Quantitative computed tomography in children and adolescents

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Introduction

Methods for quantitative assessment of the skeleton are relevant to the understanding of growth and development during normal childhood and studying the effect of disease and therapy in children with chronic diseases. Dual energy x-ray absorptiometry (DXA) is currently the most widely available and utilised technique in adults and children. The strengths of DXA are:

• The technology is widely available in most parts of the world (probably in excess of 40,000 central DXA scanners worldwide; cost approximately £80k-£100k)
• It is applicable to sites of the skeleton in which osteoporotic fractures occur in adults (lumbar spine, proximal femur, forearm)
• It can be extended beyond measurement of bone mineral density (BMD) – whole body and regional body composition, visceral adipose tissue (VAT), vertebral fracture assessment (VFA), hip strength analysis (HSA) and hip axis length (HAL)
• It involves very low doses of ionising radiation at 1-6 microSv per scan.2,3

There are some limitations also in that DXA provides a 2D image of a 3D structure so there is a depth of bone that cannot be taken into account. DXA provides areal bone mineral density (aBMD) in g/cm² and so is size dependent, a particular problem in children in whom bones are growing in length, increasing in density and changing in shape. DXA will therefore underestimate aBMD in children who are small for age, which may be the case in chronic illness or growth hormone deficiency. Additionally DXA measures integral (cortical and trabecular) bone aBMD.

Quantitative computed tomography (QCT) has advantages in that the cross-sectional imaging provides true volumetric vBMD (mg/cm³) so is not size dependent and provides separate measures of cortical and trabecular vBMD. The latter is some eight times more metabolically active than cortical bone and so more sensitive to longitudinal change in BMD. The limitation for central QCT, particularly when applied in children, is that it involves higher doses of ionising radiation than DXA and there are limited reference data available. As with other bone densitometry techniques, QCT in children is best performed by a few well trained and experienced technical staff, and good quality scans are difficult to obtain in children under five years due to movement artefact.

QCT actually predates DXA as it was introduced in 1976 whereas DXA replaced single- and dual-photon radionuclide absorptiometry in the late 1980s. However, as DXA was subsequently applied widely in epidemiological and therapeutic efficacy studies in adults it superseded QCT. Over the past decade the advantages of QCT have been recognised and consequently it has been utilised increasingly in research and epidemiology studies in adults, with the number of publications using QCT increasing from 20 per annum in 2003 to 60 in 2013, but this is compared to approximately 1,600 for DXA in 2014. This increasing application of QCT includes its application in paediatric patients with skeletal disorders.4-10

Technical aspects

QCT can be performed in central sites (usually lumbar spine) using general purpose CT scanners and in peripheral sites (femur, radius and tibia) using both general purpose and dedicated peripheral scanners that are smaller and less expensive.3,4,11 On general purposes scanners originally with ‘rotate/translate’ x-ray and detector technology, 2D single slices 5-10mm in width were performed through the midplane of three vertebral bodies between T12 to L3. Determined from the preliminary lateral scan projection radiograph (scout view), the gantry was angled to obtain a section parallel to the vertebral endplates. However, many developments have been made in CT technology since its introduction, including spiral x-ray tube rotation and multiple rings of detectors (multi-detector spiral MDCT). These improvements have allowed volumetric 3D images to be acquired with a spatial resolution of ~0.6mm for QCT of the lumbar spine and hip. QCT can now be performed rapidly in less than 30 seconds. The precision of 3D QCT is superior to 2D, with an approximate coefficient of variation of ≤1% for measuring vBMD in the lumbar spine and equivalent to that of DXA, but the radiation dose is higher. A region of interest (oval or PacMan) is placed in the trabecular bone with the margin as close as possible to, but not including, the vertebral body cortical rim and avoiding the entry posteriorly of the basi-vertebral vein (figure 1a-d).

The attenuation values, expressed in Hounsfield units (HU), corresponding to the bone tissue are converted into bone mineral equivalents (mg/cm³) by calibration with a hydroxyapatite calibration phantom and dedicated analysis software. In central QCT, the phantom is measured simultaneously with the patient (figure 1a-d). The most widely used phantoms are provided by QCT Pro, Mindways Software Inc, Austin, USA and Image Analysis Inc, Columbia, USA. Some CT manufacturers provide their own software and phantoms (Siemens Healthcare, Erlangen, Germany) and for more complex 3D volume analysis only advanced university-based research tools are available.11-14

The most widely applied phantom and software is probably the Mindways QCT Pro analysis, but this is rather large and not optimised for children. Smaller phantoms such as the Siemens Osteo phantom or the Bone Density Calibration...
phantom (QRM GmbH, Mohrendorf, Germany) allow for smaller field of views, providing optimised spatial resolution and they are less prone to cause streak artifacts, which may be present with larger phantoms when used in children.\footnote{12} The patient is positioned supine on the scanner table with the hips flexed and the calves positioned on a support to flatten the lumbar lordosis (\textbf{figure 1a}). The bone equivalent phantom is placed on the scanner table below the lumbar spine and bolus bags of water equivalent material are placed so that there is no air gap between the patient and the phantom (\textbf{figure 1b}). A calibration phantom should be scanned at least weekly or whenever QCT is to be performed and a number of factors (table height, gantry angle, scan protocol and phantom) must be kept constant in longitudinal studies. As with DXA, if scanners or phantoms have to be changed during longitudinal studies then cross-calibration with a phantom, such as the European Spine Phantom\footnote{15} or European Forearm Phantom, have to be undertaken to make results comparable. Cross-calibration between scanners using patients is more difficult with children and QCT technology.

Over the past two decades, peripheral QCT (pQCT) studies in children were almost exclusively carried out on the XCT 2000 and 3000 scanners (Stratec Medizintechnik, Germany), applied to the non-dominant radius or tibia with each slice taking one minute to acquire (\textbf{figure 2}).\footnote{16} The sites of the sections scanned have been quite variable in the radius (4%–most common site, 20%, and 66%), in the tibia (3%, 4%, 14%, 20%, 38%, and 66%) and in the femur (4% and 20%), from either the distal end of the bone, or from the metaphysis if the growth plate is unfused (\textbf{figure 2b and c}). This variability makes comparative studies problematic.\footnote{12}

A new, high resolution pQCT scanner (XtremeCT; Scanco, Switzerland) has recently been introduced. The XtremeCT operates in cone beam geometry and in standard mode acquires a 9 mm thick volume of tissue (110 slices) in about three minutes, a long acquisition time which predisposes to movement artefact, particularly in children. Three different spatial resolutions can be selected. In standard mode, the resulting 3D data set has an isotropic voxel size of 82 mm\(^3\) resulting in an isotropic spatial resolution of about 130 mm.\footnote{14} Secure fixation of the limb and a quiet scanning environment are essential to minimise movement artifacts.

**Ionising radiation doses**

The doses of ionising radiation related to QCT, other bone densitometry techniques and some comparators are given in \textbf{table 1}.\footnote{12,13,16} For single slice (2D) QCT low dose protocols using 80kVp (or 120kVp) and 120mAs (or 150-200mAs) result in effective doses of less than 200 microSv.\footnote{13} MDCT QCT radiation doses are higher and have been estimated to be as high as 1.5 mSv for the spine and 2.5-3.0 mSv for the hip,\footnote{14} precluding application of hip QCT in children.\footnote{12} As with many bone densitometry methods, QCT has been primarily developed for, and applied in, adults and there has been inadequate attention to adaption for use in children. It is possible to use a low dose technique for 3D volumetric QCT with exposure parameters of 90 kVp and 150 mAs,\footnote{13} but such settings may be inconsistent in any longitudinal studies. Ionising radiation doses from QCT performed in peripheral sites is negligible (\textbf{table 1}).

**Measurements provided**

From central QCT scans of the lumbar spine vertebral bodies in children vBMD of the trabecular bone is the measure made; a standard deviation Z score is derived from available age- and gender-matched normal data.\footnote{12,13,16} Only new bone formation is measured. Currently there is a paucity of normal reference data available.\footnote{12,13} More sophisticated analyses to include cortical bone used in adults have not yet been applied in paediatric studies.

Peripheral QCT is most commonly applied to the non-dominant forearm. The forearm length is measured as the distance between the tip of the ulnar styloid and the olecranon. The forearm is placed pronated in the pQCT gantry with the elbow resting on a block, the hand gripping the hand fixture and the arm secured with Velcro straps to prevent movement (\textbf{figure 2a}). A scout scan is performed and a reference line is placed to bisect the medial border of the end of the distal radius in adults. In children if the growth plate is visible, the reference line is positioned to bisect the medial border of the distal dense metaphysis (\textbf{figure 2b}). If the distal radial growth plate has fused, the reference line is placed to bisect the medial border of the distal articular surface of the radius (\textbf{figure 2c}). Accurate and consistent positioning of this reference line is essential in any longitudinal or multi-centre studies for results to be comparable. This is particularly important in the distal radius which changes in shape and becomes more flared towards the articular surface; even in contiguous slices in this region in adults there are significant differences in total and trabecular BMD and cross-sectional area.\footnote{17} In multi-centre studies it is advisable to have a written protocol which includes an image with the position of the reference line depicted to ensure consistency between centres. The parameters measured at the 4% site in the radius include total and trabecular bone mineral content (BMC), BMD and cross-sectional area (CSA). In the diaphyseal sites cortical BMC and BMD are measured with many geometric parameters including total and cortical area (mm\(^2\)), cortical thickness (mm), marrow cross-sectional area (mm\(^2\)), periosteal and endosteal circumference (mm). From these data can be extracted some biomechanical parameters of bone including cross-sectional moment of inertia, indicative of bone strength in torsion, and strain stress index. These parameters provide interesting research information in health and disease in adults and children, but there is a paucity of appropriate reference data available to date.\footnote{12,15} Information on CSA of muscle (and fat) can also be obtained which gives scope for study of the ‘muscle-bone unit’ in health and disease. In recent years, the effect that muscle has upon bone has received considerable attention. According to the ‘mechano-stat’ theory, the loading imposed by muscles is thought to stimulate growing bones to adapt their geometry and mineral content to preserve, or increase, bone strength. Muscle is therefore considered to be a major determinant of the strength of growing bones, and muscle and bone work together as a conceptual operational unit which is known as the ‘muscle-bone unit’.\footnote{21} These additional XCT outcome measures enable assessment as to whether an individual has deficits in bone, muscle or a combination of both. Muscle density may be a more sensitive measure of muscle status than cross-sectional muscle area alone. However, ‘muscle density’ is reported as a calcium hydroxyapatite equivalent density. Thus, muscle density as measured on XCT devices is not the physical density of muscle tissue, and the clinical value of the XCT muscle density measurement requires further investigation and validation.\footnote{12}

Peripheral sites can be scanned on MDCT scanners more quickly than on dedicated pQCT scanners, and when a volume of tissue has been obtained then it may be more feasible to retrospectively select comparable 2D slices in longitudinal studies than if only 2D sections are available at each visit.\footnote{13} The tibia is another important scanning site for XCT since it has the advantage of being an axial weight-bearing bone. Some children with disabilities, for example Duchenne muscular dystrophy, cerebral palsy, may be more comfortable and easily scanned when lying on the table of a general purpose scanner than being scanned either on DXA or dedicated pQCT scanners in which ideal positioning for the site to be scanned may be difficult or impossible.\footnote{12,15} Assessment for vertebral fracture can be made from the preliminary lateral scan projection radiograph (scout view) (\textbf{figure 1d}).

CT measurements in trabecular bone are affected by marrow fat in adults; the influence of marrow may be more complex in children as red marrow is converted to yellow marrow with age. Whereas general purpose CT scanners are calibrated to water being 0HU, so that trabecular bone does not have a negative value Stratec pQCT scanners add a constant of 60mg/cm\(^3\) to the calibrated BMD values. As a con-

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**Table 1:** Ionising radiation doses for single slice (2D) QCT low dose protocols using 80kVp (or 120kVp) and 120mAs (or 150-200mAs) result in effective doses of less than 200 microSv. MDCT QCT radiation doses are higher and have been estimated to be as high as 1.5 mSv for the spine and 2.5-3.0 mSv for the hip.

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**Figure 1a:** The bone equivalent phantom is placed on the scanner table below the lumbar spine and bolus bags of water equivalent material are placed so that there is no air gap between the patient and the phantom. **Figure 1b:** A calibration phantom should be scanned at least weekly or whenever QCT is to be performed.

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**Figure 2:** The forearm is placed pronated in the pQCT gantry with the elbow resting on a block, the hand gripping the hand fixture and the arm secured with Velcro straps to prevent movement. A scout scan is performed and a reference line is placed to bisect the medial border of the end of the distal radius in adults. In children if the growth plate is visible, the reference line is positioned to bisect the medial border of the distal dense metaphysis. If the distal radial growth plate has fused, the reference line is placed to bisect the medial border of the distal articular surface of the radius. Accurate and consistent positioning of this reference line is essential in any longitudinal or multi-centre studies for results to be comparable.
sequence results from scanners calibrated with this fat offset correction and those from scanners calibrated to water are not comparable.

The high resolution XtremeCT scanner provides outcome measures similar to those obtained by histomorphometry. Only trabecular number (Tb.N) is measured directly; bone volume/total volume, trabecular thickness, and trabecular spacing are derived from combinations of Tb.N and trabecular BMD. As a fixed bone mineralisation of 1.200mg/cm² is assumed, any disease or treatment that alters mineralisation (eg rickets) will cause inaccuracies in all the parameters measured.

Because the bone cortex is thinner in children than in adults, partial volume averaging and different spatial resolution of CT scanners result in cortical assessment being more problematic.

Reference databases and clinical applications

QCT, both central and peripheral, remains primarily a research technique. The most widely used measurement in clinical practice is pQCT at the 4% distal radial site using the Stratec scanner. There is a paucity of relevant reference databases in children from which to calculate Z scores and interpret results in individual children, and those which do exist are in children of European origin. The Manchester Healthy Children’s Study provides such reference data for the 4% and 50% radius sites in boys and girls aged 6-19 years, while the DONALD (Dortmund Nutritional and Anthropometric Longitudinally Designed) provides data for German children aged 6-20.9 years at the 4% and 65% radius sites and a USA study provides data in the tibia at the 4% and 66% sites. There is no specifically designed reference data study published for HRpQCT but there are eight reports of its application in healthy children.

Peripheral QCT has been applied in a large number of children with various diseases affecting the skeleton and there are a few studies emerging using HRpQCT. Reduced radius and tibia 4% trabecular and total vBMD are predictive of increased fracture risk in children; studies suggest that cortical vBMC may be sensitive to disease and treatment effects. Application of central QCT in children with chronic disease is limited, as is the relevant reference data available. Currently adult scan protocols are used in children so there is an urgent need for paediatric specific protocols to be developed.

Accessibility and approximate costs

There are approximately 1,700 Stratec XCT peripheral scanners worldwide and the cost of the scanners is in the region of £65k. Their small size, low radiation dose and relative portability enables more flexibility in where they are located and their utilisation. HRpQCT Scanco scanners are a more scarce and expensive commodity (cost in the region of £400k), there being about 50 such scanners worldwide, with only four in the UK. Both peripheral CT scanners must be operated in compliance with the ionising radiation legislation. General purpose CT scanners are very numerous, sited in radiology departments and in great demand for clinical use making access for QCT often problematic. The cost of phantoms and software required to perform and analyse central and peripheral QCT on a general purpose scanner is in the region of £10k to £15k.

Conclusions

Quantitative CT remains predominantly a research tool, but has advantages over DXA allowing measurement of volumetric density, separate measures of cortical and trabecular bone density, and evaluation of bone shape and size. High resolution imaging CT measures trabecular and cortical bone microstructure, however although this provides detailed insights into the effects of disease and therapies on bone, it is technically challenging, particularly in children, and not widely available, so is unlikely to be used in clinical practice.

References


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<th>Technique</th>
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<td>MDCT (children)</td>
<td>Two lumbar vertebrae L1, L2</td>
<td>80kV, 100mAs, slice thickness 0.6mm, pitch 1</td>
<td>0.59-1.09</td>
<td>Depends on gender, scan length, age</td>
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<td>Transatlantic flight (return)</td>
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<td>Spinal radiographs</td>
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TABLE 1 Ionising radiation doses QCT and some comparators.

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Central QCT: A) Patient positioned for central QCT with knees slightly flexed to flatten lumbar lordosis. B) Cross section through mid-plane of lumbar vertebra with patient lying on the bone reference phantom with cylinders of fat, water and 50, 100 and 200mg of hydroxyapatite from Mindways, and gel cushion between phantom and patient to reduce artefacts. C) Midline sagittal reformat through L1 to L3 with mid-plane lines through each vertebra (lower images) and oval region of interest of analysis placed in trabecular region to provide vBMD (upper images). D) Lateral scout view from which assessment can be made for vertebral fracture which is present in T12.
Peripheral QCT: Before scanning, the forearm length is measured from ulna styloid to olecranon with arm flexed. A) Child positioned in Stratec XCT 2000 pQCT scanner for scanning of non-dominant radius with forearm pronated in gantry and held secure with Velcro strap. B) Scout view. When the growth plate is unfused the reference line is placed to bisect the corner of the medial metaphysis of the distal radius (single line); the scan plane is then 4% proximal to this reference line (double line). C) Scout view. When the growth plates have fused in older children the reference line has to be placed to bisect the corner of the medial border of the distal articular surface of the radius. Cross-section at D) 4% distal radial site showing central trabecular bone (red) and outer cortical bone (white) and E) 50% mid diaphyseal site at which parameters of cortical bone are measured and from which biomechanical parameters can be extracted. Muscle cross-sectional area and ‘density’ can also be obtained.