

# Circulating sclerostin levels in relation to nutritional status, sex hormones and selected bone turnover biochemical markers levels in peri- and postmenopausal women

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## ABSTRACT

**Objectives:** Hormonal changes during the peri- and postmenopausal age, especially decreasing estradiol levels as the result of the expired ovarian function, are an established link of the pathogenesis of postmenopausal osteoporosis. The objective of the study was to examine the association between the circulating sclerostin levels and nutritional status, sex hormones and selected bone markers turnover levels in peri- and postmenopausal women.

**Material and methods:** The study enrolled 84 stable-body mass women (31 perimenopausal and 54 postmenopausal). Anthropometric measurements and serum estrone, testosterone, androstenedione, DHEA-S, osteocalcin,  $\beta$ -CTx, 25-OH-Vitamin D and sclerostin levels were obtained.

**Results:** There were not any differences between body mass, BMI, body fat and waist circumference between the study groups. The serum androstenedione and DHEA-S levels were similar in both study groups. However, estrone and total testosterone levels were observed to be notably higher in the perimenopausal group, unlike in the postmenopausal group (124.1 pg/mL vs. 98.3 pg/mL,  $p < 0.01$  and 0.3 pg/mL vs. 0.22 pg/mL,  $p < 0.01$ , respectively). Higher plasma osteocalcin and  $\beta$ -CTx levels were shown in the postmenopausal rather than in the perimenopausal group (19.8 ng/mL vs. 16.8 ng/mL,  $p < 0.001$  and 0.35 ng/mL vs. 0.29 ng/mL,  $p < 0.05$ , respectively). Plasma sclerostin and 25-OH-Vitamin D levels were similar. There was not any correlation between plasma sclerostin levels and the other studied parameters. In the multivariate regression analyses, sclerostin levels were proportional to the androstenedione ones ( $b = 0.06$ ;  $p < 0.05$ ) but inversely related to the  $\log_{10}(\text{testosterone})$  levels ( $b = -0.18$ ;  $p < 0.05$ ).

**Conclusions:** Circulating sclerostin levels are similar in peri- and postmenopausal women and are related to the androstenedione and testosterone levels regardless of the nutritional status.

**Key words:** sclerostin; bone turnover markers; sex hormones; nutritional status; menopause

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## INTRODUCTION

Hormonal changes during peri- and postmenopausal age, especially decreasing estradiol levels as the effect of the expired ovarian function, are an established link of the pathogenesis of postmenopausal osteoporosis. The experimental study showed that osteogenesis decreased

just 5 days after the removal of the ovary [1]. It has been suggested that estradiol inhibits the apoptosis of osteoblasts [2]. Currently, it is believed that the main signaling pathway regulating bone mass is the Wnt/ $\beta$ -catenin pathway [3, 4] and sex hormones may affect the activity of this pathway [5]. However, the main regulator of this pathway ac-

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tivity is sclerostin — Wnt antagonist produced by osteocytes. Sclerostin binds to LRP5 and LRP6 receptors and inhibits the activity of the Wnt/ $\beta$ -catenin pathway [6–9]. Higher sclerostin levels were observed in the post- rather than perimenopausal women and its levels are inversely proportional to the free estradiol index. Thus, it seems that estradiol is the factor regulating sclerostin synthesis [10]. This hypothesis confirms the observation that the administration of estradiol reduces the concentration of circulating sclerostin [11]. However, it is not known whether estradiol affects the synthesis of sclerostin directly or indirectly. Interestingly, the changes in sex hormones levels during the menstrual cycle did not affect sclerostin levels in regularly menstruating women [12]. It has also been shown that in men testosterone increased circulating sclerostin levels [11]. On the other hand, one study showed that sclerostin levels weakly correlated with bone mass density (BMD), bone turnover and parathormone (PTH) levels in postmenopausal women [13], whereas another study revealed an inverse association between bone mineral density and sclerostin in postmenopausal women. In addition, among women with osteoporosis positive association between sclerostin levels and BMI was observed. There were no correlations between sclerostin levels and circulating vitamin D, PTH, FSH, E2 and thyroid hormones [14]. However, the results assessed the relationship between circulating sclerostin levels and BMI as inconclusive. Some studies showed a positive correlation [14, 15], while others did not observe this association [16]. As a consequence, examining the association between circulating sclerostin levels and the nutritional status, sex hormones and selected bone markers turnover levels in peri- and postmenopausal women was the main objective of the study.

## MATERIAL AND METHODS

The cross-sectional study involved 31 perimenopausal and 54 postmenopausal women. The inclusion criteria for perimenopausal women were irregular menstruation, hormonal confirmation of perimenopause and for postmenopausal women the time of their last menstruation, minimum 2 years. The inclusion criteria for both groups included normal thyroid function, stable body mass in the last 3 months and not using a hypocaloric diet in the last 6 months. The exclusion criteria included using any kind of a hormonal therapy, smoking and excessive drinking. Informed consent was obtained from all of the participants and the study protocol was granted the approval of the Ethical Committee of the Medical University of Silesia.

Anthropometric measurements (body mass, height and waist circumference) were carried out, and BMI was calculated in accordance with the standard formula. The participants' body composition was measured by us-

ing the bioimpedance method with the aid of Bodystat 1500 (Douglas, Isle of Man). 10 mL samples of venous blood were taken in the morning between 8.00–9.00 a.m., after an overnight period of fasting (16 h). The blood samples were accumulated following the kit manufacturer's recommendations. All the serum and plasma samples were stored frozen in  $-70^{\circ}\text{C}$ .

## Biochemical measurements

Total testosterone, dehydroepiandrosterone sulfate (DHEA-S) were determined by the ECLIA method using Cobas E411 analyzer (Roche Diagnostics GmbH, Mannheim, Germany) with a lower limit of sensitivity 0.025 ng/mL, 0.003  $\mu\text{mol/L}$ , respectively; the respective intra- and inter-assay coefficients of variations were 4.7% and 8.4% for testosterone, 2.8% and 4.7% for DHEA-S.

Estrone (BioVendor, Czech Republic) and androstendione (DRG Instruments GmbH, Marburg, Germany) were determined by using ELISA with a lower limit of sensitivity 10.0 pg/mL and 0.019 ng/mL, respectively; and the respective intra- and inter-assay coefficients of variations 7.7% and 9.1% for estrone and 9.1% and 12.1% for androstendione.

ELISA kits, all commercially available, were used to measure plasma levels of sclerostin (TECOmedical AG, Sissach, Switzerland; the mean intra- and inter-assay coefficients  $< 4.0\%$  and the  $< 4.8\%$ , respectively), 25-OH-Vitamin D (DRG Instruments GmbH for Hybrid XL, Marburg, Germany; the inter-assay precision  $< 14.2\%$ ). Osteocalcin and  $\beta$ -CTx were assessed utilizing ECLIA (Roche Diagnostics GmbH, Mannheim, Germany for Cobas e 411 analyser) set up to sensitivity  $< 3.3\%$  and  $< 4.2\%$  respectively.

## Statistical analysis

The statistical analysis was carried out utilizing the Statistica 12.0 software (TIBCO Software Inc., Palo Alto, USA). Nominal and ordinal data were expressed as percentages, while interval data were expressed as mean value  $\pm$  standard deviation in the case of the normal distribution or as median with lower and upper quartile in the case of data with the skewed or non-normal distribution. The distribution of variables was evaluated by means of the Shapiro-Wilk test and quantile-quantile (Q-Q) plot, whereas the homogeneity of variances was assessed by using the Fisher test. To compare the data between the fitness and control group, the t-Student test for independent data (in the case of the normal data distribution or after logarithmic normalization — if appropriate — in the case of the skewed distribution) or the non-parametric U Mann-Whitney test (in non-normal data distribution) were used. The Pearson correlation coefficient was used as a measure of association between the analyzed variables. The multivariable stepwise backward regression analysis was carried

out for plasma sclerostin levels as an independent variable with potentially explanatory variables: postmenopausal status, body mass index BMI (model I), fat percentage (model II), waist (model III) and HOMA-IR values, serum levels of estrone, total testosterone, androstenedione, DHEA-S, 25-OH-Vitamin D, osteocalcin and  $\beta$ -CTx. The Cook-Weisberg test was used to test heteroskedasticity and the Ramsey RESET test was used to test the linearity of regression. The variance inflation factor VIF was calculated to check multicollinearity. The goodness of fit of the acquired regression models was assessed with the adjusted determination coefficient R<sup>2</sup>. All the tests were two-tailed. The results were regarded as statistically significant with a p-value of less than 0.05.

## RESULTS

There were no differences between body mass, BMI, body fat and waist circumference between the study groups. Serum androstenedione and DHEA-S levels were similar in study groups, whereas estrone and total testosterone levels were significantly higher in the peri- rather than the postmenopausal group (124.1 pg/mL vs. 98.3 pg/mL,  $p < 0.01$  and 0.3 pg/mL vs. 0.22 pg/mL,  $p < 0.01$ , respectively). Higher plasma osteocalcin and  $\beta$ -CTx levels were shown in the postmenopausal rather than the perimenopausal group (19.8 ng/mL vs. 16.8 ng/mL,  $p < 0.001$  and 0.35 ng/mL vs. 0.29 ng/mL,  $p < 0.05$ , respectively). However, plasma 25-OH-Vitamin D and sclerostin levels were similar. Table 1 presents the characteristics of the study groups.

There was a significant negative correlation between estrone levels and age, body mass and BMI ( $r = -0.25$ ;  $p < 0.01$ ,  $r = -0.24$ ;  $p < 0.01$ ,  $r = -0.21$ ;  $p < 0.01$ , respectively).

The negative correlation between 25-OH-Vitamin D levels and body mass, BMI, fat mass and waist circumference and positive with androstenedione levels was found ( $r = -0.24$ ;  $p < 0.01$ ;  $r = -0.24$ ,  $p < 0.01$ ;  $r = -0.25$ ,  $p < 0.01$  and  $r = -0.25$ ,  $p < 0.01$ ,  $r = 0.33$ ;  $p < 0.001$ , respectively). Plasma  $\beta$ -CTx levels correlated negatively with estrone levels ( $r = -0.26$ ;  $p < 0.01$ ) and plasma osteocalcin correlated positively with DHEA-S and androstenedione levels ( $r = 0.29$ ;  $p < 0.001$  and  $r = 0.41$ ;  $p < 0.0001$ ). No correlation between plasma sclerostin levels and the other studied parameters was detected.

Multivariate stepwise backward linear regression models for sclerostin as an independent variable, with explanatory variables: postmenopausal status, BMI values or waist circumference or fat percentage and estrone, total testosterone, androstenedione and DHEA-S levels revealed that the alterations in sclerostin levels are proportional to androstenedione levels and inversely proportional to total testosterone levels. The model with explanatory variables: vitamin D,  $\beta$ -CTx and osteocalcin did not show their effect on the changes in sclerostin levels (Tab. 2).

## DISCUSSION

So far numerous studies assessed circulating sclerostin levels and the factors affecting them in peri- and postmenopausal women [13, 14, 17, 18]. To the best of our knowledge, the study is most likely to be the first one to assess circulating sclerostin levels and the factors influencing them in peri- and postmenopausal women. In contrast to the studies which showed higher plasma sclerostin levels in postmenopausal rather than perimenopausal women [10, 11] we did not observe any differences between perimenopausal

**Table 1.** Characteristics of study group

	Perimenopausal N = 31	Postmenopausal N = 54	p
Age [years]	49.0 ± 4.0	52.2 ± 4.0	< 0.001
Body mass [kg]	76.3 ± 13.6	74.6 ± 11.5	NS
BMI [kg/m <sup>2</sup> ]	27.1 (24.0–32.5)	27.3 (24.3–30.4)	NS
Body fat [%]	37.8 ± 5.6	37.7 ± 5.8	NS
Body fat [kg]	26.5 (22.8–37.1)	28.7 (23.3–35.2)	NS
Waist circumference [cm]	88.7 ± 10.0	89.4 ± 10.2	NS
Estrone [pg/mL]	124.1 (104.3–153.3)	98.3 (74.3–118.9)	< 0.01
DHEA-S [mg/mL]	143.7 ± 77.9	141.3 ± 66.2	NS
Androstenedione [ng/mL]	2.1 ± 0.9	2.4 ± 0.9	NS
Total testosterone [pg/mL]	0.30 (0.23–0.38)	0.22 (0.13–0.29)	< 0.01
25-OH-Vitamin D [ng/mL]	28.0 (23.1–31.5)	30.0 (22.5–36.5)	NS
Osteocalcin [ng/mL]	16.84 (11.50–18.60)	19.81 (15.74–23.43)	< 0.001
Sclerostin [ng/mL]	0.63 ± 0.2	0.71 ± 0.2	NS
$\beta$ -CTx [ng/mL]	0.29 (0.21–0.36)	0.35 (0.27–0.48)	< 0.05

Mean (SD) or median (lower quartile — upper quartile)

**Table 2. A multivariate stepwise backward linear regression**

Sclerostin [ng/mL]	b	SE(b)	p
Androstenedione [ng/mL]	0.0595	0.0263	< 0.05
log <sub>10</sub> (total testosterone) [pg/mL]	-0.1786	0.0450	< 0.05
log <sub>10</sub> (β-CTx[ng/mL])	-0.1859	0.0972	0.06

sal and postmenopausal women. The factor explaining the lack of differences in sclerostin levels between our study groups is the fact that women at the age of 45 and over were enrolled in our study. This hypothesis is confirmed by the observation made by Ardavi et al. [17], which made an observation of circulating sclerostin levels increasing with age, up to the age of 45. Moreover, the results of the longitudinal study revealed that sclerostin levels increased from reproductive age to menopause and from menopause to early postmenopause [18]. Additionally, Amrein et al. [15] detected a positive correlation between sclerostin levels and age in healthy subjects regardless of gender. Among other suggested factors influencing circulating sclerostin levels is the nutritional status. However, the results of recently published studies are inconclusive. Some studies showed a positive correlation between sclerostin levels and BMI [15, 19], WHR [15] and fat mass [20] as well as the percentage of visceral and gynoid fat [21]. Contrary to these studies we did not observe any associations between sclerostin levels and BMI, waist circumference, fat mass and fat percentage. It is in line with the conclusions made by Klangjareonchai et al. [16], which found a negative correlation between sclerostin levels and BMI in men, and no association in women. It should be noted that the differences in these studies may be the result of having participants of various races with distinct patterns of fat distribution. Although one study showed similar circulating sclerostin levels in Chinese-American and white women [22], the effect of race cannot be excluded. Moreover, studies performed in a large group are necessary to explain the effect of race and nutritional status on sclerostin levels. Another explanation of these differences may be the impact of gender on the fat content. Higher sclerostin levels were observed in men rather than in women [23]. Another factor influencing sclerostin levels and its association with anthropometric parameters is physical activity. Some studies showed that regular physical activity significantly reduces circulating sclerostin levels in postmenopausal women [24, 25]. However, due to the lack of objective assessment of physical activity in our study, we did not confirm its impact on the obtained results.

The circulating estradiol levels in the postmenopausal group were very low therefore we did not assess any association between sclerostin and estradiol levels. However, it should be noted that we no association between sclerostin and estrone levels was observed. Furthermore, despite significantly higher estrone levels in the peri- rather than in the postmenopausal group, sclerostin levels were similar. It is in accordance with the study that showed that bone mass positively correlates with estradiol and estrone levels in premenopausal but not postmenopausal women [26]. On the other hand, it has been observed that a 4-week-long estrogenic hormonal therapy reduced circulating sclerostin levels [27]. It should be noted that this study was performed in a very small group. Further studies are necessary to assess the effect of estrone on sclerostin levels and the role of this hormone in bone turnover. However, our study showed that changes in sclerostin levels are proportional to androstenedione levels and inversely proportional to total testosterone levels. Contrary to our results, it has been observed that in men testosterone replacement increased circulating sclerostin levels [27]. The impact of androstenedione on sclerostin levels may be explained by the results of the experimental study that showed that androstenedione could improve the proliferation and differentiation of osteoblasts in vitro [28].

In accordance with the results of the previously published study [10, 19] no association between sclerostin and vitamin D levels was observed. However, contrary to other studies [17, 22, 28, 29], we did not observe any relationships between sclerostin and osteocalcin as well as β-CTx levels. It should be noted that the results of the studies described the association between sclerostin and β-CTx as inconclusive because both a positive [28, 29] and a negative [22] correlation were found. Multivariate stepwise backward linear regression models in our study revealed that the effect of β-CTx on sclerostin levels is negative and close to significance. Further studies are necessary to explain the association between sclerostin and bone turnover markers levels in postmenopausal women.

The main limitation of the present study is the small sample size and not including women of reproductive age in the study. Other limitations are also the assessment of body composition on the basis of the bioimpedance method, not using the DXA method, which makes it impossible to assess subcutaneous and visceral fat deposits, and the lack of assessment of bone density. However, it should be noted that our study is the first one to assess the complex association between sclerostin levels and nutritional status and sex hormone levels in perimenopausal women.

## CONCLUSIONS

Circulating sclerostin levels are similar in peri- and postmenopausal women and are related to androstenedione and testosterone levels regardless of the nutritional status.

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