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Original Research

Impact of 24-week concurrent training on bone parameters and plasma levels of osteoglycin and sclerostin in young, sedentary adults: secondary analyses from the ACTIBATE randomized controlled trial

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Abstract

Objective: To examine the effects of 24-week moderate (MOD-EX) and vigorous-intensity concurrent training (VIG-EX) on bone parameters and plasma levels of osteoglycin and sclerostin and their interplay with body composition and cardiometabolic risk factors in young, sedentary men and women.

Design: Secondary study from the ACTIBATE randomized controlled trial (ClinicalTrials.gov ID: NCT02365129).

Methods: This study was performed at the Sport and Health University Research Institute and the Virgen de las Nieves University Hospital of the University of Granada. Bone parameters were measured by dual-energy X-ray absorptiometry, and osteoglycin and sclerostin levels, by enzyme-linked immunosorbent assay.

Results: 145 young sedentary adults were assigned to a control (CON, $n = 54$), a MOD-EX ($n = 48$), or a VIG-EX ($n = 43$). 106 participants were included in the per-protocol analyses (CON, $n = 42$; MOD-EX, $n = 33$; and VIG-EX, $n = 31$). After 24 weeks of concurrent training, we observed no differences in changes in bone parameters (all P time × group ≥ .300), osteoglycin (P time × group = .250), and sclerostin levels (P time × group = .489). Moreover, we found no correlations between osteoglycin and sclerostin levels with body composition (all P ≥ .639) and cardiometabolic risk factors (all $P \geq .119$).

Conclusion: 24 weeks of concurrent training did not alter bone parameters, and plasma levels of osteoglycin and sclerostin in young, sedentary adults. Moreover, osteoglycin and sclerostin are not related with bone parameters and cardiometabolic risk factors in this population. These findings suggest that longer concurrent training interventions may be needed to enhance bone parameters in young, sedentary adults.

Keywords: bone remodeling, resistance training, endurance training, cardiometabolic health, glucose metabolism

Significance

Regular exercise enhances bone structural and endocrine function, potentially through modulating osteokines such as osteoglycin and sclerostin. However, the long-term effect of exercise training on bone parameters and both osteokines in young, sedentary adults is poorly understood. We found that 24 weeks of moderate- and vigorous-intensity concurrent training does not alter bone parameters and plasma levels of osteoglycin and sclerostin. Additionally, no associations were found between both osteokines and body composition or cardiometabolic risk factors. Baseline osteoglycin and sclerostin levels, rather than the concurrent training itself, may be more predictive of long-term changes in these osteokines in young, sedentary adults. More osteogenic interventions and/or longer concurrent training interventions may be needed to significantly enhance bone parameters in this population.

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Introduction

Regular exercise confers a myriad of health benefits and is a preventive and therapeutic "polypill' for non-communicable diseases.[1] Although there are multiple physiological and metabolic pathways underlying exercise health improvements in a tissue-specific manner, one emerging explanation involves the modulation of both the structural and endocrine function of the bone.[2] Exercise training interventions that incorporate moderate- or high-intensity progressive resistance or progressive high-impact exercises have been shown to enhance bone accrual and metabolism across the lifespan.[3] In addition to its structural role, the bone acts as an endocrine organ, regulating energy homeostasis and potentially modulating cardiovascular function and metabolism through the secretion of osteokines.[4] Identifying potential bone biomarkers associated with health could play a critical role in preventing and treating multiple chronic diseases.

Osteoglycin, a leucine-rich proteoglycan secreted by bone, skeletal muscle, and cartilage, is involved in cardiovascular function, glucose metabolism, and bone remodeling, possibly enhancing bone mineralization.[5,6] Acute moderate-intensity steady-state exercise and high-intensity interval exercise do not seem to alter serum osteoglycin levels in young adults.[7,8] In contrast, lower postprandial osteoglycin levels are associated with higher glucose and insulin levels,[7] but acute exercise prevents the postprandial decrease in osteoglycin levels after a high-glucose mixed meal in young adults, suggesting a mediating role of osteoglycin in post-exercise insulin sensitivity.[7] Thus, while osteoglycin is implicated in several physiological and metabolic processes, its specific roles and its interaction with exercise training in humans remain unclear.

Sclerostin, a glycoprotein secreted mainly by osteocytes, is an osteokine that downregulates the canonical Wnt/β-catenin signaling pathway, thereby suppressing osteoblast activity and reducing bone turnover.[9] Plasma sclerostin levels increase acutely and transiently following high-intensity interval exercise in healthy, young adults.[10] In contrast, endurance exercise training seems to decrease plasma sclerostin levels,[11] suggesting that this reduction may be one mechanism by which bone adapts to mechanical loading. Low sclerostin levels are related to enhanced body composition, cardiovascular function, and glucose metabolism.[12,13,14] Nevertheless, further research is needed to clarify its physiological and metabolic roles, and its interplay with exercise training in humans.

The long-term effect of exercise training on these osteokines both in men and women is poorly understood. Additionally, the relationship between osteoglycin and sclerostin levels and bone parameters, body composition, and cardiometabolic risk factors is still unknown. Therefore, this study aims to examine the effects of moderate- and vigorous-intensity concurrent training (VIG-EX) on bone parameters and plasma levels of osteoglycin and sclerostin and to study the relationship between these osteokines with body composition and cardiometabolic risk factors in young, sedentary adults. We hypothesized that both moderate- and VIG-EX improve bone parameters, increase osteoglycin levels, and decrease sclerostin levels, with more pronounced effects following vigorous-intensity training compared with moderate-intensity training. Moreover, we expected that baseline levels and changes in osteoglycin and sclerostin levels following the concurrent training interventions are associated with baseline measures and improvements in body composition and cardiometabolic risk factors in young, sedentary men and women.

Methods

Participants

A total of 145 young, sedentary adults aged 18-25 years old participated in the Activating Brown Adipose Tissue Through Exercise (ACTIBATE) study (Clinical- Trials.gov ID: NCT02365129; Figure 1).[15] Participants were recruited through social networks, local media, and posters in Granada, Spain. Inclusion criteria included (1) self-reporting as sedentary (ie, engaging in <20 min/day of moderate-to-vigorous physical activity on <3 days/week), (2) being a non-smoker, and (3) maintaining a stable body mass over the last 3 months. Exclusion criteria encompassed a diagnosis of diabetes, hypertension, or any significant medical condition that could interfere with or be aggravated by exercise, pregnancy, use of medication deemed to affect energy metabolism such as glucocorticoids, or frequent exposure to cold temperatures.[15]

Study design

This report includes secondary analyses from the single-center ACTIBATE randomized controlled trial (ClinicalTrials.gov ID: NCT02365129), of which the detailed study design is described elsewhere.[15] It follows the CONSORT guidelines (Table S1).

After baseline examinations, all participants were randomly assigned to 1 of 3 groups via computer-generated simple unrestricted randomization by the principal investigator[16]: (1) control group (CON; no exercise), (2) moderate-exercise intensity group (MOD-EX), and (3) vigorous-exercise intensity group (VIG-EX). The randomization was unblinded and performed by JRR using an in-house system, and no additional researcher had access to it. Participants were explicitly informed of their group assignment, and there was no delay between randomization and the start of the intervention. Rigorous standardization procedures for data collection and intervention were followed to ensure the internal and external validity of the trial.[17]

The study was conducted over 2 consecutive years in 4 different waves (from September 2015 to June 2016 and from September 2016 to June 2017) and concluded when the exercise intervention was completed. The study was carried out at the Sport and Health University Research Institute (iMUDS) and the Virgen de las Nieves University Hospital of the University of Granada. All participants were instructed not to change their daily routines, physical activity, and dietary patterns throughout the study period. No relevant changes were performed in the methodology or outcomes after the trial began, and no relevant adverse events were recorded. The study protocol and experimental design were applied following the last revised ethical guidelines of the Declaration of Helsinki. The study was approved by the Ethics Committee on Human Research of the University of Granada (no. 924) and by the Servicio Andaluz de Salud (Centro de Granada, CEI-Granada). All participants provided informed consent.

Concurrent training intervention

A detailed description of the supervised exercise training program, which combined resistance and endurance training as recommended by the World Health Organization (WHO)[18]

has been previously published.[15] Participants attended the research center 3-4 times per week, completing a total of 150 min/week of endurance exercise (performed in all sessions) and 80 min/week of resistance exercise (performed over 2 sessions per week) for 24 weeks. Both resistance and endurance training were individualized to each participant's physical fitness level. For the resistance training, participants performed a total of 8-9 strength exercises involving weight-bearing activities and guided pneumatic machines (eg, Romanian deadlift, lat pulldown, half squat, and bench press, among others). For endurance training, different ergometers including cycle-ergometer, elliptical ergometer, and treadmill were utilized.

The MOD-EX group performed resistance training at 50% of the repetition maximum (RM), whereas the VIG-EX group trained with loads equivalent to 70% RM, adjusted monthly for each participant. All endurance training in the MOD-EX group was performed at 60% heart rate reserve (HRres), while the VIG-EX group performed 75 min/week of endurance training at 60% HRres and 75 min/week at 80% HRres. HRres was calculated as the difference between the resting and maximum heart rates.

The exercise intervention was organized in 5 phases of different durations, beginning with a 4-week familiarization. Participants exercised in groups of 10-12 people at the same time of day throughout the 24-week intervention. Attendance was recorded via an electronic attendance sheet.

Anthropometrics and body composition

Body mass and height were measured barefoot and with light clothing, using a SECA scale and stadiometer (model 799; Electronic Column Scale, Hamburg, Germany), and were used to determine body mass index (BMI; kg/m^2). Participants' body composition was assessed by dual-energy X-ray absorptiometry using a Hologic Discovery Wi device (Hologic Inc., Bedford, MA, USA) equipped with analysis software (APEX version 4.0.2). The device was calibrated each day using a lumbar spine phantom. Participants were asked to remain still while being scanned in a supine position. Total body bone mineral content (BMC), total body areal bone mineral density (aBMD), total body aBMD *Z*-score, lean mass, fat mass, and visceral adipose tissue (VAT) mass were measured using a single total-body DXA scan.

Blood sample collection

Blood samples were collected 1-3 weeks prior to, and 3-4 days following the 24-week training intervention. The samples were drawn in the morning after a 10 h overnight fast using EDTA-coated Vacutainer® Hemogard™ tubes and immediately centrifuged to obtain plasma. The plasma samples were aliquoted and stored at −80 °C.

Determination of plasma levels of osteoglycin and sclerostin

The determination of osteoglycin levels was conducted in duplicate using the enzyme-linked immunosorbent assay (ELISA) method, following the protocol provided by Cloud-Clone Corp. (Houston, TX, USA). Plasma samples underwent a dilution of 1/80 prior to analysis. Precision testing yielded intra-assay and inter-assay coefficients of variation of ≤10% and ≤12%, respectively. Similarly, sclerostin levels were quantified in duplicate via ELISA, adhering to the manufacturer's protocols (Biomedica, Vienna, Austria). Precision testing for this assay indicated intra-assay and inter-assay coefficients of variation of 5% and 1%, respectively. More information about the assessment of bone metabolism, glucose metabolism, blood pressure, lipid profile, and adipokines can be found in Supplementary Material.

Statistical analyses

Sample size estimation was conducted based on the primary outcome of the ACTIBATE study.[15] The current study is a secondary analysis using data from the former study.[19] Thus, no specific sample size estimation was performed for the present study.

Descriptive data are expressed as mean and standard deviation (SD) unless otherwise stated. Data normality was checked using histograms, Q-Q plots, box plots, and the Shapiro-Wilk test. We found outliers both in osteoglycin and sclerostin levels above 3 SDs from the sample mean. After double-checking the data, we decided to exclude these outliers from the analyses. Linear mixed models were conducted to compare the effects of CON, MOD-EX, and VIG-EX on bone parameters (ie, total body BMC, total body aBMD, and total body aBMD *Z*-score), and plasma osteoglycin and sclerostin levels. *Post hoc* Bonferroni analyses were performed to obtain pairwise differences. To determine participants who experienced a clinically meaningful change from baseline to post-intervention in osteoglycin and sclerostin levels, a within-individual change distribution was calculated. Participants were grouped as osteoglycin responders if the standardized effect size for the intervention was equal to or greater than Cohen's *d* of 0.20 and as non-responders if this value was <0.20. In contrast, participants were considered sclerostin responders if the standardized effect size for the intervention was equal to or less than Cohen's *d* of 0.20 and as non-responders if this value exceeded 0.20.[20] We compared baseline levels of osteoglycin and sclerostin levels between responders and non-responders using independent Student's *t*-tests.

Furthermore, we conducted Spearman correlation analyses to determine the relationship between baseline levels and changes in levels of osteoglycin and sclerostin, and baseline and changes in body composition (ie, body mass, BMI, lean mass, fat mass, and VAT mass), bone metabolism (ie, plasma levels of calcium, phosphorus, PTH, and calcidiol), glucose metabolism (ie, fasting glucose, insulin, and HOMA-IR), blood pressure (ie, systolic, diastolic, and mean arterial pressure), lipid profile (ie, total cholesterol, HDL-C, LDL-C, triglycerides, ApoA-I, and ApoB), and adipokines (ie, adiponectin and leptin), respectively. All *P*-values were corrected by the Benjamini-Hochberg procedure for multiple comparisons by controlling the false discovery rate.[21] The level of statistical significance was set at $P < .05$. All statistical analyses and figures were performed using R version 4.3.2 (https://cran.r-project.org/, The R Project for Statistical Computing, Vienna, Austria).

Results

Of the 145 participants initially randomized into 1 of the 3 groups for the intervention, 106 participants were included in the per-protocol analyses (Figure 1). Eight participants were excluded from the main analyses as they either did not complete the study (ie, attending <70% of the total training

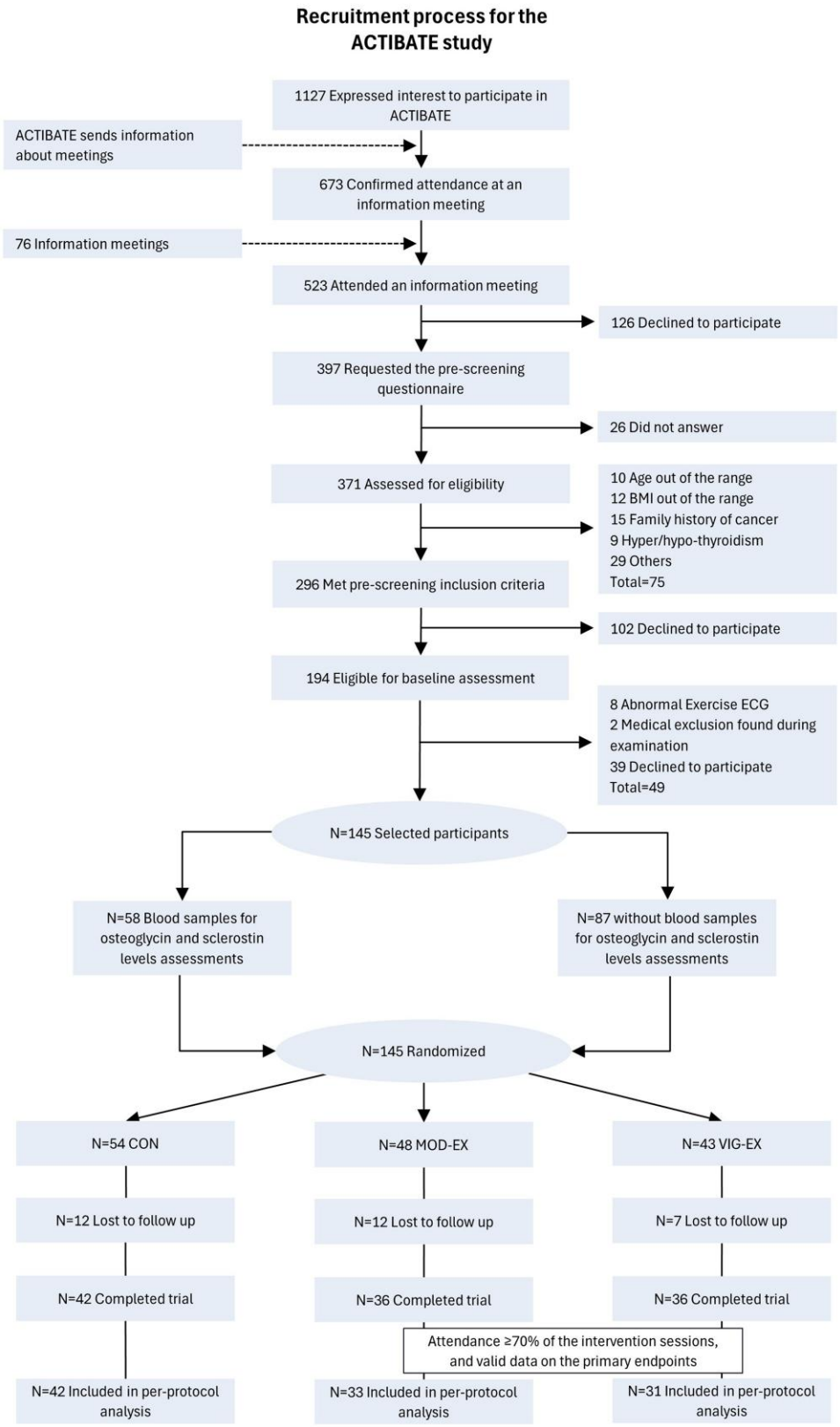

Figure 1. CONSORT flow diagram of the study. BMI, body mass index; CON, control group; ECG, electrocardiogram; MOD-EX, moderate-intensity exercise group; VIG-EX: vigorous-intensity exercise group.

sessions) or lacked valid measurements for osteoglycin and sclerostin levels (Figure 1). Of the 106 included participants, 91 participants had valid data on bone parameters, and 58 participants had valid data on osteoglycin and sclerostin levels. Of note, baseline plasma levels of osteoglycin ($P = .285$) and sclerostin ($P = .152$) were not different between men and women. The baseline characteristics of the participants included in this study are presented in Table 1.

Table 1. Baseline characteristics of the study participants.

	CON ($n = 42$) Mean (SD)	MOD-EX ($n = 33$) Mean (SD)	VIG-EX ($n = 31$) Mean (SD)
Demographics			
Age (years)	21.2 (2.1)	22.0 (2.1)	22.2 (2.4)
Male (*n*, %)	20 (48%)	10 (30%)	9 (29%)
Female (*n*, %)	22 (52%)	23 (70%)	22 (71%)
Body composition			
Weight (kg)	73.3 (20.0)	69.1 (10.3)	70.4 (15.5)
BMI (kg/m^2)	25.5 (5.8)	24.9 (3.5)	24.5 (4.1)
Total body BMC (g)	2331.5 (509.9)	2258.7 (348.4)	2355.1 (467.1)
Total body aBMD (g/cm^2)	1.1 (0.1)	1.1 (0.1)	1.2 (0.1)
Total body aBMD *Z*-score	−0.0 (1.3)	0.1 (0.9)	0.4 (1.4)
Lean mass (kg)	44.0 (11.5)	40.9 (7.4)	41.5 (9.3)
Fat mass (kg)	25.0 (9.8)	24.3 (8.0)	24.9 (8.2)
VAT mass (g)	344.3 (194.2)	336.1 (148.6)	344.0 (176.7)
Bone metabolism			
Osteoglycin (pg/mL)	17 968.7 (8110.3)	16 840.1 (5262.8)	18 238.5 (4219.3)
Sclerostin (pmol/L)	23.6 (11.6)	16.7 (6.0)	16.9 (8.5)
Calcium (mg/dL)	9.6 (0.5)	9.6 (0.4)	9.6 (0.6)
Phosphorus (mg/dL)	3.6 (0.5)	3.5 (0.4)	3.6 (0.4)
PTH (pg/mL)	28.2 (10.0)	31.8 (11.2)	33.1 (12.7)
Calcidiol (ng/mL)	25.6 (7.8)	27.1 (11.4)	25.7 (6.1)
Glucose metabolism			
Fasting glucose (mg/dL)	88.5 (7.3)	88.4 (6.6)	88.3 (5.9)
Insulin (μIU/mL)	8.9 (6.7)	8.4 (4.8)	8.6 (3.8)
HOMA-IR	2.0 (1.7)	1.9 (1.2)	1.9 (0.9)
Blood pressure and lipid profile			
Systolic blood pressure (mmHg)	117.7 (12.6)	118.3 (9.4)	117.0 (14.5)
Diastolic blood pressure (mmHg)	68.4 (8.3)	72.9 (7.0)	68.9 (9.0)
Mean arterial pressure (mmHg)	84.8 (8.0)	88.1 (6.8)	84.9 (8.6)
Total cholesterol (mg/dL)	158.0 (23.2)	169.7 (39.7)	172.0 (26.7)
HDL-C (mg/dL)	51.0 (9.2)	52.4 (11.9)	53.3 (14.3)
LDL-C (mg/dL)	91.3 (20.3)	101.4 (30.5)	101.2 (18.7)
Triglycerides (mg/dL)	78.5 (43.8)	93.0 (73.3)	87.3 (31.9)
ApoA-I (mg/dL)	139.9 (22.0)	148.6 (34.0)	148.6 (34.0)
ApoB (mg/dL)	65.7 (11.7)	73.0 (20.7)	72.5 (15.6)
Adipokines			
Adiponectin (mg/L)	9.3 (5.5)	9.1 (3.2)	9.8 (6.1)
Leptin (μg/L)	6.2 (4.6)	6.6 (4.8)	5.8 (3.1)

Data presented as mean and standard deviation (SD), unless otherwise stated.
aBMD, areal bone mineral density; ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; BMC, bone mineral content; BMI, body mass index; CON, control group; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance index; LDL-C, low-density lipoprotein cholesterol; MOD-EX, moderate-intensity exercise group; PTH, parathyroid hormone; VAT, visceral adipose tissue; VIG-EX, vigorous-intensity exercise group.

Concurrent exercise training does not modify bone parameters, nor plasma levels of osteoglycin and sclerostin

We observed no differences in changes in total body BMC (P time × group = .702; Figure 2A), total body aBMD (P time × group = .300; Figure 2D), and total body aBMD *Z*-score (P time × group = .300; Figure 2G) between CON, MOD-EX, and VIG-EX groups. Similarly, we found no differences in changes in levels of osteoglycin (P time × group = .250; Figure 2J) and sclerostin (P time × group = .489; Figure 2M) between CON, MOD-EX, and VIG-EX groups. These findings were also observed both in men (all $P \geq .081$; Figure 2B, E, H, K, and N) and women (all $P \geq .073$; Figure 2C, F, I, L, and O). Pairwise comparison of the changes in these outcomes can be found in Table S2.

Osteoglycin and sclerostin responders exhibit different baseline osteoglycin and sclerostin levels compared with non-responders

We found that osteoglycin responders had significantly lower baseline osteoglycin levels compared with non-responders ($P = .003$; Figure 3A). This pattern was also evident in women ($P = .013$; Figure 3C), whereas we did not find significant differences in baseline osteoglycin levels between responders and non-responders in men ($P = .116$; Figure 3B). Additionally, we found that sclerostin responders exhibited significantly higher baseline sclerostin levels than non-responders ($P < .001$; Figure 3D), with similar differences observed in both men ($P = .022$; Figure 3E) and women ($P = .007$; Figure 3F).

Plasma levels of osteoglycin and sclerostin are not associated with body composition and cardiometabolic risk factors

We observed no significant correlations between baseline osteoglycin and sclerostin levels with baseline body composition (all $P \geq .639$; Figure S1), bone metabolism (all $P \geq .885$; Figure S1), glucose metabolism (all $P \geq .760$; Figure S1), blood pressure (all $P \geq .885$; Figure S1), lipid profile (all $P \geq .324$; Figure S1), and adipokines (all $P \geq .639$; Figure S1). Similarly, we found no significant correlations between changes in osteoglycin and sclerostin levels and

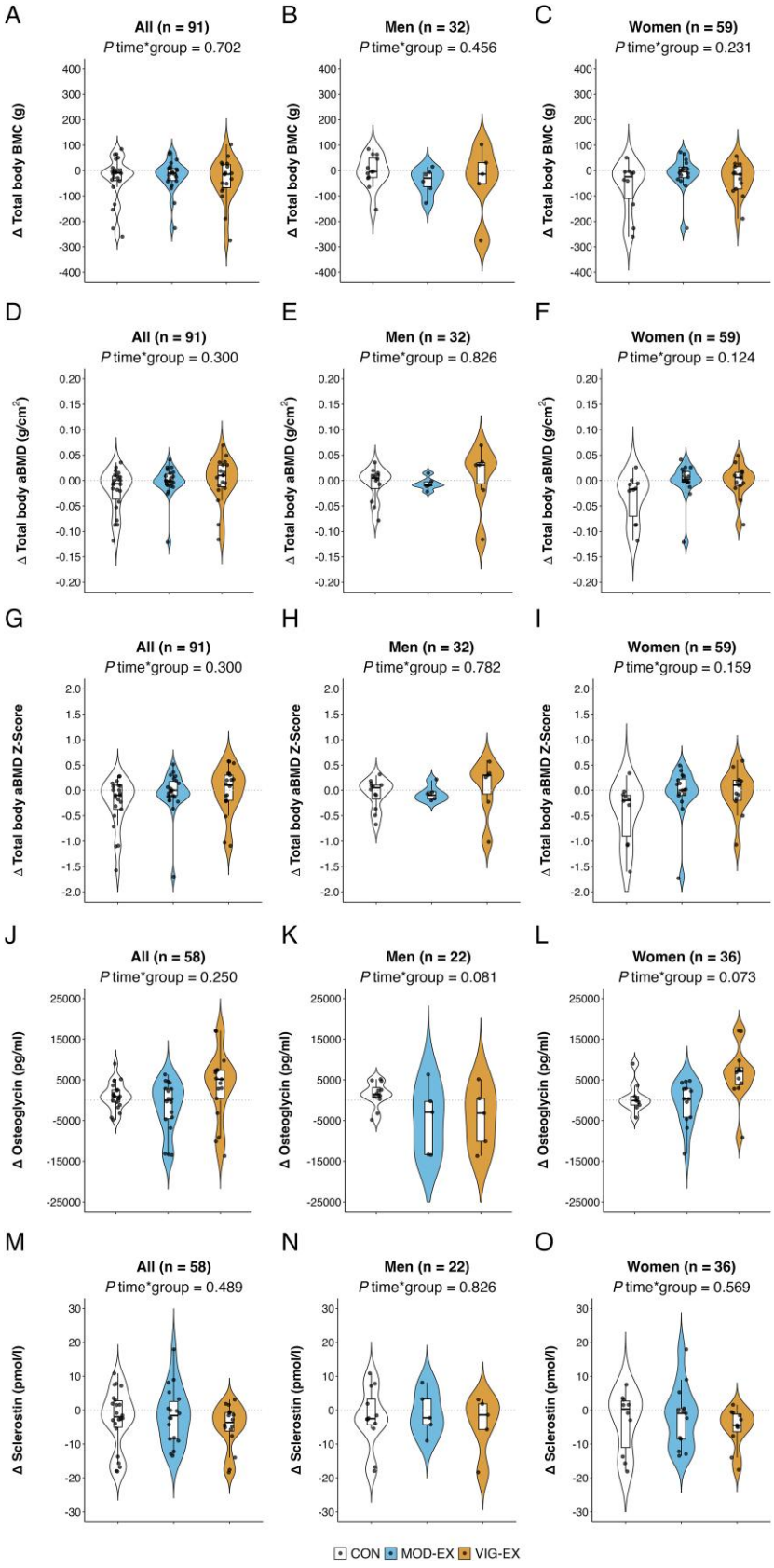

Figure 2. Effects of the 24-week supervised concurrent training on total BMC (A-C), total aBMD (D-F), aBMD *Z*-score (G-I), plasma osteoglycin (J-L) and sclerostin (M-O) levels. Δ was calculated as post-intervention minus baseline values for every outcome. *P*-values were obtained from linear mixed models. Box plots represent data as median, interquartile range (IQR) and whiskers (1.5 × IQR). Violin plots depict the distribution of the data for every outcome. CON, control group; MOD-EX, moderate-intensity exercise group; VIG-EX, vigorous-intensity exercise group.

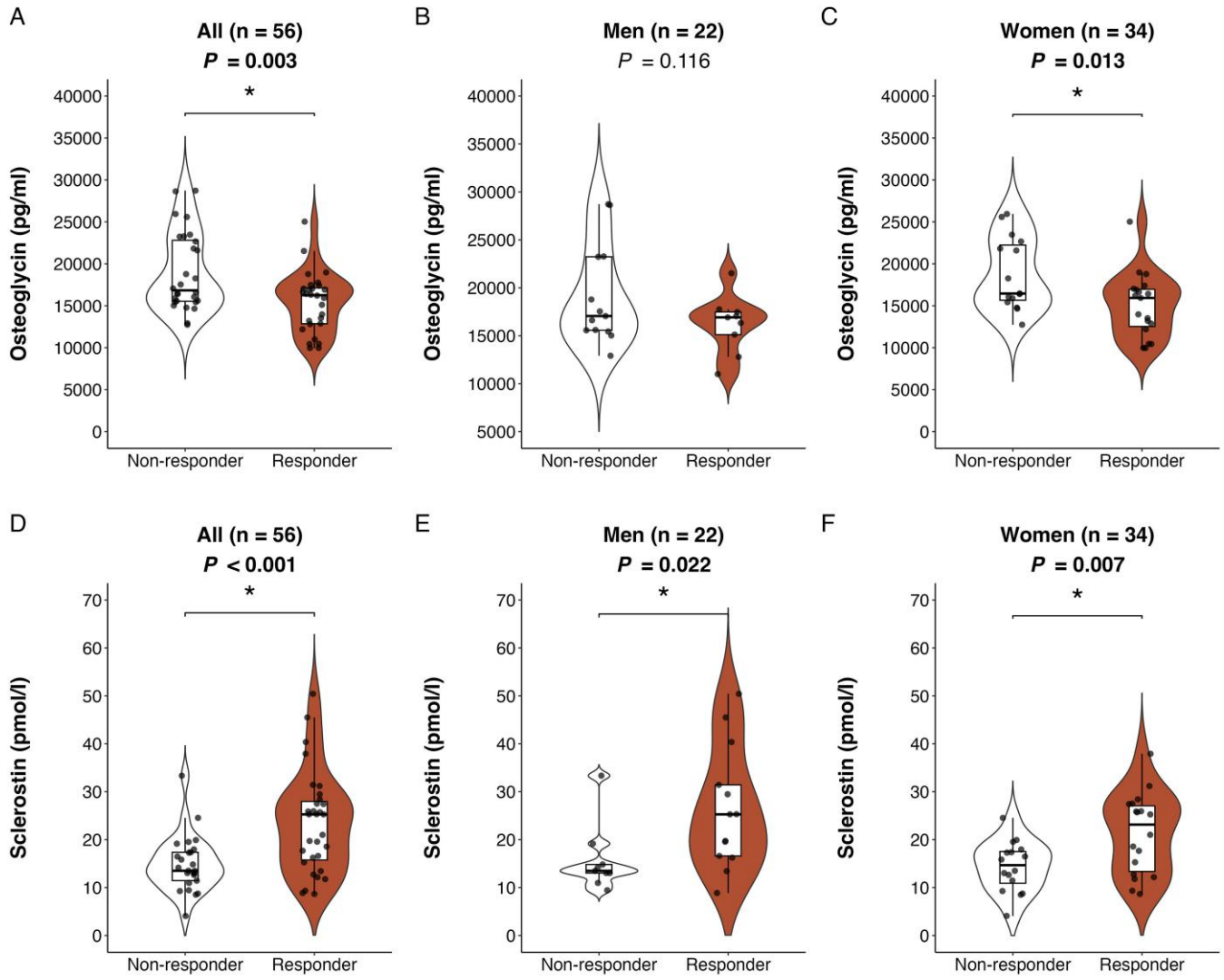

Figure 3. Baseline plasma osteoglycin and sclerostin levels (A-C and D-F, respectively) in non-responders and responders. Osteoglycin responders (A-C) were participants who increased their osteoglycin levels by 0.2 × standard deviations above the mean within-individual Δ. Sclerostin responders (D-F) were participants who decreased their sclerostin levels by 0.2 × standard deviations below the mean within-individual Δ. *P*-values were obtained from independent Student's *t*-tests. Box plots represent data as the median, IQR, and whiskers (1.5 × IQR). ***** Symbol depicts statistically significant difference between responders and non-responders ($P < .05$).

changes in body composition (all $P \geq .326$; Figure S2), bone metabolism (all $P \geq .132$; Figure S2), glucose metabolism (all $P \geq .326$; Figure S2), blood pressure (all $P \geq .119$; Figure S2), lipid profile (all $P \geq .119$; Figure S2), and adipokines (all $P \geq .326$; Figure S2) after the exercise intervention.

Discussion

This study shows that a 24-week moderate- and vigorous-intensity concurrent exercise training intervention does not alter bone parameters, nor plasma osteoglycin and sclerostin levels in young, sedentary adults. Moreover, we found that baseline and changes in osteoglycin and sclerostin levels are not correlated with baseline and changes in body composition or cardiometabolic risk factors. These results do not confirm our initial hypothesis, suggesting that longer concurrent training interventions may be needed to significantly enhance bone parameters in young, sedentary adults, and that plasma levels of osteoglycin and sclerostin are not correlated with bone parameters and cardiometabolic risk factors in this population.

Here, we demonstrate that 24 weeks of concurrent training does not modify bone parameters in young, sedentary men and women. The pro-osteogenic effects of regular exercise are well documented, with numerous studies showing that training interventions increase BMC and aBMD in older adults,[22] post-menopausal women,[23] and patients with osteopenia and osteoporosis.[24] Since peak bone mass is generally attained by around 25 years of age in both men and women, it is plausible that the long-term benefits of exercise on bone mass and density are less pronounced in young adults compared with older populations. It is plausible that MOD-EX and VIG-EX groups in the present study engaged in a suboptimal osteogenic training intervention, which may have required a longer duration or implemented more exhaustive resistance exercises to yield significant improvements in bone parameters.[25] Further research is needed to elucidate whether longer concurrent training interventions that incorporate high-impact exercises can enhance these parameters, as well as outcomes at

specific skeletal sites such as lumbar, total hip, or femoral neck in young, sedentary adults.

This study found that concurrent training does not alter plasma osteoglycin and sclerostin levels in young adults. Following acute exercise bouts, osteoglycin levels remain unchanged,[7,8] whereas circulating sclerostin levels transiently increase in young adults.[10] The post-exercise rise in sclerostin is intriguing, as this response would exert a catabolic effect on bone remodeling. However, acute responses to exercise do not always parallel long-term responses to exercise training,[26,27] and therefore it must be interpreted with caution. For instance, concurrent training augments osteoglycin expression in the skeletal muscle of middle-aged adults,[28] and decreases plasma sclerostin levels in young adults,[29,30] potentially promoting bone remodeling and the accrual of bone mass. Again, MOD-EX and VIG-EX training interventions in our study may have not provided a sufficient osteogenic stimulus to affect plasma osteoglycin and sclerostin levels in this population. Despite this, we observed that participants classified as osteoglycin responders (ie, those who showed a clinically meaningful increase in osteoglycin levels after concluding the study) and sclerostin responders (ie, those who showed a clinically meaningful decrease in sclerostin levels after concluding the study) exhibited lower baseline osteoglycin and higher sclerostin levels, respectively, compared with non-responders. These findings indicate that baseline osteoglycin and sclerostin levels, rather than the concurrent training itself, may be more predictive of long-term changes in these osteokines in young, sedentary adults. It is also plausible that plasma osteoglycin and sclerostin levels are subject to the regression to the mean, as previously demonstrated in other outcomes such as blood pressure or cholesterol levels.[31,32] More research is warranted to clarify the impact of exercise training on the plasma levels and bone expression of these osteokines, and their relationship with long-term changes in bone parameters.

We observed that baseline and changes in plasma levels of osteoglycin and sclerostin are not associated with baseline and changes in body composition, bone metabolism, glucose metabolism, blood pressure, lipid profile, and adipokines in young, sedentary adults. Osteoglycin-deficient mice display increased white adipose tissue mass, reduced β-cell mass, impaired glucose tolerance, and insulin resistance compared with wild-type mice.[33] Treatment with osteoglycin during glucose tolerance tests in these mice reduces blood glucose levels in a dose-dependent manner, suggesting that osteoglycin enhances glucose homeostasis.[33] A previous study has shown a negative association between osteoglycin levels, body fat percentage, and blood glucose levels in young men and middle-aged men with obesity,[8] a condition frequently accompanied by impairments in glucose homeostasis.[34,35] Moreover, type 2 diabetes patients exhibit higher circulating osteoglycin levels compared with healthy controls.[36] Yet, osteoglycin levels are not associated with glucose, HbA1c, or biochemical markers of bone turnover in patients with type 1 or type 2 diabetes.[37] In such clinical populations, the rise in plasma osteoglycin levels could act as a compensatory mechanism to preserve bone and glucose homeostasis,[36] although its specific metabolic functions in healthy young adults remain uncertain.

On the other hand, sclerostin-deficient mice exhibit reductions in visceral and subcutaneous fat mass, adipocyte size, and *de novo* lipogenesis, alongside increased fatty acid oxidation and insulin sensitivity, possibly through the upregulation of the Wnt/β-catenin signaling pathway in white adipocytes.[12] A previous cross-sectional study reported that plasma sclerostin levels are positively associated with fasting glucose, insulin, HOMA-IR, and indices of hepatic and adipose insulin resistance, and negatively associated with whole-body glucose disposal and insulin clearance rate both in middle-aged, normal glucose-tolerant participants and prediabetes patients.[14] Additionally, sclerostin levels are negatively correlated with diastolic blood pressure, LDL-C, and calcium in type 2 diabetes patients.[13] Altogether, sclerostin may play a protective role in the development of atherosclerosis in type 2 diabetes patients[13] and has been proposed as a biomarker of type 2 diabetes, non-alcoholic fatty liver disease, and metabolic syndrome severity.[38] However, despite the promising implications of osteoglycin and sclerostin as biomarkers in clinical populations, our findings suggest that these osteokines may not serve as indicators of cardiometabolic health in healthy, young adults. Further research is warranted to explore the relationship between osteoglycin and sclerostin levels with body composition, and cardiometabolic risk factors in healthy, young adults and other populations.

The present study has several strengths and limitations. One limitation is the inclusion of only young sedentary adults, which limits the extrapolation of the findings to other populations, such as children, older adults, trained/active individuals, or those with health conditions. Furthermore, the relatively small sample size in the assessments of osteoglycin and sclerostin levels, especially in men, could also limit the robustness of the results, although statistical methods were implemented to use all the available data. Lastly, the long-term effects of training were based on a concurrent intervention, without individually isolating the long-term effects of endurance and resistance training, and without assessing the acute effects of concurrent exercise. A key strength is the utilization of a well-characterized sample of young, sedentary men and women, with comprehensive assessments of bone parameters, osteoglycin and sclerostin levels, body composition, and cardiometabolic risk factors. Additionally, we evaluated the long-term effects of combining both resistance and endurance training.

Conclusion

In conclusion, 24 weeks of concurrent training did not alter bone parameters, and plasma levels of osteoglycin and sclerostin in young, sedentary adults. Additionally, we did not observe any associations between baseline and changes in osteoglycin or sclerostin levels and either baseline and changes in body composition or cardiometabolic risk factors. These findings suggest that osteoglycin and sclerostin are not related to bone parameters and cardiometabolic health in young, sedentary adults. Further research is needed to understand the effects of different types of training on osteoglycin and sclerostin levels, and their relationship with bone parameters, body composition, and cardiometabolic risk factors in other populations.

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Supplementary material

Supplementary material is available at *European Journal of Endocrinology* online.

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Authors' contributions

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Data availability

The data that support the findings of this study are available from the corresponding authors, J.J.M.-O., M.M.-T. and J.R.R. upon reasonable request.

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