

# Sclerostin as a novel marker of bone turnover in athletes

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**ABSTRACT:** Sclerostin is a protein secreted by osteocytes that acts as an inhibitor of bone formation. It has been shown that physical activity affects sclerostin concentration and thus bone remodelling. The aim of the study was to evaluate serum concentrations of sclerostin, selected bone turnover markers (PTH, P1NP), 25(OH)D3 and the intake of calcium and vitamin D in physically active versus sedentary men. A total of 59 healthy men aged 17-37 were enrolled in the study (43 athletes and 16 non-athletes). The mean sclerostin concentration in the group of athletes (A) was significantly higher than in non-athletes (NA) ( $35.3 \pm 8.9$  vs  $28.0 \pm 5.6$  pmol·l<sup>-1</sup>,  $p = 0.004$ ). A compared with NA had higher concentrations of P1NP ( $145.6 \pm 77.5$  vs  $61.2 \pm 22.3$  ng·ml<sup>-1</sup>,  $p = <0.0001$ ) and 25(OH)D3 ( $16.9 \pm 8.4$  vs  $10.3 \pm 4.3$  ng·ml<sup>-1</sup>,  $p = 0.004$ ) and lower concentrations of PTH ( $25.8 \pm 8.3$  vs  $38.2 \pm 11.5$  pg·ml<sup>-1</sup>,  $p = <0.0001$ ). Vitamin D deficiency was found in 77% of A and 100% of NA. A and NA had similar daily energy intake. They did not differ as to the intake of calcium and vitamin D. We observed a negative correlation between the serum concentrations of sclerostin and calcium in the studied subjects. Our results suggest that regular, long-lasting physical training may be associated with higher concentration of sclerostin. It seems that increased sclerostin is not related to other bone turnover markers (PTH, P1NP).

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## INTRODUCTION

Regular physical exercise affects bone remodelling. In recent years it has become clear that the cells actively involved in bone remodelling include not only osteoblasts and osteoclasts but also osteocytes.

Bone resorption and bone formation are assessed by measuring the concentrations of certain chemicals referred to as bone turnover markers [1]. The International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) suggest using procollagen type I N terminal peptide (P1NP) as a marker of bone formation and C-terminal telopeptide of type I collagen (CTX) as a specific marker of bone resorption [2].

It should be noted here that while the above markers of bone turnover reflect the main functions of osteoblasts and osteoclasts, they do not take into consideration the significant role of osteocytes. Sclerostin seems to be a good marker of bone turnover that is involved in bone remodelling and may reflect the activity of osteocytes [3].

Sclerostin is a product of the SOST gene, which is located in the 17q12-21 chromosomal region. Sclerostin acts as a negative regulator of bone formation, through inhibition of the Wnt signalling pathways, which is of critical importance for the development and function of osteoblasts [4]. Sclerostin is a glycoprotein that belongs

to the DAN family of bone morphogenetic protein (BMP) antagonists [5] and contains a C-terminal cysteine knot-like domain [5, 6].

The expression of sclerostin by osteocytes is regulated by mechanical forces and hormones known to affect bone metabolism, such as parathyroid hormone, calcitonin and glucocorticoids [7]. Mechanical stimulation of the skeleton induces bone formation through either exercise or experimental loading, while immobilisation increases the number of sclerostin positive osteocytes [8, 9]. Sclerostin concentrations are also affected by sex steroids [10].

Sclerostin changes bone mass through alterations in osteocyte and osteoblast Wnt and prostacyclin signalling pathways [11]. Sclerostin influences vitamin D metabolite concentrations, the concentrations of phosphaturic peptides such as fibroblast growth factor 23 (FGF-23), and the renal handling of calcium and phosphorus [12]. In the absence of sclerostin, concentrations of the active metabolite of vitamin D  $1\alpha,25(\text{OH})_2\text{D}$  are increased, whereas concentrations of the inactive metabolite of vitamin D  $24,25(\text{OH})_2\text{D}$  are decreased [13, 14]. In the absence of sclerostin the excretions of urinary Ca is diminished, suggesting a direct effect of the protein on renal Ca excretion. To respond to alterations in bone mass,  $1,25(\text{OH})_2\text{D}$

and FGF-23 concentrations are altered, as is the renal excretion of calcium, thereby resulting in a positive calcium and phosphorus balance [12, 15].

Physical exercise affects serum sclerostin levels. Sclerostin concentrations decrease in response to mechanical strain [16, 17] and increase during bed rest [9]. However, an increase of sclerostin concentration has been observed as a consequence of a 3-week bicycle race [18]. There are only a few reports in the available literature on the effects of regular physical activity of several years' duration (the case of professional athletes) on basal serum concentrations of sclerostin [19, 20, 21]. Therefore we wanted to compare concentrations of sclerostin, selected markers of bone turnover (PTH, P1NP) and 25(OH)D3 in professional athletes and male controls characterized by a low level of physical activity.

## MATERIALS AND METHODS

The study was conducted in December in 59 healthy males aged 17-37. Forty-three of them were professional football players (group A, athletes) with mean career duration of  $14.7 \pm 4.5$  years. The mean age in A was  $26.5 \pm 3.4$  years, body weight  $76.3 \pm 7.3$  kg, height  $182.0 \pm 6.6$  cm and BMI  $23.1 \pm 1.5$   $\text{kg} \cdot \text{m}^{-2}$ . The mean maximal oxygen consumption in A was  $56.09 \pm 4.29$   $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . Athletes were in the competitive phase and undertook similar exercise loads. In the winter season, they trained outdoors for about 3 hours daily in Wrocław, Poland ( $51^{\circ}10'N$ ) in uniforms covering 80% of their bodies. The control group (group NA, non-athletes) consisted of 16 healthy, non-smoking men whose mean age was  $29.5 \pm 4.3$  years and whose level of physical activity was low ( $1357.36 \pm 1720.48$  MET h  $\cdot$  week $^{-1}$ ). The mean body weight in NA was  $81.7 \pm 8.7$  kg, height  $178.7 \pm 4.1$  cm and BMI  $25.6 \pm 3.1$   $\text{kg} \cdot \text{m}^{-2}$ . All subjects from the control group worked indoors.

Neither A nor NA used any food supplements/medications containing vitamin D or calcium.

Height was measured with a stadiometer and body mass with an electronic scale.

The level of physical activity in the control group was determined using the Polish version of the International Physical Activity Questionnaire (IPAQ, short form). Food intake was evaluated by dietary recall (we evaluated foods and beverages the subjects consumed over 24 hours for 7 days). The computer software Dieta 5.0 was used to calculate the quantities of vitamin D and calcium for each of the soccer players and each of the controls.

The study was approved by the Bioethics Committee of the University School of Physical Education in Wrocław, Poland.

### Biochemical analysis

Blood sampling was carried out fasting at 8.00 am (after a 24-hour period without training in the group of football players). Serum was separated from the samples and stored at  $-70^{\circ}\text{C}$ .

Serum concentrations of 25(OH)D3, parathormone (PTH), and procollagen type I N-terminal peptide (P1NP) were determined by

electrochemiluminescence (ECLIA) using the Elecsys system (Roche, Switzerland). The intra- and interassay coefficients of variation (CVs) and the limit of detection were respectively: 5.6%, 8.0% and  $4 \text{ ng} \cdot \text{ml}^{-1}$  ( $10 \text{ nmol} \cdot \text{l}^{-1}$ ) for 25(OH)D3; 4.5%, 4.8% and  $1.20 \text{ pg} \cdot \text{ml}^{-1}$  ( $0.127 \text{ pmol} \cdot \text{l}^{-1}$ ) for PTH; and 2.3%, 2.8% and  $<5 \text{ ng} \cdot \text{ml}^{-1}$  for P1NP.

Sclerostin concentrations were determined by ELISA (Biomedica, Austria). The intra- and interassay of coefficients of variation were 5% and 4% and the limit of detection was  $2.6 \text{ pmol} \cdot \text{l}^{-1}$ . Serum calcium was determined by colorimetry using the Konelab 60 system (bioMérieux, France). The intra- and interassay CVs were 1.4% and 1.95%, and the limit of detection was  $0.36 \text{ mmol} \cdot \text{l}^{-1}$  ( $1.4 \text{ mg} \cdot \text{dl}^{-1}$ ).

### Statistical analysis

Statistical analyses were performed using PQStat for Windows (version 1.4.2.324). Serum concentrations of bone metabolic markers were compared between the groups using parametric tests (Student's t-test) for normally distributed variables and non-parametric tests (the Wilcoxon signed-rank test) for variables that did not meet the criterion for normal distribution. The relationship between serum concentrations of 25(OH)D3, bone turnover markers and calcium, and the intake of vitamin D, calcium and energy was analysed by estimating the Spearman rank correlation coefficient. Data are presented as mean  $\pm$  SD with  $p < 0.05$  being indicative of statistical significance.

## RESULTS

The results of the study are summarised in Table 1. There were no significant differences in the values of anthropometric parameters between the group of athletes (A) and non-athletes (NA).

Table 1 shows the mean and SD values of: serum concentrations of sclerostin, 25(OH)D3, markers of bone turnover (PTH, P1NP), serum calcium, values of calcium, vitamin D and energy, vitamin D and calcium intake in A and NA.

The mean concentration of sclerostin in A was significantly higher than in NA. The athletes had higher concentrations of P1NP and 25(OH)D3 and lower concentrations of PTH. We did not find any significant differences in the intake of calcium, vitamin D or energy between the two study groups.

Assuming the concentrations of serum 25(OH)D3 in the range  $30\text{--}50 \text{ ng} \cdot \text{ml}^{-1}$  are the physiological norm [22], we found that only 14% of A fulfilled this criterion while 76.7% had vitamin D deficiency. In the control group, 100% of the subjects were vitamin D deficient.

We found a significant negative correlation ( $r = -0.28$ ) between serum sclerostin and serum calcium in the studied subjects.

## DISCUSSION

The literature reports on the concentrations of sclerostin in athletes compared with non-active individuals are scarce and inconclusive.

Lombardi et al. [21], investigating sclerostin concentrations in elite athletes, found higher sclerostin concentrations in males performing weight-bearing activities as compared to those performing

**TABLE I.** Serum concentrations of bone turnover markers, 25(OH)D3 and calcium, and daily dietary intake of energy, vitamin D, and calcium in the group of athletes (A) versus non-athletes (NA).

	A (n=43)	NA (n=16)	P
Sclerostin (pmol · l <sup>-1</sup> )	35.3±8.9	28.0±5.6	0.004
P1NP (ng · ml <sup>-1</sup> )	145.6±77.5	61.2±22.3	<0.0001
PTH (pg · ml <sup>-1</sup> )	25.8±8.3	38.2±11.5	<0.0001
25(OH)D3 (ng · ml <sup>-1</sup> )	16.9±8.4	10.3±4.3	0.004
Calcium (mmol · l <sup>-1</sup> )	2.55±0.05	2.36±0.09	0.0004
Vitamin D intake (µg · d <sup>-1</sup> )	5.1±4.2	4.7±5.1	NS
Calcium intake (mg · d <sup>-1</sup> )	1072.1±373.7	1051.3±484.1	NS
Energy intake (kcal · d <sup>-1</sup> )	2655.7±448.7	2585.1±664.3	NS

Note: The values are presented as mean ± SD; P – p value; NS – not significant

non-weight-bearing activities. It is therefore possible that different types of physical activity result in differences in sclerostin levels. Lombardi et al. [21], similarly to us, also found that individuals with low levels of physical activity have lower serum concentrations of sclerostin ( $0.35 \pm 0.05 \text{ ng} \cdot \text{ml}^{-1}$ ) than professional rugby players ( $0.44 \pm 0.11 \text{ ng} \cdot \text{ml}^{-1}$ ) or endurance athletes ( $0.42 \pm 0.04 \text{ ng} \cdot \text{ml}^{-1}$ ). Fazeli et al. [20] investigated 50 adolescents between 15 and 21 years of age and also noted higher sclerostin concentrations in athletes compared to non-athletes. Grasso et al. [18] followed 9 professional cyclists during a cycling stage race and found an increasing trend for sclerostin plasma concentration (day 1, 12, 23 of race). Moreover, sclerostin concentration was correlated with the effort, the urine Ca, and the muscular activity [18].

It is not clear why sclerostin concentrations might be higher in athletes compared to non-athletes. Circulating sclerostin concentration may, for instance, reflect total-body skeletal mass, as a larger skeleton may simply produce and release more sclerostin into the circulation. In contrast to what would normally be expected, given that sclerostin is a potent inhibitor of the Wnt signalling pathway, serum sclerostin concentrations have been found to be positively associated with bone mineral mass [23]. Furthermore, it may well be that higher concentrations of sclerostin in athletes are associated with counteracting the constant increases in bone formation and bone mass from repetitive mechanical loading.

It should also be noted that our study was carried out in December, at the end of the competitive period, following a long (8-month) training period. As has been previously reported [24, 25], the concentrations of bone markers are affected by the time of sampling within the training period.

A factor that is undoubtedly adding to the divergence and inconsistency is that the available assays measure different components of the sclerostin molecule [26].

Our results are in line with those reported by Bell et al. [27], who investigated body builders versus physically inactive individuals. On the other hand, Zittermann et al. [28], comparing representatives of various disciplines (triathlon, team sports, track and field sports)

with sedentary controls, found higher concentrations of 25(OH)D3 in the group of athletes. The higher serum concentrations of 25(OH)D3 in the athletes studied by us may have resulted from the fact that they had more frequent and longer exposure to sunlight (outdoor training). We did not observe any association between serum concentrations of sclerostin and 25(OH)D3 in the studied subjects. Similar results were presented by Dawson-Hughes et al. [19]. Treatment with vitamin D did, however, increase serum sclerostin concentrations in healthy older men [29].

We observed a highly significant difference between A and NA in regard to PTH and P1NP serum concentrations. PTH in A was lower than in NA, which was consistent with the observation by Durosier et al. [26]. Several studies have demonstrated that PTH concentrations do not change or increase during exercise [27, 30, 31, 32, 33, 34]. Lower concentrations of PTH coupled with higher calcium concentrations in A may indicate that endurance exercise induces permanent suppression of PTH secretion. Another explanation of increased PTH concentrations in controls is the presence of a more pronounced vitamin D deficiency.

Both in experimental and clinical studies, PTH impacts sclerostin concentrations and PTH actually down-regulates sclerostin activation. A negative correlation is thus observed between PTH and sclerostin concentrations [26, 35, 36, 37]. Like Mirza et al. [38], in premenopausal women we did not observe correlations between the concentrations of sclerostin and PTH in the studied men.

Our findings suggest that high levels of physical activity may be associated with higher concentration of P1NP – the most specific marker of bone formation. In contrast with these, Scott et al. [39] found that exercise of high intensity did not affect the concentrations of such bone turnover markers as P1NP or bone alkaline phosphatase. They did, however, suggest that the concentrations of bone formation markers might increase after a prolonged period of physical activity. The high level of P1NP responsible for bone formation in football players may be a reflection of the dynamic changes in the bone that are associated with the repair of microinjuries caused by physical activity.

Our study also showed a negative correlation of circulating sclerostin concentrations with serum calcium levels. It is consistent with the recent findings reported by Amrein et al. [40].

Mödder et al. [10] studied men aged 20 to 39 years and similarly to us did not find any significant correlation of sclerostin concentrations with such markers of bone turnover as PTH and P1NP. Durosier et al. [26] also found no association of sclerostin concentrations with those of PTH and 1,25(OH)2D. However, after adjustment for bone mineral mass, serum sclerostin concentration was inversely associated with PTH, 25(OH)D3 and P1NP (after adjustment for sex). A weak correlation was also observed between the changes in serum sclerostin concentrations and P1NP (adjusted for age and BMI) in the group of premenopausal women [16]. Fazeli et al. [20], on the other hand, found a positive association between sclerostin and P1NP.

## CONCLUSIONS

Our results suggest that professional, years-long training in athletes may be associated with increased serum concentration of sclerostin. We did not find any significant correlation between sclerostin and the other markers of bone turnover (PTH, P1NP) in the studied subjects.

**Conflict of interests:** the authors declared no conflict of interests regarding the publication of this manuscript.

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