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EFFECT OF EXERCISE ON SCLEROSTIN CONCENTRATIONS IN BLOOD SERUM

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ABSTRACT

After entering adulthood, the quality and quantity of bone decrease with age. Bone metabolism is influenced by many factors and signaling pathways. Sclerostin is an antagonist of the Wnt signaling pathway in osteoblast lineage cells, thus causing a decrease in bone formation. Recent studies have shown that mechanical loading of the bones, for example by doing exercise, can affect the concentration of sclerostin in blood serum. However, research on this topic still has wide variations in terms of frequency, intensity, duration, and the type of exercise that can cause changes in serum sclerostin concentrations. This study was conducted using the literature review method, we reviewed and compared the latest journals that discussed the relationship between exercise and sclerostin concentrations in blood serum. Based on the studies that we have compared and analyzed, exercise with a frequency of 3x/week with a minimum duration of about 30 minutes, performed for at least 12 weeks with cardio type and intensity of 85-90% HRmax decrease sclerostin levels in blood serum. Meanwhile, a single bout of exercise will increase sclerostin levels transiently.

Keywords : bone turnover markers; sclerostin; exercise

INTRODUCTION

It is estimated that more than 9 million fractures a year are caused by osteoporosis worldwide[1]. Osteoporosis becomes a major global health problem because it decreases the quality of life and life expectancy. It reduces psychological and physical health[2]. Low bone mass is one of the characteristics of osteoporosis, besides deterioration of architecture[3,4]. A study concludes that the bone mass density of people in Southeast Asia, in general, is lower than Caucasian people[5]. Women are more at risk of osteopenia and osteoporosis than men with a prevalence of 61% and 16% for women while for men the prevalence was 38% and 4%[1]. Around one-third of postmenopausal women have osteoporosis[6]. Women in the United States over 50 years of age who are at risk of fracture in the next 10 years have percentage rates of 3.4%, 5.3%, and 6.8% and based on bone mass are classified into normal, low and osteoporosis. An important risk factor of fragility fractures later in life is the failure to achieve and maintain optimal bone mass in adulthood. Although pharmacotherapy and medical techniques are effective to treat osteoporosis, prevention is still the best option. Exercise is a contributor to bone health that is accessible, inexpensive, and can be modified[7,8]. It is supported by evidence that is increasing about the effectiveness of exercise in increasing bone mass[5,9,10].

Exercise exerts a mechanical load on bone tissue which has the combined effect of external forces and muscle contraction resulting in a higher impact on bone than other forces associated with gravity. The exercise intensity, the interval between repetitions of the same exercise and certain training sessions, these three things influence the effectiveness of the exercise in preventing osteoporosis[11,12]. What is needed and must be implemented is to design the right training program to be oriented towards the effective stimulation of the osteogenic process[13]. Regular exercise is one of the factors that stimulate bone formation.

Sclerostin is exclusively produced by osteocytes which have a function to inhibit signals sending of activation, proliferation and differentiation of osteoblasts derived from mesenchymal cells. It has an inhibitory effect on bone formation by blocking osteogenic Wnt signaling, it is a negative regulator[13–16]. Wnt pathway signaling is important for bone strength because osteoblast differentiation, formation of bone tissue, and suppression of the resorption process are stimulated by it. Inactivation of sclerostin activity in the Wnt/β-catenin signaling pathway will give an anabolic effect and influence the osteogenic mechanism prevalence[13,17,18,19]. Osteocytes have been shown to have a role in the metabolism of bone tissue in addition to osteoblasts and osteoclasts, this has been demonstrated in recent years[20]. Osteocytes have the function of suppressing sclerostin secretion to activate the process of osteogenesis and repair of bone structure[21]. Osteoblast apoptosis is stimulated by sclerostin and further processes potential mechanisms that can inhibit the process of osteogenesis. The synthesis of sclerostin may be stimulated by immobilization and lack of physical activity. The process of overexpression of sclerostin in the bone can induce osteopenia[13].

After puberty, sclerostin levels decline and regular athletic activity can alter the relationship of sclerostin to areal bone mineral density (aBMD). In healthy adults sclerostin concentrations were also positively correlated with aBMD, but not in prepubertal children. Sclerostin levels have been reported to be higher in athletes (for example gymnasts and swimmers) than in non-athletes. The increase in sclerostin can be influenced by mechanical loads[14,22]. Research on this topic still has gaps and wide variations in terms of frequency, intensity, duration, and the type of exercise that can cause changes in serum sclerostin concentrations. There are no basic standards and guidelines regarding the change of sclerostin concentrations in blood serum that is caused by exercise. Therefore, we made this literature review with the aim of comparing and analyzing several studies with different frequency, intensity, duration, and type of exercise to see the effect of exercise to sclerostin and draw conclusions from these variations.

METHODS

The method used in this literature review is search methods such as internet searches, various journal searches, journal reviews, and articles. Information used in this literature review was from Google Scholar, ProQuest, Pubmed, Science Direct, and Scopus using the keywords “Exercise” in combination with “Sclerostin” or “Sclerostin Concentrations”. The eligibility criteria include literature in the English language that were published between 2012 and 2022. The literature reporting the relationship between exercise and sclerostin concentrations in blood serum were selected. Reference lists from selected literature were also checked to identify additional relevant reports. We found 60 articles and then selected 44 articles, all articles included in this study has been checked through the Scimago Journal & Country Rank.

RESULTS

Five author teams searched for literature on Google Scholar, ProQuest, Pubmed, Science Direct, and Scopus using the keywords "Exercise" in combination with "Sclerostin" or "Sclerostin Concentrations". We include literature in the English language that were published between 2012 and 2022. The literature reporting the relationship between exercise and sclerostin concentrations in blood serum were selected. We reviewed 60 abstracts for inclusion with 44 selected for full-text review. A total of 10 studies were analyzed and compared. Information was extracted using the PICO format (ie, participants, intervention, comparison, outcomes). Descriptive findings are then reported on Table 1.

Table 1. Studies examining the effects of exercise on sclerostin

Author and year of publication	Participants	Intervention	Result's Comparison	Outcomes
Hinton et al, 2017[23].	38 men, aged 25 to 60 years with osteopenia	Participants were randomly divided into 2 group: 12 months of RT (2×/week) or 12 months of jump training (3×/week)	Baseline: 39.2 ± 11.6 pmol/L After 12 months of RT or jump training: 36.8 ± 13.3 pmol/L (p=0.012)	After 12 months of RT or jump training, sclerostin levels significantly decreased about 7% from the baseline.
Janik et al, 2018[13].	50 women, aged 50 to75 years with osteopenia	First 12 weeks: participants remained at their usual level of physical activity. Next 12 weeks: participants undergo a cardio workout on a bike ergometer, 3×/week for 36 minutes.	Baseline: 275.82±38.15 After the first 12 weeks (no physical training): 277.07±38.35 After the next 12 weeks (with physical Training): 242.60±43.04 (p<0.001)	After 12 weeks of cardio workout on a bike ergometer, sclerostin levels significantly decreased.
Ghardashi-Afousi et al, 2018[24].	59 sedentary patients (31 men, 28 women), aged 45 to 60 years with type 2 diabetes	Patients were randomly divided into 2 groups: the control group or the HIIT group. The HIIT group was trained for 6 intervals, each with a duration of 4 minutes at 85%-90% of HRmax, then interspersed with 3 minutes of training at 45%-50% of HRmax. The training was done 3 times a week for 12 weeks.	Control group (Men): 238.87 ± 84.57 HIIT group (Men): 163.38 ± 46.95 Control group (Women): 203 ± 66.27 HIIT group (Women): 170.60 ± 42.53 (p=0.001)	After 12 weeks of HIIT, sclerostin levels significantly decreased in patients with type 2 diabetes.
Sharma-Ghimire et al, 2019[25].	9 women, aged 20 to 30 years	Participants completed 2 exercise protocols in random order: RE and WBV + RE	WBV + RE PRE: 0.276 ± 0.015 POSTWBV: 0.302 ± 0.011 IP: 0.324 ± 0.025 30P: 0.268 ± 0.021 (p<0.05)	Sclerostin levels were found significantly increased from pre-exercise to immediately after resistance exercise, then decreased back to the pre-exercise level.

Guerriere et al, 2018[26].	14 men, aged 18 to 39 years	Participants completed a rest phase and a plyometric training in random order.	No significant effects were found on sclerostin levels that are measured at 0, 12, 24, 48, and 72 hours after the plyometric training is conducted. ($p>0.05$)	After an acute bout of plyometric jump exercise, there were no significant responses of sclerostin concentrations in blood serum.
Kouvelioti et al, 2018[27].	20 women, aged from 18 to 28 years	Participants completed 2 exercise trials: High-Intensity Interval Cycling (HIIC) performed on a bike ergometer and High-Intensity Interval Running (HIIR) performed on a treadmill in random order.	Sclerostin increased from pre-exercise to 5 min after exercise in both trials. HIIC: 102.3 to 135.8 pg/ml HIIR: 100.2 to 131.6 pg/ml Then returned to baseline levels by 1 hour ($p<0.001$) There is no difference between exercise modes ($p>0.05$)	After a single bout of high-intensity training, there was an increase in serum sclerostin found in young women, irrespective of the exercise mode.
Jürimäe et al, 2020[28].	16 male rowers, mean age 19.0 ± 2.2 years, who had rowing training experience: 4.3 ± 1.7 years	Participants completed a 2 hours rowing exercise, with distance 23.8 ± 0.9 km and intensity 79.8 ± 2.1% of the anaerobic threshold.	Sclerostin levels were found significantly increased about 36% from baseline. ($p<0.05$)	In trained male rowers, a 2-hour water resistance training session at 80% anaerobic threshold intensity (AnT) resulted in increased of serum sclerostin in blood.
Dror et al, 2021[29].	13 males aged 20–29 years old	Participants completed 2 exercise: cycling on a cycle ergometer (CE) or running on a treadmill (TM). For the second visit, participants completed the other exercise, cycling or a 30 minutes running at 70% heart rate reserve.	Sclerostin levels significantly increased after running (27.7%), which was not found after cycling. ($p= 0.015$)	A greater transient in sclerostin level was found in running group compared with cycling group, at the same moderate-to-vigorous exercise intensity.
Gombos et al, 2016[30].	150 females with osteoporosis or osteopenia	Participants were divided into 3 groups: resistance exercise (RG), walking group (WG), and control group (CG).	Baseline [pmol/L]: RG: 26.8 ± 14.0 WG: 23.6 ± 10.0 CG: 24.0 ± 8.8 Post-intervention [pmol/L]: RG: 29.8 ± 15.7 WG: 29.9 ± 10.8 CG: 24.2 ± 8.8 ($p<0.01$)	Sclerostin level increased in the resistance exercise (RG) and walking (WG) groups, and it was found that there was a difference after the exercise intervention between the control

				(CG) and WG groups.
Neves et al, 2021[31].	193 male and female patients with glomerular filtration rate <15 mL/min/1.73[2]	Participants were Divided randomly into three groups: CTL (n = 60), DRT (n = 66), and IRT (n = 67).	Baseline [ng/mL]: CTL: 1.93 ± 0.48 DRT: 1.86 ± 0.67 IRT: 1.82 ± 0.81 Post-intervention [ng/mL]: CTL: 1.88 ± 0.60 DRT: 1.34 ± 0.43 IRT: 1.73 ± 0.58 (p=0.0084)	There was a decrease in the levels of sclerostin in the DRT group compared to baseline, and in the CTL and IRT groups.

*Statistically Significant (p <0,05). RT: resistance training, HIIT: High Intensity Interval Training, RE: resistance exercise, WBV: whole-body vibration, PRE: before exercise, POSTWBV: immediately after WBV, IP: immediately after RE, 30P: 30 min after RE, CE: cycle ergometer, TM: treadmill, CTL: control group, DRT: dynamic resistance training, IRT: isometric resistance training.

DISCUSSION

Roles of sclerostin in bone remodeling

Bone is continually remodeled throughout life to maintain plasma calcium homeostasis and prevent the accumulation of old bone. Osteoclasts resorb bone and then the new bone is formed to replace the amount of bone reabsorbed by osteoblasts. This is called bone remodeling, and balanced bone remodeling stabilizes bone mass. The imbalance between bone resorption and bone formation results in low or high bone mass[32].

Sclerostin is a glycoprotein secreted by osteocytes. Sclerostin inhibits the intracellular Wnt signaling pathway, which activates the process of cell differentiation into osteoblasts, inhibits bone formation and the process of resorption. Wnt/β-catenin signaling function is regulated by the production of 5/6 receptor inhibitors (LRP) sclerostin and Dickkopf-1 (DKK-1), which cause phosphorylation and degradation of b-catenin, thereby inhibiting osteoblasts. The inhibitory effect of Wnt signaling on bone has led to the development of pharmacological interventions (eg sclerostin antibodies) that could be beneficial in the prevention and treatment of osteoporosis[7,13–15,33–38]

In patients with bone injuries, sclerostin secretion is inhibited by osteocytes to activate osteogenesis and bone repair processes. Overexpression of sclerostin in bone causes osteopenia. Sclerostin stimulates osteoblast apoptosis, resulting in a potential mechanism that can inhibit osteogenesis. Bones that are not exposed to mechanical stress are at risk for increased sclerostin concentrations resulting in a higher incidence of osteocyte apoptosis. This is what increases the recruitment of osteoclasts and the process of resorption and bone loss occurs[13].

Sclerostin may act as a biomarker of osteoporosis. Low lumbar bone mineral density (BMD) is associated with an increase of serum sclerostin in the elderly female of hemodialysis (HD) patients in a study conducted by Lu et al (2022)[39]. Estradiol is one of the factors that regulates sclerostin synthesis. Decreased estradiol levels are associated with the pathogenesis of postmenopausal osteoporosis. It has been suggested that estradiol inhibits osteoblast apoptosis. Higher levels of sclerostin were observed in postmenopausal women than in perimenopausal and levels were inversely related to the free estradiol index[40,41].

Effects of exercise on sclerostin concentrations in blood serum

Some studies have shown exercise can lower serum sclerostin levels, while some other studies have shown the opposite which is increase in serum sclerostin levels after certain physical activity. A study by Hinton et al (2016), showed that an exercise intervention that modulated intensity over time decreased circulating sclerostin as bone mineral density increased. It should be noted that exercise—resistance training or jumping exercise—both increases bone mass and decreases sclerostin. These results are consistent with the concept that osteocyte expression of sclerostin is capable to increase bone mass in humans by mechanical stimulation type of exercise[23,42,43].

A study from Janik et al. has shown serum sclerostin levels as one of bone turnover markers were significantly decreased after 12 weeks of physical training program in women with osteopenia. The program is interval training on a bicycle ergometer 3x/week for 36 minutes which is a moderate level. All 50 participants received calcium 500 mg and vitamin D3 1800 IU as daily supplementation during the study. The study concluded physical training effectively stimulates the formation of bone in women with osteopenia. The decrease of the serum sclerostin level after a physical training program may stimulate osteoblastogenesis. Sclerostin may be considered as a marker of physical activity and as a parameter for monitoring and predicting further therapy in osteopenia and postmenopausal osteoporosis cases[13].

Another study investigated the association between 12 weeks of high-intensity interval training (HIIT) on serum levels of sclerotin, Dkk-1, and carotid intima media thickness (cIMT). There was a decrease in cIMT, serum Dkk-1 and sclerostin levels after HIIT. The decrease in cIMT after HIIT is an effect of decreased serum levels of sclerostin and Dkk-1[24]. On the opposite, serum sclerostin levels increased after acute whole-body vibration plus resistance exercise in 9 young women. Sharma-Ghimire et al. assumed it may have been mediated by plasma volume shift[25].

Guerriere et al. determined whether an acute bout of exercise reduces serum sclerostin level, one of the biochemical markers that inhibit the Wnt signaling pathway. The study controlled dietary calcium intake to stabilize parathyroid hormone (PTH) which regulates sclerostin expression in osteocytes. As we know, the circulating concentration of calcium regulates PTH, so by regulating it, the results likely reflect the mechanical stimulus effect alone. 14 young healthy men participants did a 5 up to 10 minutes warm-up that consisted of leg presses, lightly weighted Plyo Press jumps, and stretching and were assessed several times. The result is no significant effect on serum sclerostin level after an acute bout of exercise. But, this study did not assess the serum sclerostin level immediately post-exercise and may have missed a change of it which usually increased immediately post-exercise. The duration of the plyometric exercise also may be too short to alter serum sclerostin level in this study[26].

A crossover design by Kouvelioti et al. compared the response of sclerostin to high-intensity impact exercise (running/HIIR) versus high-intensity no-impact exercise (cycling/HIIC) in the same group of young women participants. The result is there is a significant time effect on serum sclerostin level in both exercise modes 5 minutes after exercise which the level increased and returned to baseline level by 1 hour as shown in the table above. The higher serum sclerostin level after exercise is more probably because osteocytes release the previously synthesized sclerostin into the blood, rather than because of increasing gene expression of sclerostin in a short time[27,44].

The first three studies have shown the same results that serum sclerostin levels significantly decreased after regular exercise (two or three times a week) for a long period (12 weeks and 12 months). Otherwise the last three studies have shown serum sclerostin levels significantly increased or had no significant response after an acute or a single exercise only. So, according to sclerostin's role explained before, doing exercise regularly for a lifetime, may improve bone health and slow down the bone aging process, regardless of the mode of exercise.

Sclerostin secreted by bone tissue is not only involved in bone remodeling but can be used as a biological marker of energy homoestasis. A study by Jürimäe et al (2020) showed that a 2-hour water resistance training session at 80% anaerobic threshold intensity (AnT) resulted in increased serum sclerostin in trained male rowers. The distance covered was used as a marker of the metabolic demands of rowing training while the weekly training volume was used as a marker of exercise stress that would increase exercise-induced sclerostin concentration in male rowers[28].

Different types of physical exercise have different impacts on sclerotin. N. Dror et al (2021) found that moderate to vigorous intensity exercise, running appeared to produce a greater sclerostin response compared to cycling[29]. Another study by Gombos et al (2016) who observed 150 female subjects with osteoporosis or osteopenia divided their patients into 3 groups: resistance exercise (RG), walking group (WG), and control group (CG). From the observations, it was found that the level of sclerostin increased in the resistance exercise (RG) and walking (WG) groups, and it was found that there was a difference after the exercise intervention between the control (CG) and WG groups[30].

Research on dynamic resistance training (DRT) also found that DRT was able to increase bone mineral density (BMD) in various body parts. This occurs by increasing several factors of pro-osteogenic such as Klotho and calcitriol and also reducing sclerostin levels, FGF23, and PTH which affect bone loss. It was argued that the benefit did not occur after isometric RT (IRT). The researchers then recommended DRT based on the perceived exertion rating (RPE) as sufficient to provide a significant improvement. In addition, the external load can play an important role because IRT shows the same RPE for low external loads. This could explain how the process of bone remodeling[31].

Mechanism of type, duration, frequency, intensity in affecting sclerostin

As a bone formation inhibitor, sclerostin has an important role in mechanotransduction in bone[29]. The different response of sclerostin between the exercise typess may because of the different mechanical loading[16]. Some animal studies have shown that prolonged mechanical loading is followed by decreased sclerostin, while sclerostin increased during prolonged mechanical unloading[29].

High impact exercise and prolonged bed rest would increase the sclerostin. It is assumed that high sclerostin levels which is persistent will cause a catabolic effect of bone, while high sclerostin levels which is transient or intermittent will cause an anabolic effect of bone[29]. In single bout of exercise, the transient increase in sclerostin may because of the existence of previously synthesized sclerostin pool that is released into bloodstream as a response to the exercise stimulus. Physiological regulation of kidney also may relate with the increase of sclerostin[16]. It may because of a decreased excretion or an increased reabsorption of sclerostin in tubule[16]. Another speculation is it may relate to a threshold of mechanical strain intensity which bone turnover may be stimulated[35].

Sclerostin levels may depend on type, duration, frequency, and intensity of exercise. However, those mechanisms is still unclear and needs further research[16,29].

Other Factors that Influences Sclerostin Levels

Age, diabetes, BMD, male sex, weight, height, and serum uric acid levels were all linked to sclerostin levels. In patients with diabetes mellitus (DM), serum sclerostin levels increase due to lower BMD and renal function. Yamada et al. published in 2015 that serum sclerostin levels in PD patients were significantly associated to age. Sclerostin levels correlated with spinal trabecular bone loss in patients undergoing dialysis. In this investigation, lumbar BMD and serum sclerostin had a negative connection with age and female sex, but not with DKK1 HD patients. These data show that sclerostin could be used as an osteoporosis biomarker in HD patients.[39]

In perimenopausal and postmenopausal women, many studies have examined the factors that influence sclerostin levels. Ardavi et al. discovered that until the age of 45, circulating sclerostin levels increased with age. Longitudinal studies have also shown that sclerostin levels increase with age. The increase occurred from reproductive age to menopause, and also from menopause to early postmenopause. Furthermore, Amrein et al. also found an increase in sclerostin levels with age in healthy patients, which was not affected by gender.[40]

Research by Jurimae et almain showed that serum sclerostin levels were associated with the mass of body fat and serum fat-derived leptin levels, implying that bone-derived sclerostin may be involved in adipose tissue management. Resting sclerostin levels were not different between normal weight and obese teenage girls in a recent research of adolescent girls, whereas resting leptin levels were considerably greater in obese adolescent girls than in their lean counterparts.[42]

Based on the author's direct experience in the research process, there were some limitations that could be given more attention to future researchers, for example, the information provided by previous authors in describing exercise is not always complete in terms of frequency, intensity, duration, and type of exercise. Further studies are still needed with a larger number of respondents in order to describe the actual situation, and studies in a variety of populations to investigate the effect of the increase in serum sclerostin levels.

CONCLUSION

This literature review shows evidence from several studies that certain physical activity has a good impact on bone health that can be evaluated with biomarker assessment. Sclerostin which has the function to inhibit bone formation may be a marker of physical activity towards the aging of bones. Based on the studies that we have compared and analyzed, exercise with a frequency of 3x/week with a minimum duration of about 30 minutes, performed for at least 12 weeks with cardio type and intensity of 85-90% HRmax decrease sclerostin levels in blood serum. Meanwhile, a single bout of exercise will increase sclerostin levels transiently. Further studies are still needed in a variety of populations to investigate the effect of the increase in serum sclerostin levels.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1. Rinonapoli G, Ruggiero C, Meccariello L, Bisaccia M, Ceccarini P, Caraffa A. Osteoporosis in men: A review of an underestimated bone condition. Int J Mol Sci. 2021;22(4):1–22.
2. Barnsley J, Buckland G, Chan PE, Ong A, Ramos AS, Baxter M, et al. Pathophysiology and treatment of osteoporosis: challenges for clinical practice in older people. Aging Clin Exp Res. 2021;33(4):759–73.
3. Zhai T, Chen Q, Xu J, Jia X, Xia P. Prevalence and Trends in Low Bone Density, Osteopenia and Osteoporosis in U.S. Adults With Non-Alcoholic Fatty Liver Disease, 2005–2014. Front Endocrinol (Lausanne). 2022;12(January):1–12.
4. Fulzele K, Dedic C, Lai F, Bouxsein M, Lotinun S, Baron R, et al. Loss of Gsα in osteocytes leads to osteopenia due to sclerostin induced suppression of osteoblast activity. Bone. 2018;117:138–48.
5. Min C, Yoo DM, Wee JH, Lee HJ, Choi HG. High-Intensity Physical Activity with High Serum Vitamin D Levels is Associated with a Low Prevalence of Osteopenia and Osteoporosis: A Population-Based Study. Osteoporos Int. 2021;32(5):883–91.
6. Sadeghi H, Ashraf A, Zeynali N, Ebrahimi B, A Jehu D. Balance and functional mobility predict low bone

mineral density among postmenopausal women undergoing recent menopause with osteoporosis, osteopenia, and normal bone mineral density: A cross-sectional study. Geriatr Nurs (Minneap). 2021;42(1):33–6.
7. Troy KL, Mancuso ME, Butler TA, Johnson JE. Exercise early and often: Effects of physical activity and exercise on women's bone health. Int J Environ Res Public Health. 2018;15(5).
8. Hagman M, Helge EW, Fristrup B, Jørgensen NR, Helge JW, Krustrup P. High bone mineral density in lifelong trained female team handball players and young elite football players. Eur J Appl Physiol. 2021;121(10):2825–36.
9. Śliwicka E, Cisoń T, Pilaczyńska-Szcześniak Ł, Ziemba A, Straburzyńska-Lupa A. Effects of marathon race on selected myokines and sclerostin in middle-aged male amateur runners. Sci Rep. 2021;11(1):1–9.
10. Liao HW, Huang TH, Chang YH, Liou HH, Chou YH, Sue YM, et al. Exercise alleviates osteoporosis in rats with mild chronic kidney disease by decreasing sclerostin production. Int J Mol Sci. 2019;20(8).
11. Gharbia O, Hegazy A, Elhelaly R, ElGhaweet A. Serum sclerostin in rheumatoid-induced osteoporosis. Egypt Rheumatol Rehabil. 2020;47(1).
12. Turoń-Skrzypińska A, Dutkiewicz G, Marchelek-Myśliwiec M, Rył A, Dziedziejko V, Safranow K, et al. Physical activity versus sclerostin and interleukin 6 concentration in patients receiving renal replacement therapy by hemodialysis. Risk Manag Healthc Policy. 2020;13:1467–75.
13. Janik M, Stuss M, Michalska-Kasiczak M, Jegier A, Sewerynek E. Effects of physical activity on sclerostin concentrations. Endokrynol Pol. 2018;69(2):142–9.
14. Jürimäe J, Karvelyte V, Remmel L, Tamm AL, Purge P, Gruodyte-Raciene R, et al. Sclerostin, preadipocyte factor-1 and bone mineral values in eumenorrheic adolescent athletes with different training patterns. J Bone Miner Metab. 2021;39(2):245–52.
15. Holdsworth G, Roberts SJ, Ke HZ. Novel actions of sclerostin on bone. J Mol Endocrinol. 2019;62(2):R167–85.
16. Pickering ME, Simon M, Sornay-Rendu E, Chikh K, Carlier MC, Raby AL, et al. Serum Sclerostin Increases After Acute Physical Activity. Calcif Tissue Int. 2017;101(2):170–3.
17. Delgado-Calle J, Sato AY, Bellido T. Role and mechanism of action of sclerostin in bone. Bone. 2017;96:29–37.
18. Drake MT, Khosla S. Hormonal and systemic regulation of sclerostin. Vol. 96, Bone. Elsevier Inc; 2017. 8–17 p.
19. Bestaş E, Dündar Ü, Köken T, Koca B, Yeşil H. The comparison of effects of balneotherapy, water-based and land-based exercises on disease activity, symptoms, sleep quality, quality of life and serum sclerostin level in patients with ankylosing spondylitis: A prospective, randomized study. Arch Rheumatol. 2021;37(x).
20. Plinta R, Czajkowska M, Pisula M, Brzęk A, Knapik A, Olszanecka-Glinianowicz M, et al. The effect of regular fitness training, sex hormones, and turnover of selected bone markers on sclerostin levels in young women. Arch Med Sci. 2020;1–7.
21. Lapauw B, Vandewalle S, Taes Y, Goemaere S, Zmierczak H, Collette J, et al. Serum sclerostin levels in men with idiopathic osteoporosis. Eur J Endocrinol. 2013;168(4):615–20.
22. Confavreux CB. Sclerostin and energy metabolism during physical activity. Calcif Tissue Int. 2018;102(3):382–3.
23. Hinton PS, Nigh P, Thyfault J. Serum sclerostin decreases following 12 months of resistance- or jump-training in men with low bone mass. Bone. 2017;96:85–90.
24. Ghardashi-Afousi A, Davoodi M, Hesamabadi BK, Asvadi-Fard M, Bigi MAB, Izadi MR, et al. Improved carotid intima-media thickness-induced high-intensity interval training associated with decreased serum levels of Dkk-1 and sclerostin in type 2 diabetes. J Diabetes Complications. 2020;34(1):107469.
25. Sharma-Ghimire P, Chen Z, Sherk V, Bemben M, Bemben D. Sclerostin and parathyroid hormone responses to acute whole-body vibration and resistance exercise in young women. J Bone Miner Metab. 2019;37(2):358–67.
26. Guerriere KI, Hughes JM, Gaffney-Stomberg E, Staab JS, Matheny RW. Circulating sclerostin is not suppressed following a single bout of exercise in young men. Physiol Rep. 2018;6(10):1–9.
27. Kouvelioti R, Kurgan N, Falk B, Ward WE, Josse AR, Klentrou P. Response of sclerostin and bone turnover markers to high intensity interval exercise in young women: Does impact matter? Biomed Res Int. 2018;2018.
28. Jürimäe J, Purge P, Tillmann V. Serum sclerostin and cytokine responses to prolonged sculling exercise in highly-trained male rowers. J Sports Sci. 2021;39(5):591–7.

29. Dror N, Carbone J, Haddad F, Falk B, Klentrou P, Radom-Aizik S. Sclerostin and bone turnover markers response to cycling and running at the same moderate-to-vigorous exercise intensity in healthy men. J Endocrinol Invest. 2022;45(2):391–7.
30. Gombos GC, Bajsz V, Pék E, Schmidt B, Sió E, Molics B, et al. Direct effects of physical training on markers of bone metabolism and serum sclerostin concentrations in older adults with low bone mass. BMC Musculoskelet Disord. 2016;17(1):1–8.
31. Neves RVP, Corrêa HL, Deus LA, Reis AL, Souza MK, Simões HG, et al. Dynamic not isometric training blunts osteo-renal disease and improves the sclerostin/FGF23/Klotho axis in maintenance hemodialysis patients: A randomized clinical trial. J Appl Physiol. 2021;130(2):508–16.
32. Koide M, Kobayashi Y. Regulatory mechanisms of sclerostin expression during bone remodeling. J Bone Miner Metab. 2019;37(1):9–17.
33. Sharma-Ghimire P, Buchanan S, Bemben MG, Knehans A, Campbell J, Bemben DA. Sclerostin and Dickkopf-1 Characteristics According to Age and Physical Activity Levels in Premenopausal Women. J Clin Densitom. 2021;
34. Kuo TH, Lin WH, Chao JY, Wu AB, Tseng CC, Chang YT, et al. Serum sclerostin levels are positively related to bone mineral density in peritoneal dialysis patients: A cross-sectional study. BMC Nephrol. 2019;20(1):1–10.
35. Falk B, Klentrou P. Elevation in Sclerostin After Exercise: Is It Affected by Age and Sex? Calcif Tissue Int. 2018;102(3):380–1.
36. Amrein K, Amrein S, Drexler C, Dimai HP, Dobnig H, Pfeifer K, et al. Sclerostin and its association with physical activity, age, gender, body composition, and bone mineral content in healthy adults. J Clin Endocrinol Metab. 2012;97(1):148–54.
37. Ardawi MSM, Rouzi AA, Qari MH. Physical activity in relation to serum sclerostin, insulin-like growth factor-1, and bone turnover markers in healthy premenopausal women: A cross-sectional and a longitudinal study. J Clin Endocrinol Metab. 2012;97(10):3691–9.
38. Straburzyńska-Lupa A, Cisoń T, Gomarasca M, Babińska A, Banfi G, Lombardi G, et al. Sclerostin and bone remodeling biomarkers responses to whole-body cryotherapy (− 110 °C) in healthy young men with different physical fitness levels. Sci Rep. 2021;11(1):1–11.
39. Lu CW, Wang CH, Hsu BG, Tsai JP. Serum osteoprotegerin level is negatively associated with bone mineral density in patients undergoing maintenance hemodialysis. Med. 2021;57(8):1–10.
40. Czajkowska M, Plinta R, Owczarek A, Olszanecka-Glinianowicz M, Skrzypulec-Plinta V. Circulating sclerostin levels in relation to nutritional status, sex hormones and selected bone turnover biochemical markers levels in peri- and postmenopausal women. Ginekol Pol. 2019;90(7):371–5.
41. Nelson K, Kouvelioti R, Theocharidis A, Falk B, Tiidus P, Klentrou P. Osteokines and bone markers at rest and following plyometric exercise in pre-and postmenopausal women. Biomed Res Int. 2020;2020.
42. Jürimäe J, Karvelyte V, Remmel L, Tamm AL, Purge P, Gruodyte-Raciene R, et al. Serum sclerostin concentration is associated with specific adipose, muscle and bone tissue markers in lean adolescent females with increased physical activity. J Pediatr Endocrinol Metab. 2021;34(6):755–61.
43. Gaudio A, Rapisarda R, Xourafa A, Zanoli L, Manfrè V, Catalano A, et al. Effects of competitive physical activity on serum irisin levels and bone turnover markers. J Endocrinol Invest. 2021;44(10):2235–41.
44. Kouvelioti R, LeBlanc P, Falk B, Ward WE, Josse AR, Klentrou P. Effects of High-Intensity Interval Running Versus Cycling on Sclerostin, and Markers of Bone Turnover and Oxidative Stress in Young Men. Calcif Tissue Int. 2019;104(6):582–90.