ORIGINAL ARTICLE

Validation of Opportunistic Artificial Intelligence-Based Bone Mineral Density Measurements in Coronary Artery Calcium Scans

VISUAL ABSTRACT

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Abstract

Background: Previously we reported a manual method of measuring thoracic vertebral bone mineral density (BMD) using quantitative CT in noncontrast cardiac CT scans used for coronary artery calcium (CAC) scoring. In this report, we present validation studies of an artificial intelligence–based automated BMD measurement (AutoBMD) that recently received FDA approval as an opportunistic add-on to CAC scans.

Methods: A deep learning model was trained to detect vertebral bodies. Subsequently, signal processing techniques were developed to detect intervertebral discs and the trabecular components of the vertebral body. The model was trained using 132 CAC scans comprising 7,649 slices. To validate AutoBMD, we used 5,785 cases of manual BMD measurements previously reported from CAC scans in the Multi-Ethnic Study of Atherosclerosis.

Results: Mean ± SD for AutoBMD and manual BMD were 166.1 ± 47.9 mg/cc and 163.1 ± 46 mg/cc, respectively ($P = .006$). Multi-Ethnic Study of Atherosclerosis cases were 47.5% male and 52.5% female, with age 62.2 ± 10.3. A strong correlation was found between AutoBMD and manual measurements ($R = 0.85$, $P < .0001$). Accuracy, sensitivity, specificity, positive predictive value and negative predictive value for AutoBMD-based detection of osteoporosis were 99.6%, 96.7%, 97.7%, 99.7% and 99.8%, respectively. AutoBMD averaged 15 seconds per report versus 5.5 min for manual measurements ($P < .0001$).

Conclusions: AutoBMD is an FDA-approved, artificial intelligence–enabled opportunistic tool that reports BMD with Z-scores and T-scores and accurately detects osteoporosis and osteopenia in CAC scans, demonstrating results comparable to manual measurements. No extra cost of scanning and no extra radiation to patients, plus the high prevalence of asymptomatic osteoporosis, make AutoBMD a promising candidate to enhance patient care.

Key Words: Artificial intelligence, bone mineral density, deep learning, osteoporosis, quantitative computed tomography

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Dr Naghavi is the founder of HeartLung.AI. Drs Budoff, Manubolu, and Li are advisors to American Heart Technologies and HeartLung.AI and have received advisory compensation. Mr Jaberzadeh and Mr Zhang are research contractors of American Heart Technologies and HeartLung.AI. Mr Atlas is a graduate research associate of HeartLung.AI. HeartLung.AI has developed and received FDA approval for AutoBMD. The authors are non-partner/non-partnership track/employees.

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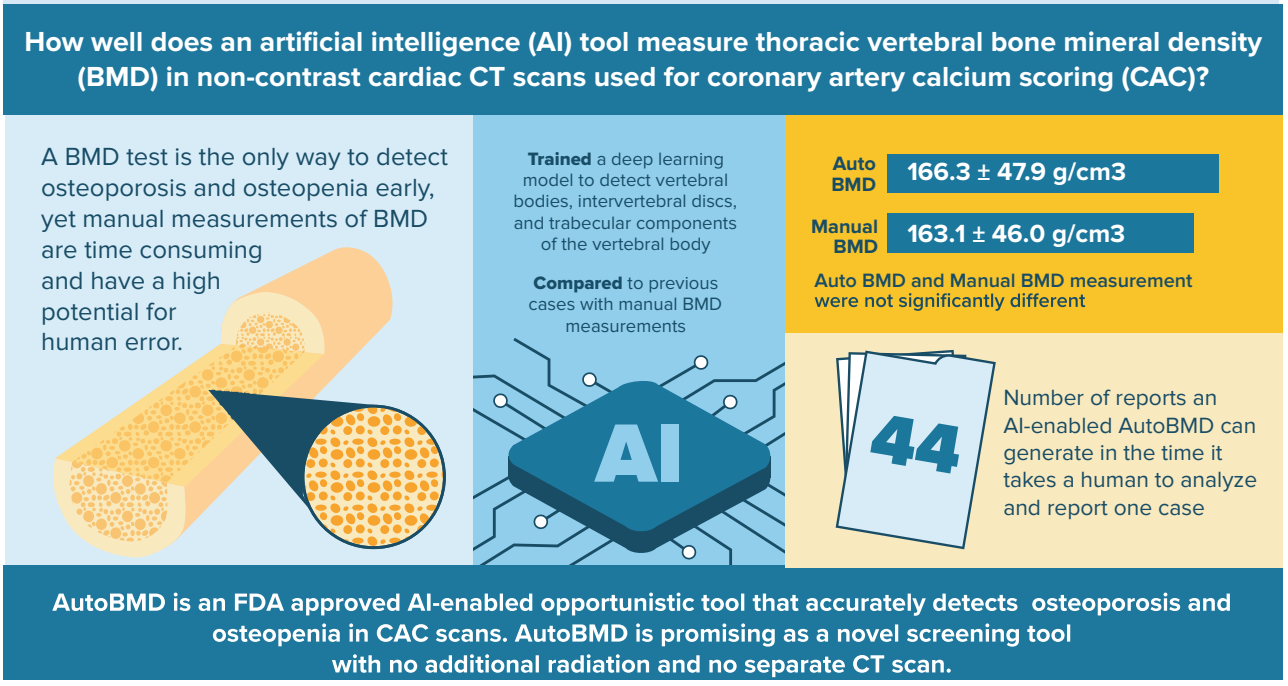
Visual Abstract



INTRODUCTION

Approximately 10 million Americans have osteoporosis and another 44 million have low bone density (osteopenia), placing them at increased risk of bone fracture [1]. This means that half of all adults aged 50 and older are suffering from accelerated bone loss, most of whom are unaware of their condition [2]. Global deaths and disability-adjusted life-years attributable to low bone mineral density (BMD) increased from 207,367 and 8,588,936 in 1990 to 437,884 and 16,647,466 in 2019, an increase of 111.16% and 93.82%, respectively [3]. About half of osteoporosis-related repeat fractures and most cases of rapid progression from osteopenia to osteoporosis and fractures can be prevented with proper treatments [4]. However, most people who have osteopenia and osteoporosis are unaware of their bone loss [5]. A BMD test is the only way to detect these individuals early and determine a treatment plan to prevent further bone loss and future bone fracture [6].

Dual-energy x-ray absorptiometry (DEXA) is widely recognized as the clinical imaging standard for assessing BMD [6]; however, less than 20% of patients with osteoporosis are currently screened with DEXA [7]. Furthermore, DEXA is limited by its 2-D planar technique, making it unable to distinguish the cortical and trabecular components of the bone, leading to an underestimation of bone density, especially in the overweight population [8]. DEXA has fundamental limitations in which cortical and trabecular bone overlap on the same 2-D images, whereas 3-D high-resolution quantitative CT (QCT) can differentiate between cortical and trabecular bone [8]. Cortical bone often contains degenerative calcifications such as osteophytes that erroneously exaggerate BMD scores in DEXA [9,10]. QCT BMD reports offer at least three unique advantages: (1) the ability to distinguish between cortical and trabecular bone; (2) the recording of actual volumetric density in milligrams per cubic centimeters; (3) 3-D photographs of bone morphometry with high resolution [11]. Notably, bone trabeculae are more sensitive to the effects of anti-osteoporosis treatment and are more likely to be observed in a state of BMD loss. Thus, routine CT scanning provides an opportunity for CT imaging for screening of the lungs and coronary artery calcium (CAC) to accurately assess BMD without increasing patient burden or radiation dose [11].

OPPORTUNISTIC SCREENING

Several groups have already reported on the clinical utility of opportunistic screening in chest CT scans [12,31,32]. Incorporating artificial intelligence (AI) to automate reporting of opportunistic findings can facilitate its adoption and improve workflow in hospitals and diagnostic imaging centers. Given that CT scans of the chest and

abdomen encompass multiple organs, it is advantageous to train AI for identification of various abnormalities within a single scan. Numerous FDA approvals are obtained each year for various clinical indications using AI as a decision support tool. In the case of BMD measurements, this added value is even more significant because manual measurements of BMD are time-consuming and have a high potential for human error.

The addition of CAC scoring to the latest guidelines issued jointly by the American College of Cardiology and American Heart Association has sparked growing interest in CAC scans [13]. Leveraging CT-based assessment of vertebral trabecular density for opportunistic osteoporosis screening in CAC scans presents an unmet opportunity, one which our group has taken from the idea stage to the FDA approval. Here, we present the validation study of artificial intelligence–based automated BMD measurement (AutoBMD) versus human experts' manual BMD measurements in CAC scans of a large longitudinal study sponsored by the National Institute of Health.

METHODS

Study Population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective, population-based, observational cohort study of 6,814 men and women without clinical cardiovascular disease (CVD) at the time of recruitment. Six field centers in the United States participated in the study: Baltimore, Maryland; Los Angeles, California; Chicago, Illinois; Forsyth County, North Carolina; and New York City, New York. As part of the initial evaluation (2000-2002), participants received a comprehensive medical history, physical examination, and laboratory tests. The basic demographic information, medical history, medication use, laboratory test results and hospitalizations were obtained from medical record. An electrocardiogram-gated noncontrast CT was performed at the baseline examination to measure CAC. MESA was chosen because it had the largest number of manual measurements of BMD using QCT.

A detailed operating manual of the CT scan methods and protocols is publicly available at the MESA website [22]. The ground truth BMD values for the MESA dataset were derived from manual measurements by trained operators using QCT-BMD Analysis Software (Image Analysis, Inc). It is important to note these ground truth BMD values are subject to human error. Manual BMD measurements are limited by highly calcified or sclerotic streaks inside the trabecular zones which can falsely elevate the BMD [25].

For our study, we removed data from 771 MESA participants who did not consent for commercial use of data. There were 258 cases that had missing slices or image processing errors in the CAC scans and were removed from analysis. The total number of cases remaining for analysis was 5,785.

Manual Method

Budoff et al reported manual BMD measurements in various MESA studies [11,14-21]. According to their methods, three consecutive thoracic vertebrae were selected for BMD measurements, beginning at the level of the left main coronary artery, and proceeding caudally[18]. The region of interest was located at the center of the vertebrae, 2-3 mm in from the cortical bone. This region was used to calculate the mean density in Hounsfield units, a standardized CT coefficient, and subsequently the BMD value in mg/cc[18]. The mean BMD for the three consecutive thoracic vertebrae was calculated in all subjects [11,14-21]. They have demonstrated thoracic QCT and lumbar QCT versus DEXA BMD measurements were reasonably correlated. Despite the reasonable correlation, the manual QCT measurement is not the standard of care today and therefore would not serve as the ultimate ground truth. Nonetheless, the purpose of this study was to compare the performance of AI-enabled AutoBMD with the manual measurements previously conducted in MESA.

AutoBMD AI Model

The deep learning model was trained using 132 cardiac CT scans from the Harbor UCLA Lundquist Institute, which comprised a total of 7,649 slices [21]. In addition to this, a training dataset (n = 73) was used to train the model to detect trabecular bone and intervertebral discs. For ground truth, 225 cardiac CT images for whole spine were used, and disk locations were manually segmented.

The deep learning model has two steps to automatically detect individual vertebrae and disks. In the first step, the model was trained to focus on the whole spine area. Transfer learning was then used to train for disk locations using the pretrained model. The architecture of the model consists of an encoder and a decoder. The encoder is a UNet with 12 layers of 2-D convolutions, skip connections, Leaky ReLu activations, and batch normalization. The decoder is three-layer convolution 2-D with Leaky ReLu activations and a sigmoid at the end. Signal processing was used to erode the borders and segment the entire vertebral bone (Fig. 1).

Ground truth labeling for the vertebral bones was performed by three trained technicians and overseen by a licensed radiologist. Software segmentation validation

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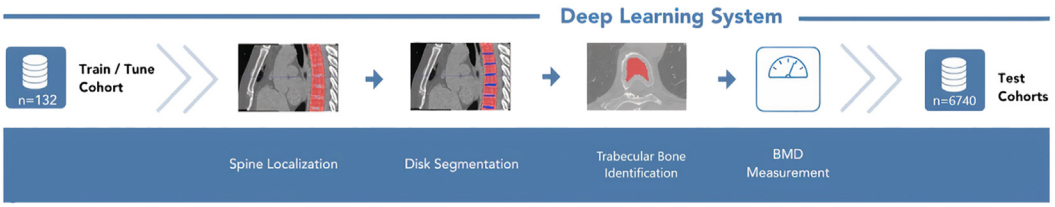

Fig. 1. Deep learning system of the AutoBMD Software. This includes spine localization, disk segmentation, trabecular bone identification, and bone mineral density (BMD) measurement. The model was trained on 132 cases and tested on 5,785 cases. This includes spine localization, disk segmentation, trabecular bone identification, and finally BMD measurement.

criteria for vertebral bones was set as a Dice coefficient of 0.95 or greater.

Figure 2 shows an example of manual BMD versus AutoBMD measurements.

Statistical Analyses

We used SAS (SAS Institute Inc., Cary, NC) and Stata (StatCorp LLC, College Station, TX) software for our statistical analyses. All values are reported as means ± SD. All

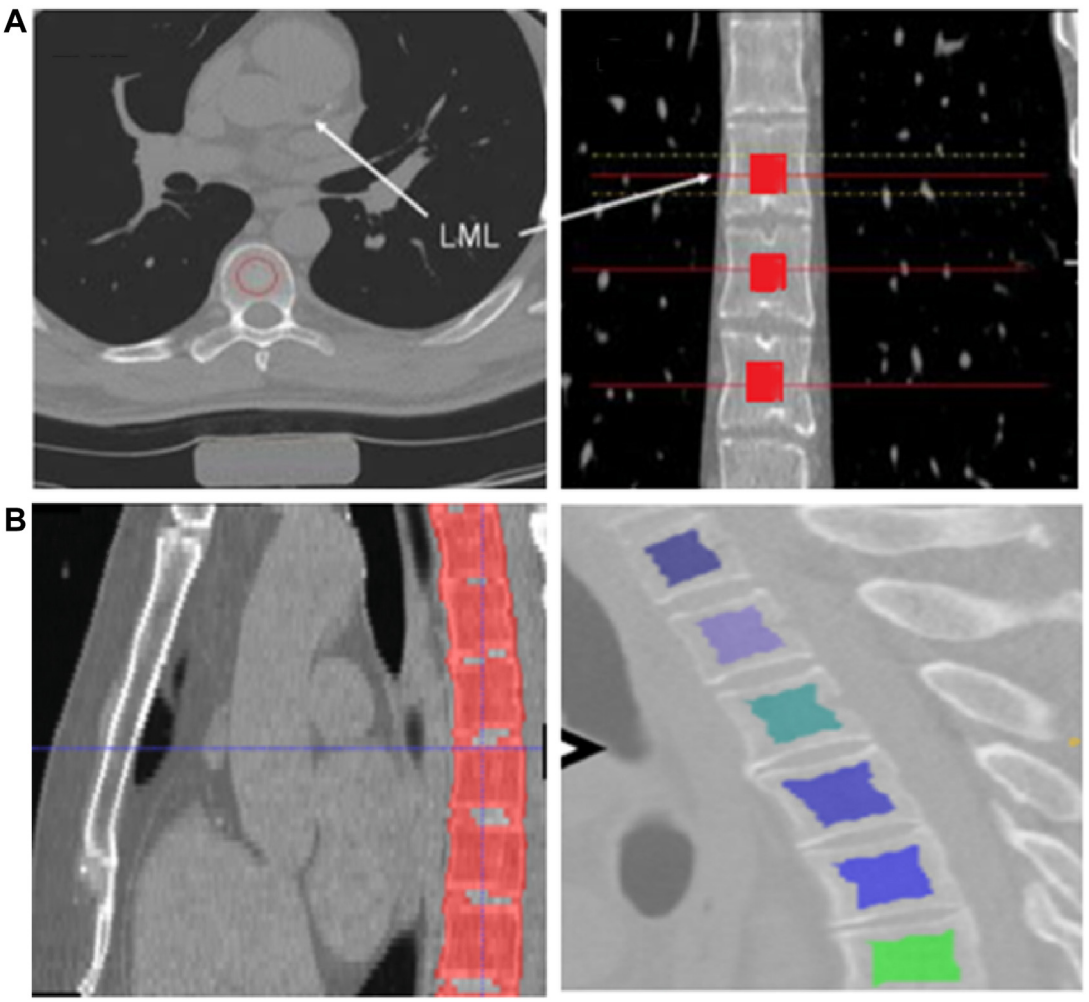

Fig. 2. (a) Manual BMD measurement on quantitative CT images. Measurements are outlined by a 10-mm circle on the axial image (left) and indicated by horizontal lines on the sagittal image (right). The 10-mm rods are placed in the middle of the vertebral bodies, depicted as red cylinders in the right image. Measurements are started at the level of the left main coronary artery and proceed caudally. (b) AutoBMD measurement on coronary artery calcium scan. The left image shows the process of vertebral bone segmentation. The right image shows segmentations for the trabecular component of the vertebral body which is used for BMD measurements. BMD = bone mineral density.

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tests of significance were two tailed, and significance was defined at the $P < .05$ level. Pearson correlation plots were conducted between manual BMD and AutoBMD.

Z-Score and T-Score

Standardized reporting of BMD uses T- and Z-scores. The T-score compares an individual's bone density to what is normally expected in a healthy young adult (30 years) of the same gender [23]. A T-score between +1 and −1 is considered normal or healthy. A T-score between −1 and −2.5 indicates that the individual has low bone mass (osteopenia), although not low enough to be diagnosed with osteoporosis. A T-score of −2.5 or lower indicates that the individual has osteoporosis. The greater the negative number, the more severe the osteoporosis. The Z-score compares an individual's bone density to a healthy person of the same age and gender. Z-scores of −2.0 or lower are classified as low BMD for that age and gender, and those between −2.0 and +2.0 are classified as within the statistically normal range [23].

It is important to note that some of the authors of this article are inventors of the AutoBMD AI technology and have financial interests in commercialization of the technology. Despite following rigorous scientific methodologies that resulted in FDA approval of AutoBMD, the readers must consider the above disclosure as a potential source of overly optimistic views, which are inherent to inventors and developers of new tools.

RESULTS

Out of 5,785 cases 47.5% were male with the average age of 62.2 ± 10.3 years. AutoBMD and manual BMD measurements were 166.1 ± 47.9 mg/cc and 163.1 ± 46.0 mg/cc, respectively ($P = .006$).

Human experts versus AutoBMD reported 26.9% versus 27% for osteoporosis ($P = .90$) and 42.7% versus 40.3% for osteopenia ($P = .10$). Compared with manual BMD, AutoBMD showed an accuracy of 99.6% for osteoporosis detection, and 94.7% for osteopenia detection. Sensitivity, specificity, positive predictive value, and negative predictive value for AutoBMD-based detection of osteoporosis were 96.7%, 97.7%, 99.7% and 99.8%, respectively (Table 1).

Pearson correlation plots between AutoBMD and manual BMD measurements showed $R^2 = 0.85$. T-Score and Z-score correlation plots between AutoBMD and manual BMD showed $R^2 = 0.85$ and $R^2 = 0.80$, respectively.

Figure 3 shows Bland Altman agreement analysis was done between AutoBMD and manual BMD measurements.

Pearson correlation plots comparing the mean Hounsfield units measured by AutoBMD and the manual BMD method are shown in Figure 4.

Table 1. AutoBMD versus manual BMD results

Variable	AutoBMD Testing	Manual BMD (Ground Truth)
n	5,785	5,785
Age, y	62.2±10.3	62.2 ±10.3
Sex, n (%)		
Male	2,748 (47.5)	2,748 (47.5)
Female	3,037 (52.5)	3,037 (52.5)
BMD, mg/cc	166.1 ± 47.9	163.1 ± 46
Osteoporosis, n (%)	1563 (27)	1558 (26.9)
Osteopenia, n (%)	2332 (40.3)	2470 (42.7)
Normal, n (%)	1890 (32.7)	1757 (30.4)
Accuracy,* %	99.6	-
Sensitivity,* %	96.7	-
Specificity,* %	97.7	-
PPV,* %	99.7	-
NPV,* %	99.8	-
Time, seconds	15	330

BMD = bone mineral density.
*For osteoporosis detection.

Correlation plots comparing the AutoBMD Software and the Manual BMD Z-score and T-score are shown in Figure 5.

DISCUSSION

We have demonstrated that automated BMD measurements using AI produce results comparable to those obtained

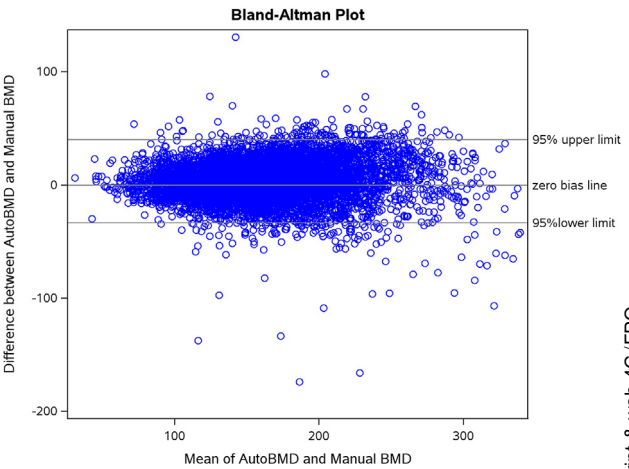

Fig. 3. Bland Altman plot of the quantitative differences between AutoBMD Software and the Ground Truth (GT) values obtained by the manual method. There is a strong agreement between the AutoBMD Software measurements and those of Ground Truth measured manually by human experts. BMD = bone mineral density.

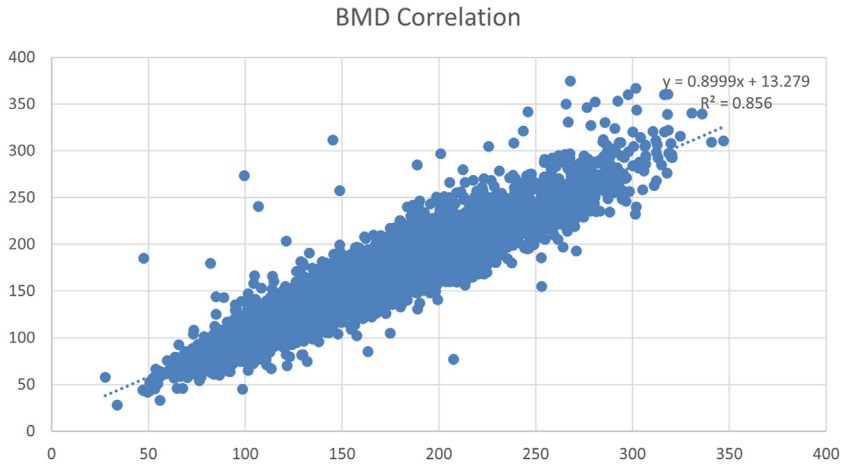

Fig. 4. Correlation plot comparing the mean Hounsfield units measured by AutoBMD Software and the manual bone mineral density (BMD) values obtained by the manual method shown below. Manual BMD scores are measured manually by Human Experts. The correlation plot between AutoBMD and Manual BMD shows strong correlation ($R^2 = 0.85$).

through manual measurements performed by human experts. Our study presents an opportunity to incorporate early detection of osteoporosis and osteopenia from routine cardiac CT scans using AI-enabled automated BMD measurements. AI-powered detection sets itself apart from manual measurements through its speed, accuracy, and reproducibility. AI-enabled AutoBMD can generate up to 44 reports in the time it takes a human to analyze and report just a single case. The repetitive nature of manual measurements may give rise to human errors, particularly as the operator becomes fatigued. AI is inherently immune to such errors and offers a compelling advantage when compared with manual human measurements [24].

Manual BMD measurements are limited by the fact it is hard to circumvent highly calcified or sclerotic streaks inside the trabecular zones, whereas AI-powered detection is trained to avoid Hounsfield units above 400, as these highly calcified areas can falsely elevate the BMD [25]. The AutoBMD model is trained to consider Hounsfield units of above 500 as pathology, excluding from measure, and therefore not falsely elevating the BMD. Another advantage of AutoBMD versus manual QCT measurements is that AutoBMD does not require phantoms. Phantomless AutoBMD measurements consider the calibration coefficient for each scanner. Budoff et al showed that phantomless versus phantom-based thoracic BMD measurements on CAC scans acquired with a wide variety of CT scanners were similar [20].

Outside of imaging, the use of AI in the context of bone health has been explored by Chiu et al [26] who implemented an artificial neural network attuned to seven predictive demographic and lifestyle variables to predict osteoporosis with a sensitivity of 78.3% and a specificity of 73.3%. Their findings contributed to the work of several others, all of which help to demonstrate the efficacy of AI in predicting osteoporotic disease [27,28].

Several epidemiological studies have suggested a relationship between coronary and aortic calcification, impaired bone metabolism, and increased mortality [29]. Recent data suggest that this association is not simply an artifact of age, stressing that the co-incidence of vascular calcification with low bone density and osteoporosis could be biologically linked [29]. The formation of bone along the spine (osteophytes) was hypothesized to share pathways with calcium deposition in the aorta [30]. A study by Harlianto et al [30] found that patients with diffuse idiopathic skeletal hyperostosis have an increased burden of thoracic aortic calcifications.

Limitations of this study include the use of manual BMD measurements from CT scans taken almost 20 years ago. It is possible that these measurements may not be entirely representative of the CT scans used today and in the next 20 years. We would need to calculate calibration coefficients for new CT scanners, which is not a major task and can be accomplished within 30 min for each scanner. Additionally, because we relied on previous publications by Budoff et al that demonstrated the agreement between the manual QCT and DEXA, those data are not presented here. Any conclusion about superiority over DEXA or equivalency is indirect and must be viewed considering these previous studies. Another limitation is that the number of vertebrae captured by AutoBMD depends on scan length and field of view used, which varies per patient. To prevent measurement variability, we have limited AutoBMD reports to the average of only three vertebrae corresponding to T7, T8, T9. Even though the BMD is measured in all visible

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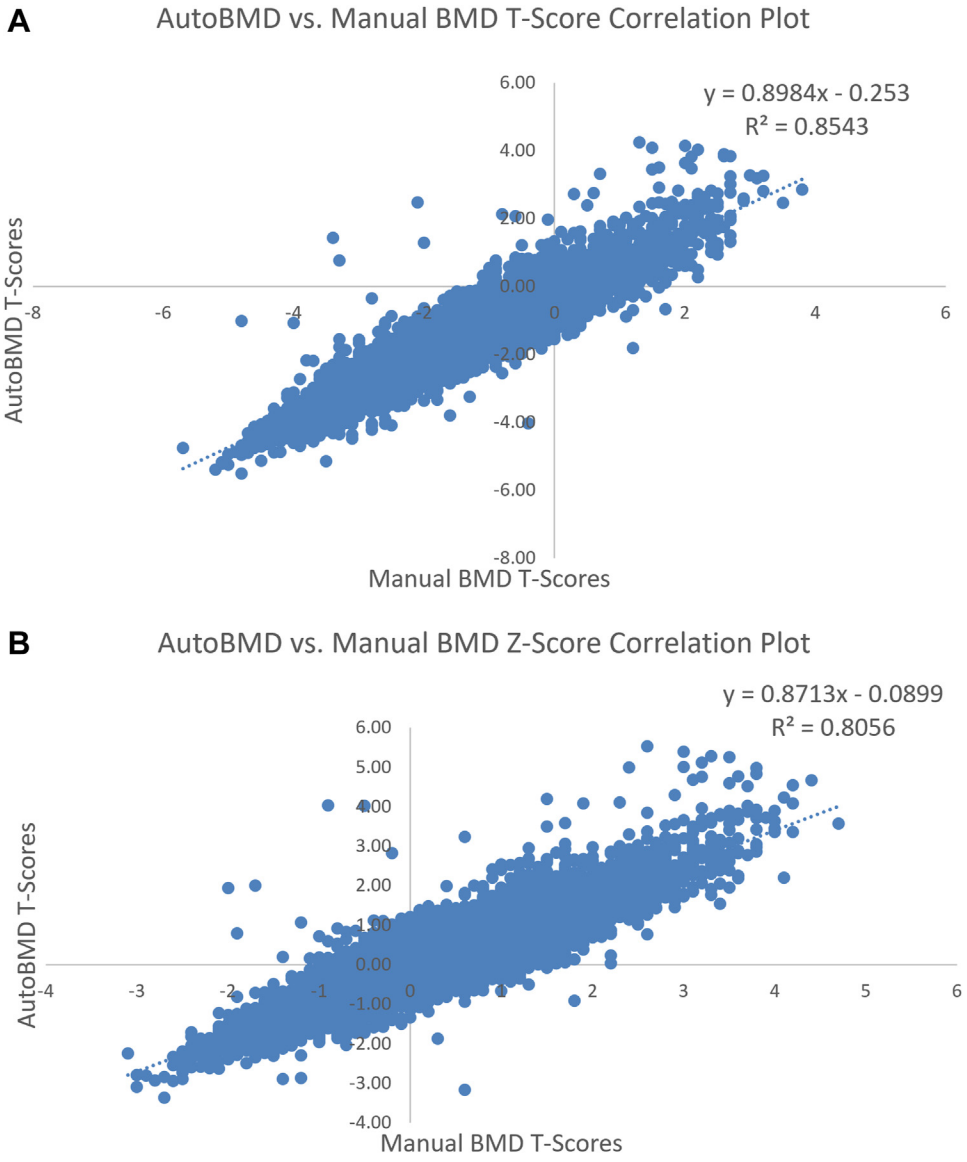

Fig. 5. (a) T-score correlation plot of AutoBMD software and manual bone mineral density (BMD) ($R^2 = 0.85$). (b) Z-score correlation plot of AutoBMD software and manual BMD ($R^2 = 0.80$).

vertebral bodies, just those three levels are used for reporting BMD and calculating T- and Z-scores. This difference in manual BMD and AutoBMD measurements ($P = .006$) is expected because the manual measurements method was limited to the cylindrical sample from the center of the bone, whereas AutoBMD covers the entire trabecular bone area and shadows the cortical bone with 2- to 3-mm distance. It is expected the center cortical bone has less heterogeneity than the peripheral area which often includes degenerative sclerotic changes. Furthermore, the 1.8% difference in mean BMD between the two groups is clinically insignificant.

In summary, opportunistic AI-enabled automated measurement of BMD in routine CAC scans offers an opportunity for early detection of subclinical osteoporosis and osteopenia. This approach can improve BMD screening rate, which is currently 20%, without additional cost or radiation exposure for the patient, ultimately improving bone health [24].

Acknowledgement

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75N92020D00004, N01-HC-95164, 75N92020D00007, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168 and N01-HC-95169 from the National Heart, Lung, and Blood Institute, and by grants UL1-TR-000040, UL1-TR-001079, and UL1-TR-001420 from the National Center for Advancing Translational Sciences (NCATS). The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org

Conflict of Interest

As stated previously, it is important to note that some of the authors of this article are inventors of the AutoBMD AI technology and have financial interests in commercialization of the technology. Despite following rigorous scientific methodologies that resulted in FDA approval of AutoBMD, the readers must consider this disclosure as a potential source of overly optimistic views, which are inherent to inventors and developers of new tools.

TAKE-HOME POINTS

- AI-enabled AutoBMD can measure BMD in patients with accuracy comparable to manual measurements by radiologists.
- Automated methods of measuring BMD are much faster on average compared with manual methods of measuring BMD (15 seconds versus 5.5 min).
- The incremental value of AutoBMD individuals undergoing CAC scans is promising as a novel screening tool with no additional radiation and no separate CT scan.

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