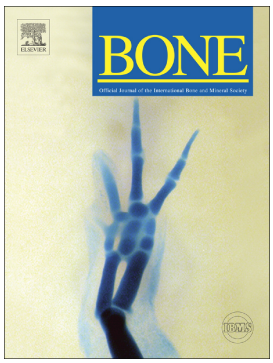

The accurate relationship between spine bone density and bone marrow in humans

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The accurate relationship between spine bone density and bone marrow in humans

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Abstract

Context: The accuracy of QCT measurements of lumbar spine trabecular volumetric bone mineral density (vBMD) is decreased due to differences in the amount of bone marrow adipose tissue (BMAT).

Objective: To correct vBMD measurements for differences in marrow composition and investigate the true relationship between vBMD and BMAT.

Design: Cross-sectional study.

Setting: University teaching hospital.

Participants: Healthy Chinese subjects (233 women, 167 men) aged between 21 and 82 yr.

Main outcome measures: vBMD and BMAT were measured using QCT (120 kV) and chemical shift-encoded MRI of the L2-L4 vertebrae. vBMD measurements were standardized to the European Spine Phantom (ESP) and corrected for differences in BMAT. Linear regression was used to analyze BMAT, ESP adjusted vBMD ($vBMD_{ESPcorr}$) and BMAT corrected vBMD ($vBMD_{BMATcorr}$) against age and corrected vBMD against BMAT.

Results: BMAT in the L2-L4 vertebral bodies increased with age in both sexes, with a faster rate of change in women compared with men (0.54%/yr vs. 0.27%/yr, $P<0.0001$). After vBMD measurements were corrected for BMAT there were statistically significant changes in the slope of the regression line with age in both sexes (women: -3.00 ± 0.13 vs. -2.57 ± 0.11 mg/cm^3/yr, $P<0.0001$; men: -1.92 ± 0.15 vs. -1.70±0.14 mg/cm^3/yr, $P<0.0001$). When $vBMD_{BMATcorr}$ was plotted against BMAT, vBMD decreased linearly with increasing BMAT in both sexes (women: -3.30 ± 0.18 mg/cm^3/%; men: -2.69 ± 0.25 mg/cm^3/%, $P=0.048$).

Conclusion: Our approach reveals the true relationship between vBMD and BMAT and provides a new tool for studying the interaction between bone and marrow adipose tissue.

Key Words: QCT; BMD; Chemical shift encoded MRI; Bone marrow adipose tissue; BMD accuracy errors

1 Introduction

With advances in stem cell research, the osteoblasts lining bone surfaces and the adipocytes occupying the marrow space are now known to be derived from the same stem cells, with the differentiation to osteoblast or adipocyte mediated by systemic and local factors (1-3). Several recent reviews have discussed the close association between osteoblasts and adipocytes and provided new insight into the role of bone marrow in the mechanisms of bone formation and bone loss (4-8).

Measurement of trabecular volumetric bone mineral density (vBMD) using QCT plays an important role in the evaluation of patients with osteoporosis and is deemed the gold standard for vBMD assessment (9-11). However, the accuracy of QCT in assessing vBMD is decreased due to differences between people in the amount of bone marrow adipose tissue (BMAT) (12-14). Although for clinical applications, including the diagnosis of osteoporosis, these errors are currently ignored. However, the accurate measurement of both bone and BMAT are critical for fundamental investigations into the interactions between trabecular bone and bone marrow, or where the bone marrow is expected to change rapidly in a short time, such as the bone marrow change after radiotherapy or chemotherapy (15).

Both Bredella and Hui reported that dual-energy CT (DECT) can accurately measure BMAT content and correct QCT vBMD for marrow composition (15,16). MRI is also a sensitive and accurate method of measuring the fat content of tissue, and we have previously shown that chemical shift encoded MRI (CSE-MRI) is a robust and precise method of measuring liver fat and BMAT (17,18). On this basis we developed and validated a method designed to correct single-energy QCT vBMD measurements for BMAT content measured by CSE-MRI (19).

To investigate the relationship between bone mass and BMAT in vivo, we sought to measure trabecular vBMD and bone marrow composition noninvasively, accurately and precisely. In the present work, we used QCT measurements of L2-L4 trabecular vBMD and CSE-MRI measurements of vertebral body BMAT content in four hundred healthy Chinese subjects aged 21 to 82 yr recruited from the nearby urban community to derive the corrected vBMD and examine the relationships between uncorrected vBMD, corrected vBMD and BMAT content.

2 Materials and Methods

2.1 Study subjects

Our study was approved by the hospital Research Ethics Committee and all subjects gave written informed consent. The participants were subjects already enrolled in two ongoing observational studies at our institution. Two hundred and fifty three subjects (156 women, 97 men) aged between 43 and 82 yr were enrolled as part of the international Prospective Urban Rural Epidemiology (PURE) Study and were scanned at their 9-yr visit. Recruitment criteria of PURE study subjects in China were published previously (20). Another 147 subjects (77 women, 70 men) aged between 21 and 52 yr were enrolled in a population study to investigate the sex- and age-stratified normative vBMD values of the cervical vertebrae by QCT and determine the correlations with lumbar vertebrae vBMD (21).

2.2 Lumbar vertebra scanning by QCT

The lumbar vertebrae from L2-L4 were scanned with a Toshiba CT scanner (Aquilion PRIME ESX-302A, Toshiba Medical Systems Corporation, Otawara, Japan). A QCT calibration phantom (Mindways Inc., Austin, TX, USA) was placed beneath the spine and scanned simultaneously according to the standard protocol of

Lang et al. (22). The scan parameters were as follows: 120 kV, 187 mAs, field-of-view 40 cm, slice thickness 1 mm, and reconstruction matrix 512 x 512. After scanning, the CT datasets were transferred to a workstation for further analysis with the QCT Pro software (version 5.0.3) (Mindways Inc.). The regions of interest were defined as the oval-shaped areas containing the largest area of trabecular bone, not including cortical bone or the basivertebral plexus. For cross-calibration a European Spine Phantom (ESP-145) (QRM GmbH, Möhrendorf, Germany) was scanned ten times. Raw vBMD measurements produced by QCT Pro software were adjusted to the manufacturer-calibrated values for the ESP-145 phantom using the following linear regression fit to the three vertebrae in the phantom:

$$vBMD_{ESPcorr}\ (mg/cm^3) = -2.16 + 1.0074 \times QCT\ Pro\ vBMD\ (mg/cm^3).$$

2.3 Bone marrow adipose tissue measurement by MRI

On the same day as their QCT study, subjects underwent a chemical shift encoded study on a 3.0-T whole-body MRI system (Ingenia, Philips Healthcare, Best, Netherlands) using a mDIXON-Quant sequence as previously described (18). After acquisition, the image data were transferred to an ISP V7 workstation (Philips Healthcare, Best, Netherlands) and the proton density fat fraction (PDFF) measured in each of the L2-L4 vertebral bodies. PDFF measurements were expressed as the percentage fat content on a scale from 0 to 100% based on the relative signal strengths of fat and water (23). Care was taken to ensure that the MRI ROI corresponded to that used in the QCT study. We have previously demonstrated that a measurement of PDFF using a mDIXON-Quant sequence provides a reliable estimate of the BMAT fraction (18). These measurements were used to correct the $vBMD_{ESPcorr}$ measurements in each vertebral body for the effects of variable marrow

composition and produce a $vBMD_{BMATcorr}$ measurement based on our previously published equation (19):

$$vBMD_{BMATcorr} = vBMD_{ESPcorr} + 0.7576 \times BMAT(\%) - 12.96\ (mg/cm^3)$$

Note that in this equation BMAT is in percentage units and can vary from 0 to 100%.

2.4 Statistical analysis

Demographic data and measurements of BMAT,$vBMD_{ESPcorr}$ and $vBMD_{BMATcorr}$ averaged over L2-L4 were presented as the mean, SD and range in men and women in each of three age groups (20-39, 40-59, 60-80 yr). Non-parametric statistical tests were used where appropriate. Scatter plots were drawn of BMAT, $vBMD_{ESPcorr}$ and $vBMD_{BMATcorr}$ against age and analyzed by linear regression to determine the Pearson correlation coefficients, the rate of change with age between age 20 and 80 yr, and the standard error of the estimate (SEE). The statistical significance of the difference in the rate of change of vBMD with age before and after applying the BMAT correction was determined by analyzing the individual differences between BMAT corrected and uncorrected vBMD values as a function of age using linear regression. The statistical significance of the change in the SEE after applying the BMAT correction was analyzed using the F-test. Scatter plots were drawn of $vBMD_{BMATcorr}$ against BMAT for men and women separately and analyzed by linear regression analysis to determine the relationship between the two measurements. A *P* value < 0.05 was considered to be statistically significant.

3 Results

QCT and CSE-MRI scans were performed in 400 subjects (233 females, 167 males) aged between 21 and 82 yr. On average the women were slightly older than

the men, although the difference as assessed by a Mann-Whitney test was not statistically significant (53.6 yr vs. 51.3 yr, P = 0.23). Full demographics are presented in Table 1.

Mean BMAT in the L2-L4 vertebral body ROIs increased progressively with age in both sexes (Table 2), but as evaluated by linear regression analysis there was a statistically significantly faster rate of increase with age in women compared with men (0.54 %/yr vs. 0.27 %/yr, P < 0.0001) (Fig. 1).

The mean of the $vBMD_{ESPcorr}$ measurements in the L2-L4 vertebral body ROIs decreased progressively with age in both sexes (Table 2). In women the mean rate of change between age 20 and 80 yr as assessed by linear regression analysis was -3.00 ± 0.13 mg/cm^3/yr (Fig. 2A). When the same data was plotted after correcting the vBMD measurements for BMAT measured by CSE-MRI there was a statistically significant change in the slope of the linear regression line (-3.00 ± 0.13 mg/cm^3/yr before correction vs. -2.57 ± 0.11 mg/cm^3/yr after correction, P < 0.0001) (Fig. 2B). In addition to the change in slope, application of the BMAT correction resulted in a statistically significant decrease in the dispersion of data points about the best fitting straight line as measured by the SEE (30.6 mg/cm^3 vs. 27.4 mg/cm^3, P = 0.047) (Fig. 2).

There were similar findings when the same plots were drawn for men, although in men the vBMD measurements declined more slowly with age than in women (Fig. 3). After applying the BMAT correction to the men the slope changed from -1.92 ± 0.15 mg/cm^3/yr to -1.70 ± 0.14 mg/cm^3/yr (P < 0.0001) and the SEE from 29.9 mg/cm^3 to 26.4 mg/cm^3 (P = 0.054) (Fig. 3).

When $vBMD_{BMATcorr}$ was plotted against BMAT, vBMD decreased linearly with

increasing BMAT in both women and men (Fig. 4). The difference in slope was marginally statistically significant (-3.30 ± 0.18 mg/cm^3/% vs. -2.69 ± 0.25 mg/cm^3/%, P = 0.048).

4 Discussion

We report a study using CSE-MRI measurements of BMAT to correct QCT measurements of trabecular vBMD for differences in the adipose tissue content of bone marrow. The short acquisition time of CSE-MRI scans makes it practical to generate more accurate vBMD results in a large number of subjects gaining a better understanding of the true association between vBMD and BMAT while avoiding the higher radiation dose of DECT scans.

The correction of vBMD for BMAT in 400 Chinese adults aged 20 to 80 yr resulted in highly statistically significant changes in the measurement of the mean annual rate of bone loss in lumbar spine trabecular bone in both women and men. There were also decreases in the SEE in both sexes. A decrease in SEE after application of the BMAT correction is expected given that the variations in adipose tissue content contribute to the random errors that increase the spread of individual data points about the regression lines in the uncorrected vBMD data plotted in Figs 2A and 3A.

Although BMAT content can be reliably measured using DECT (15,16), in the past this technique has never achieved a significant clinical role due to the increased radiation dose, reduced reproducibility and the lack of any necessity to correct vBMD measurements for marrow fat content in the routine use of QCT in the clinic for the diagnosis of osteoporosis and treatment follow-up. Dual-energy CT scanners have been introduced and shown to have advantages over single-energy CT imaging in

numerous clinical applications, including bone densitometry (24,25). More recently, the dual-layer spectral CT with simultaneous acquisition has enabled vBMD measurements using clinical scans that may have a role in opportunistic screening for osteoporosis (26). Magnetic resonance scanning is also a sensitive and accurate method of measuring the fat content of tissue, and the ^{1}H-MRS technique has been widely applied to determine BMAT content in the spine (27-30). However, ^{1}H-MRS is time-consuming, and now with a newer technique, CSE-MRI, the fat content of human tissue can be assessed quickly and accurately at sites that include the liver and spine with scan times of less than 10 min, including patient setup (18,31-33). In the present study we used CSE-MRI as a method of correcting single-energy QCT vBMD measurements as a research tool in an epidemiological study with the aim of exploring the relationship between true vBMD and BMAT or assessing the bone health when bone marrow fat changes rapidly. Rebuzzi and colleagues proposed use of the internal magnetic field gradient (IMFG), a new MR parameter that discriminates between healthy, osteopenic and osteoporotic postmenopausal women classified on the basis of BMD criteria (34). Ideally, MRI has the advantage of a radiation-free modality for evaluating bone densitometry and bone marrow. However, at present the accuracy of MRI measurement of bone is not as good as QCT or DXA.

From the basic physics of X-ray attenuation, the influence of a known amount of adipose tissue on a spine vBMD measurement is predictable, enabling the effect of vertebral adipose tissue on vBMD to be corrected once the BMAT content is known. In our previous work, we developed a method of using CSE-MRI to correct for the influence of marrow fat on vBMD and validated it against dual-energy QCT (19). In the present study we have applied this technique to a large group of healthy Chinese

adults with a wide age range and shown that correcting for BMAT results in statistically significant reductions in the apparent rate of bone loss with age and in the spread of vBMD measurements about the linear regression line as measured by the SEE.

An extensive review on the role of bone marrow and visceral fat on bone metabolism was provided by Sheu and Cauley (35). In a study of anorexia nervosa, Bredella et al. reported an inverse correlation between lumbar spine BMD measured by DXA and the BMAT of L4 measured by MRI ($r = -0.5$) (36). Shen et al. found an inverse relationship between DXA BMD and BMAT in African American and Caucasian men and women (37). The same inverse relationship was found between QCT vBMD and BMAT (38). Since these studies did not correct for the effect of variations in BMAT on vBMD, it is not possible to differentiate between the technical influence of BMAT on vBMD measurements and its true relationship with bone mass. The study presented here is the first large study to report the true relationship between marrow adipose tissue and vBMD, and this will be important for future investigations on the interaction of bone with marrow. In radiotherapy and chemotherapy patients, bone marrow fat increases rapidly after treatment (15,39). In such circumstances it is difficult to assess bone health without correcting for the influence of BMAT.

There are several limitations in this study. Our vBMD correction was not validated with histology. However, our correction using CSE-MRI was validated by comparison with DECT, and the results supported the reliability of our correction model. Our findings from vertebrae may not be valid for the other skeletal sites. Capuani and colleagues studied the calcaneus and found that bone marrow in this site differed

from the spine (40,41). Neither the accuracy nor the clinical relevance of BMAT correction of vBMD are currently known, and such validation requires further studies. No information was available about the menopausal status of the women in the study, although in urban centers in China the average age at menopause is 49 y. Strengths of the present study include the large number of subjects of both genders, their wide age range.

In conclusion, by correcting raw QCT vBMD results using CSE-MRI measurements of BMAT our findings revealed a better understanding of the relationship between BMAT and vBMD. Our approach provides a new tool for the fundamental study of the relationship between BMAT and bone mass.

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6 Tables

Women	N	Age (yr)	Weight (kg)	Height (cm)	BMI (kg/m^2)
20-39 y	59	30.8 (4.0) (22-39)	59.9 (8.1) (45-85)	161.1 (4.9) (147-171)	23.1 (3.1) (16.1-35.4)
40-59 y	72	52.6 (5.6) (42-59)	64.6 (9.5) (47-88)	159.2 (6.7) (140-178)	25.5 (3.6) (19.3-34.9)
60-80 y	102	67.5 (6.0) (60-80)	62.9 (9.7) (44-94)	156.0 (5.5) (140-171)	25.9 (3.9) (18.0-37.9)
Men					
20-39 y	49	32.7 (4.0) (21-39)	79.8 (14.5) (56-120)	172.8 (6.2) (156-187)	26.7 (4.1) (19.6-38.3)
40-59 y	53	49.6 (7.0) (40-59)	74.5 (10.3) (58-100)	169.8 (5.9) (150-181)	25.8 (3.1) (19.9-32.3)
60-80 y	65	66.7 (5.3) (60-82)	74.5 (12.2) (54-116)	169.2 (5.8) (158-187)	26.0 (3.5) (18.9-37.9)

TABLE 1

N: number of subjects in each age group; BMI: body mass index = weight (kg)/(height (m))^2. The numbers in each cell are the mean for that age group followed by the standard deviation and range of values in brackets.

Women	N	BMAT (%) (L2-L4)	$vBMD_{ESPcorr}$ (mg/cm^3) (L2-L4)	$vBMD_{BMATcorr}$ (mg/cm^3) (L2-L4)	Difference (mg/cm^3)
20-39 y	59	29.3 (7.7) (13.4-46.8)	193 (31) (127-271)	203 (28) (146-273)	9.2 (5.4) (-1.9-21.5)
40-59 y	72	42.1 (8.3) (22.3-60.0)	131 (34) (65-226)	150 (30) (96-231)	18.8 (6.1) (4.5-31.5)
60-80 y	102	50.6 (7.3) (32.7-69.0)	79 (32) (5-169)	105 (29) (44-186)	25.7 (5.5) (12.6-39.8)
Men					
20-39 y	49	36.6 (6.2) (18.4-53.4)	170 (27) (88-221)	184 (24) (108-231)	14.4 (4.5) (1.6-26.2)
40-59 y	53	41.1 (6.9) (27.9-58.6)	137 (36) (63-227)	155 (33) (93-236)	18.0 (5.2) (8.1-31.8)
60-80 y	65	46.1 (9.5) (28.6-80.1)	105 (33) (29-187)	127 (28) (60-199)	22.0 (7.1) (8.8-47.0)

TABLE 2

N: number of subjects in each age group; BMAT: bone marrow adipose tissue in L2-L4 trabecular bone measured by magnetic resonance imaging; $vBMD_{ESPcorr}$: volumetric bone mineral density measured in L2-L4 trabecular bone after correction by European Spine Phantom; $vBMD_{BMATcorr}$: $vBMD_{ESPcorr}$ after further correction for BMAT; Difference (mg/cm^3): difference between ESP and $vBMD_{BMATcorr}$ results in units of (mg/cm^3). The numbers in each cell are the mean for that age group followed by the standard deviation and range of values in brackets.

Contribution of each author to the manuscript:
X.G.C.,W.T., and G.M.B. designed the study; K.L., W.L., Y.Z., and G.M.B. analyzed the data; G.M.B. made the figure and tables; X.G.C. and G.M.B. drafted the paper; all authors made contributions during the writing and revision of the manuscript; all the authors approved the final version of the manuscript.

7 Figures

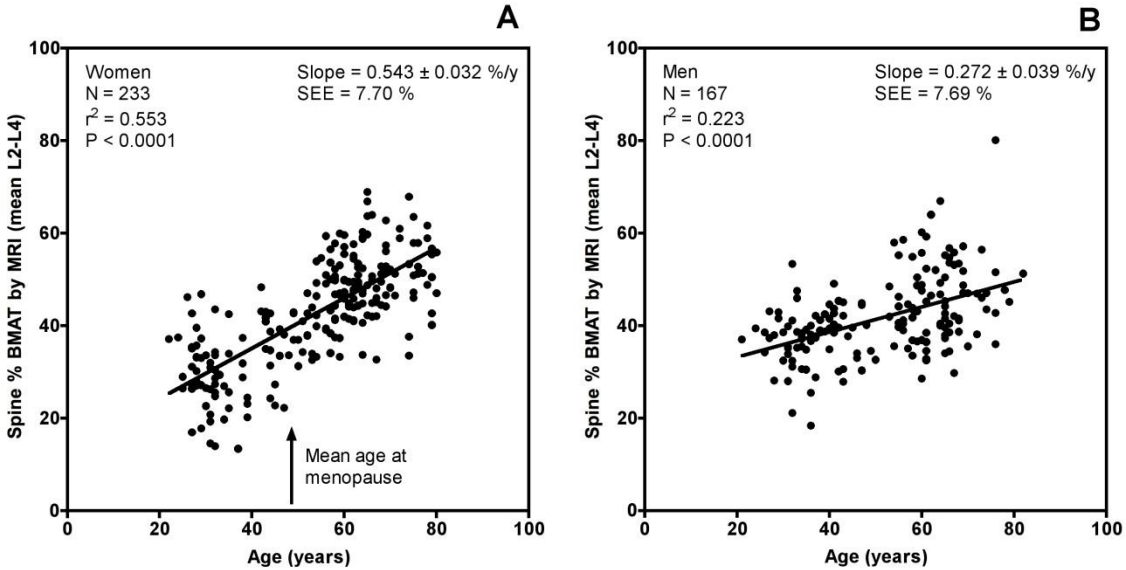

Fig. 1. Scatter plots of chemical shift-encoded magnetic resonance imaging measurements of bone marrow adipose tissue (BMAT) plotted against age. (A) Women; (B) Men. The fitted straight lines are the linear regression lines between ages 20 and 80 yr.

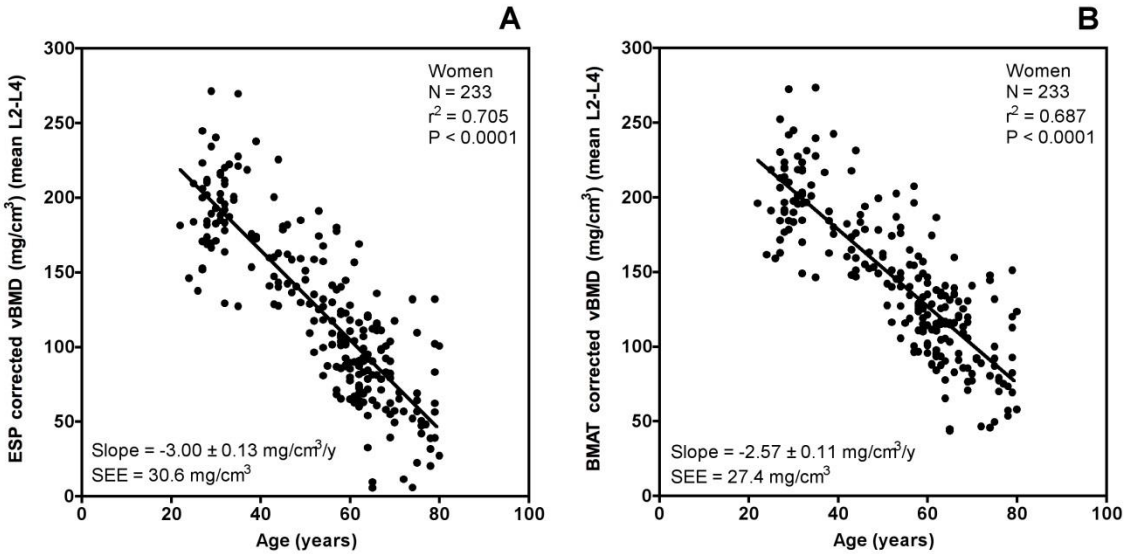

Fig. 2. Scatter plots of quantitative computed tomography measurements of volumetric bone mineral density (vBMD) plotted against age for the women in the study. (A) Plot with raw vBMD measurements standardized to the European Spine Phantom (ESP); (B) Plot after the data points in (A) have been corrected for the measurement errors caused by differences in bone marrow adipose tissue (BMAT). The fitted straight lines are the linear regression lines between ages 20 and 80 yr.

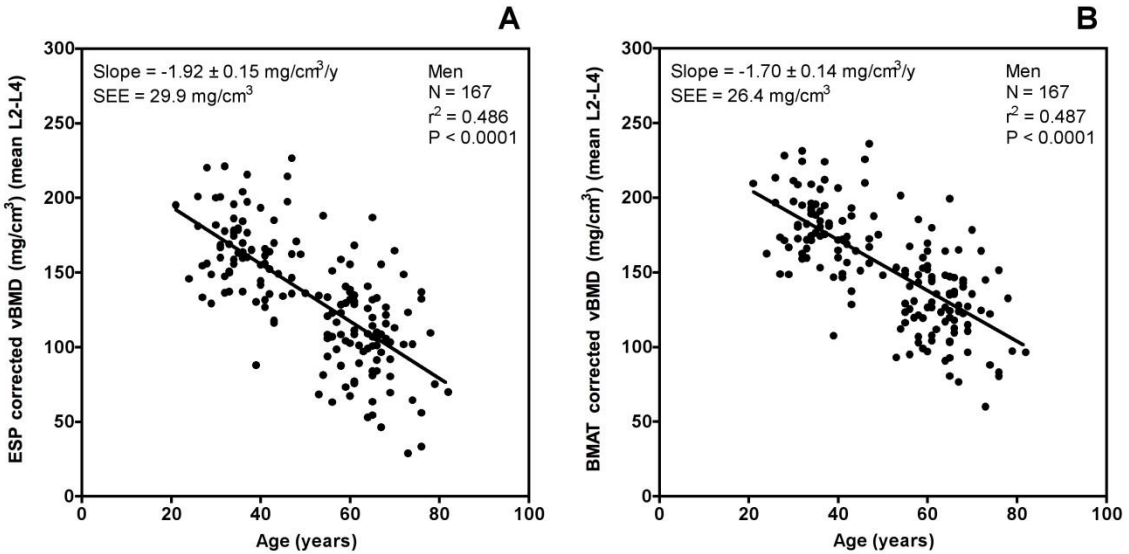

Fig. 3. Scatter plots of quantitative computed tomography measurements of volumetric bone mineral density (vBMD) plotted against age for the men in the study. (A) Plot with raw vBMD measurements standardized to the European Spine Phantom (ESP); (B) Plot after the data points in (A) have been corrected for the measurement errors caused by differences in bone marrow adipose tissue (BMAT). The fitted straight lines are the linear regression lines between ages 20 and 80 yr.

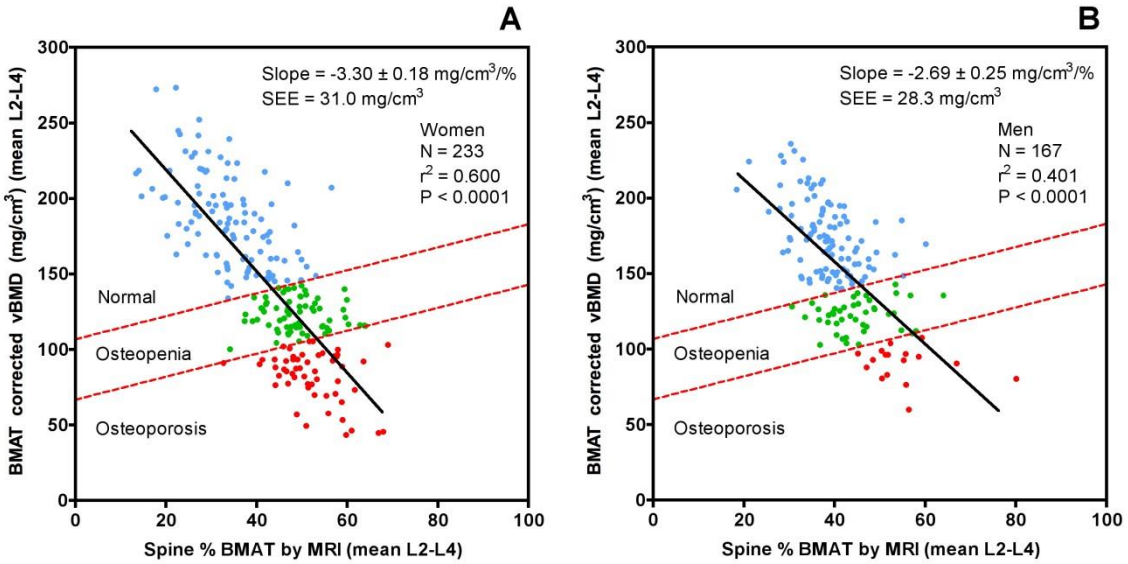

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Fig. 4. Scatter plots of QCT measurements of volumetric bone mineral density (vBMD) corrected for bone marrow adipose tissue (BMAT) plotted against BMAT. (A) Women; (B) Men. Red, green and blue dots show subjects with osteoporosis (uncorrected vBMD < 80 mg/cm^3), osteopenia (uncorrected vBMD 80-120 mg/cm^3) and normal vBMD (uncorrected vBMD > 120 mg/cm^3) respectively. Red dashed line show the thresholds of 80 and 120 mg/cm^3 after application of the BMAT correction. Straight blacks lines are the linear regression lines

We used MRI measurements of bone marrow composition to correct QCT measurements of spine bone mineral density and obtain the accurate relationship between spine BMD and bone marrow adipose tissue.