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Association of serum sclerostin levels with low skeletal muscle mass: The Korean Sarcopenic Obesity Study (KSOS)

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ABSTRACT

Background: Sclerostin is an osteocyte-derived circulating protein that inhibits the Wnt/β-catenin signaling pathway. The Wnt signaling pathway plays an important role in bone and dysregulation of the Wnt signaling pathway results in insulin resistance, inflammation, and metabolic disturbance. The aim of our study was to investigate the implication of sclerostin in low muscle mass in healthy subjects.

Methods: The cross-sectional study analyzed 240 healthy non-diabetic subjects from the Korean Sarcopenic Obesity Study (KSOS). Low muscle mass was defined as the sum of the appendicular skeletal muscle mass divided by the square of height (ASM/height^2) as proposed by the Asian Working Group for Sarcopenia.

Results: Serum sclerostin was significantly higher in the low muscle mass group than the normal muscle mass group (151.3 [79.2-187.9] vs. 74.8 [47.6-119.6] pg/mL, $p = 0.001$). In the partial correlation analyses adjusted for age, sex, and body mass index, ASM/height^2 was negatively associated with sclerostin levels ($r = -0.245$, $p < 0.001$). Furthermore, sclerostin levels decreased linearly according to the first, second, and third tertiles of ASM/height^2 even after adjusting for sex, age, body mass index, life style parameters, fasting plasma glucose, bone mineral content (BMC), and total body fat mass.

Conclusions: Serum sclerostin levels were negatively correlated to skeletal muscle mass independent of confounding factors including BMC and total body fat mass.

1. Introduction

Sarcopenia and osteoporosis are important morbidities that cause social and economic burden in the aging society [1]. Sarcopenia is defined as age-related loss of skeletal muscle mass with decreased strength or physical performance [2]. The loss of skeletal muscle mass could lead to chronic condition such as cachexia, frailty, falls, fracture, hospitalization, and mortality [3]. Osteoporosis is a systemic bone disease characterized by low bone mineral density (BMD) and microarchitectural deterioration, with an increased bone fragility and risk of fracture [4]. Skeletal muscle mass and BMD have linear association [5]. In epidemiology study in England, 50% of postmenopausal osteoporotic women diagnosed with sarcopenia [6]. Numerous factors affect the muscle and bone, which include genetic polymorphisms, insulin-like growth factor-1, malnutrition, sex hormone, and diabetes [7].

The bone acts as an endocrine organ that secretes peptides or hormones that regulate distant organs through the action of chondrocytes and osteoblasts [8]. In particular, bone-specific factors including osteocalcin, fibroblast growth factor-23, and sclerostin may act as endocrine regulators on the connection of bone and muscle [9].

Sclerostin, the product of the *SOST* gene, acts as a negative regulator of Wnt/β-catenin pathway [10]. Several studies have suggested a role for sclerostin in muscle biology [11]. Recently, the Wnt/β-catenin pathway emerged as a mediator in metabolic disease; previous studies showed the interaction between sclerostin levels and metabolic disorder such as dyslipidemia, hypertension, type 2 diabetes (T2DM), and atherosclerosis [12–16].

The Wnt/β-catenin signaling pathway plays a significant role in skeletal muscle regeneration, insulin resistance, and glucose metabolism, sclerostin might be an important moderator of muscle mass. However, to the best of our knowledge, no studies have evaluated the relationship between high sclerostin levels and low muscle mass in humans. Therefore, the current study aimed to identify whether sclerostin level is correlated to skeletal muscle mass in healthy non-diabetic individuals using population-based cohort data.

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2. Materials and methods

2.1. Study population

We analyzed the baseline cross-sectional data of the non-diabetic subgroup from the Korean sarcopenic obesity study (KSOS), which is an epidemiologic prospective observational cohort that examined the prevalence of sarcopenic obesity (SO) in diabetic/non-diabetic adults in Korea and determined the effect of SO on the development of cardiometabolic diseases and various health outcomes. We recruited the participants using local and personal advertisement in Korea university hospital, Korea university health promotion center, and public health center, which is operated by the Korean government. The exclusion criteria of KSOS study were as follows: individuals with cardiovascular disease (myocardial infarction, unstable angina, stroke, or cardiovascular revascularization), resting blood pressure ≥ 160/100 mmHg, any malignancy, acute infection, or severe renal or hepatic impairment. A total of 354 participants without diabetes were enrolled between March 2013 and August 2018. After excluding individuals with age < 40 years; body mass index (BMI) < 18 or BMI ≥ 30 kg/m^2; use of anti-diabetes medications; use of osteoporotic medications; or missing data, the final analysis was performed on 240 participants. The self-questionnaire data were used to investigate smoking, alcohol, physical activity and medication history. Physical activity minimum three times a week were considered regular exercise. A written informed consent was obtained from each participant, and the study was conducted in accordance with the World Medical Association Declaration of Helsinki. The study protocol was approved by the institutional review board of Korea University.

2.2. Laboratory measurements

After a 12-hour overnight fast, blood samples were collected in the morning and were immediately stored at −80 °C. Measurements of biochemical parameters including fasting plasma glucose (FPG), total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C), high-sensitivity C-reactive protein (hs-CRP), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were described in our previous study [17]. Serum sclerostin concentrations were measured with the Human *SOST*/Sclerostin Quantikine ELISA Kit (R&D Systems Inc., Minneapolis, MN, the USA) in an independent commercial laboratory (Woongbee Meditech, Sungnam, Korea).

2.3. Body composition assessment

Whole body dual-energy X-ray absorptiometry (DXA) scan was performed to evaluate for body composition. Data includes total and regional lean mass (kg), total body fat mass (kg), and percent total body fat. Appendicular skeletal muscle mass (ASM [kg]) was defined as the sum of the lean soft tissue mass of the four limbs [18]. We used ASM adjusted by height(m) squared (ASM/height^2) as the skeletal muscle mass index (SMI), as proposed by the Asian Working Group for Sarcopenia, with the muscle mass cutoff points for low muscle mass was 7.0 kg/m^2 for men and 5.4 kg/m^2 in women [19]. BMI was calculated as weight (kg)/height in meters squared (m^2).

2.4. Bone mineral density

Anteroposterior lumber spine (L1–4) bone marrow content (BMC) and BMD measured using DXA (Discovery-W fan-beam densitometer, Hologic, Inc., MA, the USA). Osteopenia was defined as lumbar spine T-score between −1.0 and −2.5, and osteoporosis was defined as T-score ≤ −2.5 according to the World Health Organization T-score criteria.

2.5. Statistical analysis

Data are expressed as median (interquartile range) or number (percentage). All continuous variables were non-normally distributed, and specify the Shapiro-Wilk test. Categorical variables were analyzed with the chi-square test. To evaluate correlations between sclerostin levels as well as metabolic variables and body composition variables, Spearman partial correlation analysis was conducted after adjusting for age, sex, and BMI. In addition, we used analysis of covariance (ANCOVA) to compare serum sclerostin levels between tertiles of SMI after adjusting for age, sex, BMI, smoking status, alcohol consumption, regular exercise, FPG, BMC, and total body fat mass. ANCOVA was conducted on natural-log-transformed data because the distribution of sclerostin was skewed. Data were analyzed using SPSS software (version 20.0 for Windows; SPSS, Chicago, IL, the USA), two-sided p-value < 0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics of the participants

The baseline characteristics of the 240 participants are presented in Table 1. BMI, waist circumference, diastolic blood pressure, AST, ALT, creatinine, FPG levels, ASM/height^2, BMC, BMD, smoking, and alcohol consumption were higher in men than women. However, HDL-C, triglyceride levels, percent body fat mass, and prevalence of osteoporosis were higher in women than in men. No differences in age, systolic blood pressure, total cholesterol, low density lipoprotein cholesterol, hs-CRP, prevalence of hypertension, prevalence of dyslipidemia, and percentage of regular exercise between two sexes.

Table 1
Baseline characteristics of subject.

	Men (n = 96)	Women (n = 144)	p-Value
Age (years)	68.5 (55.5–73.5)	66.0 (59.5–71.0)	0.284
Body mass index (kg/m^2)	24.6 (23.5–26.2)	23.8 (22.2–25.8)	0.012
Waist circumference (cm)	85.0 (81.5–89.5)	79.0 (74.0–83.0)	< 0.001
SBP (mmHg)	126.0 (120.0–135.0)	127.0 (115.5–136.0)	0.732
DBP (mmHg)	83.0 (76.0–88.0)	80.5 (73.0–86.0)	0.028
AST (IU/L)	26.0 (22.5–30.0)	23.0 (20.0–28.0)	0.005
ALT (IU/L)	18.5 (14.0–26.5)	15.0 (12.0–20.0)	< 0.001
BUN (mg/dL)	15.1 (12.5–19.3)	15.4 (12.8–19.1)	0.989
Creatinine (mg/dL)	0.8 (0.7–0.9)	0.6 (0.6–0.7)	< 0.001
FPG (mg/dL)	98.0 (90.0–107.0)	94.0 (88.0–103.0)	0.022
Total cholesterol (mg/dL)	181.5 (154.0–210.1)	192.5 (163.0–216.0)	0.630
LDL-C (mg/dL)	100.5 (80.2–129.3)	109.6 (92.1–133.0)	0.080
HDL-C (mg/dL)	51.0 (41.0–59.0)	57.5 (49.0–67.0)	< 0.001
Triglyceride (mg/dL)	181.5 (154.0–210.1)	192.5 (163.0–216.0)	0.029
hs-CRP (mg/L)	0.7 (0.4–1.3)	0.6 (0.3–1.1)	0.201
ASM/height^2 (kg/m^2)	8.1 (7.5–8.6)	6.5 (6.0–7.1)	< 0.001
DXA-PFM (%)	24.8 (22.4–27.6)	34.4 (31.5–38.5)	< 0.001
BMC (g)	68.84 (59.69–82.03)	49.24(43.03–57.10)	< 0.001
BMD (g/cm^2)	0.98 (0.86–1.11)	0.85 (0.79–0.96)	< 0.001
Sclerostin (pg/mL)	96.8 (61.3–162.5)	64.9 (38.9–92.5)	< 0.001
Osteopenia (%)	33 (34.4%)	73 (50.7%)	< 0.001
Osteoporosis (%)	6 (6.2%)	26 (18.1%)	0.008
Hypertension (%)	40 (41.7%)	47 (32.6%)	0.154
Dyslipidemia (%)	30 (31.2%)	32 (22.2%)	0.118
Current smoker (%)	18 (18.8%)	1 (0.7%)	< 0.001
Alcohol consumption (%)	72 (75.0%)	34 (24.1%)	< 0.001
Regular exercise (%)	58 (60.4%)	74 (52.5%)	0.227

ALT, alanine aminotransferase; ASM, appendicular skeletal muscle; AST, aspartate aminotransferase; BMC, bone mineral content; BMD, bone mineral density; BUN, blood urea nitrogen; DBP, diastolic blood pressure; DXA, dual-energy X-ray absorptiometry; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; PFM, percent total body fat; SBP, systolic blood pressure.
Data are expressed as median (inter-quartile range) or n (%).

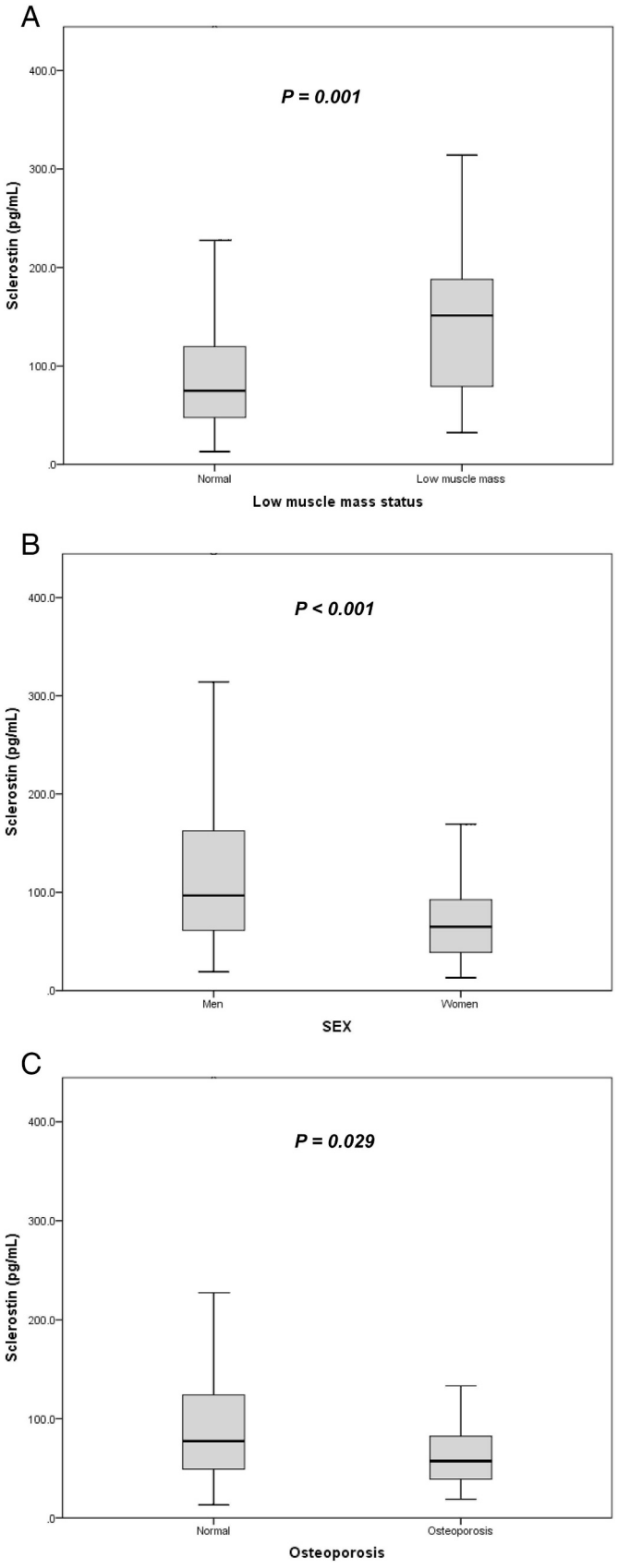

Fig. 1. Comparison of serum sclerostin level according to (A) low muscle mass status, (B) sex, and (C) osteoporosis. Low muscle mass was defined as appendicular skeletal muscle/height^2 < 7.0 kg/m^2 in men and < 5.4 kg/m^2 in women using dual-energy X-ray absorptiometry according to the Asian Working Group for Sarcopenia guidelines.

Table 2
Age- and BMI-adjusted Spearman partial correlation analysis of serum sclerostin with clinical and metabolic parameters and body composition parameters.

	Total		Men		Women	
	r	p	*r*	p	*r*	p
WC (cm)	−0.089	0.171	−0.153	0.141	−0.028	0.737
SBP (mmHg)	0.084	0.199	0.021	0.840	0.098	0.246
Total cholesterol (mg/dL)	0.034	0.598	0.072	0.489	0.011	0.895
Triglyceride (mg/dL)	0.115	0.077	0.075	0.470	0.153	0.069
LDL-C (mg/dL)	−0.004	0.957	0.047	0.652	−0.045	0.593
HDL-C (mg/dL)	−0.081	0.215	−0.166	0.111	−0.036	0.668
FPG (mg/dL)	−0.247	< 0.001	−0.329	0.001	−0.195	0.020
Creatinine (mg/dL)	0.178	0.006	0.013	0.899	0.275	0.001
hs-CRP (mg/L)	−0.002	0.979	−0.007	0.950	0.025	0.772
ASM/height^2 (kg/m^2)	−0.245	< 0.001	−0.410	< 0.001	−0.187	0.026
DXA-PFM (%)	0.274	< 0.001	0.411	< 0.001	0.284	0.001
BMC (g)	0.285	< 0.001	0.354	< 0.001	0.289	< 0.001
BMD (g/cm^2)	0.348	< 0.001	0.437	< 0.001	0.292	< 0.001

ASM, appendicular skeletal muscle; BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; DXA, dual-energy X-ray absorptiometry; FPG, fasting plasma glucose; HDL-C, high density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; LDL-C, Low density lipoprotein cholesterol; PFM, percent total body fat; SBP, systolic blood pressure; WC, waist circumference.

Men shows significantly higher sclerostin than women (median [interquartile range]: 96.8 [61.3–162.5] vs. 64.9 [38.9–92.5]) (Table 1, Fig. 1). In addition, the subjects with low muscle mass had higher sclerostin levels than subjects with normal muscle mass (151.3 [79.2–187.9] vs. 74.8 [47.6–119.6]). However, the participants with osteoporosis had lower sclerostin levels than healthy participants (57.4 [39.2–82.4] vs. 77.5 [49.1–124.2]) (Fig. 1).

3.2. Associations of sclerostin with clinical and metabolic parameters and body composition parameters

Table 2 shows the results of the partial correlation analysis of serum sclerostin levels and other metabolic parameters and body composition parameters. After adjusting for age, sex, and BMI, sclerostin level was inversely associated with FPG level ($p < 0.001$) and ASM/height^2 ($p < 0.001$) and positively associated with percent total body fat ($p < 0.001$) and BMC ($p < 0.001$) in the study population as a whole and in the men and women groups. However, creatinine was positively correlated with sclerostin level in the whole study population ($p = 0.006$) and the women group ($p = 0.001$).

3.3. Sclerostin level according to skeletal muscle mass status

ANCOVA was performed to elucidate the impact of sclerostin level on skeletal muscle mass (Table 3). In the unadjusted model, the log transformed sclerostin value was highest in the lowest SMI tertile group compared with higher tertile groups, and linearly decreased with SMI tertile (Least square mean of sclerostin was 4.50, 4.33, and 4.12 in the first, second, and third tertile of SMI). The association between sclerostin and SMI was consistent even after additional adjustment for sex, age, BMI, smoking status, alcohol consumption, regular exercise, FPG, BMC, and total body fat mass. The prevalence rate of low muscle mass was only 11.2% in all the participants.

4. Discussion

The study shows that osteocyte-derived sclerostin had a significant association with skeletal muscle mass. Importantly, sclerostin had

Table 3
Unadjusted and adjusted serum sclerostin levels by skeletal muscle mass index tertiles.

		Skeletal muscle mass index tertiles (%)						p-Value
		Q1		Q2		Q3		
		LSM	SE	LSM	SE	LSM	SE	
Sclerostin (pg/mL)	Unadjusted	4.50	0.08	4.33	0.08	4.12	0.08	0.002
	Adjusted							
	Model 1	4.49	0.07	4.34	0.07	4.12	0.07	0.001
	Model 2	4.50	0.07	4.34	0.07	4.12	0.07	0.003
	Model 3	4.49	0.08	4.34	0.07	4.10	0.08	0.002
	Model 4	4.51	0.07	4.31	0.06	4.12	0.07	0.001

BMI, body mass index; LSM, least square means; SE, standard error.
Model 1 was adjusted for sex and age. Model 2 was adjusted for sex, age, and BMI. Model 3 was adjusted for sex, age, BMI, smoking status, alcohol consumption, and regular exercise. Model 4 was adjusted for sex, age, BMI, smoking status, alcohol consumption, regular exercise, fasting plasma glucose, bone mineral content, and total body fat mass.

negative effects on skeletal muscle mass independent of age, sex, BMI, lifestyle parameters, FPG, BMC, and total body fat mass.

The bone regulates glucose and energy metabolism. Due to the increased clinical significance of osteoporosis and sarcopenia, the mechanisms of interaction between the bone and skeletal muscle mass have been examined recently. Previous studies demonstrated that lean mass and BMD are interconnected in both old men [20] and postmenopausal women [21]. Several factors that affect the muscle and bone were considered, which include genetic polymorphisms, malnutrition, obesity, estrogen, testosterone, growth hormone and diabetes [7]. However, the mechanisms involved in both sarcopenia and osteoporosis remain unclear.

The canonical Wnt signaling is one of the major component in skeletal muscle regeneration and myoblast differentiation [9]. When soluble Wnt ligands interact with frizzled and lipoprotein receptor-related protein 5/6 complex, the canonical Wnt pathway is activated. Subsequently stabilized β-catenin interacts with transcription factors such as T-cell factor-1 and lymphoid-enhancing factors-1, and contributes to skeletal muscle regeneration [22,23]. The present study showed that sclerostin levels correlated negatively with ASM/height^2. Moreover, Armamento-Vilareal et al. have shown that skeletal muscle mass was negatively correlated to the changes of sclerostin levels in older obese adults ($r = -0.24$, $p = 0.03$) [24]. However, the implication of Wnt signaling on the regulation of aged skeletal muscle is controversial. Krause et al. have revealed that *SOST* knockout mice had lower trabecular bone volume loss and higher bone marrow density and low lean muscle mass and significantly higher adipose tissue mass than wild-type mice. The authors have hypothesized that persistent sclerostin deficiency might have deleterious effect on the muscle regardless of its positive effects on the bone [25]. Furthermore, Brack et al. have indicated that the canonical Wnt pathway is associated with the fibrogenic changes in aging skeletal muscle and it accelerates aging process [26]. The difference might be associated with the pleiotropic roles of Wnt, and the Wnt pathway has complex interconnections with other pathways in skeletal muscle regeneration and myogenesis.

In addition, the Wnt pathway is one of the mechanisms associated with cardiometabolic disease, which a cluster of conditions that include abdominal obesity, hypertension, dyslipidemia, insulin resistance, and hyperglycemia [27]. Sclerostin regulates metabolic homeostasis and influences body composition. In mouse model, stimulated sclerostin production cause metabolic disturbance associated with increased fat mass [28]. Recent studies have emphasized the role of sclerostin on metabolic diseases. In patients with T2DM, those with atherosclerosis have shown higher serum sclerostin concentration than those without ($p = 0.006$). A 1 pmol/L increase in serum sclerostin level showed a 4% increased risk of developing atherosclerotic disease [13]. In postmenopausal women in Japan, circulating sclerostin levels have positive association with the proportion of abdomen, hip, breasts and thigh fat, markers of inflammation, LDL-C, uric acid, and homocysteine levels [12]. In a study of prediabetes participants, Daniele et al. have shown that sclerostin levels were significantly correlated to the index of insulin resistance ($r = 0.62$, $p < 0.001$) and higher sclerostin levels were observed in the impaired glucose regulation subjects than in the normal glucose tolerance subjects (50.8 ± 2.4 vs. 38.7 ± 2.3 pmol/L, $p = 0.01$) [15]. In accordance with previous studies, García-Martin et al. have presented that patients with diabetes have higher sclerostin levels than those with normal glucose tolerance [16]. Skeletal muscle is the primary organ responsible for insulin-related glucose homeostasis and low muscle mass could mediate insulin resistance [29]. Insulin resistance itself contributes to the pathophysiology of low muscle mass [30]. Hence, the Wnt signaling pathway could be a common pathology for sarcopenia and cardiometabolic disease. Measuring serum sclerostin level could be used to identify participants at risk of sarcopenia related to insulin resistance.

In our partial correlation analysis, sclerostin level was negatively correlated to FPG level independent of sex, age, and BMI. This finding contradicted the results of previous cross-sectional studies. A possible explanation for this unexpected negative correlation is the use of only one FPG measurement in non-diabetic participants in the study. FPG levels fluctuate, and a single value may not fully reflect glucose tolerance. Another possible reason is that the determination of T2DM was based on the answers of a questionnaire and the use of antidiabetic medications, therefore, patients with undiagnosed diabetes but with a normal FPG level might have been enrolled. In accordance with our study, Yu et al. demonstrated that sclerostin level was not significantly associated with FPG levels in 1778 non-diabetic subjects. There was no causal relationship was observed between sclerostin levels and increased risk of T2DM over 7.5 years of follow up [31]. A large-scale longitudinal study should be conducted to elucidate the direction of causality in sclerostin and glucose homeostasis in healthy participants.

In the Spearman's correlation analysis, an association of age and BMI with sclerostin was not found. Previous studies have reported inconsistent results about their relationship. Moreover, we analyzed sclerostin levels according to sex and presence of osteoporosis. Men have shown higher serum sclerostin levels than women, as previously reported [32]. Sclerostin could reflect whole-body skeleton, and men produces a higher sclerostin level than women due to their high skeletal mass. Furthermore, estrogen suppresses the effects of sclerostin. Mirza et al. have reported that premenopausal women had lower sclerostin values than postmenopausal women [33]. Although serum sclerostin inhibits osteoblastic activity and bone formation; our participants with osteoporosis had lower sclerostin levels than the healthy participants ($p = 0.029$), which is consistent with previous studies that higher sclerostin levels are associated with higher BMD [34]. Serum sclerostin level could be used as a marker of osteocyte production [35]. Currently, it is still unclear whether circulating sclerostin bears any significance to

what is happening inside the skeleton. The relationship between sclerostin and muscle mass may be driven by the relationship between BMD and muscle mass, rather than a direct relationship between sclerostin and muscle mass. Considering the close relationship between muscle, bone, and body fat, the association between sclerostin and muscle mass could be affected by body composition. Interestingly, our study demonstrated sclerostin levels were negatively associated with skeletal muscle mass even after adjusting for confounding factors including BMC and total body fat mass.

Our study had several limitations. First, we cannot find a causality between sclerostin level and low muscle mass due to the limitation of cross sectional design. Second, we analyzed only Korean men and women, and our findings are based on relatively small sample size that is not representative of the Korean population. A large-scale study in various populations should be conducted to validate our results. Third, muscle strength and performance were not considered. Fourth, sclerostin was measured by immunoassay and that future studies should consider mass spectrometry. Finally, we could not observe sclerostin as an independent risk factor in low muscle mass due to the small number of individuals with low muscle mass in our cohort. Our study participants were relatively young and healthy, and a large study that include elderly population should be conducted. Nevertheless, this study also had strengths. To the best our knowledge, this study first assessed the association between serum sclerostin levels and skeletal muscle mass. We found that the independent relationship between high sclerostin level and low muscle mass.

5. Conclusion

High serum sclerostin levels are independently correlated to low muscle mass in non-diabetic men and women in Korea. Further studies required to explore the physiological relevance of circulating sclerostin as a local hormone within the muscle-bone unit.

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Author contributions

Study design: JAK and KMC. Study conduct: JAK, HJY, and KMC. Data collection: JAK and KMC. Data analysis: JAK, ER, YBL, SHH, HJY, and KMC. Data interpretation: JAK, HJY, and KMC. Drafting manuscript: JAK and KMC. Revising manuscript content: NHK, JAS, SGK, NHK, JAK and KMC. Approving final version of manuscript: NHK, JAS, SGK, NHK, and SHB. JAK and KMC takes responsibility for the integrity of the data analysis.

Declaration of competing interest

All authors state that they have no conflicts of interest.

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