Circulating sclerostin associated with vertebral bone marrow fat in older men but not women

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Introduction

- Marrow fat (MF) and bone density (BMD) are negatively correlated. Proposed mechanisms include 1) a shift in stem cell lineage allocation from osteoblasts towards adipocytes, and 2) an increase in osteoclast-promoting cytokines with greater MF.
- Sclerostin is expressed by osteocytes and reduces bone formation by inhibiting the Wnt/B-catenin pathway.
- Circulating sclerostin is also associated with higher BMD. However, the relationship between circulating sclerostin and MF is not known.
- Circulating sclerostin increases with weight loss but little is known about relationships with the separate compartments of fat and lean mass.

PRIMARY OBJECTIVE

To characterize the relationships between circulating sclerostin and MF, QCT measurements of hip and spine, and body composition parameters, we used data from the Iceland AGES-Reykjavik cohort of older adults.

Methods

COHORT

- 303 participants at AGES-Reykjavik follow-up visit had measurements of vertebral MF and hip/spine QCT.
- Participants with inadequate serum (N=3) or no MR (N=1) or use of bone-active medication (N=44) were excluded.
- 137 women and 118 men were included in analyses.

QUANTITATIVE COMPUTED TOMOGEAPHY (QCT)

- Scans were obtained for lumbar spine (L1 and L2, 120kVp, 150mAs, 1mm ST) and hip (140mAs, 1mm ST), mid-thigh (129kVp, 10mm ST) using 4-detector CT system (Sensation, Siemens Medical Systems, Erlangen, Germany).
- Cortical and trabecular volumetric BMDs (vBMDs) for vertebra and hip, vertebral compressive strength, hip geometry, subcutaneous fat at mid-femur and visceral fat at L4/L5 intervertebral space, and muscle attenuation at mid-thigh were calculated from QCT data.

PROTON MAGNETIC RESONANCE SPECTROSCOPY (^{1}H-MRS) FOR VERTEBRAL MF

- Single voxel Point Resolved Spectroscopy (PRESS) ^{1}H-MRS was acquired in vertebral bodies L1 to L4 using a 1.5 Tesla scanner (GE Healthcare, Milwaukee, WI) with an eight-channel spine coil (TR/TE = 2000/37ms, 64 averages without water suppression, voxel size = 12x12x20mm^3).
- Peak areas for water at 4.67ppm and fat at 1.3ppm were calculated using GE SAGE software. The average MFs (*Fat/(Fat+Water)*100%*) from all four vertebral levels were used in analyses.

DUAL-ENERGY X-RAY ABSORPTIOMETRY (DXA)

- Scans of lumbar spine, proximal femur and whole body were obtained with GE Healthcare Lunar iDXA scanner (software version 11.4).

ASSAY FOR SCLEROSTIN AND BONE TURNOVER MARKERS

- Serum was collected fasting and stored at -70°C.
- Sclerostin and markers for bone formation (amino-terminal propeptide of type 1 procollagen; P1NP) and bone resorption (serum C-terminal cross-linking telopeptide of type I collagen; CTX) were assayed in one batch.

STATISTICAL ANALYSIS

- Least square means of selected bone and body composition parameters were compared across tertiles of serum sclerostin level in a linear model adjusted for age, diabetes status, and BMI and ran separately by gender.
- P-values for linear trend across tertiles was used to assess association from models.

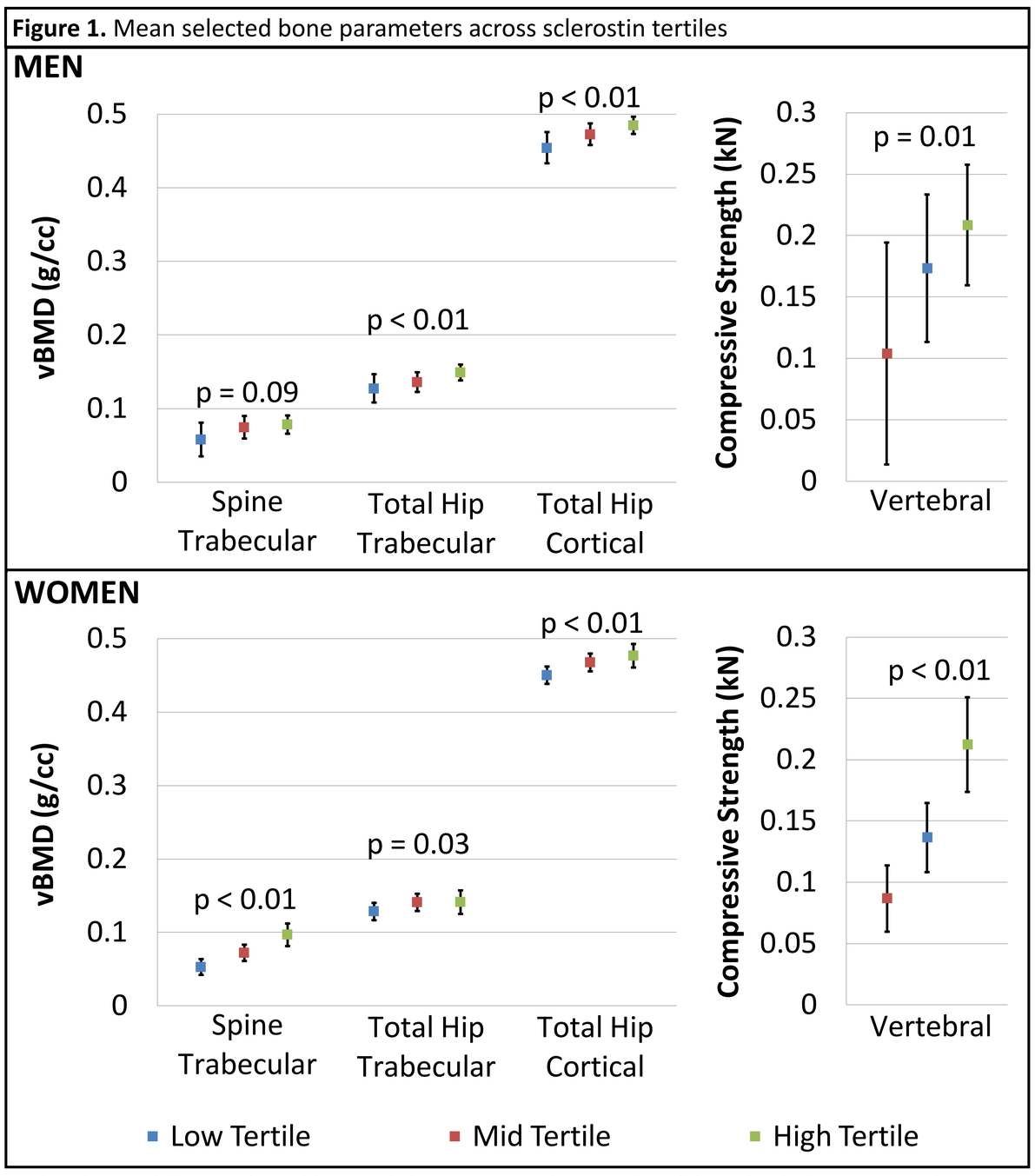
Results

Table 1. Descriptive analysis of participants included in analyses

	Men	Women
N	118	137
Age at BMA visit (year)	80.0 ± 3.1	78.6 ± 3.0
Diabetes	7 (5.9)	10 (7.3)
Marrow Fat (%)	53.5 ± 8.1	55.0 ± 8.4
BMI (kg/m^2)	27.2 ± 3.6	28.0 ± 3.9
Sclerostin (ng/mL)	1.27 ± 0.41	0.84 ± 0.27

Results are shown either as n(%) or mean±SD.

Figure 1. Mean selected bone parameters across sclerostin tertiles

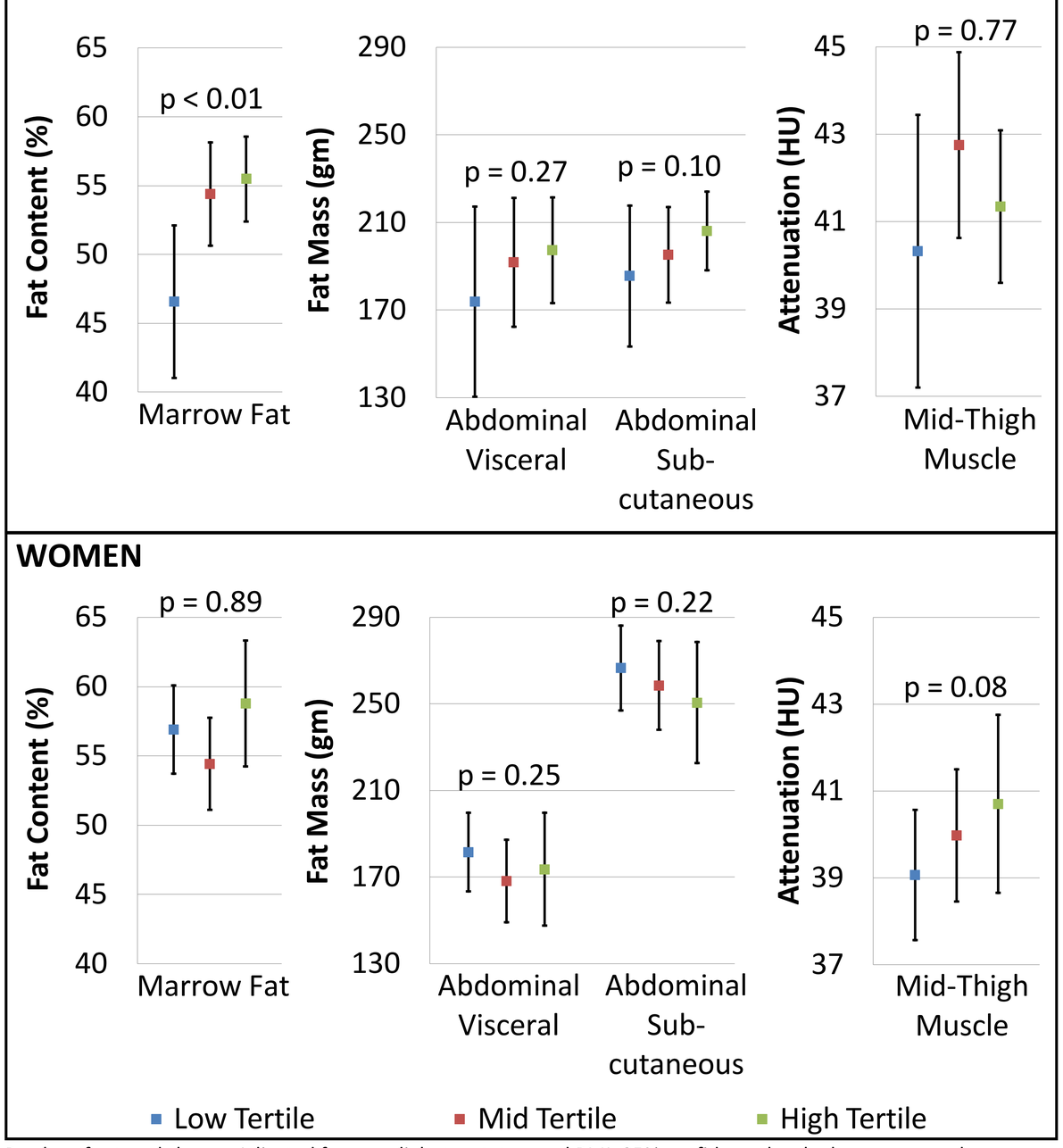


P-values for trend shown. Adjusted for age, diabetes status, and BMI. 95% confidence levels shown as error bars.

Results - Continued

- Total hip cortical and trabecular vBMD increased significantly with higher sclerostin for men and women (Figure 1).
- Spine trabecular vBMD increased significantly with higher sclerostin for women. The same positive trend, although not significant, was found in men (p=0.09) (Figure 1).
- Areal BMDs measured by DXA increased significantly across sclerostin tertiles at spine, femoral neck, and total hip for both men and women.
- Vetebral cross-sectional area (CSA) non-significantly increased with higher sclerostin for both men (p=0.23) and women (p=0.16).
- PINP and CTX were negatively associated with sclerostin in women, but not men.
- MF increased significantly with higher sclerostin in men, but not women (Figure 2).
- There was a trend towards positive association between sclerostin and body mass index (BMI) in women (p=0.09), and weight in men (p=0.06).
- Total fat and lean mass measured by DXA and abdominal visceral and subcutaneous fat mass measured by QCT were not significantly associated with sclerostin levels (Figure 2).
- Thigh muscle attenuation by QCT was not significantly associated with sclerostin levels (Figure 2). However, there was a positive trend for women (p=0.08).

Figure 2. Mean selected body composition parameters across sclerostin tertiles



P-values for trend shown. Adjusted for age, diabetes status, and BMI. 95% confidence levels shown as error bars.

Discussion

- As previous report showed a negative association between MF and BMD[1], it is surprising that sclerostin is positively associated with both MF and BMD in men. However, higher MF was also associated with prevalent vertebral fracture in the same cohort[1], independent of BMD. Sclerostin may be a marker of bone fragility, but this remains controversial.
- Previous reports on sclerostin and MF are not available. Further investigation is needed to understand the gender difference.
- Both trabecular and cortical vBMDs were positively associated with sclerostin, consistent with the only previous report on central QCT and sclerostin[2].
- Previous studies have reported positive[3,4,5] or no[6,7] association between sclerostin and weight or BMI. Another previous study found no association between sclerostin and lean mass or fat mass[7]. Interestingly, sclerostin increases in response to weight loss[8]. Longitudinal studies are needed to fully understand the relationship between sclerostin and body composition.
- A limitation of this study is that the cohort lacks racial and age diversity.

Conclusion

- MF is positively associated with circulating sclerostin levels in men, providing additional evidence that MF and bone formation are linked.
- Circulating sclerostin is positively correlated with both trabecular and cortical vBMDs.

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