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Sclerostin as a biomarker of physical exercise in osteoporosis: A narrative review

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Osteoporosis, a disease of low bone mass, is characterized by reduced bone mineral density (BMD) through abnormalities in the microarchitecture of bone tissue. It affects both the social and economic areas, therefore it has been considered a lifestyle disease for many years. Bone tissue is a dynamic structure exhibiting sensitivity to various stimuli, including mechanical ones, which are a regulator of tissue sclerostin levels. Sclerostin is a protein involved in bone remodeling, showing an anti-anabolic effect on bone density. Moderate to vigorous physical activity inhibits secretion of this protein and promotes increased bone mineral density. Appropriate exercise has been shown to have an osteogenic effect. The effectiveness of osteogenic training depends on the type, intensity, regularity and frequency of exercise and the number of body parts involved. The greatest osteogenic activity is demonstrated by exercises affecting bone with high ground reaction forces (GRF) and high forces exerted by contracting muscles (JFR). The purpose of this study was to review the literature for the effects of various forms of exercise on sclerostin secretion.

KEYWORDS

sclerostin, osteoporosis, bone mineral density, physical activity, exercise, physical training

Introduction

Osteoporosis, as a disease of low bone mass, has been the subject of numerous studies worldwide for many years. The underlying cause of this disease is a disturbance of metabolic processes in bone tissue leading to excessive bone fragility (1). Recently, increasing scientific attention has focused on the protein called sclerostin, which, while

influencing the balance between bone tissue formation and resorption, simultaneously exhibits sensitivity to mechanical stimuli (2). This fact became the basis for research on the effects of physical exercise on bone tissue metabolism, including the processes that cause osteoporosis (3–5). In the present study, the relationship between the physical activity and exercise level and the preservation or increase in bone mineral density was correlated with the level of sclerostin in bone tissue.

Osteoporosis – low bone mass disease

Osteoporosis is a disease of the skeletal system characterized by increased bone fragility due to decreased bone mass and disruption of the microarchitecture of bone tissue. It is a disease that does not manifest obvious symptoms for a long time, despite its progressive, destructive effects on bone tissue. The first noticeable symptom is an osteoporotic fracture, otherwise known as a low-energy fracture (a spontaneous fracture caused by falling from one's standing position height or minor trauma) (4). Osteoporosis is diagnosed when bone mineral density (BMD) reaches a value of less than 2 standard deviations, compared to the average BMD value in young people (6, 7).

Osteoporosis as a lifestyle disease

Osteoporosis is recognized as a lifestyle disease on a global scale (8, 9). In 2010, 22 million women and 5.5 million men were diagnosed with low bone mass disease in European Union countries, while the number of new fractures was 3.5 million (7), 800,000 more have already been recorded in 2019 (6, 7). The most numerous fractures occurred in the proximal femur. In 2019, 25.5 million women and 6.5 million men were estimated to have osteoporosis in the European Union plus Switzerland and the United Kingdom. The population age 50 years or more is projected to increase by 11.4% in men and women between 2019 and 2034 and the annual number of osteoporotic fractures in those countries will increase by 25% (10). In Poland, 2 million patients over 50 years of age suffered from osteoporosis in a given year, and among them 168,000 suffered a fracture, 60% of them were women (7).

An osteoporotic fracture occurring as a result of decreased bone mass can lead to disability, especially in the case of femoral neck fractures. It devastates stabilization of life and leads to the reduction of its quality (11). Nowadays, 1 of 3 women over 50 years old (over breast cancer) and 1 of 5 men over 50 years old (over prostate cancer) are affected by osteoporosis (11, 12).

Osteoporosis is not only a social problem, but also an economic one. There is an increase in the aging population in developed countries. The economic burden of incident and prior fragility

fractures in 2019 was estimated at € 57 billion in European Union countries with Switzerland and United Kingdom (13). The population of elderly people (aged 65 years or more) in European Union countries will increase significantly, rising from 90.5 million at the start of 2019 to reach 129.8 million by 2050. This age structure of population and increased percentage of elderly people will increase the prevalence of osteoporosis. Consequently, this will increase the monetary outlay associated with both the treatment immediately following the fracture and the lengthy rehabilitation and subsequent care. The cost of treatment is estimated to increase from 593 million euros in 2010 to 753 million euros in 2025 (14, 15).

Causes and risk factors

The main cause of osteoporosis is low bone mineral mass, which depends on two types of factors: non-modifiable (impossible to eliminate) and modifiable (possible to change or eliminate).

Non-modifiable factors:

- age (there is a slow decline in bone mass after the age of 30);
- sex (women develop the disease four times more often than men);
- ethnic group (most common in Caucasian and Asian women);
- genetic conditions.

Modifiable factors:

- diet, eating habits (too little in the diet: vit. D, C and K, magnesium, phosphorus, potassium, omega 3 fatty acids, isoflavonoids; excess in diet: protein, vitamin A, sodium, alcohol, caffeine; smoking cigarettes);
- reduced physical activity;
- presence of other diseases (including hyperthyroidism, diseases affecting bone metabolism, diseases associated with impaired absorption, anorexia);
- use of certain medications (e.g., anticonvulsants, heparin, glucocorticoids) (14, 16, 17).

Symptoms of osteoporosis

Osteoporosis is a disease that is asymptomatic, especially in its early stages. Very often, the first symptom of already advanced disease is the so-called osteoporotic fracture (or low-energy fracture) (18). These fractures usually involve the proximal end of the femur, the proximal end of the tibia, the

spine, the pelvis, the proximal forearm, the proximal humerus and the ribs (19). According to Perry et al. (20), an osteoporotic fracture is a fracture that is disproportionate to the forces causing it, and occurs after a fall from one's own standing height level, after ruling out another cause such as a pathological fracture. The risk of fracture doubles with a 10% decrease in BMD from the mean value (5). Low-energy fractures are followed by pain of varying degrees of intensity when performing simple motor activities, such as sitting down, bending the trunk, and even when standing. As the disease progresses, along with successive fractures, there is a limitation of mobility, a decrease in body height by about 2–4 cm, skeletal deformation, deepening of spinal kyphosis (the so-called widow's hump), and symptoms of the respiratory, circulatory and digestive systems appear as a result (16).

According to many authors physical exercise ought to be one of the most suitable strategy in prophylaxis of osteoporosis, especially in postmenopausal women but not only, as a crucial element of life style (21–24).

Sclerostin – bone remodeling protein

Sclerostin is a human bone tissue protein encoded by the SOST gene. It is located on chromosome 17 in the 17q12-q21 region (25). Sclerostin belongs to the bone morphogenetic protein (BMP) family of antagonists, and is involved in the anti-anabolic processes of bone formation (26). There are several regulatory elements in the SOST gene responsible for its transcription in bone tissue cells (27). Sclerostin was first detected in adult human osteocytes through the study by Winkler et al. (26). Studies have also shown the presence of

this protein in hypertrophic chondrocytes (28). Sclerostin is a strong inhibitor of osteoblastogenesis (29, 30).

This protein plays a key role in maintaining the balance between the processes of bone formation and resorption (bone remodeling) (Figure 1). It is a specific negative regulator of bone formation. Expression of this protein occurs in bone, cartilage, kidney, liver, pancreas and heart, among others, but it is mainly produced in bone tissue by mature osteocytes and cementocytes, and is detectable in plasma (31). Studies in genetically modified mice have shown that deletion of the SOST gene in the rodent genome resulted in high bone mass, a characteristic of humans with hereditary sclerostin deficiency (27). Sclerostin is released to inhibit bone formation. Its production is mainly regulated by mechanical loads on bone tissue and hormones affecting bone metabolism (calcitonin, parathyroid hormones, glucocorticoids). Calcitonin inhibits osteoclast resorption and up-regulates sclerostin expression by osteocytes. Glucocorticoids increase sclerostin expression *in vivo* and *in vitro* as well but there is a difference between results, probably due to different treatment regimens (32). Moreover studies have shown that serum sclerostin concentration in humans and expression in rodent bone tissue decreased in response to PTH treatment. Although sclerostin acts in a paracrine manner, changes in bone cell activities partly regulated by osteocytes may be reflected by circulation of sclerostin concentrations (33).

Mechanical stimuli damaging the bone tissue are perceived by osteocytes as changes in cytoplasmic space. This leads to inhibiting the expression of sclerostin and to initiation of the bone tissue repair and formation processes (34). Exogenous sclerostin added to osteogenic cultures inhibits proliferation and differentiation of mouse and human osteoblastic cells. Moreover it decreases their life span by stimulating their apoptosis. Since sclerostin inhibits osteoblasts stimulation and

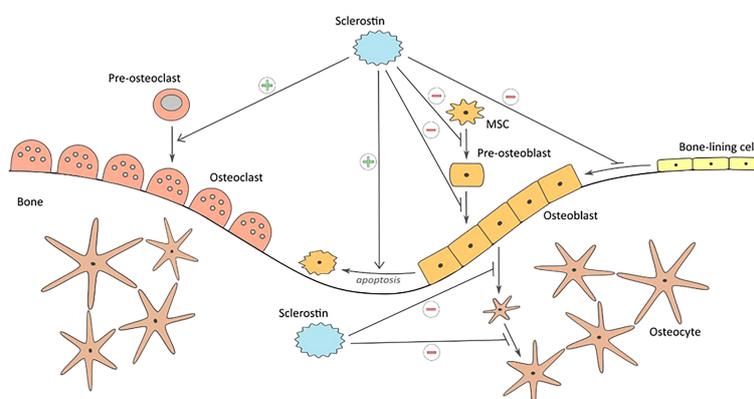


FIGURE 1

Influence of sclerostin on bone formation and resorption: inhibiting proliferation and differentiation of mesenchymal cells to osteoblasts, keeping the bone lining cells in dormant state, inhibition of bone matrix formation, inhibition of osteoblasts differentiation to osteocytes, promoting osteoblast apoptosis, and stimulating bone resorption.

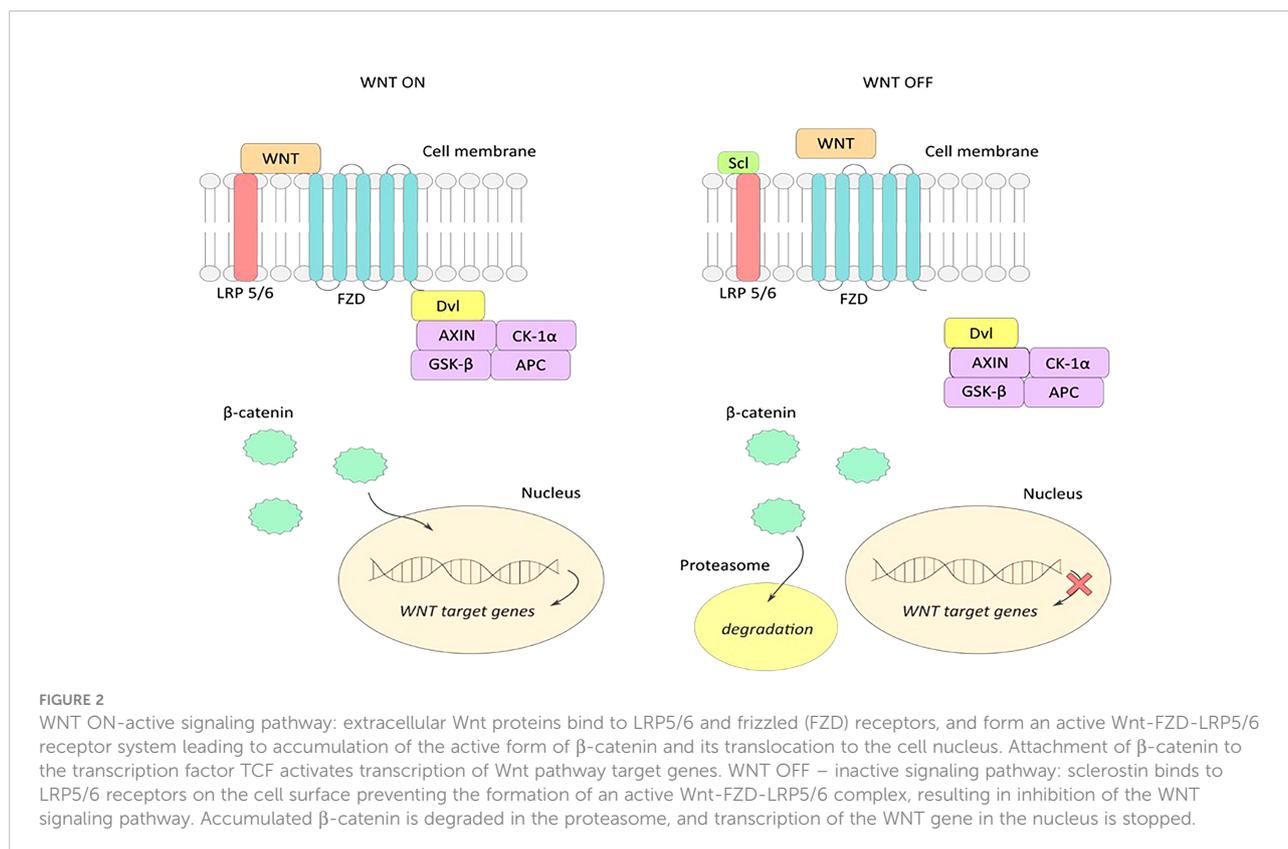
bone formation processes, it leaves cells lining the bone tissue at rest (35). Moreover, studies have shown that another extracellular matrix protein – periostin – impacts on inhibition of sclerostin (36). The activity sclerostin as a regulator in bone tissue metabolism is dependent on the Wnt/ β -catenin signaling pathway, whose modulator is periostin (37). The protein reacts directly with sclerostin and inhibits its antagonistic effect on this signaling pathway. As a consequence periostin promotes bone formation process. The study conducted by Bonnet et al. (38) has shown that periostin presence inhibits sclerostin expression and thereby increases level of osteoblasts. Mutual interaction of these two proteins has impact on bone tissue formation process in response to biomechanical loads.

Sclerostin as an inhibitor of the Wnt/ β pathway – catenin

The Wnt pathway proteins form a ligand for Frizzled and lipoprotein receptor-related proteins (LPRs) located in the plasma membrane of the target cell. As low-density lipoproteins (LDL), LPR receptors have transport and signaling roles in the pathway (30). Once proteins bind to their receptors, the conduction of signals from the cell membrane to the cell nucleus is triggered, where gene expression occurs. The combination of Dvl (Dishevelled)

protein with Frizzled receptor and axin with LRP receptor further leads to the activation of β -catenin, which then combines with TCF/LEF (T- cell transcription factor/ lymphocyte enhancer factor) transcription factors to form an active complex leading to the expression of target genes. Lack of Wnt protein expression or inhibition of their attachment to receptors degrades β -catenin and inactivates the signaling pathway (39). As an inhibitor of the Wnt pathway, sclerostin binds to LRP5/6 receptors and masks them from Wnt proteins (27). This blocks the formation of the Wnt-Frizzled-LRP5/6 system leading to inactivation of signaling pathway transmitters. This ultimately leads to inhibition of anabolic processes of bone tissue by deactivating osteoblast differentiation (40) (Figure 2). Additionally, *via* the Wnt pathway, the lifespan of osteoblasts is prolonged by inhibiting their apoptosis (39).

The discovery of the effect of sclerostin on Wnt pathway signaling may be crucial in the prevention and treatment of bone remodeling disorders. Studies in mice and rats have shown that increased mechanical loading on bone tissue resulted in decreased sclerostin activity by osteocytes (41). Similar studies in wild-type mice have shown that mechanical stress relief of tissue has the effect of increasing sclerostin production, which in turn reduces the activity of the Wnt pathway (42). According to Sharif et al. (43) downregulation of sclerostin might be effective in the treatment of osteoporosis (44). conducted an experiment in which 7180 postmenopausal women suffering from



osteoporosis were randomly divided into two groups – one group received romosozumab, a monoclonal antibody binding sclerostin, and the second group received placebo for 12 months. The risk of vertebral fractures in women receiving romosozumab was 73% lower, compared to placebo group. Also according to Brandenburg et al. (45) blocking sclerostin is a quite promising treatment perspective against osteoporosis moreover authors underly the Wnt signaling pathway and sclerostin secretion with evident cardiovascular calcification observed in different diseases.

Effect of physical activity on sclerostin and bone mass

The precise influence of physical training on sclerostin level stays unclear. Many studies show a negative correlation between increased physical activity and sclerostin level. Ardawi et al. (32, 46) conducted two experiments including premenopausal women divided into two groups, one of which consisted of physically active women, and the second one - sedentary women. In both experiments, blood and urine levels of sclerostin were significantly lower in physically active women. Similar results were obtained in women aged 50-75, suffering from osteopenia, by Janik et al. (47). Exposing osteocytes to sera of obese women undergoing physical activity program shows negative correlation between duration of the program (sera were collected 48 hours before training program, and then after 4, 6 and 12 months of training) and sclerostin level (48). Similar results were achieved by Wannenes et al. (49), who also noted lower mRNA levels of some key osteogenic factors, like Runx2, BNP4 and BALP, compared to control group. There was also a significant decrease in expression of cMyc and axin2, specific target genes of canonical Wnt/ β -catenin signaling pathway.

Studies including male participants show corresponding results. Hinton et al. (50) conducted a study in apparently healthy men aged 25 to 60 years whose physical activity in the past 24 months was ≥ 4 hours per week. The study group was divided into those doing resistance training or jump training and underwent their 12 month intervention. After this time, a significant decrease in serum sclerostin levels was examined and observed.

However, there are many experiments showing results contrary to the above. Pickering et al. (51) subjected young, healthy women to a 45-minute treadmill run. They achieved a significant increase in sclerostin level. Similar results were obtained by Gombos et al. (52), who observed an increase in sclerostin level after a single exercise session in both the resistance exercise and walking groups, compared to its baseline level.

Kouvelioti et al. (53) studied young, healthy women and subjected them to two exercise tests: interval running on a treadmill and cycling on a cycle ergometer. They obtained an increase in sclerostin level after training in both trials.

Interestingly, sclerostin levels returned to baseline values one hour after the end of training regardless of the exercise regimen.

During a study conducted by Armamento-Villareal et al. (54) older, obese individuals were randomly assigned to a control group that included diet or exercise, and exercise combined with diet. Attempts were made to see how weight loss would affect serum sclerostin levels. After a 12-month study, there was an increase in sclerostin in the diet group. It remained unchanged in the other groups. Śliwicka et al. (55) conducted a study in healthy men after a marathon. Sclerostin levels were observed to increase 1.3-fold 72 hours after the marathon compared to baseline.

Detailed information of different studies about influence of various form of physical activity/training in healthy/obese/athletes are presented in Tables 1, 2.

Next to sclerostin there are some other bone formation and resorption biomarkers which can be considered in relation to physical effort. Studies conducted by Kouvelioti et al. have shown that sclerostin level increase after five minutes in response to high intensity exercises but PINP (procollagen type I amino-terminal propeptide) and CTXI (cross linkedtelopeptide of type I collagen) do not correspond to the sclerostin response. Moreover, no correlation between sclerostin and PINP or CTXI values at any time of exercises was noted (56). Gombos et al. conducted experiments on three groups: resistance exercise group, walking group and control group. Increase in sclerostin level in both study groups with significant difference was observed but there was no significant change in BALP values in any of the groups. Next, the changes in CTX concentrations were significant in the resistance exercise group but not in the walking group. Physical effort of appropriate type, intensity and duration may affect bone formation and resorption causing detectable changes in serum concentrations of biochemical markers of bone metabolism such as PINP, CTXI, BALP and sclerostin. Forces generated by muscle contraction play an important role in stimulating bone resorption (58).

Physical activity of professional athletes and sclerostin level in bone tissue

Previous studies on the effects of physical activity levels on bone tissue sclerostin levels have shown that mechanical loading of bone tissue increases bone density, promotes tissue formation processes, and inhibits resorption. Are sclerostin levels at similar levels at very high exercise loads in professional athletes whose bones are subjected to daily high mechanical loads?

Many studies seem to support that thesis. Zagrodna et al. (53) compared sclerostin levels in professional football players and in healthy individuals with low levels of physical activity. A significantly higher mean level of sclerostin was observed in the football players group compared to the control group. Similar

TABLE 1 Studies showing the effect of physical activity on changing sclerostin levels.

Ref:	Group	Group Characteristic	Type of physical activity/ /exercise/ training	Sclerostin	Other biochemical parameters	Additional effects/ Comments
(32)	♀ n=120	Age: 30-42 years Premenopausal; BMI: 30.0 kg/m ² or less; sedentary lifestyle; stable body mass; not being on the special diet; lack of participation in another program during the study; randomly classified to PA training group (PAT) or sedentary (SG);	<u>Duration: 8-week</u> 120 min/ session, 4d/wk; (20 min walking, 25 min running, 10 min cycling, 10 min step ups, 35 min stretching and mobilizing the spine, upper and lower body);	↓ Sclerostin level by 33.9% (26.06 pmol/L pre-test and 19.46 pmol/L post-test) in PAT group; CG: no changes 25.69 pmol/L before, 26.41 pmol/L post-test;	PAT : ↑ IGF-1 pre- 50.26 ng/ml to 87.54ng/ml; ↑ BALP pre 8.16 U/L to 12.01 U/L after test; ↓ CTX from 166.5 to 151.5pg/ml; ↑ intact parathormone (PTH) from 2.76pmol/L to 3.38 pmol/L;	Exclusion criteria as in ref (46); No correlation were observed between Sclerostin and bone resorption markers in PAT group;
(32)	♀ n=1235	Age: 33.83 ± 8.41 years; Healthy; Premenopausal; Serum FSH level ≤ 15 mIU/L and a normal cycle; normal blood count, renal and hepatic tests; All inclusion data as above;	All group divided into four groups based on PA level: <30, 30-60, 60-120, >120 (min/week);	↓ Sclerostin level by 36% (17.60 pmol/L) in the group with PA >120 min/wk compared to the PA < 30 min/wk. (27.84 pmol/L). Sclerostin level in group with PA = 30-60 min/wk = 27.11 pmol/L, and in group with PA = 60-120 min/wk Sclerostin level = 21.64 pmol/L;	IGF was the highest in PA group >120min/wk (101.89ng/ml) and the lowest in PA group <30 min/ wk (49.27ng/ml); BALP was the highest in PA group >120min/wk (11.13U/L) and the lowest in PA group < 30min/wk (8.93U/L); CXT was also the highest in PA group >120min/wk (238.5pg/ml) and the lowest in PA group <30 min/ wk (191.7 pg/ml);	Exclusion criteria the same as ref (46); No correlation were observed between Sclerostin and bone resorption markers in PAT group;
(41)	♂ n=8	Age: 25.0 ± 4.0 years Range: 18-30 years; Obese; exercised no more 2-3x /week (150 min); waist circumference > 98cm; no cardiometabolic diseases, no medication, non-smoking; BMI = 35 ± 4 kg/m ² ;	<u>Duration: 4 weeks</u> of sprint interval training (SIT); 4 session/week /4 weeks on cycle ergometer; Session: 5 min warm-up, 8 x 20s work at 170% work rate at VO _{2peak} / 10s rest, total time = 9 min; Post training serum and subcutaneous white adipose tissue (WAT) biopsy have been taken;	↓ Sclerostin in serum 15 % pre- to post- SIT, 5/7 showed decrease, n.s.); WAT - ↓ sclerostin (37% pre v post);	↑ Wnt/ β-catenin signaling in WAT (52%); ↓ TNF-α (-0.36 pg/ml) and IL-6 (-1.44 pg/ml);	VO _{2 peak} increased (5%); no anthropometric changes after 4 weeks; Sclerostin in regulating human adipose tissue in response to exercise training;
(46)	Women (♀) n=50	Age: 64.8 ± 5.0 years; Range: 50-75 years; With clinically diagnosed osteopenia;	<u>Duration: 12-week</u> observation /12-weeks physical activity; Interval training on a cycle ergometer 4 min exercise/2 min rest, 3 times a week for 40 min);	↓ Sclerostin 12.04% (275.82 ng/mL pre-test and 242.60 ng/mL post-test);	↑ Osteocalcin (OC) level from 21.67 ng/mL to 23.64 ng/mL after the study; ↑ vit.D ₃ from 23.7 ng/ml to 32.55 after study; no changes of C-terminal telopeptide type 1 collagen (β-CTX/ β-CrossLaps); no changes of Alkaline Phosphatase (ALP) activity, Phosphorus and Calcium (Ca) level;	Supplementation with vit. D ₃ (1800IU) and Ca (500mg) during entire study in all women. No significant correlations between OC and Sclerostin;
(50)	♀ n=28	Age - 53 ± 8.2 years Obese; BMI ≥ 30 kg/m ² ; Body mass; 101.3 ± 3.9 kg; Sedentary lifestyle;	<u>Duration: 12-months</u> ; daily aerobic training; individualized prescribe physical activity and hypocaloric diet. Time of training session varied from 30 min/2 months and 60 min to the end of study;	↓ Sclerostin levels after 4, 6 and 12 months compared to baseline;	Decrease of insulin and leptin levels; increased of adiponectin receptor-1 (Adipo R1) after 6 and 12 months; time-dependent total β-catenin increase and others intracellular markers;	Significant reduction of body mass (to 91.0 ± 9.5 kg after 12 months due to fat and fat free mass; Body composition variation achieved after 4 months and maintained for for the end of study;
(52)	Men (♂) n=38	Age: 43.7 ± 10.1 years Range: 25-60 years. Healthy, physically active (≥4 hours of leisure-time physical activity/ week with low lumbar spine	<u>Duration: 12 months</u> ; All group randomized into two groups: (RT) resistance training and (JUMP) jump training; 8 cycles of 6 weeks	↓ Sclerostin levels by about 7% from 39.2 ± 11.6 pmol/L to 36.8 ± 13.3 pmol/L in both group; Mean % of change was	IGF-1 increase of 26% from 203 ± 71 ng/mL to 239 ± 109 ng/mL in both group; PTH - no changes; Whole body and LS BMD increased after 6 months	All participants were provided supplementation with Ca (1200mg calcium

(Continued)

TABLE 1 Continued

Ref:	Group	Group Characteristic	Type of physical activity/ /exercise/ training	Sclerostin	Other biochemical parameters	Additional effects/ Comments
		or hip BMD (>-2.5 SD T-score ≤ -1.0 SD);	training/1 week rest, progressive intensity; JUMP – 3x/wk; RT 2x/wk;	–4.5 ± 3.6% for JUMP and –9.5 ± 3.5% for RT;	in both groups; Hip BMD significantly increased at 6 and 12 months only in RT;	carbonate/d) and vit. D (10 µg/d);
(53)	♀ n=32	Healthy, Two groups: Practicing PA less than 120min/wk (age: 22.9± 1.5years) n=23; Resting test (age: 26.1±3.1 years) n=9;	<u>Duration: 45 min</u> low-speed, treadmill running test;	↑Sclerostin levels in practicing PA group by 44.3% from 290 ± 19 pg/mL before test to 410± 27pg/mL after Resting test: Stable level (303 vs 294 pg/ml);	Increase in level by 7.7% from 370.9+/-31.5 to 386.2+/-28.5 pg/mL);	
(54)	♀ n=150	Age: 58.80±7.5 years; With diagnosed osteoporosis/ osteopenia. Randomly assigned to three groups: Resistance (RG), Walking (WG), Control (CG);	<u>Duration: 46 min</u> RG: 8min warm-up, 30 min exercises with elements of core stabilization and muscle strengthening 3 sets/ 2 min rest, 8 min cool-down; WG: 46 min outdoor walking (3–6 MET), rhythm 100 steps/min CG: any intervention;	↑ Sclerostin levels in RG: pre - 6.8 pmol/L to 29.8 pmol/L post intervention; WG: pre- 23.6 pmol/L to 29.9 pmol/L post-; CG: Pre - 24.0 pmol/L v 24.20 pmol/L post intervention;	RG: ↑CTX/β-CrossLaps) (303.60 to 276.40 pg/mL post intervention) WG: ↑Bone-Specific Alkaline Phosphatase (BALP);	<u>Exclusion criteria:</u> Any condition influencing Ca and bone metabolism (expect dietary Ca and vit. D supplementation), Ongoing hormone replacement therapy, renal and hepatic diseases, cardiovascular disease, physical injury, anabolic steroids, anticoagulants, diuretics within last 6 months;
(55)	♀ n=20	Age: 22.5±2.7 years Range: 18-28 years. Healthy, recreationally active (2 to 5x/ wk , free of injuries or chronic conditions, having no fracture in the last year, nonsmokers, and not taking any medication or dietary supplements (protein, vit. D, and calcium);	<u>Duration: 16 min</u> Two exercise tests: High intensity interval running (HIIR) on a treadmill and HI cycling on a cycle ergometer (HIIC); HIIR and HIIC lasted 8 x 1 min running /cycling at ≥90% of HR _{max} separated by 1 min passive recovery between work; During both trials 5x blood samples were collected: pre and 5 min, 1h, 24h, and 48h post exercise;	↑Sclerostin level in 5 min after exercise in both trials, in HIIR from 100.2 to 131.6 pg/mL and from 102.3 to 135.8 pg/mL in HIIC. Recorded significant effect of time but not exercise mode; at 1h after exercise Sclerostin level returned to pre- test value;	No significant time effect for CTXI in both trials; A significant time effect for procollagen type I amino-terminal propeptide (PINP) was found only in HIIR; No significant differences in CTXI and PINP concentrations between both trials at any time point. No significant correlations were found between the sclerostin, CTXI and PINP levels at any time point;	During both training mean heart rate was >90% of HR _{max} (93.2 ±4.7% for HIIR and 90.2 ±4.8% for HIIC) Borg rating of perceived exertion (RPE) was recorded in both trials = 19;
(56)	♀♂ n=107	Age: ≥65 years, Obese (BMI ≥30kg/m ²); no physically active; stable body weight (±2 kg) in past year; on stable medications within last 6 months;	<u>Duration: 12 weeks</u> ; All participants divided into four groups: control group, with diet induced weight loss, exercise training group, diet and exercise group. Exercised groups: 90 min (15 min flexibility exercise, 30 min aerobic, 30 min progressive resistant exercises 15 min balance exercise);	↑ Sclerostin levels in the diet group by 6.6± 1.7% and 10.5% ± 1.9% in 6 and 12 month compared to baseline. There was no changes in the other groups;	Body weight decreased in diet and in diet + exercise but not in exercise and control;	All received with Ca (1500 mg/d) and vit. D (1000 IU/day); Exclusion of subjects taking bone-acting drugs, sex-steroid compounds within last year;
(53)	♂ n=14	Age: 22.1 ± 4.05 years; Range: 18-39 years; Volunteers; Healthy, Active Duty Army Soldiers; not having used glucocorticoids in the past 2 years; BMI: 27.3±3.8 kg/m ²	Single bout of exercise; Randomized crossover study; 10 sets /10 repetitions of plyometric jumps at 40% of 1 -RM leg press or a nonexercised control period; Blood was drawn at baseline, 12, 24, 48, 72h following exercise or rest	No significant effect of time or exercise on sclerostin levels;	Markers of bone metabolism: (PTH, Ca); markers of bone formation: bone Alkaline Phosphatase (BAP); osteocalcin (OCN); markers of bone resorption (CXT (lower in 12h in comparison to baseline), Dickkopf-1 (DKK-1));	Calcium controlled diet (1000mg/day) was implemented;

(Continued)

TABLE 1 Continued

Ref:	Group	Group Characteristic	Type of physical activity/ /exercise/ training	Sclerostin	Other biochemical parameters	Additional effects/ Comments
(57)	Girls and boys ♀ n=12 ♂ n=12	Age: ♀ - 11.00 ± 0.5 years, ♂ - 10.2 ± 0.3 years. All girls premenarcheal; all children recreationally active; no difference between ♀ and ♂ in daily energy intake and Ca intake, but below recommendation for children in this year. BMI <85 th percentile for their age; no fracture (within 6 past months); growth no premature or delayed, no pharmaceuticals;	<u>Duration and exercise:</u> High impact of plyometric exercise protocol in form of circuit training stations (3x): 5 min warm-up, different stations, 3 min rest between stations; exercises: jumping jacks, lunge jumps, single-leg hops, hurdle jumps, tuck jumps, drop jumps (entire session about 100-144 jumps);	↑Sclerostin in ♀ in comparison to boys before (♀-187.1 pg/ml v ♂-161.4 pg/ml) and at 24h post exercise (♀-200.3 pg/ml v ♂-162.9 pg/ml); In girls post exercise the level was lower in comparison to the pre exercise at 5 min and 1h, at 24h much higher than in previous stages. No changes in boys post exercise;	DKK-1 - ↓in ♀ than in ♂ at the same time; no changes post exercise in both groups. OPG - ↓ in ♀ than in ♂ at the same time, except 24h; RANKL (receptor activator of nuclear factor kappa-β ligand) ↓ in ♀ than in ♂ in each stage of study; In ♀ post exercise lower than pre exercise; no changes in ♂ post exercise;	Plyometric training induces osteokine response favoring osteoblastogenesis than osteoclastogenesis;

♀, women, ♂ men, ↓ reduced level, ↑ decreased level.

TABLE 2 Studies depicting the effects of physical activity on the bone mass of professional athletes.

Ref:	Group	Group Characteristic	Type of physical activity/ training	Sclerostin	Other biochemical parameters	Additional effects/Comments
(58)	♂ n=10	Age: 41±7.7 years Range: 32-51 years Healthy; recreational runners;	Visegrad Marathon (42.195 km);	↑ Sclerostin levels 1.3-fold 72 h after the marathon in comparison to the baseline;	24 h after marathon, an increase in myostatin (1.2-fold), osteoprotegerin (OPG) (1.5-fold) and PTH (1.3-fold), high-sensitive interleukin-6 (hsIL-6) (1.9-fold), myoglobin (4.1-fold), hs C-reactive protein (hsCRP) (5-fold), and tumor necrosis factor α (TNFα) (2.6-fold); After 72h and in myostatin (1.2-fold), irisin (1.1-fold), OPG (1.3-fold) and PTH (1.4-fold), hsIL-6 (1.4-fold), TNFα (1.9-fold);	Sclerostin was correlated with hsIL-6; negative correlation was noted for sclerostin and myostatin and PTH and OPG;
(59)	♂ n=59	Range: 17-37 years; Healthy; Athletes- footballers (A) n=43; aged 26.5 ± 3.4 years body mass 76.3 ± 7.3 kg, BMI 23.1 ± 1.5kg/m ² ; Mean career duration 14.7 ± 4.5 years; Non-athletes (NA) n=16; Aged 29.5 ± 4.3 years, non-smokers; low physical activity per week; body mass 81.7 ± 8.7 kg; BMI 25.6±3.1 kg/m ² ; All NA participants worked indoors;	Winter season; Training lasted every day by 3 h/d in uniforms covered 80% of their body;	↑ sclerostin in A group (35.3 ± 8.9 pmol/L) than in the NA group (28.0 ± 5.6 pmol/L);	A group had higher concentrations of P1NP (145.6 ± 77.5 vs 61.2 ± 22.3 ng/ml; and vit. D ₃ (16.9±8.4 vs 10.3 ± 4.3 ng/ ml; lower concentrations of PTH (25.8 ± 8.3 vs 38.2 ± 11.5 pg/ml in comparison to NA. VO ₂ max = 56.09 ± 4.29 ml/kg/min in A group;	Vitamin D deficiency was found in 77% of A and 100% of NA;
(60)	♂ n=9	Age 28.8 +/- 3.6 years; Healthy, cyclists;	The 3-week stage cycling race Giro d'Italia 2012 Saliva was collected at days:-1, 4, 8, 12, 14,	↑Sclerostin; average level of sclerostin on the 1 st day: 254.5 ± 134 pg/ mL, in 12 th day:	Cortisol remained constant, testosterone decreased at day 4, estradiol and DHEA firstly increased and then	DHEA and estradiol correlated with the physical effort and the bone-muscular markers;

(Continued)

TABLE 2 Continued

Ref:	Group	Group Characteristic	Type of physical activity/ training	Sclerostin	Other biochemical parameters	Additional effects/Comments
			19, 23; Blood and urine were collected at days: -1, 1, 23;	477.5± 137.9 pg/mL, in 23th day: 762.1 ± 143.3 pg/mL;	returned to basal levels. LDH, CK, AST, and urinary Ca and phosphorus increased;	
(61)	♀ n=62	Age - 14-18 years; Eumenorrheic adolescents; Healthy;	Three study groups: rhythmic gymnasts (RG), swimmers (SW), untrained control group (UC);	↑ Sclerostin levels was higher in RG: (129.35 ± 51.01 pg/ml; by 74%) and SW; (118.05 ± 40.05 pg/ml; by 59%) v UC: (74.32± 45.41 pg/ml);	No differences between groups in preadipocyte factor-1 (Pref-1), Osteocalcin and CTx;	Adolescent have higher sclerostin compared to UC; Sclerostin correlated with whole-body BMD and lumbar spine (LS) areal bone mineral density (aBMD) in RG, and femoral neck aBMD in UC. No correlation was found between sclerostin and BMD in SW;
(61)	♂, ♀ n=61 Control n=16 8 ♂ 8 ♀	Age: 27.2 ± 6.8 years; 15 – Italian national rugby team (29.1 ± 1.7 ys; 13 professional cycling team (31.1 ± 2.7 years); 6 professional tennis players (23.2 ± 6.2 years); 11 professional endure motorcycling team (29.1 ± 11.8 years); 8♀ professional basketball players first Italian league (27.0 ± 3.0 s); 8♀ figure ice skaters Italian national (19.5 ± 4.9 years);	All athletes classified into three group based on work-load: - (1) weigh bearing, (WB: rugby, endure, basket), (2) non-weight bearing (NWB: cycling), (3) high impact sports (HI: ice skating, tennis); Blood taken after 10 min resting;	Sclerostin level was the same for entire group of athletes and control (0.42 ± 0.09 ng/ml, n.s.); Significant differences between genders in whole cohort: ♂-0.45 ± 0.07 ng/ml, ♀-0.40 ± 0.09 ng/ml) and sedentary group: ♂-0.36 ± 0.05 ng/ml, ♀-0.46 ± 0.09 ng/ml; Differences between men in athletes – rugby players (0.44 ± 0.11ng/ml) and endure (0.42 ± 0.04 ng/ml) had much higher Sclerostin level than cyclists (0.34 ± 0.08 ng/ml);	ALP – 22.4 ± 7.6U/L in athletes and 24.3 ± 8.5U/L in sedentary; Differences of ALP between whole cohort of men and women (21.3 ± 6.8 U/L v 26.1 ± 8.8 U/L) and in athletes: men (20.4 ± 5.5U/L v women (28.4 ± 9.8U/L); No differences in sedentary group. No differences in athletes men and women between sport categories;	Significant correlation were noted for sclerostin level and age; no differences within gender in entire athletes group. No correlation between sclerostin level and category of sport in females. No gender differences in athletes group (♂-0.41 ± 0.09 ng/ml v ♀-0.45 ± 0.07 ng/ml); No differences in ♀ group of athletes within sport category and to sedentary; In WB athletes sclerostin much higher (0.43 ± 0.0ng/ml) than in NWB athletes (0.34 ± 0.08 ng/ml);
(62)	♀ n=64	Age: 9-10 years Healthy; Gymnasts (RG), n=32; Untrained control (UC), n=32;	Comparison between two groups;	RG: Sclerostin 19.8 ± 6.3 pmol/l was higher in comparison to UC;	RG: Pref-1 (1.6±1.0 ng/ml) was higher than in control (untrained);	Sclerostin and Pref-1 levels are higher in RG compared to UC girls. Sclerostin was related to adiponectin in UC;
(63)	♂ n=9	Age: median 45 years; No specific inclusion and exclusion criteria; Healthy; amount of training about 100km during winter time and more than 200km during summer, up to 7000km/year;	Spartathlon race 246 km (ultramarathon food race). Runners start in Athens and have to reach Sparta with 36h; It took them 34h 3 min (32h 29 min; 35h 3 min) to reach Sparta;	↓Sclerostin after the race (pre- 29.15 pmol/L v 27.75 pmol/L, post- race (n.s.);	Significant ↑myostatin (23.73 ng/ml v 26.73 ng/ml); ↑↑Follistatin (300.8 pg/ml v 1211 pg/ml; ↓ Dkk-1 (38,68 pmol/L v 38.14 pmol/L); ↓ P1NP (54.37 ng/ml v 41.14 ng/ml); ↑ CTX (0.299 ng/ml v 0.542 ng/ml); The increase of myostatin can reflect muscle catabolism processes induced by over strenuous exercise;	

♀, women, ♂ men, ↓ reduced level, ↑ decreased level.

conclusions may be drawn from comparing sclerostin levels in athletes from many other sports with different workloads to people who do not practice any sports (60, 64).

Sclerostin levels, already high in professional athletes before physical effort, seem to grow even higher during long-term exercise. The study conducted by Grasso et al. (59) involved 9 professional cyclists who raced a total distance of 3503.8 km during the 3-week stage cycling race Giro d'Italia 2012. One of the many parameters measured was the mean sclerostin level in

the blood samples of the competitors taken in the morning during the intervals between successive stages. The authors showed that the blood sclerostin level in the cyclists increases during the race in successive stages. The implication is that prolonged high-intensity exercise, as during a 3-week cycling race, may lead to increased bone resorption by steadily increasing serum sclerostin levels during exercise and maintaining high levels between activity stages. This wouldn't be surprising, since there's already data showing that consistent

high loads due to continuous training stimulus increase the sclerostin level through increased bone metabolism (60), which is especially evident in strength sports (61).

Physical training in the prevention of osteoporosis

Physical training to prevent bone mass loss and to maintain or increase BMD levels is based on different principles than training to improve cardiovascular or muscular capacity. When properly selected, composed and conducted, the training has an osteogenic effect, while improper training can lead to the so-called saturation of the osteogenic response to a mechanical stimulus. The bone tissue then becomes resistant to the training stimulus (5).

Exercise as a mechanical stimulus to the skeletal system increases bone mineral density through a mechanotransduction mechanism in bone, involving the sclerostin protein as described previously (62, 65). Based on that, the effectiveness of physical training in the prevention of skeletal disorders can be assessed by BMD, depending on factors such as:

- type of training (66);
- exercise intensity (63, 67);
- frequency of exercises, breaks between exercises and series (63, 67)
- the number of body parts involved (68)
- systematic approach (69)

Exercise to prevent osteoporosis must be of such intensity that bone tissue shows a threshold sensitivity to mechanical stimulus, because bones show an osteogenic effect only when this threshold is exceeded (70). Studies among menopausal women have confirmed the effect of high-intensity walking on increasing BDM, particularly in the lower body. The threshold for osteogenic activity in the study group occurred at a speed of just over 6.14 km/h and a load of 872.3 N, which translated to 80% of age-specific maximum heart rate (HRmax), 74% of VO₂max, and 115% of ventilation threshold (71). If the stimulus intensity is increased during training or a training cycle, the potentiation of the osteogenic effect will occur until the so-called saturation of the osteogenic response (72).

As per Bailey et al. (69) daily exercises results in greater osteogenic activity. Moreover, Ardawi et al. (32) showed that physical activity levels above 120 min per week result in significantly higher serum sclerostin levels, leading to increased bone mineral density. Exercise should involve as many body parts as possible because of the fact that osteogenic activity occurs in the part of skeleton directly loaded by the mechanical stimulus (68). Breaks between repetitions of a given exercise in a cycle allow the mechanical stimulus to activates more bone-forming cells or osteoblasts and achieve an osteogenic effect with fewer repetitions, but also to shift the threshold at which saturation of the osteogenic response occurs later (73, 74). Moreover exercise should be repeated several to a dozen times, and the intervals between exercise cycles should be more than 4 - 8 hours in order to avoid saturation of the osteogenic response (72, 73).

Research to date confirms that exercise has a beneficial effect on bone health (75). However, the size of osteogenic effect obtained depends not only on the factors mentioned above, but also on the type of physical training performed (5). Exercise exerts two types of mechanical load on the bone in the form of JFR e.g. running, walking, climbing stairs and GRF e.g. rowing, weightlifting. A study of 39 postmenopausal women found that both types of exercise resulted in a significant increase in BDM, but GRF-based training resulted in a greater increase in both the entire body, and the individual skeletal parts tested (76). Table 3 lists the types of exercise along with the degree of osteogenic effects (77).

High- and moderate-intensity exercise involving both JFR and GRF causes a strong osteogenic effect. The greatest osteogenic activity is found in running, tennis, and weight training using equipment, among others. In addition, a slightly higher mean BDM (across skeletal parts) was observed among women performing GFR-based exercise training (76). Power training based on dynamic exercises will be more effective in preventing osteoporosis than training based on strength exercises (72).

There is also an interesting question of the influence of the level of physical activity during childhood and adolescence on bone mass in elderly people. There's data showing that peripubertal exercise causes at least two types of skeletal adaptations: periosteal expansion and better trabecular microarchitecture (78). Especially high sensitivity of the

TABLE 3 Types and examples of exercises with their corresponding osteogenic effect coefficient.

Type of physical exercise	Example	Osteogenic effect coefficient
Exercises without or with small GRF and JRF	cycling, swimming	0
Exercises or games with small GRF and JRF	bowling, walking	1
Exercises or games with moderate GRF and JRF	dancing, aerobic exercises with light loads rhythmic	2
Exercises or games with GRF > 1000μE	Running, aerobic exercise with heavy loads, tennis, squash	3
Exercises with large JRF	strength training using equipment	3

skeleton to exercise at this time of life may be due to high growth hormone level. The extent to which the forementioned skeletal changes may last to the old age remains unclear. Nevertheless, it is worth mentioning that structural changes may persist despite the loss of bone mass (79, 80)

Studies have shown that exercise programs which includes at least two kinds of activities such as weight-bearing activities, progressive resistance training (PRT) and/or power training and balance/mobility training have positive effect on skeletal system and fall-related risk factors (81). Detailed training program recommended in osteoporosis and osteoporotic fractures prevention with physical activities, frequency, intensity and sets/repetitions descriptions is presented in Table 4.

Exercising regularly has a beneficial effect on health but not every type of activity shows equal osteogenic effect. Previous studies about aerobic training such as swimming, cycling or walking and its positive impact on all body systems are contrary to those suggesting that these activities do not provide notable stimulus to bone and next to that do not cause an osteogenic effect. However there are types of activities which have positive influence

on bone health. A lot of bone adaptive responses depends on magnitude, rate and frequency of loading. They must be dynamic, cyclic and induce relatively high bone strains. In order to elicit a bone system adaptive response relatively few loading cycles with adequate load intensity are required. Moreover breaks between repetition are equally or even more important than number of repetitions in cycle. Finally, loading diversification is required to stimulate an adaptive skeletal response (83).

Summary

Based on the foregoing considerations, sclerostin is a marker to determine the effect of exercise on bone tissue processes. By inhibiting tissue formation processes, this protein mediates bone remodeling. In recent years, numerous studies have shown that properly selected physical training has a preventive effect on skeletal diseases, especially osteoporosis, by increasing bone mineral density (82, 84). This disease, which is considered to be a civilization disease, is a huge problem both socially and economically, so the

TABLE 4 Training program recommended in osteoporosis and osteoporotic fractures prevention (82).

Type	Progressive resistance training	Weight-bearing impact exercise	Challenging balance, stepping and mobility
Exercises	Exercises: squats, lunges, hip abduction/adduction, leg press, thoracic/lumbar extension, plantar/dorsi-flexion, abdominal/postural exercises, bent over row, wall/counter/floor pushup, triceps dips and lateral shoulder raises.	Multidirectional and novel loading activities: jumping, bounding, skipping, hopping, bench stepping and drop jumps or participation in weight-bearing sports (e.g., tennis, dancing, netball, recreational gymnastics and football).	Include static and dynamic movements: reduce base of support, shift weight to limits of stability (e.g., leaning/ reaching), perturb center of mass, stepping over obstacles, alter surface (foam mats) and multi-sensory activities (e.g. reduce vision) and dual tasking. Consider Tai Chi and rapid stepping movements in different directions.
Frequency	≥2 days per week	4- 7 times per week	Accumulate at least 2- 3 h per week. This could be achieved within other exercise bouts during the course of a week.
Intensity	Start with slow and controlled movements and emphasize correct lifting technique. Progress to 75-85% of 1-RM (5-7/8 on Borg 0-10 point RPE scale or hard-very hard). Consider progressing to high velocity (power) resistance and functional training for lower extremities to increase rate of loading and improve movement speed and power. Light-to-moderate loads (30-70% 1-RM) can be used.	Moderate to high impact activities (>2-4 BW), as tolerated. Increase height of jump, step height, weights or a weighted vest and incorporate change of direction movement. For sedentary individual and those with poor muscle strength or function, start with PRT for 6-12 weeks to strengthen lower limb muscles and/or introduce low impact exercises and core muscle training.	Must be progressively challenging (close to limit of balance) and preferably specific to everyday functional tasks. Progress to dynamic/mobility and rapid stepping exercises and introduce secondary motor or cognitive tasks to improve dual task performance.
Sets/Repetitions	≥8 exercises targeting muscles attached too or crossing the hip and spine At least 2 sets 8- 12 repetitions 1- 3 min rest between sets	50-100 jumps per session divided into 3-5 sets of 10-20 repetitions. 1-2 min rest between sets.	Incorporate into daily activities or combine with resistance or impact exercise (e.g., balance for 10-30 s while waiting for kettle to boil, cooking or watching TV).
Precautions	Emphasize exercises performed in a standing (weight-bearing) position. Use caution with lifting weights higher than shoulder height to limit rotator cuff injury. For individuals with low spine BMD avoid spine flexion or twisting and encourage spine-sparing strategies. Include core stability and postural strengthening/endurance exercises as well as pelvic floor activities.	Teach correct landing technique. Progress slowly. Intersperse between strength and balance exercises. For those with incontinence issues first strengthen pelvic floor muscles and avoid jumping exercises with feet wide apart. For those with (osteo)arthritis, prescribe within limits of pain.	For individuals with impaired balance or high fracture risk, start with static and progress to dynamic balance exercises.

BW, body weight; RPE, Rating of Perceived Exertion; 1-RM, one-repetition maximum.

In accordance with most national physical activity guidelines, women should accumulate ≥150 min per week of moderate to vigorous intensity physical activity. To realistically accomplish all of the above therapeutic goals, one could combine activities e.g., lunges as a leg strengthening exercise that also challenges balance, step class that includes impact exercise and moderate/vigorous aerobic challenge and simultaneously challenges balance (91).

fact of the beneficial effect of physical exercise as the cheapest and most beneficial cure is all the more convincing. This study demonstrates the relationship between the physical activity level and serum sclerostin level and bone mineral density, as osteogenic factors. This raises the question: why do near-maximal mechanical stress and high bone mineral density in athletes not correlate with reduced blood sclerostin levels, as in people with low or moderate activity levels? Are there other mechanisms involved in the osteogenic response with very high mechanical loading? Furthermore, it has been noted that not every type of physical activity results in a significant increase in BMD. According to selected studies osteogenic activity is affected by the load of exercise, type of physical training, and its effectiveness depends on the intensity and frequency of exercise, and the intervals between repetitions, among other factors. Moreover the very essential factors are gender and season, because in bone turnover markers secretion the seasonal variations was observed (85). The question remains, will osteoporosis be preventable and treatable in the near future with well-timed physical training as an alternative to medication?

There is still a need for further research to answer this question and to clearly establish the dynamics of sclerostin changes in relation to the factors influencing its secretion.

Author contributions

Conceptualization: EM-C, AO, and AK. Writing—original draft preparation: AO, AK, MK, MC, EA, AS, FC and EM-C.

Supervision: EM-C and FC. Project administration: EM-C. Funding acquisition: EM-C and AK. All authors have contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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