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Non-contrast Cardiac Computed Tomography Image-based Vertebral Bone Mineral Density: the Multi-Ethnic Study of Atherosclerosis (MESA)

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INTRODUCTION

Cardiac computed tomography (CT), especially the latest generation multi-detector computed tomography (MDCT), is a noninvasive imaging tool which has been increasingly

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applied for early atherosclerosis detection, quantification of coronary artery calcification, and coronary artery stenosis assessment. Some initial studies have indicated that cardiac CT may have the potential to assess vertebral BMD while assessing cardiovascular disease (CVD) risk with no extra cost or radiation(4–6), but the results show population diversity. Method validation is extremely important, especially in a community-based, multiethnic (Caucasian, African American, Asian and Hispanic) population.

The Multi-Ethnic Study of Atherosclerosis (MESA) is a population-based study of eight large gender-ethnic sub-populations with cardiac CT scan across the United States. This study provides an opportunity to evaluate vertebral BMD based on non-contrast cardiac CT image. Compared with dual-energy X-ray absorptiometry (DXA), the predominant screening tool for BMD, cardiac CT has at least three unique advantages: 1) ability to clearly separate cortical and trabecular bone; 2) offer “real” volumetric density in units of mg/cm^3 ; 3) high-resolution three-dimensional (3D) images of bone morphometry. Notably, compared to cortical bone, trabecular bone loses first and quick response to medical therapies as well. So trabecular bone may offer a more realistic reflection of bone mineral metabolism and bone density status (7–9). In this study, we use cardiac CT image to garner vertebral bone information and then to assess trabecular BMD (tBMD) and related fractures while assessing cardiovascular disease risk.

METHODS

CT image acquisition

The CT image from MESA, which the goal of identifying CAD risk factors and also the presence of subclinical atherosclerosis by using different modalities, including cardiac CT scanning for evaluation of Coronary Artery Calcium (CAC). The specific number of images and the image source included the following: total 443 (21.8%) sets of cardiac CT images from Wake Forest University, total 376 (18.5%) sets of cardiac CT images from Columbia University, total 54 (2.7%) sets of cardiac CT images from Johns Hopkins University, total 400 (19.7%) sets of cardiac CT images from University of Minnesota, total 386 (19.0%) sets of cardiac CT images from Northwestern University, and total 369 (18.2%) sets of cardiac CT images from University of California, Los Angeles.

The CT scanning parameters were 130 kVp and 630 mA current (Chicago, Los Angeles, and New York field centers) or 120 – 140 kVp, 600 mA current (Baltimore, Forsyth County, and St. Paul field centers). Vertebral tBMD was reviewed on the NVivo workstation (Columbia, Kentucky).

Measurement of tBMD

As described earlier in Dr. Budoff’s protocol (10), the Regions-of-Interest (ROIs) was positioned in the center of each vertebral body, and at least 2 mm away from the spinal cortical edge. This includes default options-maximum radius of the ROI The software automatically positions an elliptical ROI within the without operator interaction and the software also automatically flags any reconstructed CT slices, which may result in a poor vertebral ROI, such as inhomogeneity resulting from reconstructed slice clipping of vertebral endplates, extra-osseous calcium deposits, vertebral fracture, or high image noise in large patients. The major anterior portion of the vertebral body was segmented by the software, and all the bones were measured as a composite density of both cortical and trabecular bone components. Because the external cortical shell has been large contrasts with the surrounding soft tissue, it can be segmented with relatively greater accuracy and precision than trabecular bone. Thoracic spine BMD was measured at the level of the left main (LM) coronary artery. Finally, an experienced physician oversaw all measurements to

ensure an accurate assessment. Any vertebra with a crush fracture or other gross abnormalities was excluded from measurement results. Briefly, a total of five samples was excluded. Among of them, two for trauma, one for the spread of tumor to the spine, one for neuromuscular scoliosis, and one for vertebrae deformity.

Measurement of vertebral fracture

Though many different approaches have been used to diagnose and characterize vertebral fractures and vertebral fractures can happen for a number of reasons, including trauma, osteoporosis-related low bone mineral density (BMD) or even the spread of a tumor to the spine, in this paper, osteoporosis-related fracture and the vertebral fracture (Vfx) were classified based solely on morphometry measurements using Genant's criteria(11) and Lenchik methods (12, 13). Briefly, posterior heights of the T-1 to L-5 vertebrae were measured. The degree of vertebral deformity was derived by comparing a ratio of heights with the adjacent upper and lower vertebral body when on visual inspection, it exhibited more than 15% height loss and fractures were graded as mild (15–24% reduction), moderate (25–49% reduction) or severe (more than 50% reduction) based on the degree of height loss.

Statistical Analysis

All analyses were guided by three principles: 1) descriptive analysis accompanied complex models; 2) models accommodate the outcome measurement scale, data structure, and objectives; 3) multiple findings were evaluated for coherence rather than by individual p-values. Primary analysis focused on characterizing tBMD distribution and variation across ethnic groups as well as age and gender. In order to accurately assess tBMD, covariate include sex, age, race-ethnicity, BMI, current tobacco smoking, daily alcohol consumption of 3 or more units daily, and other causes of secondary osteoporosis. This enabled us to establish a population-based norm for integral and tBMD. Covariates were entered into the models based on their potential role as confounders due to their association with BMD. Pearson's correlation analysis was used to correlate thoracic and lumbar tBMD stratified by gender, race and age. In the univariate analysis model, overweight participants (BMI ≥ 25 kg/m²) were compared with participants who had normal BMI (18.5–24.9 kg/m²). Multiple regression analysis was also performed for thoracic tBMD, lumbar tBMD and BMI to determine the association between vertebral tBMD and BMI. All statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC).

RESULTS

Community-based multiethnic reference values for vertebral BMD

Among these 2028 men and women, 1011 were women (49.9%) and then a race/ethnic composition of the subgroup was as follows: 837 (41.3%) Caucasian, 258 (12.7%) Chinese American, 423 (20.9%) African-American, and 510 (25.1%) Hispanic. The mean age was 62 ± 10 years (95% CI 61.5, 62.3 years) in full populations.

A Multi race/ethnicity reference value for vertebral BMD was shown in Table 1A and 1B. Overall, thoracic BMD is about 16.3% higher than lumbar BMD (140.8 ± 42.1 mg/cm³ vs. 121.0 ± 39.1 mg/cm³, $P=0.02$) independent of age, gender and BMI. When stratified by gender, the mean tBMD was significantly higher in men versus women for thoracic vertebrae (143.2 ± 41.2 mg/cm³ vs. 138.7 ± 42.7 mg/cm³ respectively, $p=0.014$), and also for lumbar vertebrae (125.0 ± 37.9 mg/cm³ vs. 117.2 ± 39.4 mg/cm³ respectively, $p<.0001$). In addition, our data also confirmed ethnic differences in BMD. African-Americans had the highest mean thoracic tBMD (167.9 ± 47.6 mg/cm³), followed by Hispanics (143.8 ± 37.9 mg/cm³), Chinese American (129.8 ± 37.4 mg/cm³), and Caucasians (128.9 ± 35.7 mg/cm³). For lumbar tBMD, African-Americans had highest mean lumbar tBMD (144.3 ± 44.2 mg/cm³),

followed by Hispanics ($120.9 \pm 35.7 \text{ mg/cm}^3$), Caucasians ($112.3 \pm 33.8 \text{ mg/cm}^3$), and Chinese American ($111.6 \pm 34.8 \text{ mg/cm}^3$).

Table 2 demonstrates correlation between thoracic and lumbar tBMD. The correlation was high regardless of race, age and gender (correlation coefficients 0.87, $p < .001$). The correlation of thoracic and lumbar tBMD was higher in women than in men, and the highest correlation coefficient appeared to be in Chinese American women ($r = 0.92$, $P < .0001$). The correlation coefficients in a descending order were as follows: $r = 0.89$, 0.87 , 0.85 , and 0.84 for Chinese American, African-American, Caucasian, and Hispanic populations respectively. Our data clearly indicated that the correlation between thoracic and lumbar tBMD is independent of age and other confounders.

Influence of cardiovascular disease risk factors on vertebral BMD

Given cardiac CT image-based BMD measurement has the additional advantages of evaluating vertebral bone health while assessing CVD risk, multiple regression analysis was also performed to investigate the Influence of CAD risk factors on vertebral BMD. African-American population had higher mean values of tBMD than Hispanic, Chinese American or Caucasian at both thoracic and lumbar. Taking thoracic as an example, mean tBMD among African-American, Hispanic, and Caucasian population was $167.9 \pm 47.6 \text{ mg/cm}^3$, $143.8 \pm 37.9 \text{ mg/cm}^3$, $129.8 \pm 37.4 \text{ mg/cm}^3$, and $128.9 \pm 35.7 \text{ mg/cm}^3$, respectively. In other words, these represent 39.3 mg/cm^3 (95% CI 34.7, 43.8), 14.8 mg/cm^3 (95% CI 10.4, 19.1) higher thoracic BMD values among African-American and Hispanic population compared with Caucasian population.

Generally, the incidence of osteoporosis of the hip is lower in men. However the effects of gender may differ in vertebrae tBMD. In our study, a similar trend was also observed in vertebral bone. Men had higher thoracic tBMD and lumbar tBMD than women (5.2 mg/cm^3 , 95% CI 1.6–8.9 for thoracic and 8.4 mg/cm^3 , 95% CI 5.1–11.8 for thoracic, respectively).

Age-related decrements in vertebrae BMD was also observed in this study population. Though this occurs more commonly in patients above the age of 65 years, our data indicated that in both genders over 65 years of age, there are 21.1% (32.7 mg/cm^3) lower thoracic tBMD when compared with those subjects with aged less than 65 years. Similarly, the numerical value for lumbar tBMD is 22.9% (30.7 mg/cm^3).

Being overweight, defined as $\text{BMI} > 25$, was associated with increased both thoracic and lumbar tBMD even after adjustment for age, sex and race/ethnicity. Compared to the normal body weight group ($\text{BMI} < 25$), overweight individuals had a 12.2% ($13.0 \pm 1.8 \text{ mg/cm}^3$, 95% CI 9.4–16.5 mg/cm^3) higher mean thoracic tBMD and an 8.7% ($7.5 \pm 1.7 \text{ mg/cm}^3$, 95% CI 4.3–10.8 mg/cm^3) higher lumbar tBMD.

DISCUSSION

More epidemiological data indicated that the coexistence of osteoporosis and coronary artery disease (CAD) is not just a by chance event, but the underlying mechanism is unclear. Evidence-based studies have shown that trabecular bone is more metabolically active compartments, and it is the most sensitive indicator of osteoporosis and future fracture risk. Obviously, detecting abnormal tBMD and evaluate the association of bone density and CAD risk may provide deeper insight into the coexistence of osteoporosis and CAD. Cardiac CT increasingly being utilized to evaluate the risk for CAD and prognosis has been potential as a diagnostic device for osteoporosis and related fractures. Especially in clinical practice, the ability to garner both CAD risk factors and vertebral BMD information without additional patient imaging or radiation exposure is highly desirable.

Compared with DXA, cardiac CT's 3D high resolution image is the only method that provides a really volumetric measurement of bone density that is capable of distinguishing between the exterior cortical bone and the interior trabecular bone. However, no multi-center, multiethnic data on thoracic tBMD measurement based on non-contrast cardiac CT image has been reported. Here, we have presented detailed epidemiological data on both thoracic and lumbar tBMD, showing high correlation between the two and across multiple gender, ethnic and age subgroups. These results may help to fill the gap in clinical data, which is related to lacking of references for tBMD. It also may provide baseline information for future longitudinal studies on osteoporosis, utilizing widely available thoracic spine images, which are taken as part of lung and cardiac CT scans.

A large number of experimental and epidemiological data have indicated that there are ethnic differences in BMD (14–17), however, whether ethnic diversity effects on the correlation of thoracic and lumbar BMD has remained unclear. Our data indicated that thoracic and lumbar tBMD are closely correlated, independent of age and other confounders. This finding is very important and can have a high clinical value due to if thoracic and lumbar tBMD highly correlated (correlation coefficients 0.866 95% CI 0.81–0.92, $P < .0001$) even stratified by race and gender, in clinical practice, the physician may assess bone density by using either thoracic or lumbar spine available from chest scan (lung or cardiac) or abdominal CT scans. It makes the estimated 72 million CT scans done annually in the United States, as potential treasures for bone health evaluation without extra radiation exposure or economic burden.

There is good evidence that there is a gender difference in BMD, and that age is inversely related to BMD (18–20). Indeed, our data confirmed it. Additionally, our data indicated that, for thoracic tBMD, compared to men; women under 48 years have higher thoracic tBMD (179.9 mg/cm^3 vs. 166.2 mg/cm^3). However, for lumbar vertebrae, until 50 years old, compared to men, women keep higher tBMD (157.8 mg/cm^3 vs. 147.8 mg/cm^3).

In summary, vertebral BMD assessment based on non-contrast cardiac CT image in a large multicenter, multiethnic population. Cardiac CT imaging is a reliable source to assess vertebral tBMD. In clinical, cardiac CT has potential in evaluating the quality and quantity vertebral bone while assessing CAD risk with no extra cost or radiation exposure. Our findings may fill crucial gaps in epidemiological data on vertebral BMD and provide a better understanding of racial and ethnic specific differences in vertebral tBMD. This information could be potentially used in future studies in correlating bone health with coronary atherosclerosis in different populations with different risk factors for CAD.

There are several limitations that may affect our results. Our results just based on cross-sectional study design, and we only analyzed vertebral tBMD data. Additionally, we did not evaluate the consistency between vertebral tBMD and hip and lumbar spine BMD measured by DXA. Finally, some of our participant's osteoporosis medication records were missing, and these medications might have increased our tBMD measurements. However, we controlled for most known confounding factors.

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Figure 1.
Measurement of the tBMD with the standard elliptical ROI positioned within the trabecular region.

Figure 2.
Figure 2A–2B. The association between tBMD and age.

Figure 3.
Correlation plots of thoracic and lumbar BMD.

Table 1
Community-based multi race/ethnicity reference values for vertebral bone mineral density (BMD) among men

	Thoracic trabecular BMD(mg/cm ³)				Lumbar trabecular BMD(mg/cm ³)			
	Caucasian	Chinese	African-American	Hispanic	Caucasian	Chinese	African-American	Hispanic
Overall	131.1±36.0	134.1±34.7	171.9±46.9	148.1±37.2	115.1±33.1	115.3±31.5	151.7±43.7	127.9±34.5
80–85 yrs	95.0±37.8	109.5±16.3	105.4±21.4	130.1±30.9	79.6±34.2	96.1±21.9	85.4±21.7	106.4±31.2
75–80 yrs	105.8±30.7	119.7±36.9	151.1±46.8	116.3±32.3	90.3±29.0	100.6±33.2	128.3±50.7	102.1±27.4
70–75 yrs	123.9±27.3	124.6±37.4	147.6±32.1	122.3±29.6	105.8±30.6	97.2±18.0	137.2±45.2	106.8±26.6
65–70 yrs	118.0±35.2	125.4±23.5	172.4±38.8	131.7±30.5	105.1±28.7	108.5±25.7	156.8±49.1	115.3±33.1
60–65 yrs	133.2±33.3	126.0±34.0	181.3±38.1	146.3±32.2	115.1±32.1	107.7±32.5	149.0±29.7	123.0±32.3
55–60 yrs	140.7±32.6	138.5±27.4	173.4±52.0	157.9±38.2	123.9±25.6	115.3±22.7	149.0±35.9	140.4±33.1
50–55 yrs	150.2±30.2	143.8±29.4	180.2±45.3	163.3±37.1	135.3±31.6	127.9±22.8	161.3±38.3	138.5±33.3
45–50 yrs	150.4±35.9	160.6±38.3	201.0±53.9	167.0±31.2	133.6±25.4	147.7±35.2	183.2±35.7	144.6±30.9

Table 1B
Community-based multi race/ethnicity reference values for vertebral bone mineral density (BMD) among women

	Thoracic trabecular BMD (mg/cm ³)				Lumbar trabecular BMD(mg/cm ³)			
	Caucasian	Chinese	African-American	Hispanic	Caucasian	Chinese	African-American	Hispanic
Overall	126.3±35.2	124.9±39.8	164.8±48.0	139.5±38.1	109.1±34.4	107.5±37.8	138.7±43.9	114.0±35.6
80–85 yrs	93.3±25.0	94.1±17.7	115.1±38.3	108.0±25.4	74.8±24.5	91.7±22.3	93.0±46.3	80.1±16.6
75–80 yrs	93.8±24.8	77.5±21.6	114.8±27.0	107.9±33.6	75.4±21.8	62.9±20.9	94.5±25.5	84.8±28.5
70–75 yrs	109.2±28.6	93.8±21.5	143.6±43.1	108.8±30.8	91.8±33.4	75.7±24.1	115.5±39.2	86.4±28.1
65–70 yrs	122.3±34.3	103.7±28.1	153.4±38.7	128.7±30.2	103.6±30.4	95.9±37.3	124.7±34.4	105.1±30.6
60–65yrs	135.3±27.7	132.2±32.1	162.0±35.4	132.9±23.7	115.1±29.5	109.3±30.9	146.6±34.1	109.4±25.1
55–60 yrs	130.7±31.2	136.4±29.8	184.7±49.1	151.7±38.0	114.0±27.8	116.4±28.4	151.6±41.6	122.1±31.2
50–55 yrs	145.6±31.1	154.3±34.4	188.4±32.3	155.1±30.1	131.3±26.4	136.2±29.7	162.0±30.4	129.1±30.3
45–50 yrs	154.0±43.6	155.9±28.2	207.3±50.6	187.5±31.0	139.2±39.2	139.9±28.1	182.9±39.7	159.1±29.2

Table 2
Correlation of thoracic and lumbar BMD as a whole and stratified by race & Gender

	<u>Total population</u>		<u>Women</u>		<u>Men</u>	
	<i>r</i>	<i>P-value</i>	<i>r</i>	<i>P-value</i>	<i>r</i>	<i>P-value</i>
Full population	0.87	<.0001	0.9	<.0001	0.85	<.0001
Caucasian	0.84	<.0001	0.88	<.0001	0.81	<.0001
Chinese	0.89	<.0001	0.92	<.0001	0.84	<.0001
African-American	0.86	<.0001	0.9	<.0001	0.82	<.0001
Hispanic	0.83	<.0001	0.86	<.0001	0.81	<.0001

* *r* stands for Pearson correlation coefficients, significant *P*-value for *r*

Table 3

Influence of cardiovascular disease risk factors on vertebral BMD

	n	Thoracic BMD (mg/cm³)			Lumbar BMD(mg/cm³)				
		Mean±SD	β (se)	95% CI	P Value	Mean±SD	β (se)	95% CI	P Value
Race/Ethnic									
Caucasian	846	128.9±35.7	0 (Ref)			112.3±33.8	0 (Ref)		
Chinese	260	129.8±37.4	1.0(2.8)	-4.4,6.5	0.71	111.6±34.8	0.8(2.6)	-5.9,4.4	0.77
African-American	431	167.9±47.6	39.3(2.3)	34.7,43.8	<001	144.3±44.2	32.3(2.2)	28.0,36.6	<.001
Hispanic	523	143.8±37.9	14.8(2.2)	10.4,19.1	<001	120.9±35.7	8.4(2.1)	4.3,12.5	<.001
Gender									
Women	1027	138.7±42.7	0 (Ref)			117.2±39.4	0 (Ref)		
Men	1033	143.2±41.2	5.2(1.9)	1.6,8.9	0.005	125.0±37.9	8.4(1.7)	5.1,11.8	<.001
Age, yrs									
<65	1205	154.5±39.9	0 (Ref)			133.9±35.4	0 (Ref)		
65	855	121.9±37.2	-32.7(1.8)	-36.1,-29.2	<001	103.1±36.3	-30.7	-33.9,-27.5	<.001
Body weight									
Normal	583	129.6±39.6	0 (Ref)			114.0±37.0	0 (Ref)		
Obesity	1477	145.4±42.1	15.8(2.0)	11.9,19.9	<001	123.9±39.2	9.9(1.7)	6.1,13.6	<.001