Bone 112 (2018) 145–152

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Full Length Article

Evaluation of cross-sectional and longitudinal changes in volumetric bone mineral density in postmenopausal women using single- versus dual-energy quantitative computed tomography

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ARTICLE INFO

Keywords:
Menopause
Osteoporosis
DXA
Quantitative computed tomography

ABSTRACT

Central quantitative computed tomography (QCT) is increasingly used in clinical trials and practice to assess bone mass or strength and to evaluate longitudinal changes in response to drug treatment. Current studies utilize single-energy (SE) QCT scans, which may be confounded both by the amount of bone marrow fat at baseline and changes in marrow fat over time. However, the extent to which marrow fat changes either underestimate volumetric BMD (vBMD) measurements at baseline or under-/overestimate longitudinal changes in vivo in humans remains unclear. To address this issue, 197 early postmenopausal women [median age (IQR) 56.7 (54.4–58.7) years] underwent spine and hip QCT scans at baseline and 3 years using a 128-slice dual-source dual-energy (DE) scanner. The scans were analyzed as either SE scans (100 kVp) or DE scans (100 kVp and 140 kVp), with the latter accounting for bone marrow fat. At baseline, vertebral trabecular vBMD was (median) 17.6% lower ($P < 0.001$) while femur neck (FN) cortical vBMD was only 3.2% lower ($P < 0.001$) when assessed by SE vs DE scanning. SE scanning overestimated the 3 year rate of bone loss for trabecular bone at the spine by 24.2% ($P < 0.001$ vs DE rates of loss) but only by 8.8% for changes in FN cortical vBMD ($P < 0.001$ vs DE rates of loss). The deviation between SE and DE rates of bone loss in trabecular vBMD became progressively greater as the rate of bone loss increased. These findings demonstrate that SE QCT scans underestimate trabecular vBMD and substantially overestimate rates of age-related bone loss due to ongoing conversion of red to yellow marrow. Further, the greater the rate of bone loss, the greater the overestimation of bone loss by SE scans. Although our findings are based on normal aging, recent evidence from animal studies demonstrates that the skeletal anabolic drugs teriparatide and romosozumab may markedly reduce marrow fat, perhaps accounting for the disproportionate increases in trabecular vBMD by SE QCT as compared to dual-energy X-ray absorptiometry with these agents. As such, future studies using recently available DE scanning technology that has satisfactory precision and radiation exposure are needed to evaluate changes in trabecular vBMD independent of changes in marrow fat with aging and drugs that may alter marrow fat composition.

1. Introduction

In humans, bone marrow occupies about 85% of the bone cavity, with the remainder of the cavity consisting of trabecular bone [1]. During normal physiologic aging, as well as in various disease states, red hematopoietic marrow is progressively converted to yellow fatty marrow. Importantly, during the perimenopausal transition, a period characterized by rapid bone loss in women, changes in the amount of marrow fat can impact the assessment of bone mineral density (BMD) due to the fact that marrow fat has lower radiodensity relative to bone, thereby leading to underestimation of volumetric BMD (vBMD) using conventional single energy (SE) quantitative computed tomography

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https://doi.org/10.1016/j.bone.2018.04.023
Received 15 January 2018; Received in revised form 9 March 2018; Accepted 24 April 2018
Available online 25 April 2018
8756-3282/

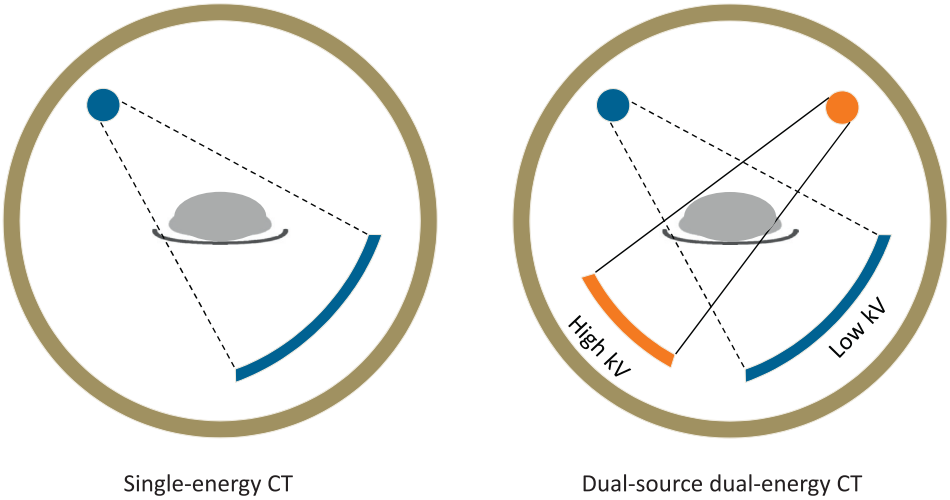

Fig. 1. Schematic comparing the energy sources in a SE versus DE CT scanner.

(QCT) methods.

Central QCT has been increasingly employed in both clinical trials and practice to assess bone mass and strength and to evaluate longitudinal skeletal changes in response to pharmacologic intervention. Current studies utilize SE QCT scans which offer the advantages of 3-dimensional evaluation of bone structure and estimations of vBMD due to the ability of QCT to allow for the separate evaluation of cortical and trabecular compartments. The trabecular compartment is of particular importance due to its high metabolic activity and consequent susceptibility to changes in vBMD, but image assessment is highly influenced both by the degree of marrow fat at baseline and changes in marrow fat over time [2,3]. It has long been recognized that accounting for marrow fat in the assessment of vBMD, using techniques such as dual energy (DE) QCT, provides a more accurate estimation of both bone mass and mineral content [4,5], although previous studies have been performed in cadaveric specimens and there is currently no data on longitudinal changes in DE QCT vBMD in vivo in humans. In particular, SE QCT scans have routinely been used for research and clinical purposes due to concerns regarding radiation exposure and increased variability of DE QCT scans [4,5].

Given these considerations, in this study we sought to quantify the underestimation of vBMD at the lumbar spine and femoral neck when assessed by SE QCT versus DE QCT as well as the potential overestimate of rates of bone loss by SE QCT during longitudinal 36-month follow-up imaging. For this comparison, we used DE QCT technology to assess postmenopausal bone loss in women independent of changes in marrow fat.

2. Methods

2.1. Study subjects

We recruited 199 women aged 50–61 years between 2011 and 2012. The sample size was based on power calculations to provide 90% power to detect 0.8%/year (and 80% power to detect 0.7%/year) changes in lumbar spine trabecular vBMD using DE QCT in early postmenopausal women. In our previous studies, the average changes over 3 years in lumbar spine trabecular vBMD by SE QCT were 1.7%/year in similar age women [6], so we planned for a sample size that would allow as much as a 50% overestimation of rates of bone loss by SE versus DE QCT. Inclusion criteria were postmenopausal status (absence of menses for ≥ 1 year and serum FSH level > 20 IU/L) as well as total hip or lumbar spine BMD T-score between −1 and −2.5. Exclusion criteria included: 1) Total hip or lumbar spine BMD T-score at or below −2.5; 2) abnormality in any of the following screening laboratory studies: serum calcium, phosphorus, alkaline phosphatase, aspartate aminotransferase, or creatinine; 3) presence of significant liver or renal disease, malignancy, malabsorption syndrome, hypo- or hyperparathyroidism, acromegaly, Cushing's syndrome, hypopituitarism, or severe chronic obstructive pulmonary disease; 4) history of oral or inhaled corticosteroid use > 3 months, anticonvulsant therapy (within previous year), sodium fluoride (any history), pharmacological doses of thyroid hormone (causing decline of thyroid stimulating hormone below normal), or treatment within the past 3 years with bisphosphonates, denosumab, parathyroid hormone, calcitonin, strontium, estrogen, or a selective estrogen receptor modulator. Subjects with a clinical history of an osteoporotic fracture (spine, hip, or distal forearm) were also excluded. Of the 199 women enrolled in the study, we excluded two women from analyses who did not have valid baseline QCT data for either the femur neck or lumbar spine.

2.2. Study protocol

The protocol was approved by the Mayo Clinic Institutional Review Board and all studies were performed in the Mayo Clinic Clinical Research and Trials Unit (CRTU). Blood samples were obtained fasting at 8 am. Spine and hip DXA measurements were obtained using a Lunar Prodigy scanner (GE Medical Systems). QCT scans of the spine and hip were performed at baseline and again at 36 months using a 128-slice DE scanner (SOMATOM Definition FLASH, Siemens Healthcare, Germany). Fig. 1 provides a schematic comparing the energy sources in a SE versus DE CT scanner. The FLASH scanner provides two simultaneous SE scans using the two X-ray sources, one at 100 kVp (tube A) and the other at 140 kVp (tube B). A tin-filter was added to tube B to allow for better separation of the X-ray spectra of the 140 kVp scan from the low kVp scan than in older instruments [7,8]. Since spectra separation is one of the primary limiting factors influencing the precision of DE QCT, this technique provides much improved precision as compared to previous scanners. The reason why the 100 kVp was selected as the low kVp instead of traditional 80 kVp in the DE scan was because the 100 kVp allows better penetration of high attenuating body regions, such as pelvis, and thus improves image noise and the precision of QCT results as compared to 80 kVp. The scanning and reconstruction techniques were as follows: rotation time, 0.5 s; detector configuration, 32 × 0.6 mm; automatic exposure control was on (CAREDose4D, Siemens Healthcare) with the quality reference mAs of 155 for 100 kVp and 120 for 140 kVp; nominal CTDIvol, 12.3 mGy; reconstruction kernel, D30 with a slice thickness of 2 mm and slice interval of 2 mm. Table height was fixed for all patients. A calibration phantom (Mindways Inc.) was scanned together with the patient to provide the basis