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Sclerostin and its association with insulin resistance in children and adolescents

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ABSTRACT

Introduction: Recent studies have shown that sclerostin, which is mainly known as a negative regulator of bone formation, could play an important role in the crosstalk between bone and glucose metabolism. The aim of this study was to investigate the relationship between sclerostin, other bone and fat related factors as osteocalcin (OC), Receptor Activator of Nuclear Factor NF-κB ligand (RANKL), leptin and adiponectin with glucose metabolism and insulin action in children and adolescents with obesity compared with healthy children and adolescents.

Methods: Fifty-five obese children and adolescents, a mean age of 13.2 ± 3.4 yrs., BMI 28.89 ± 5.5 kg/m^2, and 26 healthy controls (mean age 13.0 ± 4.3 yrs., BMI 19.96 ± 3.1 kg/m^2), sex-, and Tanner stage-matched were included into the study. Fasting blood samples for measurement of sclerostin, glucose, lipid profile, HbA1c, C-peptide, OC, RANKL, leptin and adiponectin, and vitamin D were taken at 8.00 AM.

Results: Sclerostin, osteocalcin, RANKL, and adiponectin levels did not differ between obese patients and the control group. Leptin and fasting insulin levels were significantly higher in obese subjects compared with controls ($p < 0.01$, $p = 0.01$, respectively). A positive correlation between sclerostin and OC ($r = 0.417$, $p = 0.027$) and negative correlations between sclerostin and HOMA-IR and between sclerostin and age ($r = -0.24$, $p = 0.045$, $r = -0.23$, $p = 0.037$, respectively) were found in all of the subjects. Sclerostin did not correlate with HbA1c, lipids, RANKL and fat-derived leptin and adiponectin. Partial correlation analysis adjusted for age, SDS-BMI and Tanner staging only revealed a negative correlation between sclerostin and HOMA-IR ($r = -0.3$, $p = 0.01$). In obese patients this correlation was stronger than in the whole group ($r = -0.39$, $p = 0.005$). Moreover, a negative correlation between sclerostin and insulin was found in obese patients ($r = -0.39$, $p = 0.006$). In the healthy cohort, sclerostin had a negative correlation only with C-peptide ($r = -0.79$, $p = 0.02$).

Conclusions: Sclerostin could play an important role in the regulation of glucose metabolism in children and adolescents, regardless of other fat and bone-derived factors. In obese young patients it's action could be associated with decreasing insulin resistance.

1. Introduction

Recent evidence has shown that the skeleton can affect energy metabolism [1]. In children and adolescents bone turnover is extremely high with the physiological dominance of bone formation over bone resorption. It has been found that both osteoblasts and osteoclasts, which are responsible for the bone turnover, are also associated with glucose metabolism. Bone tissue could cooperate in this action with fat tissue. Osteoblast-derived osteocalcin (OC), which is a specific marker of bone formation, is pharmacologically active in glucose metabolism [2,3]. It has been reported that intermittent injections of OC improve glucose metabolism and could prevent type 2 diabetes in mice [4]. Simultaneously, OC acts on adipocytes to induce adiponectin expression, which secondarily reduces insulin resistance [5,6]. Leptin is another fat-derived hormone, that influences energy metabolism by modulating the expression of *Esp*, a gene that inhibits the bioactivity of OC, thereby modulating insulin signaling in osteoblasts [7]. In healthy children, weight-dependent relationships between OC, adiponectin and insulin secretion have been observed [8].

Another osteocyte-secreted molecule, sclerostin, is a potent

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antagonist of the Wnt/β-catenin pathway, which is a major regulator of bone mass. This pathway increases bone mass through a number of mechanisms including renewal of stem cells, stimulation of pre-osteoblast replication, induction of osteoblastogenesis, and inhibition of osteoblast and osteocyte apoptosis [9]. It's biological importance is underlined by clinical observations in subjects with sclerosteosis and van Buchem disease, two genetic disorders with impaired sclerostin production and markedly increased bone mass [10,11]. A neutralizing antibody to sclerostin has recently been shown to increase bone formation and reduce bone resorption in both mice [12] and humans [13]. Moreover, Wnt/β-catenin signaling pathway is one of the most important regulators of adipogenesis. These recent findings show that circulating sclerostin could affect the development of all types of adipocytes. However, sclerostin levels vary significantly depending on age, gender, and disease conditions. Moreover, significant variation is present among adipocytes depending on developmental stage and tissue location [14]. It was hypothesized that the antagonism of Wnt signaling by oxidative stress during aging may be a common molecular mechanism that contributes to the development of not only involutional osteoporosis, but also several other pathologies, such as atherosclerosis, insulin resistance, and hyperlipidemia [15]. Increased sclerostin levels were observed in adult patients with type 2 diabetes mellitus (DM) and atherosclerotic diseases [16].

Osteoclasts, which play an opposing role to osteoblasts in the bone turnover process, form by differentiation and fusion of monocytic precursors of the macrophage lineage in response to macrophage colony stimulating factor (M-CSF) and receptor activator of nuclear factor kappa B ligand (RANKL). The RANKL can therefore be considered as a bone turnover marker. During RANKL-induced osteoclast differentiation from murine bone marrow macrophages, both glycolysis and oxidative phosphorylation (OXPHOS) as well as lactate production were found to increase. Interestingly, osteoclastogenesis appeared to be optimal in a normoglycemic state, whereas high levels of glucose were less effective even though cell proliferation was maximally stimulated [17].

Based on previous data indicating that skeleton and fat tissue are involved in the endocrine regulation of glucose homeostasis in animals and adult men, the present study was performed to assess the biological importance of these tissues and better understand the energy metabolism in children and adolescents. The role of sclerostin in link with glucose homeostasis has not been yet studied extensively in children. The aim of this study was to investigate the relationship between sclerostin and other bone-derived molecules such as OC, and RANKL, fat tissue-derived leptin and adiponectin, and glucose metabolism in obese and healthy children and adolescents.

The hypothesis of our study is that sclerostin is associated with glucose metabolism due to sclerostin's influence on insulin action and glucose metabolism independent of other bone-derived or fat derived factors.

2. Methods

Fifty-five children and adolescents with simple obesity, recruited as an random sample among the patients of the outpatient clinic of our Department, with a mean age of 13.2 ± 3.4 yrs., BMI 28.89 ± 5.5 kg/m^2, and 26 control, healthy age-matched, sex-matched and Tanner stage-matched children (mean age 13.0 ± 4.3 yrs., BMI 19.96 ± 3.1 kg/m^2) were included into the study in the years 2015–2017. The control group was recruited among other inpatients not being obese and not having diseases affecting carbohydrate metabolism and bone turnover. The Local Ethical Committee approved the study. All participants and their parents gave their written, informed consent.

The patients' heights were measured to the nearest millimeter using a rigid stadiometer. Height standard deviation score (height SDS) was calculated from national normative data. The patients' unclothed weights were measured to the nearest 0.1 kg using a calibrated balance scale. Reference data for Polish children were used [18]. Each patient's body mass index (BMI) was calculated as weight in kilograms (kg) divided by the square of height in meters (m^2). Obesity was defined as equal or above the 95th percentile of the sex-specific BMI for the age growth charts. The sexual development was assessed using the Tanner scale in all participants of the study by one physician.

The fasting blood samples were collected from the antecubital vein at 8.00 AM to measure the bone-derived sclerostin, OC, and RANKL levels, fat tissue-derived leptin and adiponectin levels, as well as vitamin D, lipid profile, glucose, C-peptide, insulin, and HbA1c concentrations. The HbA1c, glucose, and lipids levels were measured at once on the same day. The serum samples were stored at -80 °C until the remaining parameters were measured.

The serum levels of sclerostin (Biomedica, Wien, Austria, detection limit: 7.5 pmol/l, intra-assay precision: ≤7%, inter-assay precision: ≤10%), OC (Diasource, Louvain-la-Neuve, Belgium, detection limit: 0.08 ng/ml, intra-assay precision: ≤4.7%, inter-assay precision: ≤5.6%), RANKL (Biomedica, Wien, Austria, detection limit: 0.02 pmol/l, intra-assay precision: ≤9%, inter-assay precision: ≤6%), leptin (Diasource, Louvain-la-Neuve, Belgium, detection limit: 0.04 ng/ml, intra-assay precision: ≤13.3%, inter-assay precision: ≤12.7%) and adiponectin (Diasource, Louvain-la-Neuve, Belgium, detection limit: 0.6 ng/ml, intra-assay precision: ≤4.7%, inter-assay precision: ≤6.7%) were measured by ELISA. The 25(OH)D3 concentration was measured with HPLC. The HbA1c levels were measured using a standardized IFCC method. The serum glucose levels and lipid profile were measured by routine chemical methods. The homeostatic model assessment (HOMA-IR) was calculated as a product of the glucose [mmol/l] and insulin [uIU/ml]) concentrations divided by 22.5.

Statistical analysis was performed using the Dell Statistica 13.1 64-bit package (StatSoft, Poland, Kraków). Variables are presented as mean with SD. Parameters with skewed distribution were logarithmically transformed before use in parametric procedures. Differences between obese and healthy children and adolescents were determined either by Student's *t*-test or by χ^2 test depending upon the distribution of variables. Age, SDS-BMI and Tanner stage – adjusted partial correlations of sclerostin levels with other bone-derived, fat-derived, and metabolic parameters, were identified by Pearson or partial correlation analysis where appropriate. Univariate analysis of covariance (ANCOVA) was used to evaluate the differences of sclerostin levels between obese and healthy children and adolescents, controlling the effect of age, SDS-BMI and Tanner stage. All statistical tests were two-sided. A p value < 0.05 was used as statistically significant.

Table 1
Clinical characteristics of the patients with obesity and the healthy ones. Abbreviations: BMI – body mass index, TS – Tanner stage. P value refers to differences between obese patients and controls. Student's test and χ^2 test were used as appropriate.

Group	No	Age [year]	Height SDS	BMI SDS	TS 1	TS 2	TS 3	TS 4	TS 5
Obese	55	13.2 ± 3.4	0.47 ± 1.6	7.97 ± 11.13	10	7	7	8	23
Healthy	26	13.0 ± 4.3	−0.43 ± 2.6	1.50 ± 1.83	5	3	3	5	10
		$p = 0.75$	$p = 0.08$	$p < 0.001$	$\chi^2 = 17.3$, $p = 0.87$				

Table 2
The mean values (± SD) of serum concentrations of sclerostin, osteocalcin (OC), leptin, adiponectin, and C-peptide, HbA1c, fasting serum glucose (FG), vitamin D, and lipids in the obese patients and controls. P value refers to differences between obese patients and controls. Student's test and ANCOVA test were used as appropriate.

Parameter	Obese children and adolescents	Healthy controls	p
Sclerostin [pmol/l]	33.1 ± 12.4	29.7 ± 9.4	F = 1.57, p = 0.19
OC [ng/ml]	27.6 ± 17.6	21.7 ± 15.9	F = 2.39, p = 0.08
Leptin [ng/ml]	8.1 ± 5.8	2.5 ± 0.9	F = 22.67, $p < 0.0001$
Adiponectin [μg/ml]	6.9 ± 5.9	7.7 ± 3.3	F = 0.57, $p = 0.57$
C-peptide [ng/ml]	1.8 ± 1.3	0.96 ± 0.3	0.1
Insulin [μIU/ml]	20.0 ± 11.9	11.8 ± 7.7	0.01
FG [mmol/l]	4.7 ± 0.5	4.6 ± 0.6	0.63
HbA1c [%]	5.3 ± 0.3	5.4 ± 0.1	0.86
HOMA	2.4 ± 1.6	4.2 ± 2.7	0.01
$25(OH)D_3$ [ng/ml]	20.9 ± 10.1	19.5 ± 7.1	0.62
Chol [mmol/l]	4.3 ± 0.9	4.1 ± 0.7	0.21
TGL [mmol/l]	1.3 ± 0.78	1.2 ± 1.3	0.62
HDL [mmol/l]	1.1 ± 0.3	1.5 ± 0.4	< 0.001
LDL [mmol/l]	2.7 ± 0.8	2.0 ± 0.6	< 0.001
HDL/TC [%]	26.8 ± 7.6	37.3 ± 10.1	< 0.0001

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3. Results

The clinical characteristics of the cohorts of the obese and healthy children and adolescents is presented in Table 1.

The levels of bone-derived sclerostin, OC and RANKL were not different between the obese and healthy group (Table 2). The results of ANCOVA, controlling the effect of age, SDS-BMI and Tanner stage confirmed lack of differences regarding sclerostin level between both groups ($F = 1.57$, $p = 0.19$). There were no differences regarding sclerostin between male and females ($F = 0.94$, $p = 0.44$). The leptin levels of obese patients were significantly higher compared to healthy subjects, while the levels of adiponectin did not differ between groups. There were significant differences in the C-peptide, insulin, HOMA-IR, HDL-cholesterol, and LDL-cholesterol levels, as well as the HDL-cholesterol/total cholesterol ratio between the examined groups. The levels of fasting blood glucose, HbA1c, total cholesterol, triglycerides, and vitamin D did not differ between obese and healthy subjects (Table 2).

Pearson correlation coefficients revealed a positive association between serum sclerostin levels and OC ($r = 0.417$, $p = 0.027$) and a negative correlation between serum sclerostin levels and HOMA-IR as well as age ($r = -0.24$, $p = 0.045$, $r = -0.23$, $p = 0.037$) in all of the subjects. No significant correlation was found between sclerostin and HbA1c, lipids, RANKL and fat-derived leptin and adiponectin. The correlation between sclerostin and HOMA-IR remained significant after adjustments for age, SDS-BMI and Tanner stage ($r = -0.3$, $p = 0.01$). The distribution of sclerostin in regard of Tanner stage in the healthy group is presented in Fig. 1. The linear correlation between sclerostin and HOMA-IR in all participants of the study is presented in Fig. 2.

In the group of obese patients, Pearson correlation coefficients revealed a negative association between serum sclerostin levels and insulin ($r = -0.29$, $p = 0.04$), HOMA-IR ($r = -0.3$, $p = 0.037$), age ($r = -0.35$, $p = 0.008$), height ($r = -0.3$, $p = 0.02$), and body mass ($r = -0.3$, $p = 0.024$). However, when adjusting the analysis adjusted to the age, SDS-BMI and Tanner staging, only negative correlations between sclerostin and insulin as well as HOMA-IR ($r = -0.39$, $p = 0.005$, $r = -0.39$, $p = 0.006$, respectively) were observed. The correlation between sclerostin and HOMA-IR was much stronger in the obese patients than in the whole group. The linear associations between the sclerostin and insulin levels in obese children and adolescents are presented in Fig. 3.

In the healthy group, a negative correlation between sclerostin and C-peptide ($r = -0.79$, $p = 0.02$) was found. The significant correlation was present after adjustment to the age, SDS-BMI and Tanner stage. The linear association between the sclerostin and C-peptide levels in healthy children and adolescents is presented in Fig. 4.

4. Discussion

For first time we presented that bone-related sclerostin could be associated with insulin action and perhaps influence glucose metabolism in children and adolescents.

The effects of the skeleton on glucose metabolism have been postulated over the last decade [19,20], including studies in children and adolescents [8,21]. A recent study demonstrated that the changes in the circulating sclerostin levels reflect similar changes in the sclerostin levels in bone marrow plasma [22]. Sclerostin distribution in children and adolescents with type 1 diabetes mellitus was presented by Tseniditis et al. [23]. They found that sclerostin levels correlated with bone resorption and formation markers and also with bone mass indices, gender, and pubertal stage. Physiologically, sclerostin inhibits the canonical Wnt/β-catenin signaling pathway and thus osteoblast activity [24]. We found that the sclerostin levels were significantly negatively correlated with HOMA-IR in children and adolescents. In obese patients this correlation was much stronger, moreover the correlation between sclerostin and insulin level was found. Our data suggest the possible association between sclerostin and glucose metabolism via influence on insulin action. The question is whether sclerostin influences glucose metabolism independently or through the inhibition of osteoblast activity and OC production? Bone-derived osteocalcin, a marker of bone formation, was shown to play a major role in this process [2–4]. In our previous study we presented that OC could be potentially associated with glucose control in children and adolescents with type 1 diabetes mellitus [25]. Although a strong positive correlation was observed between sclerostin and OC levels in our current study, this correlation disappeared after considering the age of the patients. It was observed that both of these parameters are dependent on the age and pubertal stage of the children [26,27]. We did not find any correlations between sclerostin and RANKL nor correlations between sclerostin and fat-derived leptin and adiponectin.

In adults, sclerostin levels are increased in individuals with prediabetes and are correlated with insulin resistance [28]. Circulating sclerostin is also increased in patients with type 2 diabetes independent of gender and age. In this group of patients serum sclerostin was correlated with the duration of type 2 diabetes mellitus, glycated hemoglobin, bone turnover markers, and bone mineral density [29]. Another study reported that circulating sclerostin is increased in patients with type 2 diabetes mellitus and atherosclerotic lesions [17]. Conversely, Gaudio et al. presented in their study, that there was a significant negative correlation between sclerostin and carotid intima media thickness in patients with type 2 diabetes. These study suggests that sclerostin, an established modulator of the canonical Wnt signaling, may protect against progression of vascular complications in diabetic patients. A possible mechanism may be the attenuating upregulation of β-catenin activity in the vascular cells [30]. Last, very important publication presented that in obese adult patient circulating sclerostin level was not associated with cardiovascular disease [31].

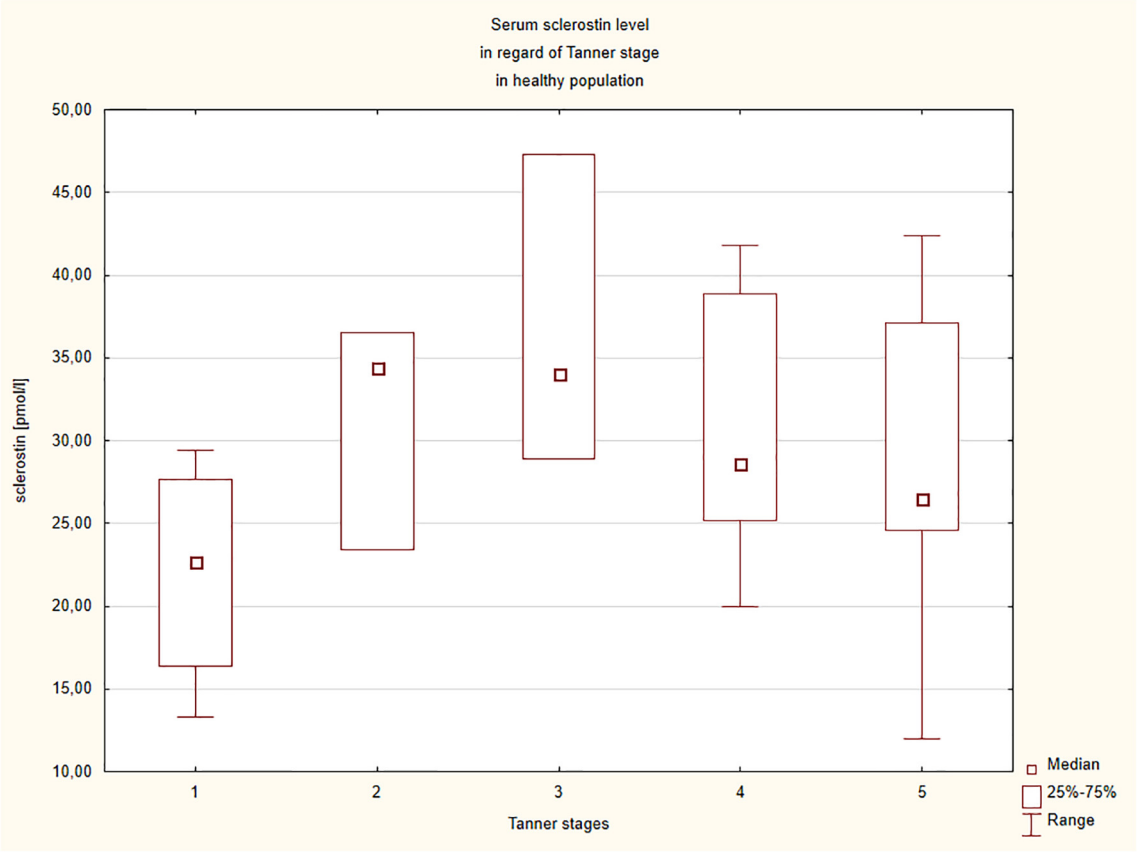

Fig. 1. The distribution of sclerostin in regard of Tanner stage in the healthy group.

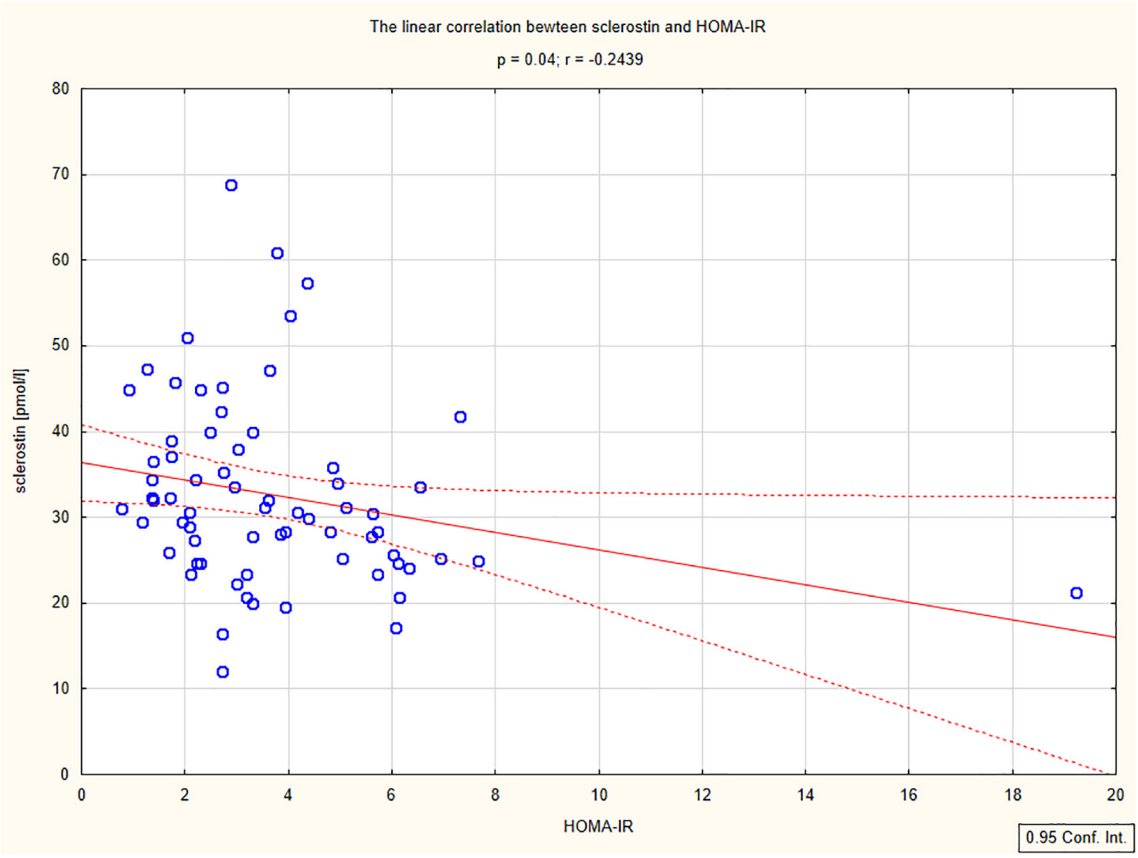

Fig. 2. The linear correlation between sclerostin and HOMA-IR in children and adolescents (Pearson correlation coefficients).

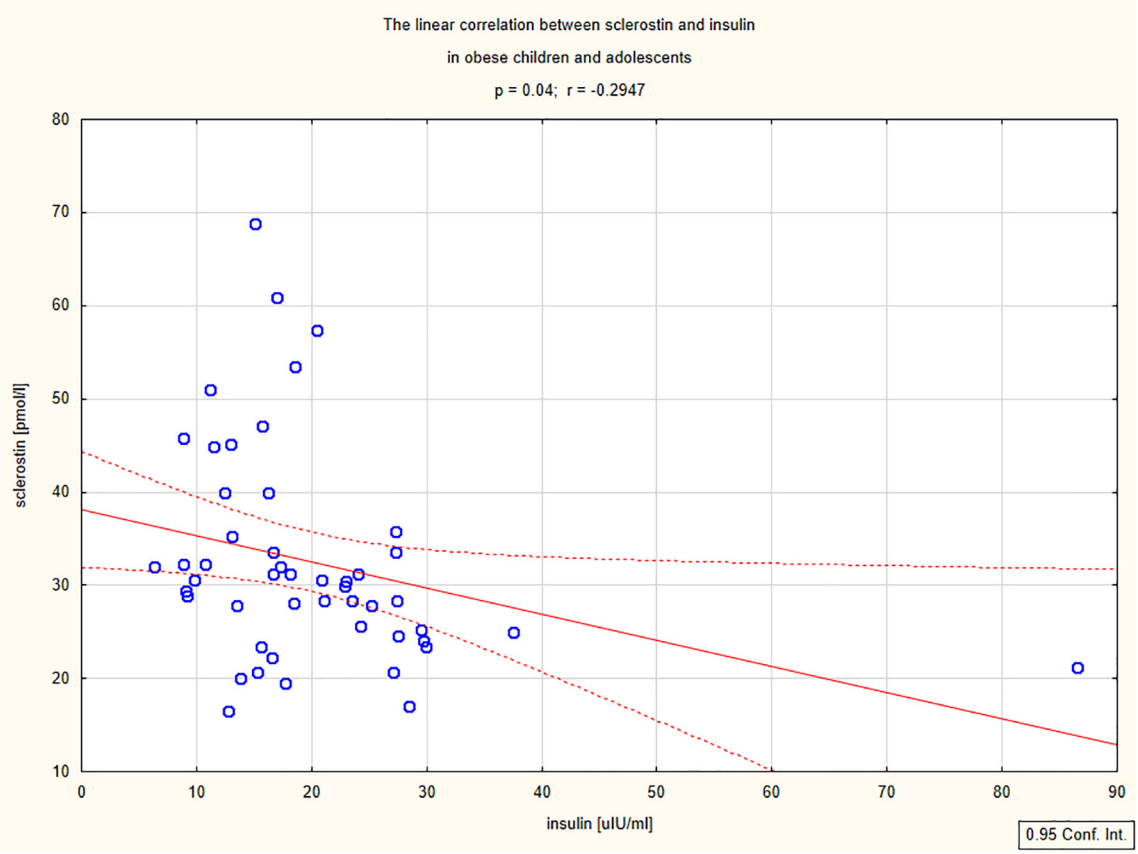

Fig. 3. The linear correlation between sclerostin and insulin in obese children and adolescents (Pearson correlation coefficients).

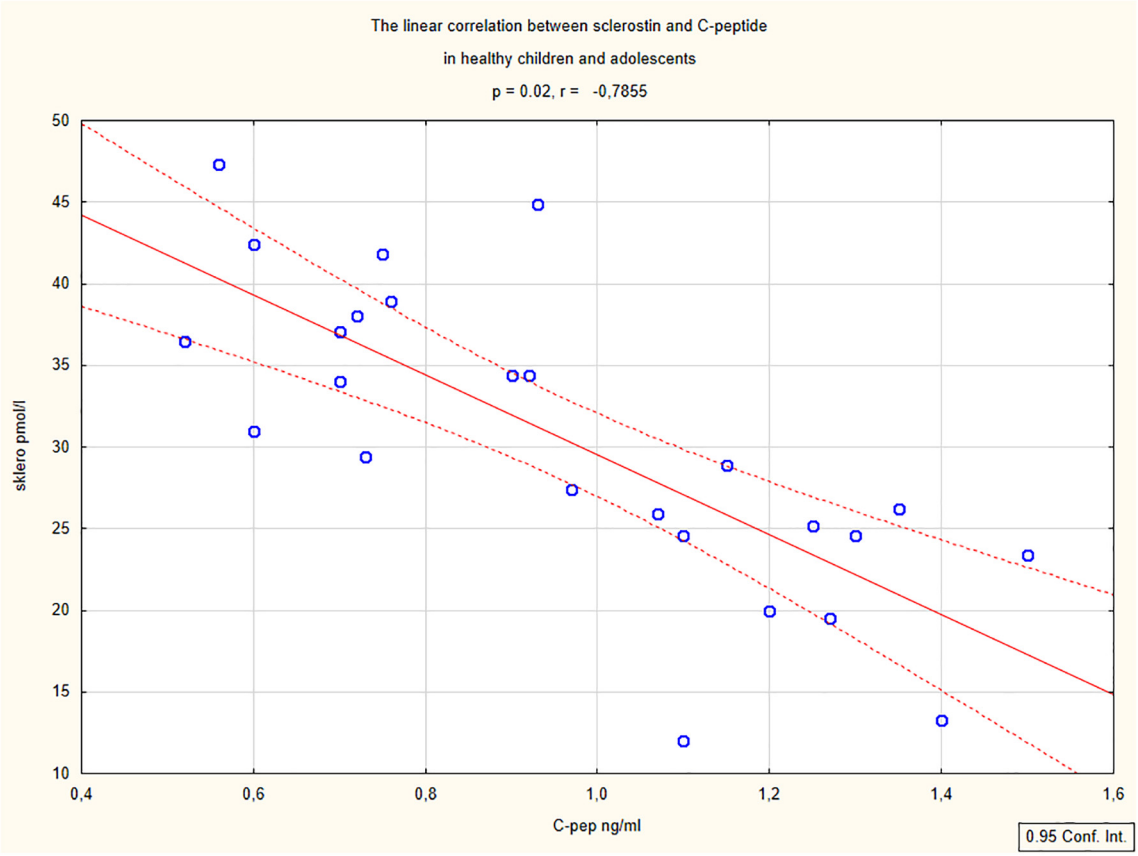

Fig. 4. The linear correlation between sclerostin and C-peptide in healthy children and adolescents (Pearson correlation coefficients).

The above-mentioned studies, although contradictory, are an evidence of a cross talk between bone and glucose metabolism. Tsentidis et al. presented in their study, that sclerostin was correlated with both resorption and formation markers in children and adolescents [23]. It is worth highlighting that bone metabolism is very active in childhood and adolescence. Osteoblasts and osteocytes, which combine the action of sclerostin and OC, play a major role in the process of bone formation. The OC and sclerostin levels are likely increased and positively correlated because of the increased bone turnover [26,27]. Our data suggest that sclerostin could have the possible influence on insulin action both in obese children and adolescents as well as their healthy peers. The increasing level of sclerostin, which is characteristic for childhood, could be associated with decreased insulin resistance. During adolescence, when physiologic insulin resistance is present, the reduction of sclerostin level in Tanner stage IV according to the data of Tsentidis was simultaneously observed [23]. Also our data show that there is a decrease of sclerostin levels in Tanner stage 4 in comparing with previous Tanner stages (Fig. 4).

The results of our study could suggest that sclerostin, which levels are inversely related to the markers of insulin resistance, could possibly contribute to insulin action and indirectly decrease several complications caused by insulin resistance.

The strength of our study includes the presentations of sclerostin distribution in healthy subjects and obese Caucasian children. The cohort was homogeneous therefore representing the pediatric population of Central Europe. The study presents new data suggesting a role of sclerostin in the known crosstalk between bone and energy homeostasis. There is a novel study that links serum sclerostin to metabolic parameters in pediatric population.

The limitations of our study are the relatively small sample sizes and the cross-sectional design. The conclusions drawn from our data must be applied with caution to other populations.

In summary, the bone-derived sclerostin could play an important role in the regulation of glucose metabolism in children and adolescents. In young patients, the crosstalk between bone-derived sclerostin and carbohydrate metabolism appear to be independent of other fat and bone-derived factors. In young patients who are obese, sclerostin's action could be associated with decreasing insulin resistance. This observation is a novel finding, which demands further investigation due to important implications in the aspect of the risk of cardiovascular diseases in the future of this patient population.

Declaration of conflicts of interest

None of the authors have a conflict of interest.

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Authorship

AW - the conception and design of the study, the acquisition of data, the analysis and interpretation of data, drafting the article and revising the design and edition of the study critically for important intellectual content after first reviewing process in Bone;

KS - revising the study critically for important intellectual content and final approval of the version to be submitted;

JS – the final revise and an approval of the version to be submitted.

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