Direct Comparison of Unenhanced and Contrast-Enhanced CT for Opportunistic Proximal Femur Bone Mineral Density Measurement: Implications for Osteoporosis Screening

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OBJECTIVE. For patients undergoing contrast-enhanced CT examinations that include the proximal femur, an opportunity exists for concurrent screening bone mineral density (BMD) measurement. We investigated the effect of IV contrast enhancement on CT-derived x-ray absorptiometry areal BMD measurement.

MATERIALS AND METHODS. Our cohort included 410 adults (mean age, 65.3 ± 10.0 years; range, 49–95 years) who underwent split-bolus CT urography at 120 kVp. Areal femoral neck BMD in g/cm^2 was measured on both unenhanced and contrast-enhanced CT series with asynchronous phantom calibration. Constant offset and multiplicative factor corrections for the contrast-enhanced series were derived from the Bland-Altman plot linear regression slopes.

RESULTS. Mean unenhanced and contrast-enhanced areal femoral neck BMD values were 0.681 ± 0.118 and 0.713 ± 0.123 g/cm^2, respectively. The SD of the distribution of residuals for the constant offset and multiplicative model corrections were 0.0232 and 0.0231, respectively. The constant offset correction associated with contrast enhancement was 0.032 ± 0.023 g/cm^2, which corresponds to 0.29 ± 0.21 T-score units using the CT-derived x-ray absorptiometry young normal areal femoral neck BMD reference SD of 0.111 g/cm^2.

CONCLUSION. For the purposes of opportunistic osteoporosis screening, contrast-enhanced abdominopelvic CT studies are equivalent to unenhanced CT and can therefore be used for femoral neck BMD assessment. This measure could greatly enhance osteoporosis screening.

Osteoporosis is a major public health concern. It is estimated that up to 50% of women and 20% of men in the United States are at risk for developing an osteoporosis-related fracture during their lifetime, with a major impact on quantity and quality of life [1]. Screening is successful in identifying patients at risk for fracture, increasing effectiveness of treatment, and preventing fractures in patients at risk [2–4]. Despite these statistics, osteoporosis screening with dual-energy x-ray absorptiometry (DXA) remains underused [5–7]. At the same time, abdominopelvic CT is a relatively common procedure, with 130.6 studies performed in every 1000 Medicare beneficiaries in the United States annually [8]. Prior studies have shown that CT performed for other indications can be used opportunistically to assess bone mineral density (BMD) [9–11]. Although these CT measures may be applicable to exclude low BMD, few provide information that can truly guide clinical treatment because the reported values cannot be used to calculate a 10-year fracture risk.

The World Health Organization Fracture Risk Assessment tool (WHO FRAX) (World Health Organization Collaborating Center for Metabolic Bone Diseases, University of Sheffield) enables estimation of 10-year fracture risk. This tool is being used worldwide to guide treatment of patients with low BMD [12]. This tool uses a combination of clinical risk factors plus femoral neck BMD to calculate the risk, and this BMD evaluation must come from DXA or CT. For CT, the only BMD measurement that can be currently used in the FRAX tool is femoral neck measurement from the QCT (Quantitative CT) System (Mindways Software). Previously, QCT has been shown to have a significant correlation with DXA on unenhanced CT [13]. However, there is a paucity of data regarding the effect IV contrast administration has on QCT BMD values of the hip [14]. Therefore, the purpose of this study was to investigate the effect of IV contrast enhancement on areal BMD measurement compared with the established DXA-equivalent unenhanced QCT analysis (CT-derived x-ray absorptiometry) of the hip.

Keywords: bone mineral density, contrast-enhanced CT, musculoskeletal system, osteoporosis, quantitative CT, screening

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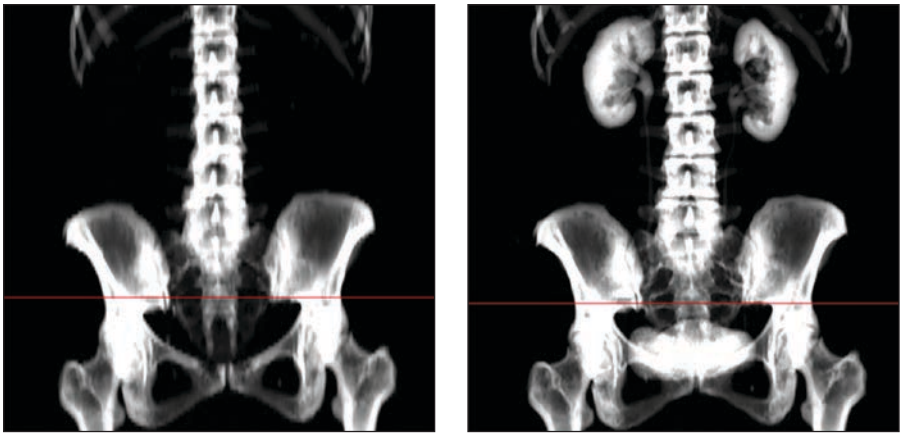

Fig. 1—A and **B,** Unenhanced CT urography image (**A**) shows interactive volume definition. Contrast-enhanced CT urography image (**B**) shows interactive volume definition. Red line shows superior extent of chosen volume.

Materials and Methods

Patient Cohort

Our cohort included 410 adults (261 men, 149 women; mean age, 65.3 ± 10.0 years; range, 49–95 years) who underwent split-bolus CT urography at 120 kV between August 2011 and May 2013. Ninety-two patients were excluded before selection of the final cohort due to bilateral hip arthroplasties (seven patients) or the inferior scanning extent not including the lesser trochanters (85 patients).

CT Acquisition

MDCT scanning of the abdomen and pelvis was performed on 16- or 64-MDCT scanners (LightSpeed series, GE Healthcare) using a 120-kVp setting and variable tube current. The variable tube current does not have an effect on CT attenuation numbers because this parameter is affected by beam energy (kVp). The variable tube current may cause differences in image noise, although it has no effect on QCT measurements as proven in previous work [15]. All CT scanners underwent routine daily, weekly, and monthly quality assurance (QA) calibration over the entire study period to ensure reliable Hounsfield unit measurement. All patient examinations included an unenhanced and contrast-enhanced series. The contrast-enhanced series included a split-bolus contrast-injection technique with an injection of 50 mL of contrast material followed by a 10-minute delay and subsequent second injection of 100 mL of contrast material with scanning occurring 100 seconds after the second bolus. This results in excreted contrast within the urinary bladder as well as marrow enhancement. This biphasic (dynamic and delayed) protocol provides a greater challenge for matching unenhanced and contrast-enhanced BMD measurement, resulting in an ideal comparison setting for assessing the effect of IV contrast administration.

Asynchronous QCT Calibration

Asynchronous QCT calibration has been described in detail elsewhere [13]. In brief, QA and calibration studies were obtained for each of the CT scanners used for the study. Because the CT studies were performed at a variety of table heights, a set of asynchronous QA and calibration scans at increments of 10-mm table height over a 100-mm range spanning the table heights typically used for contrast-enhanced CT scanning were obtained. For each QA and calibration study, 8–10 slice images of the Mindways QA phantom and calibration phantom were acquired using the same technique as for contrast-enhanced CT subjects. QCT Pro QA analysis software (Mindways Software) was used to determine individual CT scanner performance. For asynchronous QCT calibration, contrast-enhanced CT images were referenced to the appropriate QA and calibration results by matching both the individual CT scanner and table height (within 5 mm).

QCT Image Analysis

As a preprocessing step, we used the Slicepick tool (Mindways Software) to produce an anteroposterior projected display of the CT volume to allow a limited number of slices to be chosen to create a 3D image. Using this tool, the most superior and inferior slices of interest are chosen interactively (Fig. 1). Below the red line is the ROI, from just above the most superior aspect of the femoral head to approximately 1 cm below the lesser trochanter of the femur. This simulates the usual QCT process of choosing a scanning volume at the hip using an anteroposterior localizer on the CT scanner.

Therefore, CT volumes of the hip were produced following an accepted standard workflow except that the CT scanners were calibrated

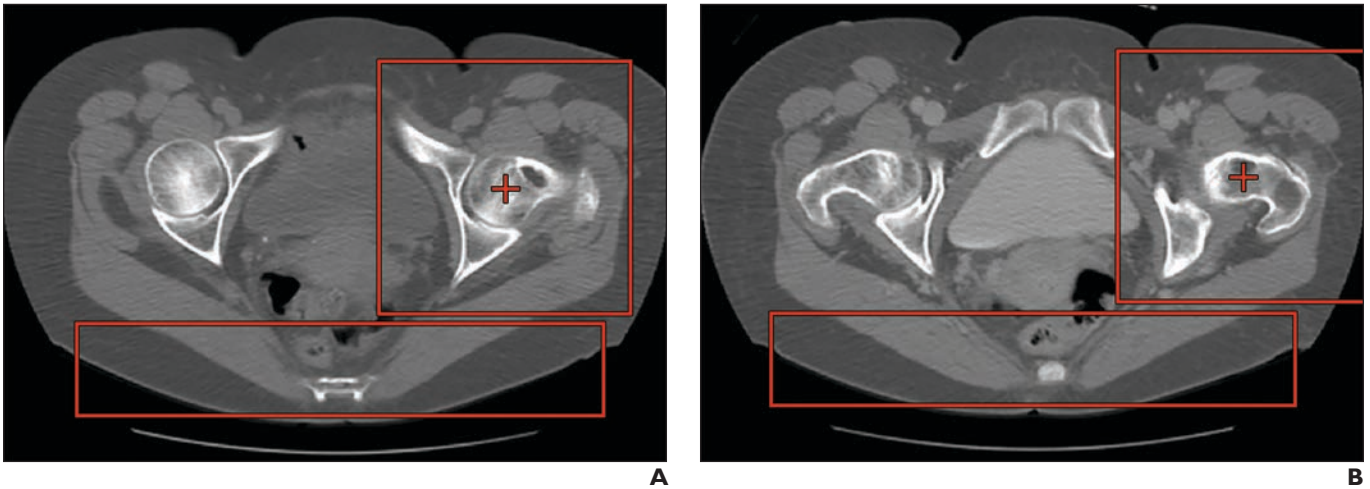

Fig. 2—A and **B,** Unenhanced axial slice (**A**) and contrast-enhanced axial slice (**B**) through pelvis. Red cross and associated box indicate location of anatomy of hip for automated analysis.

asynchronously by phantoms scanned in August 2012—that is, either before or after the actual CT examination without the subject present. From the patient standpoint, the examination is phantomless. Typical axial views can be seen in Figure 2, in which no calibration phantom is present on the CT table.

Areal BMD in g/cm^2 of the femoral neck was measured on both unenhanced and contrast-enhanced CT series using QCT Pro Version 5.1 (Mindways Software). The QCT-derived areal BMD was determined according to the directions provided by the manufacturer. This has been described in detail elsewhere [16]. ROIs similar to those used in Hologic DXA devices for proximal femur analysis (total hip, femoral neck, intertrochanter, and trochanter) were identified automatically on the projected image by the software (Fig. 3). The left hip was chosen for analysis in 404 cases in accordance with the vendor recommendations, with the right hip used in six cases because of metallic hardware at the left hip. The automatically identified ROIs were visually checked to verify that the lower extent of the intertrochanter ROI was set at the lower junction of the lesser trochanter and the femoral shaft and that the femoral neck axis and femoral neck ROI position and size were appropriate. Results for areal BMD (g/cm^2) were reported in terms of equivalent calibrated aqueous potassium phosphate density and were stored in the QCT Pro database for export as text files. Femoral neck T scores were calculated using the manufacturer's CT-derived x-ray absorptiometry reference database. T scores were considered normal if greater than or equal to –1.0, osteopenic if less than –1.0 to –2.4, and osteoporotic if less than or equal to –2.5.

Data Analyses

Constant additive offset and constant multiplicative factor corrections for the contrast-enhanced series were derived from Bland-Altman plot linear regression slopes.

Results

Mean unenhanced and contrast-enhanced areal BMDs of the femoral neck were 0.681 ± 0.118 and 0.713 ± 0.123 g/cm^2, respectively. This correlated with a mean T score of –1.03 ± 1.05 and –0.73 ± 1.10, respectively. Although the estimated slope of a correction (Fig. 4) was significantly different from zero ($p < 0.0001$), the SD of the distribution of residuals for a constant offset (or additive) model and a constant slope (or multiplicative) model correction were very similar at 0.0232 and 0.0231, respectively.

To determine whether a constant offset or constant slope factor may be more appropriate as a model for unenhanced and contrast-enhanced areal BMD difference, we tested the hypothesis that the Bland-Altman plot (Fig. 5) linear regression slopes were significantly different from zero. The estimated p value for this test was significant at 0.00002. The constant offset correction associated with contrast enhancement was 0.032 ± 0.023 g/cm^2, which corresponds to 0.29 ± 0.21 T score units using the CT-derived x-ray absorptiometry young normal areal BMD reference SD of 0.111 g/cm^2.

There were 30 patients (7.3%) in the osteoporotic range on unenhanced CT and 182 patients (44.4%) in the osteopenic range. T-score categorization of normal, osteopenic, or osteoporotic changed between unenhanced and contrast-enhanced series in 56 (13.7%) of 410 patients before constant offset correction (i.e., subtracting 0.3 T-score units from the contrast-enhanced value) compared with 19 (4.6%) patients after constant offset correction. Evaluating the categorization between osteopenic and normal findings, the T-score value changed from osteopenic to normal range in 21.2% (40/182) patients on contrast-enhanced studies before correction. After correction, 2.7% (5/182) remained in the normal range, with the highest corrected T score of –0.65 in a patient who had an unenhanced T score of –1.32. Eight patients (4.0%) who were categorized in the normal range on unenhanced CT had T-score values in the osteopenic range on contrast-enhanced imaging with simple correction.

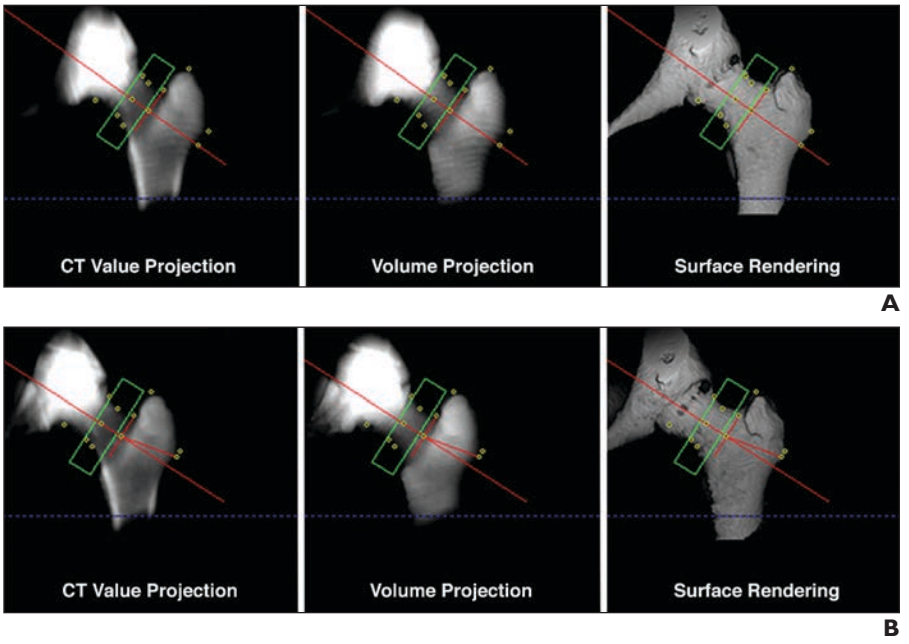

Fig. 3—A, Unenhanced CT images. Projectional analysis of proximal femur is done automatically with ROI (*green box*) placed over femoral neck, similar to dual-energy x-ray absorptiometry (DXA).
B, Contrast-enhanced CT images. Again, projectional analysis of proximal femur is done automatically with ROI (*green box*) placed over femoral neck, similar to DXA.

Discussion

Femoral neck BMD can be acquired on CT studies obtained for any indication that includes the pelvis. This study shows the ability to obtain BMD measurements on CT scans obtained with IV contrast enhancement that are nearly equivalent to those on an unenhanced examination, thereby expanding the clinical utility of this technique. Theoretically, BMD measurement obtained by QCT with asynchronous calibration could be performed on a CT obtained for virtually any indication, either prospectively or retrospectively, when requested by a referring physician. Obtaining these BMD results requires postprocessing that can be efficiently performed by a CT technologist, and the results can be included with the original CT report or in a separate report.

To our knowledge, only one study has previously investigated the use of contrast-enhanced CT examinations for QCT areal BMD measurement at the hip using an external calibration standard [14]. That study used a much smaller cohort of 21 subjects, but our results of a contrast-enhanced offset of around 0.032

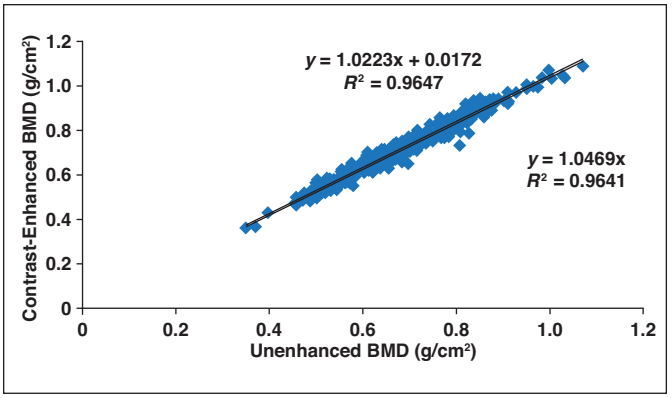

Fig. 4—Graph shows linear regression analysis of unenhanced and contrast-enhanced femoral neck areal bone mineral density (BMD) results.

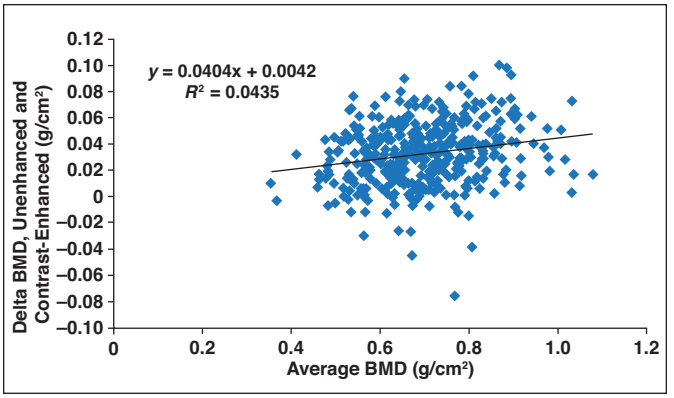

Fig. 5—Bland-Altman plot shows femoral neck areal bone mineral density (BMD) difference between unenhanced and contrast-enhanced examinations.

g/cm^2 (approx. 4.7%) is similar to their result of 4.1% at the femoral neck. Our analysis of the Bland-Altman plot indicates that we may more accurately describe the areal BMD difference introduced by contrast enhancement using a multiplicative (linear model with a nonzero slope) relative to a constant model. However, the improvement in standard error in doing so does not appear to be clinically significant, particularly in a screening situation. In a study evaluating the precision of DXA, 0.4 T-score units was determined to be the variability at the femoral neck [17]; our 0.3 T score offset between unenhanced and contrast-enhanced QCT compares favorably to this DXA variability. Therefore, we would suggest not correcting for the small adjustment in T score for a screening population because the adjustment falls within the range of variability of DXA scanners and has minimal effect on the FRAX-estimated 10-year risk. For example, taking a 65-year-old woman (mean age in this cohort) and assuming she is a white United States resident who weighs 140 pounds (63.5 kg), is five feet 5 inches (165 cm) tall, and has no additional clinical risk factors, her 10-year major fracture risk is 7.2% at a T score of –0.7, 7.7% at –1.0, and 8.2% at –1.3.

The lack of correction for IV contrast material would greatly simplify this approach for opportunistic osteoporosis screening. The design of this study, using combined delayed and nephrographic phases, enables simultaneous marrow enhancement and contrast enhancement extrinsic to the marrow within the bladder that could attenuate the beam and creates a worst-case scenario of effect on BMD measurement. Therefore, these results should be applicable to CT studies including oral and IV contrast administration regardless of the timing of contrast administration. Formal DXA examination would still be required before treatment intervention for monitoring purposes, which would likely be covered by third-party payers in addition to the screening QCT study.

QCT performed with CT scans obtained for other indications is reasonable to use for osteoporosis screening. This could be performed with an order that occurs at the time of the routine CT order or even after the study results are reported. As mentioned, it is likely that all patients who begin therapy on the basis of the results of this screening will undergo baseline DXA to monitor treatment response, preferably at a consistent location. The cost-effectiveness of screening with CT is beyond the scope of this article, but it arguably fits a need because of the number of eligible patients who are not screened and is a potential area for future study [2, 7].

The changes required for a routine contrast-enhanced body CT workflow to facilitate QCT of the hip are easily accommodated and consist of asynchronous calibration scans obtained periodically every few months and a small amount of extra work in the definition of a volume of slices from the original scan. This postprocessing of CT data can be performed by a dedicated technologist after a short training period with QA of the resultant images by the interpreting physician. This interpretation can occur at the time of the CT interpretation or in a separate setting remote from the initial CT interpretation, an approach that may be preferred to minimize impact on radiologist workflow.

Obtaining the relevant clinical risk factor data to enable FRAX estimation of risk is another task to consider. The potential clinical implications of extracting hip BMD data from contrast-enhanced CT examinations in this study extend the concept of opportunistic screening for osteoporosis beyond the use of unenhanced CT scans. Given the large volume of contrast-enhanced body CT currently performed in older adults for a wide variety of clinical indications, this represents a unique opportunity to expand osteoporosis screening [8]. Importantly, this opportunistic screening requires no additional patient time or radiation exposure, further enhancing the clinical yield of the CT study. This capability also has the possibility to expand screening guidelines, especially for men. Screening of men is currently limited by the resource cost of significantly increasing the number of DXA scanners [18].

Although previous studies have indicated that uncalibrated Hounsfield unit values from CT scanners may be used for the opportunistic screening of low bone mass [9], the use of a calibration standard in this study means that the derived areal BMD results and T-score computations will be consistent across CT scanners from different manufacturers and consistent at different scanning x-ray energies [19]. In contrast with QCT spine BMD measurements made from abdominal CT studies ordered for another purpose [14, 20], or CT colonography examinations [10, 11] on the basis of the comparability shown in this study, femoral neck QCT CT-derived x-ray absorptiometry T scores may be used to estimate fracture risk and assist in therapeutic decision making. Indeed, both T scores and areal BMD measurements from QCT CT-derived x-ray absorptiometry at the femoral neck may now be used to calculate the 10-year risk of osteoporotic fracture using the WHO FRAX tool [12], making this a potentially powerful opportunistic approach for BMD screening.

This study has limitations, the most relevant of which was the asynchronous nature

of the phantom calibration. The CT scanners did, however, undergo routine daily calibration scanning and the evaluation was limited to only studies performed at 120 kVp, which should make the numbers relatively reproducible. A prospective evaluation with concurrent monthly calibration could be performed to ensure this method is reproducible and is a reasonable next step. The study was limited to scans obtained at 120 kVp, which limits applicability to scans obtained at other energies. As Hounsfield unit values move away from zero, the effect of beam energy change is magnified. Calibration can account for energy changed, but the effect of contrast enhancement at these energies is a potential area for future study. Although correlation of unenhanced QCT and DXA has been previously reported, direct comparison of contrast-enhanced QCT and DXA is another reasonable step that is planned for a separate cohort in which both studies are available. This study also does not evaluate the clinical effect or cost-effectiveness of reporting BMD with contrast-enhanced CT. These would be areas of interest for further study.

In conclusion, for the purposes of opportunistic osteoporosis screening, routine contrast-enhanced abdominopelvic CT is essentially equivalent to unenhanced CT and therefore can be used for femoral neck BMD assessment. The simple addition of this postprocessing technique to routine abdominopelvic CT could greatly enhance osteoporosis screening because it can be applied regardless of the clinical indication for CT.

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