3D phantom-based method it is about 5%, in the case of consecutive vertebral should be evaluated, usually L2 and L3 [13]. To avoid unnecessary radiation, scans should be performed from endplates to endplates only. Vertebrae with obvious or known abnormalities such as fractures, deformities, hemangiomas or metastases should not be included (Figures 3 and 4).

To optimize image quality and minimize radiation dose, general guidelines for CT imaging should be followed, like placing the arms over head and avoiding metal objects within the scan range. The lateral scout view assists in selecting suitable vertebrae. It is also used for fracture detection and should therefore cover the spine from T6 to L5 (Figure 4).

The QCT scan protocol has to be kept consistent for best reproducibility, especially for follow-up scans. For scans of the spine using the phantom-less method, a helical scan protocol with 120 kV and 100 mAs has proven to be sufficient for non-obese patients. The same table height should be used for all scans, and the same CT system and the same analysis system should be used in follow-up scans.

A QCT report should first of all include technical information, such as the system and technique used, for example 2D single slice QCT, 3D QCT or the phantom-less 3D method. The corresponding minimal monitoring time interval should also be stated. The trabecular BMD should be indicated as the most important parameter, and should be interpreted using the Felsenberg classification [31], based on the following cut-off values:

- Normal BMD > 120 mg/cc
- Osteopenia < 120 mg/cc
- Osteoporosis < 80 mg/cc
- Very high fracture risk < 50 mg/cc.

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References


