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Chronic Kidney Disease Is Associated With Greater Bone Marrow Adiposity

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Abstract

Bone marrow adiposity is associated with aging, osteoporosis, and reduced hematopoiesis, as well as anorexia nervosa, but little is known about the underlying mechanisms that affect marrow adiposity. Chronic kidney disease (CKD) may influence bone marrow adipose tissue (BMAT), possibly through loss of lean mass or higher circulating levels of sclerostin. To test these hypotheses, we investigated the cross-sectional association between estimated glomerular filtration rate (eGFR) as a measure of kidney function and ^{1}H-MRS-based measurement of vertebral BMAT (L1 to L4) in 475 older adults from the Age Gene/Environment Susceptibility (AGES)-Reykjavik study. Mean BMAT was compared in those with eGFR >60 (n = 297) versus those with eGFR 45 to 60 (n = 120) or eGFR <45 (n = 58) using linear regression models. Participants had a mean age of 81.5 (SD 4.1) years, mean eGFR of 64.3 (SD 16.1) mL/min/1.734 cm^2, mean BMAT of 54.5% (SD 8.5); 48.2% were women. In unadjusted and adjusted models (age, visit window, gender, diabetes and visceral adipose tissue), BMAT was higher in those with eGFR <45 (adjusted mean 58.5%; 95% CI, 56.2 to 60.7) compared with those with eGFR >60 (adjusted mean 53.8%; 95% CI, 52.8 to 54.8) (p = 0.0002). BMAT did not differ in those with eGFR 45 to 60 (adjusted mean 54.3%; 95% CI, 52.8 to 55.9) compared with those with eGFR >60 (p = 0.58). In a subgroup of

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Disclosure

The authors have no conflicts of interest to disclose.

participants with serum sclerostin available (n = 253), additional adjustment for sclerostin attenuated the difference in adjusted mean vertebral BMAT between those with eGFR <45 versus >60 from 3.7% (p = 0.04) to 2.4% (p = 0.20). CKD stage 3b or worse was associated with greater bone marrow adiposity; this association may be partially mediated by sclerostin. © 2018 American Society for Bone and Mineral Research.

Introduction

Bone marrow adiposity (BMA) is associated with aging, anorexia nervosa, impaired hematopoiesis, and osteoporosis.[1] In older adults, high vertebral bone marrow adipose tissue (vBMAT) is associated with low bone mineral density (BMD) and vertebral fractures,[2] although the underlying mechanisms remain incompletely understood. Although its physiologic importance is increasingly appreciated, little is known about the factors that influence the accumulation of BMAT. Impaired kidney function is associated with reduced lean mass and anemia; thus, we hypothesized it may also influence BMAT. One previous study reported higher vertebral BMAT (vBMAT) in those with chronic kidney disease (CKD) compared with age-matched healthy controls.[3] However, this study had a small sample size (n = 16) and did not include a full range of kidney function. The primary goal of the current study was to determine if impaired kidney function is associated with vBMAT in older adults enrolled in the Age Gene/Environment Susceptibility (AGES)-Reykjavik study.

A secondary goal was to assess whether lean mass or sclerostin are intermediaries in any association between kidney function and vBMAT. In states of severe caloric restriction, when other adipose depots are severely depleted, BMAT paradoxically expands. Advanced CKD is associated with a loss of lean body mass and protein energy wasting,[4,5] which may also influence BMAT. Thus, we hypothesized that lean body mass may be an intermediary in any association between CKD and BMAT.

In CKD, there is repression of the Wnt signaling pathway, which directs lineage allocation of skeletal stem cells toward the osteoblast at the expense of marrow adipogenesis.[6] Sclerostin, an osteocyte-derived Wnt signaling inhibitor, circulates at elevated levels in the setting of CKD; higher sclerostin levels may be associated with greater BMAT.[7] We hypothesized that sclerostin may be an intermediary in any association between CKD and BMAT. We used data from the AGES-Reykjavik study of older adults in Iceland to assess whether kidney function is associated with vBMAT, and whether lean mass or sclerostin might be an intermediary in any association.

Subjects and Methods

Participants

The AGES-Reykjavik study is a longitudinal, observational study of older adults in Iceland, designed to examine genetic susceptibility and gene/environment interactions contributing to phenotypes of old age.[8] The baseline AGES-Reykjavik visit, conducted from 2002 to 2006, included 5764 participants between the ages of 67 and 93. From 2007 to 2011, 3411 participants attended a second visit. Two subgroups of participants attending this second

visit were enrolled in the BMA ancillary study. The first subgroup was recruited from 2010 to 2011 from eligible participants. Eligibility criteria included no contraindication to MRI. Of the 403 participants that were approached to participate in the BMA study, 303 (subgroup A) enrolled and had measurements of BMAT at the time of their second AGES-Reykjavik visit. From November 2014 to August 2015, a second group was recruited for enrollment in AGES-BMA from the 3411 participants who attended the second AGES visit, but did not have BMAT measured. Of the 548 participants who were invited to participate in 2015, 241 (subgroup B) completed the BMA study visit. Thus, the BMAT measurement was obtained in 2010 to 2011 for subgroup A and in 2014 to 2015 for subgroup B. Of the 544 participants from subgroups A and B enrolled in the AGES-BMA study, 3 were excluded based on missing or inadequate BMAT measurements, and 66 participants were excluded for using medications known to affect BMAT, leaving 475 participants in the analytic sample. The ancillary study was approved by the National Bioethics Committee in Iceland, the National Instituteon Aging, and the University of California, San Francisco. All participants provided written informed consent.

Vertebral bone marrow adipose tissue

BMAT was measured with a 1.5-T MRI scanner (GE Healthcare, Milwaukee, WI) with an eight-channel cervical-thoracic-lumbar spine coil (using the three lower elements; GE Healthcare). Single-voxel magnetic resonance spectroscopy (MRS) was acquired in vertebral bodies from L1 to L4 using single-voxel proton MRS (^{1}H-MRS) based on a point resolved spectroscopy (PRESS) sequence. The PRESS box was positioned in the middle of the vertebral body and the PRESS-box size was kept the same for each vertebral level for all subjects.

The spectral data were analyzed with in-house developed software using a Lorentzian model fitting in time domain. Two peaks were identified, a water peak at 4.67 ppm and a lipid peak (bulk CH_2 methylene protons) at 1.3 ppm. The area under each peak was calculated, and BMAT was calculated as ratio of fat to water plus fat (%). The mean (L1 to L4) BMAT was used in this analysis. Daily quality-assurance testing was performed at the AGES-Reykjavik imaging center, in addition to weekly stability and calibration testing.

There was one software upgrade during the study period (2012) that occurred between the baseline visits for subgroup A (2010 to 2011) and B (2014 to 2015). For quality control purposes, 4 subjects were scanned before (May 2011) and after the software upgrade (March 2013).

The measured fat contents were significantly higher after the software upgrade as opposed to before the upgrade. The average difference was 3.4% ($P = 0.005$). Models included an adjustment for subgroup, which corresponded to measurement before or after the software upgrade.

Kidney function

For both subgroups, serum creatinine was measured from fasting blood samples obtained at the time of the BMAT measurement. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration)

equation.[9] Participants were stratified by eGFR >60, eGFR 45 to 60, and eGFR <45 in analyses.

Sclerostin

Sclerostin was measured in subgroup A using archived serum from fasting blood samples obtained at the time of the BMAT measurement in 2010 to 2011. Serum was stored at —80°C. Assays were obtained in one batch in 2012. Sclerostin was measured by ELISA (TECOmedical AG, Sissach, Switzerland)[10] at the Maine Medical Center Research Institute Laboratory (Scarborough, ME). Sclerostin measurements were not available for subgroup B.

Other measurements

Height and weight were measured by study personnel at the AGES-BMA study visit. An interviewer administered a questionnaire including demographics and history of medical conditions. Participants were asked to bring in all medications and supplements used in the previous 2 weeks, which were recorded and coded according to the Anatomical Therapeutic Chemical Classification System. Participants reporting current use of medications that affect BMAT (thiazolidinediones, oral glucocorticoids, hormone therapy, aromatase inhibitors, antiandrogens, and bisphosphonates) were excluded from this analysis. Fasting glucose was measured in serum obtained at the AGES-BMA study visit. Diabetes was defined by self-report, diabetes medication use, and/or fasting glucose > 7mMol/L at the study visit. Visceral adipose tissue (VAT) area (cm^2) was obtained by CT (Sensation; Siemens Medical Systems, Erlangen, Germany) using a 10-mm cross-section through the L4/L5 intervertebral space at 140 kilovolt peak (kVp), 330 milliamp seconds (mAs). The VAT compartment was first outlined manually. Analysis of abdominal images was carried out using a program adapted to characterize the VAT compartment. Lean body mass (g) of the arms and legs was obtained from whole-body DXA (GE Healthcare Lunar iDXA scanner, software version 11.4; GE Healthcare Lunar, Madison, WI). Appendicular lean mass index (ALMI) was calculated as [appendicular lean mass (arms + legs)/$height^2$] (kg/m^2).

CT measures of trabecular spine bone mineral density

QCT scans were obtained for the lumbar spine using a 4-detector CT system (Sensation; Siemens Medical Systems). A reference standard (3-sample calibration phantom; Image Analysis, Columbia, KY) was placed under the participant's spine and scanned simultaneously. The lumbar spine scanning included a helical study of the LI and L2 vertebrae (120 kVp, 150 mAs 1-mm slice thickness, pitch = 1). QCT images were transferred to a network of computer workstations and processed to extract measures of volumetric BMD using analysis techniques previously described.[11] Spine trabecular BMD was calculated from an elliptical region in the midvertebra.

Statistical analyses

Baseline characteristics of participants were summarized using means and SDs for continuous measures and counts and percentages for categorical measures. BMAT and eGFR were normally distributed. The least squares means procedure was used to determine the

association between the three eGFR categories (eGFR >60, 45 to 60, and <45) and vBMAT, with results presented as unadjusted or adjusted means and 95% CIs. Mean vBMAT was compared in those with eGFR >60 (reference group) versus those with eGFR 45 to 60 or eGFR <45 using linear regression models, both unadjusted and adjusted for age, subgroup (A or B), gender, diabetes, and VAT. These covariates were selected a priori based on known[1] or biologically plausible associations with BMAT and CKD. ALMI, trabecular spine BMD, and sclerostin were added to the adjusted models as potential intermediaries between CKD and BMAT. Interactions between continuous eGFR and gender were evaluated by including cross-products in the linear regression models. We found no evidence of interaction by gender for BMAT outcomes; therefore, results are presented for men and women combined. Because serum sclerostin measurements were obtained in subgroup A only, all analyses were repeated in this subgroup. All analyses were performed with SAS software (version 9.4; SAS Institute Inc., Cary, NC).

Results

Baseline characteristics of the cohort of 246 men and 229 women are presented in Table 1. Participants had a mean age of 81.5 (SD 4.1) years, mean eGFR of 64.3 (SD 16.1) mL/min/1.734 cm^2, and mean (L1 to L4) BMAT of 54.5% (SD 8.5). When stratified by eGFR category, 62.5% of the cohort had an eGFR >60 (mean 74.5 ± 8.6 mL/min/1.734cm^2),25.3% had an eGFR 45 to 60 (mean 53.1 ± 4.2 mL/min/1.734cm^2), and 12.2% had an eGFR <45 (mean 35.1 ± 8.4mL/min/1.734cm^2). Those with lower eGFR were significantly older, had a higher prevalence of diabetes, greater VAT, and higher serum sclerostin levels. There were no differences in gender, ALMI, or trabecular spine volumetric bone mineral density (vBMD) based upon category of kidney function. In this cohort, BMAT was not strongly associated with age ($r = 0.07$, $p = 0.29$ for men; $r = 0.02$, $p = 0.75$ for women), VAT ($r = 0.05$, $p = 0.43$ for men; $r = -0.1$, $p = 0.12$ for women), or diabetes (difference = 2.5%, $p = 0.14$ for men; 1.4%, $p = 0.53$ for women).

Greater BMAT was observed in those with eGFR <45 in both unadjusted and adjusted analyses, compared with eGFR >60 (Table 2 and Fig. 1). Compared with those with eGFR >60, there was no difference in BMAT in those with eGFR 45 to 60 in either unadjusted models or models adjusted for potential confounders including age, subgroup, gender, diabetes, and VAT. Adjustment for potential intermediaries including ALMI and trabecular spine vBMD did not alter the mean vBMAT by eGFR levels (Table 2 and Fig. 1).

In the analysis of subgroup A, as in the full cohort, BMAT was higher in those with eGFR <45 in both unadjusted and analyses adjusted for potential confounders (Table 2 and Fig. 2). The difference in the mean BMAT levels comparing eGFR <45 with eGFR >60 was 3.7% ($p = 0.04$) after adjustment for confounders. The addition of sclerostin attenuated this difference in mean vBMAT between those with eGFR <45 and those with eGFR >60 to 2.4% ($p = 0.20$).

Discussion

The physiologic importance of BMAT has been increasingly appreciated. BMAT is expanded in conditions such as aging, osteoporosis, anorexia nervosa, and with use of medications such as glucocorticoids and thiazolidendiones.[12] This study convincingly demonstrates that CKD is among the conditions associated with greater marrow adiposity in humans. In particular, we found those with eGFR <45 (CKD stage 3b to stage 5) had greater BMAT than those with eGFR >60, whereas BMAT for those with eGFR 45 to 60 (CKD stage 3a) did not differ from those with eGFR >60. The magnitude of difference in BMAT by eGFR category was relatively large. For example, the 4.9% difference in unadjusted mean BMAT between the groups with eGFR <45 versus >60 is similar to the 3.7% higher BMAT observed in individuals with versus without prevalent vertebral fracture in this cohort.[2]

Adjustment for potential confounders including age, gender, diabetes, and VAT did not change the magnitude of these associations. This is somewhat surprising given the reported associations between BMAT and these variables in other cohorts.[13,14] However, in the AGES-Reykjavik cohort these associations were only modest, perhaps as a result of the advanced age and relatively narrow age range of this cohort.

Our results are consistent with a previous report comparing vBMAT in a small sample of participants with CKD stages 3b to 4 ($n = 8$) and healthy controls ($n = 8$).[3] Those with CKD (mean eGFR 24 mL/min/1.734cm^2) had 13.8% higher (L2 to L4) vBMAT compared with the control group.[3] Participants in our study with eGFR <45 (mean eGFR 35 mL/min/1.734cm^2) had a mean (L1 to L4) vBMAT of 58.5%, which is similar to that reported in the 8 CKD subjects (57.8% at L2, 56.9% at L3, and 59.8% at L4). The magnitude of difference in vBMAT between the CKD subjects and controls was greater (13.8%) than the difference we observed (4.9%). This may be based on the younger age of the healthy control group (mean age 58.1 years) compared with participants in the present study (mean age 81.5 years), or the fact that the 8 CKD subjects were selected based on the presence of CKD-MBD (elevated PTH). To our knowledge, there are no other published reports evaluating the association between kidney function and BMAT.

In this study, adjustment for ALMI did not affect the difference in BMAT by eGFR category, suggesting that loss of lean body mass does not explain the expanded BMAT among individuals with CKD in this cohort. In this cohort, ALMI was not associated with eGFR. Protein energy wasting is typically described in end-stage renal disease (CKD stage 5, eGFR <15), whereas the mean eGFR was only 35 among our participants in the lowest category of kidney function. Our results suggest that ALMI is not an important intermediary in the relationship between eGFR and BMAT at the levels of kidney function observed in this cohort.

Adjustment for BMD did not attenuate our findings, but these models are difficult to interpret. BMD is not a confounder of the relationship between eGFR and BMAT because BMD is affected by eGFR. If BMD is an intermediary in this relationship, ie, if low BMD is a cause of higher BMAT, then it is appropriate to include BMD in the models. However, we think it is more likely that BMAT influences bone, ie, greater marrow adiposity leads to

lower BMD based on animal models.[15] If also true in humans, then BMD would be considered a “collider” in the relationship between kidney function and BMAT and should not be included in models. Adjusting for a collider, ie, BMD, may introduce bias into the association between eGFR and BMAT.[16] Thus, our finding that adjustment for BMD did not substantially alter the association between eGFR and BMAT can be interpreted as evidence that BMD is not playing an important intermediary role or that BMD is not an important collider in the association between eGFR and BMAT, depending on whether BMD primarily affects BMAT or vice versa.

In our subgroup analysis of participants in whom sclerostin measurements were available, adjustment for sclerostin modestly reduced the relationship between vBMAT and eGFR. We have previously reported in this cohort that higher sclerostin is associated with higher BMAT in men. A similar association was not observed in women.[7] In this present analysis, we found that higher sclerostin was associated with lower eGFR. Taken together, these results suggest that sclerostin may be a partial mediator in the relationship between kidney function and BMAT.

Sclerostin is an osteocyte-derived Wnt signaling inhibitor that circulates at higher levels in the setting of CKD, starting at CKD stage 3 (eGFR 30 to 60),[17] possibly providing one mechanism by which CKD is associated with greater BMAT. Bone marrow adipocytes and osteoblasts are derived from the same skeletal stem cell whose preferential differentiation toward the adipocyte lineage may occur at the expense of osteoblast formation.[18] Antagonized by sclerostin, the osteoanabolic Wnt/β-catenin signaling pathway influences skeletal stem cell fate and inhibits marrow adipogenesis.[6,18,19] As noted above, in the AGES-Reykjavik study, sclerostin levels were positively associated with BMAT in men.[7] Consistent with other published data, sclerostin levels were higher in men than in women in the AGES-Reykjavik cohort.[7,17] No other studies have reported the association between endogenous sclerostin levels and BMAT in older adults.

Kidney function may also influence BMAT through other pathways that we were not able to evaluate. PTH has been shown to decrease marrow adipogenesis in both mice and humans.[20] Clinical studies have shown that treatment with teriparatide reduces bone marrow adiposity in postmenopausal women[21] and men with idiopathic osteoporosis.[20] Skeletal resistance to the effect of PTH is implicated in low turnover bone disease, which has been increasingly recognized to occur in both early and advanced stages of CKD.[22,23] Elevated circulating FGF23, another osteocyte-derived Wnt signaling inhibitor, is also implicated in the pathogenesis of renal osteodystrophy.[24,25] Resistance to PTH and/or elevated FGF23 levels may explain other mechanisms by which CKD is associated with greater BMAT. In a prior study by Moorthi and colleagues, in which patients were selected based on the presence of both CKD and PTH levels above the reference range, there was no correlation between circulating PTH and BMAT.Toour knowledge, human studies of the association between FGF23 and BMAT have not been reported.

The strengths of this study include concurrent serum measurements of kidney function and ^{1}H-MRS measurements of BMAT in a large, well-characterized cohort of older adults with a range of kidney function that included both men and women. Results could be adjusted for

key potential confounders, including VAT. We were also able to explore potential mediators including sclerostin.

The study also has important limitations. This is an observational study; therefore, the presence of unmeasured or poorly measured confounders may have influenced our findings. This study has a cross-sectional design; hence, it is not possible to determine the temporal relationship between kidney function and BMAT. Also, the cohort was limited to older adults in Iceland; these results may not apply to younger ages or to other ethnic groups. We were unable to evaluate whether PTH and FGF23 act as intermediaries in the association between CKD and BMAT because these measurements were not available. Finally, our ability to determine whether sclerostin is a mediator in the association between CKD and BMAT was limited by the possibility that sclerostin levels may be greater in CKD based in part on the decreased clearance of circulating sclerostin. However, at least one study has demonstrated greater sclerostin expression in the setting ofCKD in both mouse and human bone.[26]

In conclusion, moderate-to-severe CKD (stage 3b to stage 5) is associated with greater bone marrow adiposity in older adults; this association may be partially mediated by elevated sclerostin. Further work is needed to investigate other possible mechanisms underlying this association.

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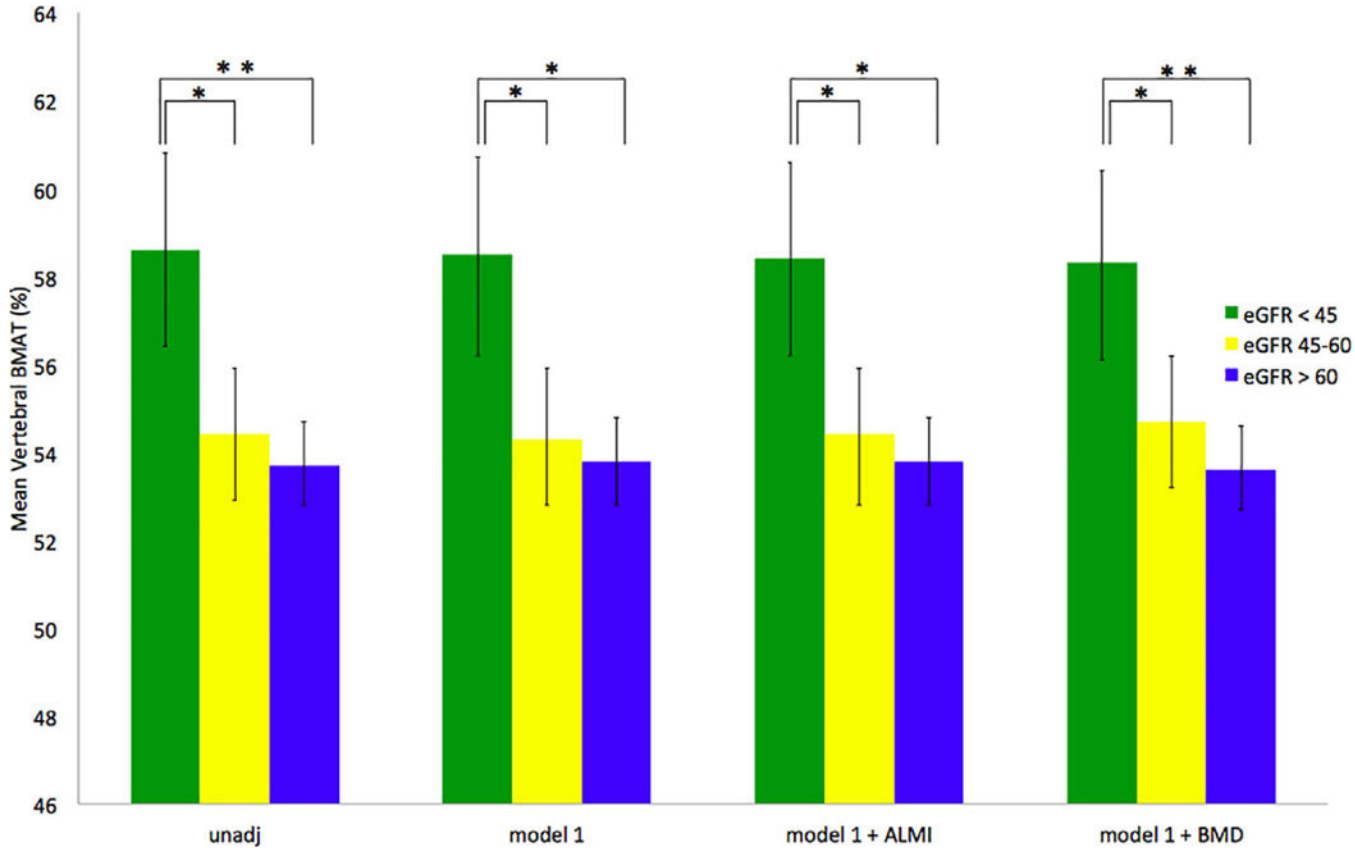

Fig. 1.

Comparison of mean (L1-L4) bone marrow adipose tissue (%) between those with eGFR<45 (n = 58) and those with eGFR 45–60 (n = 120) or eGFR >60 (n = 297). Model 1 adjusted for age, gender, subgroup (A or B), diabetes and visceral adipose tissue. ALMI = appendicular lean mass index; BMD = trabecular spine volumetric bone mineral density. *$p < 0.05$ **$p \leq 0.0001$.

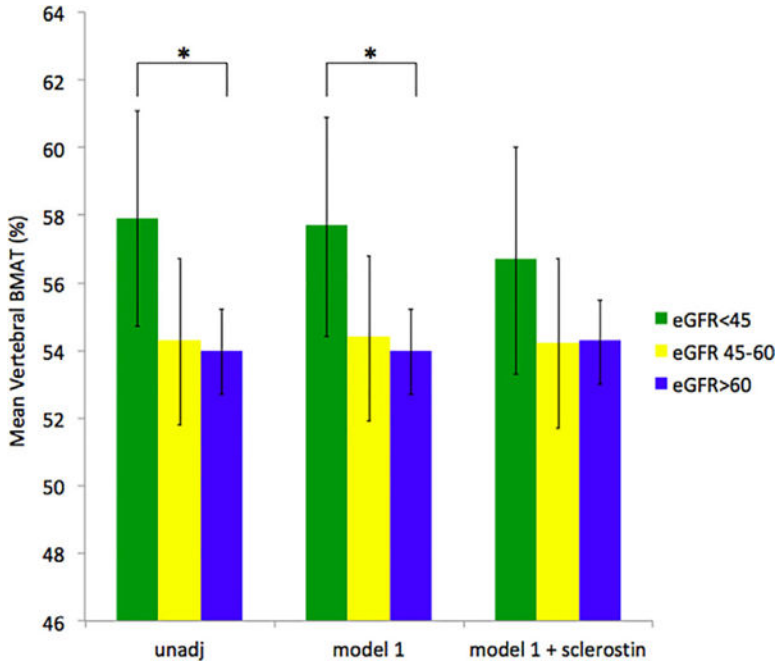

Fig. 2.

Comparison of mean (L1-L4) bone marrow adipose tissue (%) in subgroup A between those with eGFR <45 ($n = 27$) and those with eGFR 45–60 ($n = 46$) or eGFR > 60 ($n = 180$). Model 1 adjusted for age, gender, diabetes and visceral adipose tissue. *$p < 0.05$.

Table 1.

Baseline Characteristics

	eGFR <45 (*n* = 58)	**eGFR 45 to 60 (*n* = 120)**	**eGFR >60 (*n* = 297)**	***P*-value**
eGFR, mL/min/1.734 cm^2, mean ± SD	**35.1 ± 8.4**	**53.1 ± 4.2**	**74.5 ± 8.6**	**<0.0001**
Age, years, mean ± SD	**82.8 ± 4.3**	**82.9 ± 4.5**	**80.7 ± 3.7**	**<0.0001**
Male, *n* (%)	34 (58.6)	64 (53.3)	148 (49.8)	0.44
Subgroup A, *n* (%)	**27 (46.6)**	**46 (38.3)**	**180 (60.6)**	**0.0001**
BMI, kg/m^2, mean ± SD	27.9 ± 4.7	27.0 ± 3.3	27.1 ± 4.0	0.30
Appendicular lean mass index, kg/m^2, mean ± SD	7.0 ± 1.0	6.9 ± 0.9	6.9 ± 1.0	0.56
Visceral fat area, cm^2, mean ± SD	**227.7 ± 103.4**	**196.2 ± 76.4**	**188.4 ± 82.4**	**0.005**
Diabetes, *n* (%)	**12 (20.7)**	**14 (11.7)**	**20 (6.7)**	**0.003**
Sclerostin, ng/mL, mean ± SD (subgroup A only)	**1.37 ± 0.54**	**1.22 ± 0.48**	**0.94 ± 0.31**	**<0.0001**
Trabecular spine BMD, g/cm^3, mean ± SD	0.067 ± 0.034	0.074 ± 0.036	0.069 ± 0.032	0.37
Average BMAT (L1-L4), %, mean ± SD	**58.6 ± 7.1**	**54.4 ± 8.4**	**53.7 ± 8.7**	**0.0003**

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Table 2.

Vertebral BMAT (%) by eGFR Category

	Full cohort			Subgroup A		
eGFR	**Mean**	**95% CI**	***p*-Value**	**Mean**	**95% CI**	***p*-Value**
Unadjusted						
<45	**58.6**	**56.4, 60.8**	**0.0001**	**57.9**	**54.7, 61.1**	**0.03**
45–60	54.4	52.9, 55.9	0.46	54.3	51.8, 56.7	0.84
>60	53.7	52.8, 54.7	REF	54.0	52.7, 55.2	REF
Model 1[a]						
<45	**58.5**	**56.2, 60.7**	**0.0002**	**57.7**	**54.4, 60.9**	**0.04**
45–60	54.3	52.8, 55.9	0.58	54.4	51.9, 56.8	0.78
>60	53.8	52.8, 54.8	REF	54.0	52.7, 55.2	REF
Model 1 plus sclerostin						
<45	N/A	N/A	N/A	56.7	53.3, 60.0	0.20
45 to 60	N/A	N/A	N/A	54.2	51.7, 56.7	0.97
>60	N/A	N/A	N/A	54.3	53.0, 55.5	REF
Model 1 plus ALMI						
< 45	**58.4**	**56.2, 60.6**	**0.0002**	**57.7**	**54.4, 61.0**	**0.04**
45 to 60	54.4	52.8, 55.9	0.57	54.4	52.0, 56.9	0.75
> 60	53.8	52.8, 54.8	REF	54.0	52.7, 55.2	REF
Model 1 plus BMD						
<45	**58.3**	**56.1, 60.4**	**0.0001**	**57.6**	**54.4, 60.8**	**0.03**
45 to 60	54.7	53.2, 56.2	0.25	55.1	52.7, 57.5	0.34
> 60	53.6	52.7, 54.6	REF	53.8	52.6, 55.0	REF

No evidence of interaction by gender; therefore, pooled results are presented. Bolded results indicate significance at $p < 0.05$ for comparison of mean BMAT for given eGFR category versus eGFR >60 (reference).

BMAT = bone marrow adipose tissue; eGFR = estimated glomerular filtration rate; ALMI = appendicular lean mass index; BMD = trabecular spine volumetric bone mineral density (g/cm3); Ref = reference; N/A = not applicable.

[a] Model 1: Adjusted for age, gender, diabetes, visceral adipose tissue, and subgroup (A or B) for full cohort.