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FULL PAPER

Population-based opportunistic osteoporosis screening: Validation of a fully automated CT tool for assessing longitudinal BMD changes

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Objective: To validate a fully automated CT-based spinal trabecular bone mineral density (BMD) tool and apply it to a longitudinal screening cohort.

Methods: The automated BMD tool was retrospectively applied to non-contrast abdominal CT scans in 1603 consecutive asymptomatic adults (mean age, 55.9 years; 770 M/833 F) undergoing longitudinal screening (mean interval, 5.7 years; range, 1.0–12.3 years). The spinal column was automatically segmented, with standardized L1 and L2 anterior trabecular ROI placement. Automated and manual L1 HU values were compared, as were automated supine-prone measures. L1–L2 CT attenuation values were converted to BMD values through a linear regression model. BMD values and changes were assessed according to age and gender.

Results: Success rate of the automated BMD tool was 99.8 % (four failed cases). Both automated supine vs prone and manual vs automated L1 attenuation measurements showed good agreement. Overall mean annual rate of bone loss was greater in females than males (–2.0% vs –1.0%), but the age-specific rate declined

faster in females from age 50 (–2.1%) to age 65 (–0.3%) compared with males (–0.9% to –0.5%). Mean BMD was higher in females than males at age 50 (143.6 vs 135.1 mg cm^{–3}), but post-menopausal bone loss in females reversed this relationship beyond age 60. By age 70, mean BMD in females and males was 100.8 and 107.7 mg cm^{–3}, respectively.

Conclusion: This robust, fully automated CT BMD tool allows for both individualized and population-based assessment. Mean BMD was lower in men than women aged 50–60, but accelerated post-menopausal bone loss in women resulted in lower values beyond age 60.

Advances in knowledge: This fully automated tool can be applied to routine abdominal CT scans for prospective or retrospective opportunistic BMD assessment, including change over time. Mean BMD was lower in men compared with women aged 50–60 years, but accelerated bone loss in women during this early post-menopausal period resulted in lower BMD values for women beyond age 60.

INTRODUCTION

Osteoporosis is an important yet underdiagnosed and undertreated bone disease whose direct and indirect costs are estimated to substantially increase in the coming decades.^{1–4} As such, efforts to increase osteoporosis screening and treatment are important for reducing the impending global public health burden of fragility fractures. Dual-energy X-ray absorptiometry (DXA) is the most widely used screening tool for low bone mineral density (BMD), but its planar nature precludes direct trabecular assessment of the spine. An additional opportunity for osteoporosis screening exists using bone data obtained from body CT scans, which are frequently performed in

older adults for a wide variety of indications.^{5–10} In particular, manual CT-based L1 trabecular attenuation measurements have been shown to correlate with DXA-based BMD categories, is predictive of future fragility fractures, and this level is imaged on both thoracic and abdominal CT scans.^{11,12}

Advances in radiology image processing have the potential to provide fully automated measurements of CT-based images that are more objective than manual human measures, and can be applied to larger patient cohorts.^{13–15} In this study, we implemented an image-processing algorithm that performs automatic volumetric segmentation of the lumbar trabecular space on CT scans and then estimates

BMD. Utilizing a large, unique CT-based adult screening cohort undergoing longitudinal colonography assessment,¹⁶ we sought to validate this BMD tool, including both measurement fidelity and objective population-based assessment according to age and gender over time.

METHODS AND MATERIALS

Patient population

This was a HIPAA-compliant retrospective cohort study performed at a single academic medical center. The need for patient consent was waived by the IRB. Asymptomatic, generally healthy outpatient adults aged 50–70 years at the time of their initial screening CT colonography (CTC) study, and who had at least two CTC studies over time at the University of Wisconsin between January 2004 and March 2017, were eligible for inclusion. For patients with more than one follow-up CTC, the initial and last scans were utilized for primary analysis. Patients whose scans were performed less than 1 year apart were excluded as relevant decreases in BMD would be less likely over such a short follow-up period. A total of 1607 patients were initially eligible for inclusion. We also searched the electronic medical records of included patients for evidence of osteoporosis screening with central DXA (spine and/or hips), either before or after their initial CT examination used in this study.

Age at initial CT, length of time between CT studies, and gender were collected as exposure variables. After excluding four failed cases, the final cohort consisted of 1603 adults (833 females and 770 males), with a mean age at initial CT of 55.9 ± 5.0 years. The mean interval to follow-up CT was 5.7 ± 1.9 years (range, 1.0–12.3 years). Outcome variables were the automated CT-derived L1 trabecular attenuation values [in Hounsfield units (HU)] and the calculated BMD values, which were based on the average trabecular HU at L1 and L2.

CT image acquisition

Per standard CTC screening technique,^{17,18} breath-hold supine and prone acquisitions were performed without i.v. contrast on a variety of 8–64 channel multidetector CT scanners (GE Healthcare, Waukesha, WI). These CT scanners undergo daily QA, including HU calibration testing. Scan parameters included 1.25 mm collimation and slice thickness, 120 kV, variable low-dose mAs settings, and 1 mm reconstruction interval. The 1.25 mm supine series was utilized for primary BMD analysis, include rate of change over time; prone series BMD measurements were also obtained for intra patient comparison.

Automated trabecular spine segmentation and BMD estimation

A fully automated method was developed to segment the trabecular spine from CT images, which was developed and tested on a separate patient cohort.¹⁹ The CT images were sent offline from PACS for anonymization prior to accessing the BMD tool. The algorithm first extracts the spinal column based on thresholding, region growing, watershed, and directed graph search. Second, the segmented spinal column is then partitioned into individual vertebrae using curved planar reformation and dynamic programming. For each vertebral body, the cortical bone was automatically eroded to isolate the trabecular space.

An oval region of interest (ROI) was automatically placed in the middle transverse (axial) cross-sections of extracted L1 and L2 vertebrae (Figure 1). The location of the ROI was set at the anterior one-third of the anteroposterior center axis of the vertebral body, to simulate the established manual method.^{11,20,21} The size of the ROI was standardized at one-half of the vertebral body lateral width by one-fourth of the vertebral body anteroposterior height, using a single slice at the vertebral midline. Mean HU values were calculated within the ROIs for L1 and L2 and converted to BMD estimation through a linear regression model trained by a set of QCT images with calibration phantoms.

Figure 1. Automated CT BMD tool in asymptomatic 59-year-old male at initial evaluation, evaluated over a 10-year interval. (A) 3D volume-rendered image from the initial CT scan performed in 2007 when the patient was 59 years old shows the relative placement of the automated ROI (green cylinder) within the anterior trabecular space of the L1 vertebral body. (B) Collage of 2D transverse images at the L1 level from CT in 2007 (top row) and 2017 (bottom row). Bone windows (left images) and soft tissue windows (middle images) are shown, as well as placement of the automated ROI (green ovals) with resulting mean HU values (right images). The HU values correspond to an estimated BMD of 186.9 mg cm^{-3} in 2006 and 131.6 mg cm^{-3} in 2016, reflecting a 30% loss, or annual mean rate of BMD change of $-3\%/ \text{year}$. Note also the significant interval weight loss. 3D, three-dimensional; BMD, bone mineral density; ROI, region of interest.

To estimate BMD from HU, we used a previously derived calibration curve obtained from phantoms used in dedicated QCT scans, which demonstrated excellent correlation ($r^2 = 0.98$).¹⁹ The curve maps CT attenuation in HUs to BMD in milligrams per milliliter.

Comparison of manual and automated trabecular attenuation values

To further assess the automated L1 HU measurement, we compared manual L1 attenuation measurements in a random subset of 588 patients, using a previously validated method, with placement of a single ROI in the anterior L1 trabecular space, just off the mid-vertebral level.^{8,11,21}

Statistical analysis

Annual rate of change in BMD was assessed in overall and percentage-based terms. The rate of annual BMD change was estimated by calculating the difference between initial and follow-up BMD and dividing it by the scan interval in years (Figure 1). The full patient range at initial CT (50–70 years) was utilized for age-specific BMD values; age-specific rates of BMD loss were considered for the 50–65 year-old range, as there were insufficient data points for rates of change beyond 65 years.

Inpatient comparison between automated L1 HU values on the supine and prone CT series were compared as an internal quality assurance measure in a subset of 2851 CT scans. For all other purposes, BMD values for the supine CT series were utilized. Multivariate linear regression was performed to estimate the effects of age and gender on annual change in BMD and to model expected annual change in BMD. Interaction of the effects of age and gender on outcome variables were included in the regression analyses. Bland-Altman analysis was utilized for comparing manual and automated L1 attenuation measurement, and for comparing automated supine and prone BMD measurements. In addition, the square of the Pearson correlation coefficient (r^2 , the correlation of determination) was derived for these

comparisons. All statistical analyses were performed using R software (R Core Development Team, v3.3.2).

RESULTS

QA performance of the BMD algorithm

The automated BMD tool successfully derived an L1 HU and BMD value in 99.8% (1603/1607) of cases. There was good agreement ($r^2 = 0.90$) between the automated supine and prone BMD measurements (Figure 2), with a mean difference of -0.15 mg cm^{-3} , without bias. Bland-Altman 95% limits of agreement were -21.7 to 21.4 mg cm^{-3} . In the subset of 588 patients, supine manual and automated L1 attenuation measurements also showed good linear agreement (Figure 3; $r^2 = 0.80$). The Bland-Altman 95% limits of agreement for the attenuation difference were -32.8 to 22.4 HU . Automated L1 attenuation measurements were slightly increased relative to manual measurements by 5.2 HU on average, without bias.

BMD change over time at CT

Overall results for the entire cohort, not stratified by age, are shown on Table 1. The overall mean annual change in BMD was -2.0% per year in females and -1.0% per year in males (-1.5% per year for the entire cohort). However, a deeper understanding is gained when the results are stratified by age and gender (Table 2). As expected, mean BMD decreased with increasing age from 50 to 70 years for both males and females (Figure 4). Mean BMD in females was higher than males at 50 years of age (143.6 vs 135.1 mg cm^{-3}), but accelerated post-menopausal bone loss in females reversed this relationship beyond 60 years of age. However, the rate of bone loss progressively declined more rapidly with increasing age in females compared with males (Figure 5). By 65 years of age, the mean rate of annual bone loss was slightly greater in males compared with females ($-0.5\%/ \text{year}$ vs $-0.3\%/ \text{year}$). By 70 years of age, mean BMD in females and males was 100.8 and 107.7 mg cm^{-3} , respectively. Age at initial CT, sex, and their interaction term were all significantly associated ($p < 0.001$) with mean BMD at initial CT, annual mean rate of change

Figure 2. Automated supine vs prone measurements (A), Plot of automated BMD measurement of the supine vs prone CT series ($r^2 = 0.90$) (B), Corresponding Bland-Altman plot with 95% limits of agreement. No bias is noted. BMD, bone mineral density.

Figure 3. Manual vs automated L1 trabecular attenuation measurements in 588 subjects. (A) Plot of manual single-slice ROI and automated volumetric measurements for L1 trabecular attenuation (in HU). ($r^2 = 0.80$). (B) Corresponding Bland-Altman plot with 95% limits of agreement. Note that the automated measures are approximately 5 HU higher on average, without bias according to variation of the mean. HU, Hounsfield unit; ROI, region of interest.

in BMD, and annual percent change in BMD at multiple linear regression modeling.

Clinical osteoporosis screening with DXA

A total of 377 patients underwent DXA for osteoporosis screening prior to their initial CT screening study, corresponding to 23.5% (377/1603) of the cohort. Another 17.3% (278/1603) of patients underwent DXA study after the date of the initial CT study. Nearly 90% of patients screened with DXA were females. To date, 59.1% (948/1603) of patients from this study have not been screened by DXA.

DISCUSSION

In this study, we determined annual age- and gender-specific rates of trabecular spine BMD change in an adult screening cohort using fully automated CT-based software. We found that annual rates of BMD loss peaked in females ages 50–55 years, corresponding to the early post-menopausal period (mean age of menopause in females is 51 years). This is in agreement with prior DXA²² and qCT^{23–25} data that demonstrated accelerated bone loss in females during late perimenopause and early post-menopause. Prior to this accelerated post-menopausal BMD loss in females, we found that age-matched males actually

Table 1. Characteristics for overall patient cohort

		Female	Male	All
	N=	833	770	1603
Age at initial CT (years)	Mean (SD)	56.0 (5.0)	55.8 (5.0)	55.9 (5.0)
CT Interval (years)	Mean (SD)	5.8 (1.8)	5.7 (1.9)	5.7 (1.9)
L1 Attenuation at Initial CT (HU)	Mean (SD)	177.4 (40.8)	171.1 (39.5)	174.3 (40.3)
BMD at Initial CT (mg cm ⁻³)	Mean (SD)	130.7 (30.5)	127.5 (28.5)	129.1 (29.6)
	Min	55.4	54.3	54.3
	Max	253.9	253.1	253.9
BMD at follow-up CT (mg cm ⁻³)	Mean (SD)	119.1 (29.0)	121.6 (28.7)	120.3 (28.8)
	Min	39.5	58.1	39.5
	Max	237.22	244.8	244.8
Change in BMD (mg cm ⁻³)	Mean (SD)	-11.6 (17.2)	-5.6 (12.5)	-8.7 (15.5)
% Annual Change in BMD	Mean	-2.0%	-1.0%	-1.5%

BMD, bone mineral density; HU, Hounsfield Unit; SD, standard deviation.

Table 2. Mean BMD values and rates of change according to gender and age

Age at initial CT	Sex	Mean BMD (mg cm ⁻³)	Mean rate of annual change in BMD (mg cm ⁻³ /year)	% Rate of annual change in BMD
50	Female	143.6 (140.6, 146.5)	-3.1 (-3.4, -2.8)	-2.1% (-2.3, -1.9)
55	Female	132.9 (130.9, 134.8)	-2.2 (-2.4, -2.0)	-1.5% (-1.5, -1.7)
60	Female	122.2 (119.8, 124.6)	-1.3 (-1.6, -1.1)	-0.9% (-1.1, -0.8)
65	Female	111.5 (107.7, 115.4)	-0.4 (-0.8, -0.1)	-0.3% (-0.7, -0.09)
70	Female	100.8 (95.3, 106.4)	-	-
50	Male	135.1 (132.1, 138.1)	-1.2 (-1.5, -0.9)	-0.9% (-1.1, -0.6)
55	Male	128.3 (126.3, 130.3)	-1.0 (-1.2, -0.8)	-0.8% (-0.2, -0.6)
60	Male	121.4 (118.9, 124.0)	-0.8 (-1.0, -0.5)	-0.6% (-0.8, -0.4)
65	Male	114.6 (110.5, 118.7)	-0.6 (-1.0, -0.2)	-0.5% (-0.8, -0.2)
70	Male	107.7 (101.8, 113.6)	-	-

BMD, bone mineral density.

have lower lumbar trabecular BMD than females, on average. Although not widely appreciated, this lower BMD level in males has been previously shown for adults in the third decade of life.²⁶ We also found that rates of BMD loss progressively slowed after menopause in females, which is also in accordance with previously published results. In combination, these data stress the potential importance and possible preventive opportunity for this accelerated BMD loss seen in the early post-menopausal period in females. Because these changes occur before the age of recommended osteoporosis screening, other interventions might be considered.

Perhaps more important than redemonstrating normative BMD levels and rates of BMD loss according to age and gender is the fact that all our CT-based measurements were obtained automatically without reader input. This robust automated tool, representing an improvement over an earlier version,¹⁹ demonstrated a very low failure rate, and correlated well with

the manual L1 trabecular ROI measurements. Manual L1 HU measures have been previously validated for clinical important outcomes,^{6,8,11,12,20} and are now being used every day in our routine clinical practice to provide opportunistic BMD information. Use of an automated tool could greatly expand utilization of this opportunistic screening approach, and enhance the value of our CT interpretations. In addition, this tool could be applied retrospectively within a group or practice to provide population-based screening. As we have shown, there is a substantial subset of patients who may otherwise not be screened by DXA, and opportunistic screening with CT could therefore have a meaningful impact. Although one could argue that many of these patients were not yet of the recommended age for osteoporosis screening, many osteoporotic fractures occur prior to initial DXA screening. Furthermore, the majority of patients undergoing DXA who have a fragility fracture will have a non-osteoporotic T-score (*i.e.* greater than -1.0),¹¹ which may relate in part to the planar nature of DXA. As a volumetric cross-sectional imaging technique, CT is able to directly assess the trabecular bone without the issues of overlying cortical bone and degenerative changes.

Figure 4. Automated mean BMD values at initial CT according to age and gender. Plots using lines of best fit show that males have lower BMD values on average in the 50–60 age range, whereas females have lower values on average at older ages. The shaded areas around lines correspond to the 95% CIs for the mean BMD values. BMD, bone mineral density.

Figure 5. Annual rates of BMD change according to age at initial CT and gender. BMD, bone mineral density.

In general, rapid advances in artificial intelligence and machine learning applied to cross-sectional imaging could eventually lead to fully automated measurements that provide objective assessment to complement a radiologist's interpretation.^{13–15} Beyond this BMD tool, we are currently investigating a number of abdominal CT-based machine learning algorithms to automatically measure abdominal aortic calcification, hepatic attenuation, muscle mass for sarcopenia, and visceral and subcutaneous fat. While potentially providing useful information in isolation, the combination of these tools could conceivably synergize to provide meaningful cardiometabolic risk assessment and stratification. In addition, a companion machine learning algorithm for automatically detecting vertebral compression fractures was not applied in this study but could be used in concert with automated BMD assessment.²⁷

One strength of our study design was the relatively unique longitudinal CT series in an asymptomatic screening cohort, which was ideal for applying this automated tool to assess for age- and gender-based differences in BMD values and rates of BMD loss. In addition, CT has intrinsic advantages over the clinical standard of DXA, which is a planar technique that cannot directly assess the spinal trabecular space. However, we also acknowledge limitations of the current study. The small but measurable increased offset in automated L1 attenuation over 5 HU over the manual technique likely relates to placement of the automated ROI in the central aspect of the anterior trabecular space, where a stripe of increased linear density can be seen on sagittal CT reconstructions and at gross anatomy.²⁸ In addition, one would expect some offset in HU measurements between supine and prone measurements given the known effects related to positional changes within the scanner.²⁹ The phantomless technique with calibration on one scanner in a limited data set could potentially lead to inaccuracies or variability in the conversions from HU to mg/cc. However, HU values are calibrated as part of daily quality control, and a recent study found that phantomless

BMD results based on HU values represent good estimates across different scanners.³⁰ We did not investigate the impact of other risk factors, such as those included in the FRAX tool,³¹ nor did we search for prevalent or incident fractures, all of which would require a detailed patient-by-patient search. We plan to investigate the predictive ability of this automated BMD tool by applying it to a large retrospective cohort both with and without future fragility fractures.

In conclusion, this fully automated BMD tool can be applied opportunistically to routine abdominal CT scans for prospective clinical or retrospective population-based assessments, including monitoring changes over time.

Numbers in parentheses represent 95% confidence intervals. Accelerated bone loss in the early post-menopausal period in females leads to overall lower BMD values beyond age 60. Note, however, that the rate of BMD loss progressively decreases faster in females than in males, resulting a lower rate of BMD loss by age 65. Data for rates of change beyond age 65 were too sparse for accurate reporting.

Plots using lines of best fit show that females demonstrate accelerated bone loss over the post-menopausal 50–60 year age range, but that this rate of loss progressively declines faster than males. Shaded areas around lines correspond to 95% CIs for the mean annual rate of BMD change.

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DISCLOSURE

Dr Pickhardt serves as an advisor to Bracco and is a shareholder in SHINE and Elucet.

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