EnM ENDOCRINOLOGY AND METABOLISM

Original Article

Endocrinol Metab 2024 Forthcoming.
https://doi.org/10.3803/EnM.2024.2100
pISSN 2093-596X · eISSN 2093-5978

Elevated Circulating Sclerostin Levels in Frail Older Adults: Implications beyond Bone Health

Ji Yeon Baek[1,*], Seong Hee Ahn[2,*], Il-Young Jang[1,*], Hee-Won Jung[1], Eunhye Ji[3], So Jeong Park[3], Yunju Jo[4], Eunju Lee[1], Dongryeol Ryu[4], Seongbin Hong[2], Beom-Jun Kim[5]

[1]Division of Geriatrics, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul; [2]Division of Endocrinology and Metabolism, Department of Internal Medicine, Inha University Hospital, Inha University College of Medicine, Incheon; [3]Asan Institute for Life Sciences, Asan Medical Center, University of Ulsan College of Medicine, Seoul; [4]Department of Biomedical Science and Engineering, Gwangju Institute of Science and Technology, Gwangju; [5]Division of Endocrinology and Metabolism, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Background: Sclerostin, initially recognized for its pivotal role in bone metabolism, has gained attention for its multifaceted impact on overall human health. However, its influence on frailty—a condition that best reflects biological age—has not been thoroughly investigated.

Methods: We collected blood samples from 244 older adults who underwent comprehensive geriatric assessments. Sclerostin levels were quantified using an enzyme-linked immunosorbent assay. Frailty was assessed using two validated approaches: the phenotypic model by Fried and the deficit accumulation frailty index (FI) by Rockwood.

Results: After controlling for sex, age, and body mass index, we found that serum sclerostin levels were significantly elevated in frail individuals compared to their robust counterparts ($P<0.001$). There was a positive correlation between serum sclerostin concentrations and the FI ($P<0.001$). Each standard deviation increase in serum sclerostin was associated with an odds ratio of 1.87 for frailty ($P=0.003$). Moreover, participants in the highest quartile of sclerostin levels had a significantly higher FI and a 9.91-fold increased odds of frailty compared to those in the lowest quartile ($P=0.003$ and $P=0.039$, respectively).

Conclusion: These findings, which for the first time explore the association between circulating sclerostin levels and frailty, have significant clinical implications, positioning sclerostin as one of potential blood-based biomarkers for frailty that captures the comprehensive physical, mental, and social aspects of the elderly, extending beyond its traditional role in bone metabolism.

Keywords: Sclerostin; Frailty; Aging; Biomarkers

Received: 17 July 2024, **Revised:** 5 August 2024, **Accepted:** 7 August 2024

Corresponding author: Beom-Jun Kim
Division of Endocrinology and Metabolism, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea
Tel: +82-2-3010-5876, **Fax:** +82-2-3010-6962, **E-mail:** umkbj0825@amc.seoul.kr

*These authors contributed equally to this work.

INTRODUCTION

In a super-aging society, where the proportion of elderly individuals is rapidly increasing, frailty emerges as a critical public health issue due to its association with adverse health outcomes such as disability, hospitalization, and mortality [1,2]. The "phenotypic frailty" model and the "frailty index" are the most commonly used tools for assessing frailty, each offering distinct characteristics [3]. The phenotypic frailty model, based on observable clinical criteria such as weight loss, exhaustion, and physical activity, provides a straightforward approach to identifying frail individuals [4]. Conversely, the frailty index utilizes a cumulative deficit model, encompassing a broad range of health deficits including comorbidities, disabilities, and laboratory abnormalities [5]. Both tools have their respective advantages and limitations [3]; the phenotypic model is simple and easy to apply in clinical settings, while the frailty index offers a comprehensive and nuanced assessment. Therefore, these complementary tools should be employed in biomarker discovery research to identify high-risk frailty groups and support healthy aging initiatives.

Sclerostin is a glycoprotein primarily expressed in osteocytes that has garnered significant attention for its role in inhibiting bone formation by serving as a negative regulator of the Wnt signaling pathway [6]. Beyond its local effects on bone tissue, sclerostin has been reported to function hormonally in non-skeletal tissues such as adipocytes, vessels, muscles, and kidneys, where it influences endothelial function, energy homeostasis, glucose metabolism, physical performance, and kidney function [7-10]. This broader systemic role underscores its potential impact on overall health. Importantly, sclerostin circulates in the bloodstream as a secreted protein and can be easily measured, making it a promising biomarker for several age-related conditions, including osteoporosis, sarcopenia, and cardiovascular diseases [11-13]. However, despite the significant interest in sclerostin, the relationship between serum sclerostin concentrations and frailty—a condition that best reflects biological age—has not been thoroughly investigated. To bridge this gap, we conducted a clinical study to explore the association between circulating sclerostin levels and frailty, utilizing both the phenotypic frailty model and the frailty index in a cohort of older adults.

METHODS

Study participants

This clinical study involved Korean individuals aged 65 and older who underwent a comprehensive geriatric assessment (CGA) at the Division of Geriatrics or Endocrinology, Department of Internal Medicine, Asan Medical Center (AMC) in Seoul, Korea, from April 2019 to January 2021. The participants visited the clinic to evaluate non-specific symptoms such as fatigue and loss of appetite, which are common among older adults, or to manage chronic conditions like osteoarthritis, hypertension, and hyperlipidemia. They were ambulatory and community-dwelling individuals, not residing in nursing homes or hospitals. Exclusion criteria included the presence of end-stage renal disease, malignancies, or symptomatic heart failure with a life expectancy of less than 1 year. Blood samples were collected from 244 eligible participants during the CGA visit, following informed consent and exclusion of ineligible individuals. The study received approval from the AMC Institutional Review Board (no. 2020-0259) and complied with the ethical guidelines for human experimentation set forth by the Declaration of Helsinki. Written informed consent was obtained from all participants.

Comprehensive geriatric assessment

Experienced nurses conducted the CGA for each participant. Through detailed interviews and review of medical records, data on demographic characteristics, medical history, and surgical history were obtained. The assessment utilized previously validated CGA-frailty index variables [14], which cover geriatric domains such as comorbidities, functional status, physical performance, nutritional status, and common geriatric syndromes like cognitive dysfunction, depression, and polypharmacy.

The CGA included the assessment of 18 conditions considered multimorbidities: hypertension, stroke, peripheral vascular disease, myocardial infarction, heart failure, coronary artery disease, atrial fibrillation/flutter, angina, diabetes, depression, sensory impairment, degenerative spine disease, cancer within the past 5 years, chronic kidney disease (estimated glomerular filtration rate of <60 mL/min/1.73 m^2), chronic obstructive pulmonary disease, asthma, arthritis, and anxiety disorder.

Disability was defined as requiring assistance from another person to perform any of the seven activities of daily living (ADLs) (bathing/showering, toileting, getting in and out of bed, walking, grooming, dressing, and feeding) or seven instrumental ADLs (IADLs) (managing money, taking medications, doing housework, cooking, shopping, using transportation, and making telephone calls). Social frailty was assessed using a five-item social frailty questionnaire, which included items such as not talking with someone every day, being alone, feeling unhelpful to friends and family, rarely visiting friends' homes, and going out less frequently. Cognitive dysfunction was defined as

scoring less than 24 points on the mini-mental status examination for participants who tested positive on the mini-cognitive screening test. Depression was indicated by a score of 10 or more on the Korean version of the short form of the 15-item Geriatric Depression Scale for participants who screened positive on the patient health questionnaire-2 (PHQ-2).

Frailty assessment

Phenotypic frailty

Frailty was assessed using the Cardiovascular Health Study frailty criteria, a widely validated definition proposed by Fried et al. [4]. The frailty phenotype scale assigns a point for each of the following five components: unintentional weight loss, slowness, weakness, low physical activity, and self-reported exhaustion. The method used in our study for these assessments has been previously described [15]. Participants were classified as robust (0 points), prefrail (1–2 points), or frail (3–5 points) based on their total score.

Deficit accumulation frailty index

The frailty index, as proposed by Rockwood and Mitnitski [5], is a sensitive predictor of adverse health outcomes and is based on the cumulative effect of psychosocial, medical, and functional age-related deficits. In this study, we calculated a frailty index validated in other studies (see the complete list of assessed items in Supplemental Table S1) [14,16]. The ratio between the number of identified deficits and 50 evaluable items is calculated, ranging from 0 to 1, indicating that a higher frailty index corresponds to greater frailty.

Assessment of body composition and functional status

Body composition, encompassing muscle mass (total body lean mass excluding bone mineral content) and fat mass, was evaluated with a bioelectrical impedance analyzer (InBody S10, InBody, Seoul, Korea). This device uses measurement frequencies of 1, 5, 50, 250, 500, and 1,000 kHz [17]. To reduce the impact of recent food and water intake, participants fasted for over 8 hours prior to the assessment. Appendicular skeletal muscle mass (ASM) was determined by summing the muscle mass of both arms and legs. The skeletal muscle index (SMI) was calculated by normalizing ASM to the square of the participant's height, facilitating objective muscle mass comparisons [18].

Handgrip strength on the dominant side was gauged using the Jamar hydraulic hand dynamometer (Patterson Medical, Warrenville, IL, USA) [19]. Participants were seated comfortably, with their elbows bent at a 90º angle, and instructed to grip the dynamometer as forcefully as possible. Each test was conducted twice, with a minimum 1-minute interval, and the highest value was recorded. Usual gait speed was measured over a 4-m distance, and the time taken to complete five chair stands was also recorded. The short physical performance battery (SPPB) encompassed repeated chair stands, standing balance, and gait speed tests. In the standing balance test, participants attempted side-by-side, semi-tandem, and tandem stances, each for up to 10 seconds. An SPPB score ranging from 0 to 12 indicated the level of lower extremity function, with higher scores signifying better performance.

Sclerostin measurements in human serum

Blood samples were collected following at least 8 hours of overnight fasting. Post-centrifugation at 3,000 rpm for 5 minutes at 4°C, the supernatants were carefully separated to eliminate cell components. Samples exhibiting hemolysis or clotting were discarded. The serum samples were stored at −80°C prior to concentration analysis. Serum sclerostin levels were quantified using a competitive enzyme-linked immunosorbent assay (ELISA) kit (Cat. No. BI-20492, Biomedica, Vienna, Austria) per the manufacturer's protocol. The ELISA kit had a lower detection limit of 3.2 pmol/L and intra- and inter-assay coefficients of variation at 7% and 5%, respectively.

Statistical analysis

Data are expressed as mean±standard deviation or as numbers and percentages unless stated otherwise. Baseline characteristics of participants, categorized by phenotypic frailty status, were compared using analysis of variance with *post hoc* Tukey's honest significance test for continuous variables, and chi-square test for categorical variables. Analysis of covariance was employed to generate and compare estimated means with 95% confidence intervals for serum sclerostin levels by phenotypic frailty status and for the Rockwood frailty index by serum sclerostin quartiles, adjusting for sex, age, and body mass index (BMI). Associations between frailty-related factors and serum sclerostin levels were examined via linear regression analysis. Logistic regression was used to determine odds ratios (ORs) for phenotypic frailty relative to serum sclerostin level increases and quartiles. All statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA), with significance set at $P<0.05$.

RESULTS

Table 1 presents the baseline characteristics of the 244 study

Table 1. Clinical Characteristics of Study Participants according to Phenotypic Frailty Status

Variable	Robust (n=83)	Prefrail (n=135)	Frail (n=26)	P value
Sex				0.435
Male	15 (18.1)	22 (16.3)	7 (26.9)	
Female	68 (81.9)	113 (83.7)	19 (73.1)	
Age, yr	74.5±5.2	76.2±5.4	80.9±6.0[a]	<0.001
Weight, kg	56.7±8.7	57.4±10.4	53.5±8.5	0.168
Height, cm	155.5±6.4	153.7±6.8	150.4±6.8	0.003
BMI, kg/m^2	23.4±3.0	24.4±3.8	23.7±3.3	0.126
Serum albumin, g/dL	3.9±0.2	3.9±0.2	3.8±0.3	0.157
Frailty index (range, 0–1)	0.052±0.037	0.101±0.070[a]	0.236±0.109[a]	<0.001
Grip strength, kg	26.8±7.1	24.0±5.9[a]	18.3±5.9[a]	<0.001
Gait speed, m/sec	1.16±0.16	0.93±0.23[a]	0.62±0.24[a]	<0.001
Chair stand, sec	9.1±2.6	12.1±8.5[a]	19.4±15.2[a]	<0.001
SPPB score (range, 0–12)	11.6±0.8	10.5±1.9[a]	7.3±2.8[a]	<0.001
ASM, kg	15.0±3.1	14.3±2.9	12.9±3.0[a]	0.005
SMI, kg/m^2	6.27±0.87	6.02±0.83	5.64±0.79[a]	0.022
Sarcopenia	2 (2.4)	38 (28.1)	20 (76.9)	<0.001
Use of ≥5 prescription of drugs	29 (34.9)	69 (51.5)	22 (84.6)	<0.001
Multimorbidity	46 (55.4)	90 (66.7)	23 (88.5)	0.007
ADL disability	3 (3.6)	6 (4.4)	8 (30.8)	<0.001
IADL disability	0	12 (8.9)	15 (57.7)	<0.001

Values are expressed as number (%) or mean±standard deviation. P values were analyzed by analysis of variance (ANOVA) for continuous variables or chi-square test for categorical variables.
BMI, body mass index; SPPB, short physical performance battery; ASM, appendicular skeletal muscle mass; SMI, skeletal muscle index; ADL, activities of daily living; IADL, instrumental activities of daily living.
[a]P<0.05 vs. robust group by *post hoc* analysis using Tukey's method.

participants. According to Fried's criteria, the cohort consisted of 83 (34.0%) robust, 135 (55.3%) prefrail, and 26 (10.7%) frail older adults. The proportions of women in these groups were 68 (81.9%), 113 (83.7%), and 19 (73.1%) respectively (P=0.435). The mean ages for the robust, prefrail, and frail groups were 74.5±5.2, 76.2±5.4, and 80.9±6.0 years, respectively (P<0.001). No significant differences were observed between the groups in terms of weight, BMI, and serum albumin levels. Compared to the robust and/or prefrail groups, the frail group exhibited significantly lower height, grip strength, gait speed, SPPB score, ASM, and SMI (P<0.001 to 0.022). Additionally, the frail group had higher Rockwood frailty index scores, longer times to complete five chair stands, and greater prevalence of sarcopenia, polypharmacy, and multimorbidity (P<0.001 to 0.007). The frail group also showed higher rates of deficiencies in ADL and IADL (both P<0.001).

Before adjusting for sex, age, and BMI, the frail group had 52.4% and 45.2% higher serum sclerostin levels compared to the robust and prefrail groups, respectively (both P<0.001) (Fig. 1A). This statistical significance persisted even after adjustments (both P<0.001) (Fig. 1B).

Univariate linear regression analyses indicated that serum sclerostin levels were positively associated with the Rockwood frailty index and time to complete five chair stands, and inversely associated with gait speed (P<0.001 to 0.011) (Table 2). However, after adjusting for sex, age, and BMI, serum sclerostin concentration remained significantly correlated only with the frailty index (P<0.001), losing significance with other variables.

Multiple logistic regression analyses were conducted to explore the risk of frailty in relation to serum sclerostin levels, as detailed in Table 3. Before adjusting for confounders, the OR for frailty per standard deviation increase in serum sclerostin level was 2.17 (P<0.001). This increased risk of frailty associated with higher serum sclerostin levels remained significant

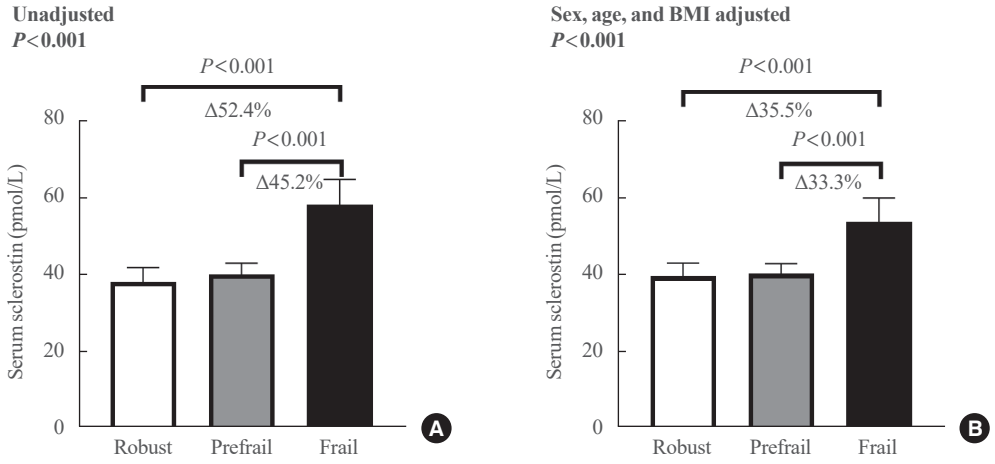

Fig. 1. Differences in serum sclerostin levels according to phenotypic frailty status (A) before and (B) after adjusting for sex, age, and body mass index (BMI). The estimated means with 95% confidence intervals were generated and compared using an analysis of covariance. *Post hoc* analysis was performed with Bonferroni correction. Delta (Δ) indicates a change in the value of a variable between groups. Phenotypic frailty is defined based on Fried's criteria.

Table 2. Association between Serum Sclerostin Levels and Frailty-Related Parameters before and after Adjusting for Sex, Age, and BMI

Frailty-related parameters	Unadjusted				Sex, age, and BMI adjusted			
	B	SE	β	*P* value	B	SE	β	*P* value
Frailty index[a]	0.002	0.000	0.354	<0.001	0.001	0.000	0.240	<0.001
Grip strength	0.047	0.024	0.126	0.052	–0.002	0.021	–0.005	0.934
Gait speed	–0.003	0.001	–0.225	<0.001	–0.002	0.001	–0.125	0.054
Chair stand	0.077	0.030	0.162	0.011	0.062	0.034	0.131	0.066

P values were analyzed by linear regression analysis before and after adjusting for sex, age, and BMI.
BMI, body mass index; B, unstandardized regression coefficient; SE, standard error; β, standardized regression coefficient.
[a]Frailty index is calculated based on the Rockwood's proposal.

Table 3. Odds Ratios for Phenotypic Frailty[a] according to the Increase in Serum Sclerostin Levels before and after Adjusting for Sex, Age, and BMI

Model	ORs per SD increments in serum sclerostin	95% CI	*P* value
Unadjusted	2.17	1.51–3.13	<0.001
Sex, age, and BMI adjusted	1.87	1.24–2.81	0.003

P values were analyzed by logistic regression analysis before and after adjusting for sex, age, and BMI.
BMI, body mass index; OR, odds ratio; SD, standard deviation; CI, confidence interval.
[a]Phenotypic frailty is defined based on the Fried's criteria.

even after adjusting for sex, age, and BMI (P=0.003).

To determine if there was a threshold effect between serum sclerostin levels and the Rockwood frailty index, participants were divided into four groups based on their serum sclerostin concentrations (Fig. 2). Participants in the highest sclerostin quartile (Q4, >49.9 pmol/L) had a frailty index at least 57% higher than those in the lowest quartile (Q1, ≤29.4 pmol/L), regardless of the adjustment model used (P<0.001 to 0.003). Additionally, logistic regression analyses of the unadjusted model showed that older adults in Q4 had a 17.6-fold higher OR for frailty compared to those in Q1 (P=0.007) (Fig. 3A). This elevated OR for frailty in the Q4 group remained statistically significant even after adjustments for sex, age, and BMI (P=0.039) (Fig. 3B).

DISCUSSION

In a cohort of ambulatory, community-dwelling older adults, we observed that circulating sclerostin levels were significantly

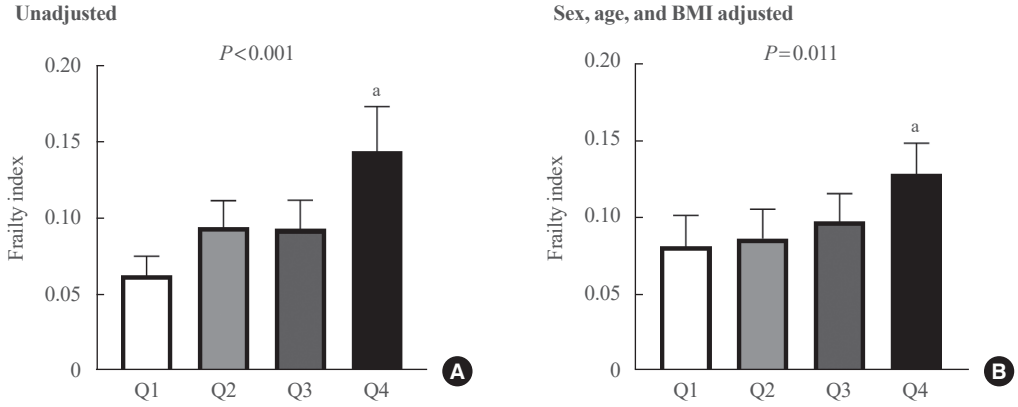

Fig. 2. Differences in the frailty index according to serum sclerostin quartiles (A) before and (B) after adjusting for sex, age, and body mass index (BMI). The estimated means with 95% confidence intervals were generated and compared using an analysis of covariance. *Post hoc* analysis was performed using Tukey's method. Serum sclerostin quartiles: Q1=13.6 to 29.4 pmol/L; Q2=29.5 to 37.9 pmol/L; Q3=38.0 to 49.8 pmol/L; Q4=49.9 to 138.8 pmol/L. The frailty index is calculated based on Rockwood's proposal. [a]Statistically significant difference from the lowest quartile (Q1).

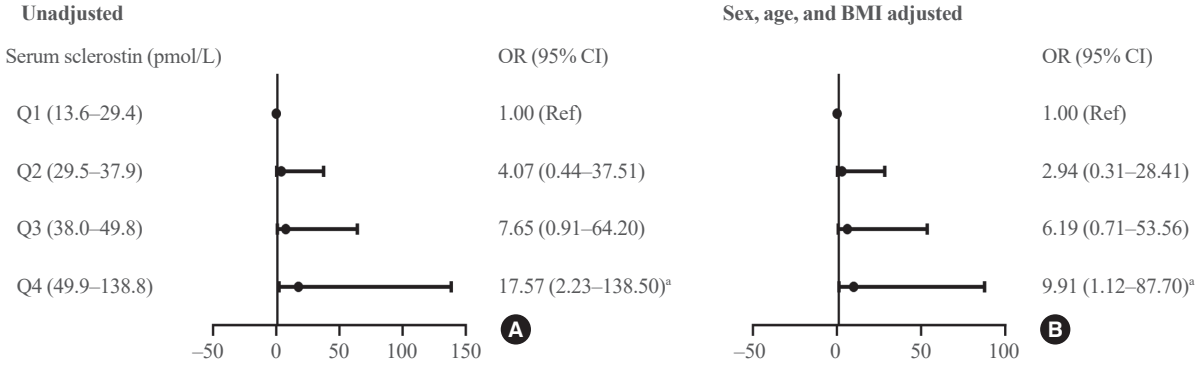

Fig. 3. Odds ratios (ORs) for phenotypic frailty according to serum sclerostin quartiles (A) before and (B) after adjusting for sex, age, and body mass index (BMI). *P* values were analyzed by logistic regression analysis before and after adjusting for sex, age, and BMI. Phenotypic frailty is defined based on Fried's criteria. CI, confidence interval. [a]Statistically significant difference from the lowest quartile (Q1).

higher in frail individuals, even after adjusting for sex, age, and BMI. Moreover, as serum sclerostin concentrations increased, there was a corresponding rise in both the frailty index and the risk of phenotypic frailty. This study is the first clinical investigation to examine the association between blood sclerostin levels and frailty. The findings have significant clinical implications, positioning sclerostin as one of potential blood-based biomarkers for frailty that captures the comprehensive physical, mental, and social aspects of the elderly, going beyond its traditional role in bone metabolism.

Sclerostin, initially recognized for its pivotal effects in bone metabolism through the inhibition of the Wnt/β-catenin signaling pathway, has significantly influenced the field of osteoporosis treatment with the development of romosozumab [6,20]. This therapeutic breakthrough exemplifies a quintessential 'bench to bedside' success story, demonstrating the translation of molecular biology insights into effective clinical therapies. In addition to its established role in skeletal health, sclerostin's expression in a variety of organs suggests a broader physiological relevance, implicating it in the regulation of systemic metabolic processes [10]. The inhibitory effects of sclerostin on the Wnt/β-catenin pathway, essential for cellular homeostasis, indicate its possible involvement in various physiologic and pathologic conditions in humans [7-9,21,22]. This multifaceted role underscores the potential of sclerostin not only as a therapeutic target but also as a biomarker for frailty, a geriatric syndrome characterized by an overall diminished physiological capacity, leading to increased vulnerability to various environmental and biological stressors [3].

The association between elevated circulating sclerostin levels

and increased frailty risk can be interpreted through various underlying mechanisms. Sclerostin inhibits the Wnt/β-catenin signaling pathway, which is crucial for maintaining cell proliferation, differentiation, and tissue regeneration, leading to impaired osteoblast function, decreased bone formation, and overall reduced skeletal integrity [6,23], which are critical components of frailty. Furthermore, the suppression of Wnt/β-catenin signaling by sclerostin may also negatively impact other tissues, contributing to diminished muscle strength, impaired cognitive abilities, and altered immune responses [24-27]. These deficits collectively reduce physiological resilience, a hallmark feature of frailty. Indirectly, elevated sclerostin levels may be indicative of broader systemic dysfunctions often associated with aging, such as chronic inflammation, endocrine changes, and decreased physical activity [28]. Chronic inflammation, for instance, can upregulate sclerostin expression, creating a feedback loop that exacerbates both bone resorption and systemic deterioration [29,30]. Hormonal imbalances, including reduced levels of sex hormones like estrogen and testosterone, are known to elevate sclerostin levels [31,32] and are also implicated in the pathophysiology of frailty. Moreover, reduced physical activity in frail individuals can lead to increased sclerostin production due to decreased mechanical loading of bones [33,34]. Therefore, there is a possibility that sclerostin could serve as a biomarker reflecting these cumulative age-related changes rather than a sole causative agent. Its elevated levels might signal an ongoing decline in multiple physiological systems, making it a valuable marker for identifying individuals at higher risk of frailty. Further research is essential to delineate whether sclerostin acts primarily as a mediator or an indicator of the complex interplay of processes leading to frailty, and to explore potential therapeutic interventions targeting this pathway to mitigate frailty in the older adults.

Although age-related sarcopenia is a key component of frailty [35], a previous study has shown that older adults with sarcopenia, particularly those with low muscle mass, have significantly lower serum sclerostin levels [12]. In contrast, our current study found that higher serum sclerostin levels are associated with an increased risk of frailty. This discrepancy creates considerable confusion regarding the clinical use of circulating sclerostin as a biomarker. It is well-established that bone is the primary source of sclerostin [6] and that bone and muscle undergo parallel changes throughout life [36]. In sarcopenia patients, reduced muscle mass leads to decreased mechanical stimulation of adjacent bones, resulting in reduced bone strength. To compensate for this bone fragility, there may be increased mechanical stimuli to other parts of the bone, reducing the expression of sclerostin. Additionally, recent report suggests that muscle tissue may also be a source of sclerostin [37]. Therefore, the decrease in muscle cell-secreted sclerostin in sarcopenia patients could contribute to the observed reduction in serum sclerostin levels. On the other hand, the association between higher sclerostin levels and increased frailty risk found in our study supports the notion that, once expressed, sclerostin may have a systemic negative impact on human health through various mechanisms. However, given the complex and context-dependent role of sclerostin, ongoing research is crucial to fully understand its implications.

The principal strength of our study is that we utilized both the phenotypic frailty and the Rockwood frailty index, highlighting the complementary nature of these two assessment tools. Phenotypic frailty, based on the Fried criteria, is widely favored in clinical and research settings due to its simplicity, efficiency, and focus on physical aspects, allowing for rapid evaluations [4]. On the other hand, the Rockwood frailty index, encompassing a broader range of deficits including cognitive, psychological, and social factors, is acknowledged as a more comprehensive tool [5]. Although it requires more time to administer, it is strongly correlated with adverse outcomes such as hospitalization, disability, and mortality, and it better reflects biological age [38-40]. By integrating both methodologies in our research, we uniquely explore the association between frailty and sclerostin. This dual approach not only enhances the reliability and depth of our findings but also differentiates our study from other frailty biomarker research.

Our study has several limitations that must be acknowledged. Firstly, due to its cross-sectional design, we are unable to determine a causal relationship between serum sclerostin levels and frailty, leaving it unclear whether sclerostin is a bystander or a direct contributor to the development of frailty. This issue could be overcome by conducting intervention studies to explore whether sclerostin-blocking antibodies can alleviate the onset or progression of frailty. We anticipate that our research will serve as a valuable foundation for these future investigations. Secondly, our study population was exclusively composed of Korean individuals, which limits the generalizability of our findings to other ethnic groups. Additionally, there are uncontrolled factors that may influence circulating sclerostin levels, potentially introducing bias into our results.

In conclusion, this study of individuals aged 65 and older revealed that serum sclerostin levels were significantly elevated in those with phenotypic frailty compared to those without, and these levels were positively associated with the frailty index.

Given that frailty is a multifaceted geriatric syndrome encompassing physical, mental, and social components, and serves as a key indicator of overall health and functional ability, our findings provide clinical evidence suggesting that sclerostin may play critical roles in maintaining various aspects of homeostasis in humans, beyond its known effects on bone metabolism. Future large-scale longitudinal studies are warranted to elucidate the potential of circulating sclerostin as a blood biomarker for predicting the onset or progression of frailty.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

This research was supported by grants from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: RS-2024-00401934); from the Asan Institute for Life Science, Asan Medical Center, Seoul, Republic of Korea (grant number: 2022IP 0072); and from the Young Medical Scientist Research Grant through the Seokchunnanum Foundation (grant number: SC-Y2306P).

AUTHOR CONTRIBUTIONS

Conception or design: J.Y.B., S.H.A., I.Y.J., B.J.K. Acquisition, analysis, or interpretation of data: J.Y.B., H.W.J., E.J., S.J.P., Y.J., E.L., D.R., S.H., B.J.K. Drafting the work or revising: J.Y.B., S.H.A., I.Y.J., B.J.K. Final approval of the manuscript: J.Y.B., S.H.A., I.Y.J., H.W.J., E.J., S.J.P., Y.J., E.L., D.R., S.H., B.J.K.

ORCID

Ji Yeon Baek *https://orcid.org/0000-0001-7547-8015*
Seong Hee Ahn *https://orcid.org/0000-0003-2558-2118*
Il-Young Jang *https://orcid.org/0000-0003-3617-3301*
Beom-Jun Kim *https://orcid.org/0000-0001-8591-1759*

REFERENCES

1. Vermeiren S, Vella-Azzopardi R, Beckwee D, Habbig AK, Scafoglieri A, Jansen B, et al. Frailty and the prediction of negative health outcomes: a meta-analysis. J Am Med Dir Assoc 2016;17:1163.
2. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013;381:752-62.
3. Lee H, Lee E, Jang IY. Frailty and comprehensive geriatric assessment. J Korean Med Sci 2020;35:e16.
4. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146-56.
5. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. J Gerontol A Biol Sci Med Sci 2007;62:722-7.
6. Baron R, Kneissel M. WNT signaling in bone homeostasis and disease: from human mutations to treatments. Nat Med 2013;19:179-92.
7. Wang JS, Mazur CM, Wein MN. Sclerostin and osteocalcin: candidate bone-produced hormones. Front Endocrinol (Lausanne) 2021;12:584147.
8. Dirckx N, Moorer MC, Clemens TL, Riddle RC. The role of osteoblasts in energy homeostasis. Nat Rev Endocrinol 2019;15:651-65.
9. Kocełak P, Puzianowska-Kuznicka M, Olszanecka-Glinianowicz M, Chudek J. Wnt signaling pathway and sclerostin in the development of atherosclerosis and vascular calcification. Adv Clin Exp Med 2024;33:519-32.
10. Dreyer TJ, Keen JA, Wells LM, Roberts SJ. Novel insights on the effect of sclerostin on bone and other organs. J Endocrinol 2023;257:e220209.
11. Lim Y, Kim CH, Lee SY, Kim H, Ahn SH, Lee SH, et al. Decreased plasma levels of sclerostin but not dickkopf-1 are associated with an increased prevalence of osteoporotic fracture and lower bone mineral density in postmenopausal Korean women. Calcif Tissue Int 2016;99:350-9.
12. Ahn SH, Jung HW, Lee E, Baek JY, Jang IY, Park SJ, et al. Decreased serum level of sclerostin in older adults with sarcopenia. Endocrinol Metab (Seoul) 2022;37:487-96.
13. Sanabria-de la Torre R, Gonzalez-Salvatierra S, Garcia-Fontana C, Andujar-Vera F, Garcia-Fontana B, Munoz-Torres M, et al. Exploring the role of sclerostin as a biomarker of cardiovascular disease and mortality: a scoping review. Int J Environ Res Public Health 2022;19:15981.
14. Kim DH, Afilalo J, Shi SM, Popma JJ, Khabbaz KR, Laham RJ, et al. Evaluation of changes in functional status in the year after aortic valve replacement. JAMA Intern Med 2019;

179:383-91.
15. Jang IY, Lee S, Kim JH, Lee E, Lee JY, Park SJ, et al. Lack of association between circulating apelin level and frailty-related functional parameters in older adults: a cross-sectional study. BMC Geriatr 2020;20:420.
16. Koo CM, Kim SH, Lee JS, Park BJ, Lee HK, Kim HD, et al. Cannabidiol for treating Lennox-Gastaut syndrome and Dravet syndrome in Korea. J Korean Med Sci 2020;35:e427.
17. Oh JH, Song S, Rhee H, Lee SH, Kim DY, Choe JC, et al. Normal reference plots for the bioelectrical impedance vector in healthy Korean adults. J Korean Med Sci 2019;34:e198.
18. Nga HT, Jang IY, Kim DA, Park SJ, Lee JY, Lee S, et al. Serum GDF15 level is independent of sarcopenia in older Asian adults. Gerontology 2021;67:525-31.
19. Roberts HC, Denison HJ, Martin HJ, Patel HP, Syddall H, Cooper C, et al. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. Age Ageing 2011;40:423-9.
20. Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, et al. Romosozumab treatment in postmenopausal women with osteoporosis. N Engl J Med 2016;375:1532-43.
21. Golledge J, Thanigaimani S. Role of sclerostin in cardiovascular disease. Arterioscler Thromb Vasc Biol 2022;42:e187-202.
22. Donham C, Manilay JO. The effects of sclerostin on the immune system. Curr Osteoporos Rep 2020;18:32-7.
23. Marini F, Giusti F, Palmini G, Brandi ML. Role of Wnt signaling and sclerostin in bone and as therapeutic targets in skeletal disorders. Osteoporos Int 2023;34:213-38.
24. Kim JA, Roh E, Hong SH, Lee YB, Kim NH, Yoo HJ, et al. Association of serum sclerostin levels with low skeletal muscle mass: the Korean Sarcopenic Obesity Study (KSOS). Bone 2019;128:115053.
25. Sclerostin secreted from bone mediates cognitive decline in the brains of aged and Alzheimer's disease mice. Nat Metab 2024;6:394-5.
26. Yuan J, Pedrini S, Thota R, Doecke J, Chatterjee P, Sohrabi HR, et al. Elevated plasma sclerostin is associated with high brain amyloid-β load in cognitively normal older adults. NPJ Aging 2023;9:17.
27. Sun M, Chen Z, Wu X, Yu Y, Wang L, Lu A, et al. The roles of sclerostin in immune system and the applications of aptamers in immune-related research. Front Immunol 2021;12:602330.
28. Iwamoto R, Koide M, Udagawa N, Kobayashi Y. Positive and negative regulators of sclerostin expression. Int J Mol Sci 2022;23:4895.
29. Gharbia O, Hegazy A, Elhelaly R, ElGhaweet A. Serum sclerostin in rheumatoid-induced osteoporosis. Egypt Rheumatol Rehabil 2020;47:22.
30. Jaskiewicz L, Chmielewski G, Kuna J, Stompor T, Krajewska-Wlodarczyk M. The role of sclerostin in rheumatic diseases: a review. J Clin Med 2023;12:6248.
31. Modder UI, Clowes JA, Hoey K, Peterson JM, McCready L, Oursler MJ, et al. Regulation of circulating sclerostin levels by sex steroids in women and in men. J Bone Miner Res 2011;26:27-34.
32. Di Nisio A, De Toni L, Speltra E, Rocca MS, Taglialavoro G, Ferlin A, et al. Regulation of sclerostin production in human male osteocytes by androgens: experimental and clinical evidence. Endocrinology 2015;156:4534-44.
33. Spatz JM, Wein MN, Gooi JH, Qu Y, Garr JL, Liu S, et al. The Wnt inhibitor sclerostin is up-regulated by mechanical unloading in osteocytes in vitro. J Biol Chem 2015;290:16744-58.
34. Koide M, Kobayashi Y. Regulatory mechanisms of sclerostin expression during bone remodeling. J Bone Miner Metab 2019;37:9-17.
35. Ji S, Jung HW, Baek JY, Jang IY, Lee E. Sarcopenia as the mobility phenotype of aging: clinical implications. J Bone Metab 2024;31:1-12.
36. Kim BJ. Beyond bone: embracing osteosarcopenia for comprehensive fracture prevention. Endocrinol Metab (Seoul) 2024;39:531-3.
37. Magaro MS, Bertacchini J, Florio F, Zavatti M, Poti F, Cavani F, et al. Identification of sclerostin as a putative new myokine involved in the muscle-to-bone crosstalk. Biomedicines 2021;9:71.
38. Theou O, Brothers TD, Mitnitski A, Rockwood K. Operationalization of frailty using eight commonly used scales and comparison of their ability to predict all-cause mortality. J Am Geriatr Soc 2013;61:1537-51.
39. Blodgett J, Theou O, Kirkland S, Andreou P, Rockwood K. Frailty in NHANES: comparing the frailty index and phenotype. Arch Gerontol Geriatr 2015;60:464-70.
40. Li X, Ploner A, Wang Y, Magnusson PK, Reynolds C, Finkel D, et al. Longitudinal trajectories, correlations and mortality associations of nine biological ages across 20-years follow-up. Elife 2020;9:e51507.

Supplemental Table S1. Items for Comprehensive Geriatric Assessment-Frailty Index

Medical history (21 items)
Angina
Anxiety disorder
Arthritis
Asthma
Atrial fibrillation/flutter
Cancer within 5 years
Chronic kidney disease (eGFR <60 mL/min/1.73 m^2)
COPD
Coronary artery disease
Degenerative spine disease
Dementia
Depression
Diabetes
Fall within the past year
Heart failure
Hypertension
Myocardial infarction
Peripheral vascular disease
Sensory impairment
Stroke/TIA
Use of ≥5 prescription drugs
Functional status (21 items)
Activities of daily living
Feeding
Dressing/undressing
Grooming
Walking (or use of a walker)
Getting in and out of bed
Toileting
Bathing or shower
Activities of daily living
Using telephone
Using transportation
Shopping
Preparing own meals
Housework
Taking own medications
Managing money
Nagi and Rosow-Breslau activities
Pulling or pushing a large object
Stooping, crouching or kneeling

(Continued to the next)

Supplemental Table S1. Continued

Lifting or carrying 10 lbs
Reaching arms above shoulder
Writing or handling small objects
Walking up/down a flight of stairs
Heavy work around house
Performance tests (4 items)
Mini-mental status examination
27–30 points (0 points)
24–26 points (0.3 points)
21–23 points (0.7 points)
<21 points (1 point)
5 Repeated chair stands
<11.20 sec (0 points)
11.20–13.69 sec (0.25 points)
13.70–16.69 sec (0.5 points)
16.70–60.90 sec (0.75 points)
≥61.0 sec (1 point)
Gait speed
≥1 m/sec (0 points)
0.80–0.99 m/sec (0.3 points)
0.60–0.79 m/sec (0.7 points)
<0.60 m/sec (1 point)
Dominant handgrip strength
M, ≥32 kg; F, ≥20 kg (0 points)
M, ≥26–31 kg; F, 16–19 kg (0.5 points)
M, <26 kg; F, <16 kg (1 point)
Nutritional status (3 items)
Weight loss >4.5 kg in past year
Body mass index <21 kg/m^2
Serum albumin <3.5 g/dL

eGFR, estimated glomerular filtration rate; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack; F, female; M, male.