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Sclerostin and its significance for children and adolescents with type 1 diabetes mellitus (T1D)

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ABSTRACT

Introduction: Recent studies have shown that sclerostin, which is a negative regulator of bone formation, could play an important role in the crosstalk between bone and glucose metabolism. The role of sclerostin and its link with glucose homeostasis in type 1 diabetes mellitus (T1D) has not been yet studied extensively in children. The aim of this study was to assess sclerostin and its relationship between other bone and fat related factors as well as glucose metabolism in children and adolescents with T1D in comparison to their healthy peers.

Methods: Forty patients with T1D, 18 girls, mean age 12.3 ± 4.7 yrs, and 28 healthy as controls (13.1 ± 4.2 yrs), sex and Tanner stage-matched were included into the study. Fasting blood samples for measurement of sclerostin, osteocalcin (OC), leptin, adiponectin, vitamin D, fasting glucose, lipid profile, HbA1c, and C-peptide were taken at 8.00 AM.

Results: Sclerostin levels were significantly higher in patients with T1D than in the control group ($p = 0.04$) without significant differences between genders. Pearson correlation coefficients revealed a positive association between serum sclerostin levels and leptin OC ($r = 0.59$, $p < 0.001$) and a negative correlation between serum sclerostin levels and leptin ($r = -0.32$, $p = 0.02$) in all of the subjects and no significant correlations between sclerostin and adiponectin, 25(OH)D3, nor lipids.

In the group of T1D patients a strong positive association between serum sclerostin levels and OC ($r = 0.62$, $p < 0.001$), and a negative association between serum sclerostin levels and HbA1c and leptin levels ($r = -0.33$, $p = 0.04$; $r = -0.33$, $p = 0.03$, respectively) were found. These associations were significant also after adjusting the analysis to the age, SDS-BMI and Tanner staging.

In the healthy group after adjustment to age, SDS-BMI and Tanner stage, a negative correlation between sclerostin and C-peptide ($r = -0.79$, $p = 0.02$) was found.

Conclusions: Our data suggest a possible relationship between sclerostin and glucose metabolism in children and adolescents with T1D. It would be worth to investigate if an increase in sclerostin levels could present as a potential cause of the reduction of bone formation in T1D. Both bone-derived OC as well as fat-derived leptin seems to possibly modulate the participation of sclerostin in metabolic regulation in T1D.

1. Introduction

Recent studies have shown that skeleton and fat tissue are newly discovered important endocrine organs. Moreover there is evidence that there is crosstalk between skeleton and fat tissue, as well as between those both tissues and glucose metabolism [1,2]. Animal studies revealed that bone-secreted osteocalcin (OC) stimulates insulin secretion and β-cell proliferation [3]. Other studies indicate that leptin can cooperate in this action with OC. Moreover another adipokine – adiponectin can also influence glucose metabolism [4]. The results of our previous study had suggested that fat and bone tissue could influence glucose metabolism in children and adolescents, potentiality in an insulin-dependent manner. Our previous data could also be an explanation of the known clinical observation that poor metabolic control is associated with reduced bone formation [5]. In continuation of this clinical issue, in the present study we focus on sclerostin, an osteocyte-secreted molecule and a potent antagonist of the Wnt/β-catenin pathway, which is a major regulator of bone mass. This pathway mediates increased bone formation through the expansion of osteoprogenitor cells, as well as, reduced apoptosis of mature osteoblasts

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[6,7]. Sclerosteosis and van Buchem disease are genetic disorders with impaired sclerostin production and markedly increased bone mass [8,9]. A neutralizing antibody to sclerostin has recently been shown to increase bone formation and reduce bone resorption in both mice [10] and humans [11]. Intriguingly, the attenuation of Wnt-mediated transcription, resulting from an autosomal-dominant missense mutation in LRP6, a co-receptor for the Wnt-signaling pathway, has been recently linked to not only hereditary premature osteoporosis, but also to coronary artery disease, as well as, several features of metabolic syndrome including hyperlipidemia, hypertension, and diabetes [12]. In animal models, the Wnt/β-catenin signaling pathway has been shown to contribute to modulation of insulin secretion, β-cell function and insulin signaling in skeletal muscle [13]. Increased sclerostin levels were observed in adult patients with type 2 diabetes mellitus (DM) and atherosclerotic diseases [14]. Several recent studies have evaluated sclerostin levels in adult patients with type 1 DM (T1D) and type 2 DM (T2D). Sclerostin was found higher in adult T2D patients [15,16], while adult T1D patients had either higher [17] or comparable values of sclerostin with controls [16]. Sclerostin level was also assessed in women with gestational diabetes, which can serve as a model of prediabetes type 2, in comparison with non-diabetic pregnant women and no differences regarding serum sclerostin levels and any associations between sclerostin and adverse metabolic profile were found in this study [18]. According to the study by Tsenidis, in pediatric and adolescent populations with T1DM, sclerostin levels demonstrated a Gaussian distribution with no significant difference between patients and controls. Significantly lower values were found in girls and prepubertal children. Sclerostin values were significantly and gradually increased in children through pubertal Tanner stages 1–3. Values were reduced at stage 4 and increased again at pubertal stage 5 [19].

The aim of this study was to assess sclerostin level in children and adolescents with T1D and healthy controls and to investigate the relationship sclerostin, bone-derived osteocalcin (OC), fat tissue-derived leptin and adiponectin, and glucose metabolism.

The hypothesis of the study is that sclerostin is a potential link connecting poor metabolism control and increased bone fragility in patients with T1D.

2. Methods

Forty children with T1DM: 18 girls and 22 boys, and 28 healthy, sex- and Tanner stage-matched controls treated in our department were included in the study. The clinical characteristic of the groups is presented in Table 1. There were no differences relating to the age, and BMI between the groups. The Local Ethical Committee approved the study. All participants and their parents gave their written, informed consent.

All patients with T1D, were treated with an intensive insulin therapy regimen. Insulin analogs were administered to 36 patients, including 19 patients who were treated with CSII. Regular and NPH insulin were administered to 9 patients. The mean daily insulin dose of the entire group of patients reached 0.75 ± 0.52 IU/kg body weight. The mean duration of diabetes was 4.3 ± 2.9 years. The mean level of HbA1c in the group of patients with T1D was 7.7 ± 1.6% [61 mmol/mol].

The control group was selected among patients of our outpatient clinic and their healthy relatives not having diabetes and other disorders influencing bone, fat, and glucose metabolism.

The height of each patient was 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. Each patient's body mass index (BMI) was calculated as her/his weight in kilograms (kg) divided by the square of her/his height in meters (m^2). BMI standard deviation score (BMI SDS) was calculated in the same way as height SDS. The reference data for Polish Children were used [20]. 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 of the bone-derived sclerostin, and osteocalcin (OC), fat tissue-derived leptin and adiponectin levels, as well as the vitamin D, lipid profile, glucose, C-peptide, 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%), 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 by HPLC. The HbA1c levels were measured by a standardized IFCC method. The serum glucose levels and lipid profile were measured by routine chemical methods.

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 T1D patients 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 T1D patients 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.

3. Results

Serum sclerostin levels were significantly higher in patients with T1D then in the control group ($p = 0.04$). The results of ANCOVA, controlling the effect of age, SDS-BMI and Tanner stage confirmed the significant differences regarding sclerostin levels between both groups ($F = 6.028$, $p = 0.017$). There were no differences regarding serum sclerostin levels between genders as well in patients with T1D as in the control group. OC, leptin, and adiponectin levels did not differ

Table 1
Clinical characteristics of the patients with type 1 diabetes mellitus (T1D) and controls, BMI – body index, TS – Tanner stage. The data are presented as mean ± SD. p value refers to differences between patients with T1D and controls. Student's test and χ^2 test were used as appropriate.

Group	Age [year]	Height SDS	BMI SDS	TS1	TS2	TS3	TS4	TS5
T1D	12.3 ± 4.7	−0.16 ± 1.1	1.45 ± 1.92	9	5	5	8	13
Healthy	13.1 ± 4.2	−0.4 ± 2.6	1.50 ± 1.83	5	3	3	5	10
p	0.47	0.54	0.61	$\chi^2 = 20.4$, $p = 0.72$				

Table 2
The mean (± SD) serum levels of osteocalcin (OC), sclerostin, leptin, adiponectin, C-peptide, HbA1c, fasting serum glucose (FG), vitamin D and lipids in the patients with type 1 diabetes mellitus (T1D) and controls, TC – total cholesterol, TGL – triglycerides, HDL – HDL-Cholesterol, LDL – LDL-cholesterol. p value refers to differences between patients with T1d and controls. Student's test and χ^2 test were used as appropriate.

Group	T1D	Controls	p
Sclerostin [pmol/l]	34.8 ± 10.7	29.6 ± 9.1	0.04
OC [ng/ml]	26.4 ± 16.6	21.7 ± 15.9	0.41
Leptin [ng/ml]	2.5 ± 0.9	2.4 ± 0.9	0.82
Adiponectin [ug/ml]	9.5 ± 4.5	7.7 ± 3.3	0.22
C-peptide [ng/ml]	0.4 ± 0.2	1.0 ± 0.4	< 0.0001
HbA1c [%]	7.7 ± 1.6	5.3 ± 0.1	< 0.001
FG [mmol/l]	8.1 ± 3.1	4.7 ± 0.6	< 0.001
25(OH)D_3 [ng/ml]	21.1 ± 9.7	20.0 ± 7.1	0.64
TC [mmol/l]	4.4 ± 0.7	4.0 ± 0.7	0.02
TGL [mmol/l]	1.1 ± 0.8	1.1 ± 1.3	0.83
HDL [mmol/l]	1.4 ± 0.4	1.4 ± 0.3	0.09
LDL [mmol/l]	2.3 ± 0.6	2.1 ± 0.5	0.08
HDL/TC [%]	36.2 ± 8.1	37.3 ± 10.1	0.71

significantly between both groups. Patients with T1DM had statistically significant higher levels of fasting glucose, HbA1c, and total cholesterol in comparison with controls ($p < 0.001$, $p = 0.04$, $p = 0.02$, respectively) and significantly lower level of C-peptide than healthy ones ($p < 0.001$) [Table 2].

Pearson correlation coefficients revealed a positive association between serum sclerostin levels and OC ($r = 0.59$, $p < 0.001$) and a negative correlation between serum sclerostin levels and leptin ($r = -0.32$, $p = 0.02$) in all of the subjects. Both correlations remained significant after adjustment for age, SDS-BMI and Tanner stage ($p < 0.001$, $p = 0.024$). No significant correlation was found between sclerostin, adiponectin, 25(OH)D3, nor lipids.

In the group of T1D patients, Pearson correlation coefficients revealed a strong, positive association between serum sclerostin levels and OC ($r = 0.62$, $p < 0.001$) and a negative association between serum sclerostin levels and HbA1c and leptin levels ($r = -0.33$, $p = 0.04$, $r = -0.33$, $p = 0.03$, respectively). When adjusting the analysis to the age, SDS-BMI and Tanner staging, all correlations in T1D group remained significant ($p < 0.05$). The linear positive correlation between sclerostin and OC is presented in Fig. 1. The linear associations between sclerostin and HbA1c level and between sclerostin and leptin level in T1D patients are presented in Figs. 2 and 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.

4. Discussion

The crosstalk between the skeleton and glucose metabolism has been postulated over the last decade in the general population and also in children and adolescents [21,22]. Bone-derived osteocalcin, a marker of bone formation, was shown to play a major role in this process [22]. The results of the present study suggest that sclerostin could also be associated with glucose metabolism. We have shown the marked increase in circulating sclerostin levels in children and adolescents with T1D in comparison with age- and sex-matched controls. In the previously cited study by Tseniditis et al., there were no differences in regards to sclerostin levels between children and adolescents with T1D and their healthy peers [19]. But in adult patients with T1D, which included men and premenopausal women, the serum sclerostin levels, like in our study, were higher than those in the control group, irrespective of gender [17]. In adults sclerostin levels were also increased in individuals with prediabetes compared with healthy individuals [23]. A recent study demonstrated that the changes in the circulating sclerostin levels reflect similar changes in the sclerostin levels in bone marrow plasma [24]. Sclerostin is a recently discovered Wnt antagonist that is almost entirely produced by osteocytes and plays a major role in the suppression of bone formation. Together with other factors such as Dickkopf1, sclerostin can bind to LRP5 and LRP6 leading to the inhibition of the Wnt/β-catenin signaling pathway in the osteoblast and thus osteoblast activity [25]. This in turn leads to reduced osteoblast proliferation, differentiation, and lifespan [26]. Increased sclerostin serum levels is associated with bone formation and resorption markers in patients with immobilization-induced bone loss [27]. Inhibiting the osteocyte-specific protein sclerostin increases bone mass and fracture resistance in multiple myeloma [28]. Several clinical and experimental observations suggest an increased skeletal fragility in T1D patients, although the pathophysiology of reduced bone strength in diabetes remains to be clarified [29]. Our data could point toward an increase in sclerostin levels as a potential cause of the reduction of bone formation in T1D. The same observations were reported by Faienza et al. Their study highlighted the high serum levels of DKK-1 and sclerostin in T1D children and their relationship with altered glycemic control and further the effect of CSII on the improvement of glycemic control and bone health [30]. The possible cooperation between bone tissue and glycemic control via sclerotin is probably long-term process. It could be a reason for why women with gestational diabetes did not show such correlations [13].

The question is whether sclerostin influences glucose metabolism independently or through the inhibition of osteoblast activity and OC production. Surprisingly, a strong positive correlation was observed between the sclerostin and OC levels in our study. Similar results were reported by Tsentidis et al. In their study, sclerostin was correlated with both resorption and formation markers in children and adolescents [19]. In adults with prediabetes, the sclerostin level and correlated with insulin resistance [23]. Results of the above-mentioned studies are evidence of the crosstalk relationship between bone and glucose metabolism. The negative correlation between sclerostin and HbA1c could not confirm that sclerostin is a main contributor the relationship between inadequate metabolic control of diabetes and bone complications. However, they do not deny its role in the origin of this complication. It is worth highlighting that bone metabolism is very active in childhood and adolescence. Moreover, there is a physiological prevalence of bone formation compared to bone resorption. Osteoblasts and osteocytes, which secrete sclerostin as well as OC, play a major role in the process of bone turnover. The OC and sclerostin levels are likely increased and positively correlated because of the increased bone turnover. It was observed that both of these parameters are dependent on the age and pubertal stage of the children [19]. In healthy pediatric populations serum sclerostin levels were higher in boys in comparison to girls and declined in both sexes following the onset of puberty [31]. We did not find such differences between sexes of individuals with T1D and healthy peers and we cannot find the possible cause of that observation. However, gender differences in sclerostin were described as well in children and adults with T1D, but the results were contradictory. In most publications sclerostin levels were higher in males with T1D, but the opposite was seen in the study of Catalano et al. where women with T1DM exhibited higher sclerostin levels than men [32]. A completely different observation was reported in adults with type 2 diabetes mellitus. The sclerostin concentrations did not differ between males and females with diabetes, although they were higher in non-diabetic men when compared with women [33].

Most likely, the difference in the insulin levels and its mode of action in the two types of diabetes can explain for their influence on the role of sclerostin in glucose metabolism. Moreover, the results of our study could suggest that another cause of the differences between type 1 and 2 diabetes mellitus could be the participation of leptin in this process. Despite the significant negative correlation between the sclerostin and HbA1c levels, we found a negative correlation between the sclerostin and leptin levels in children with T1D. Adipocyte-derived

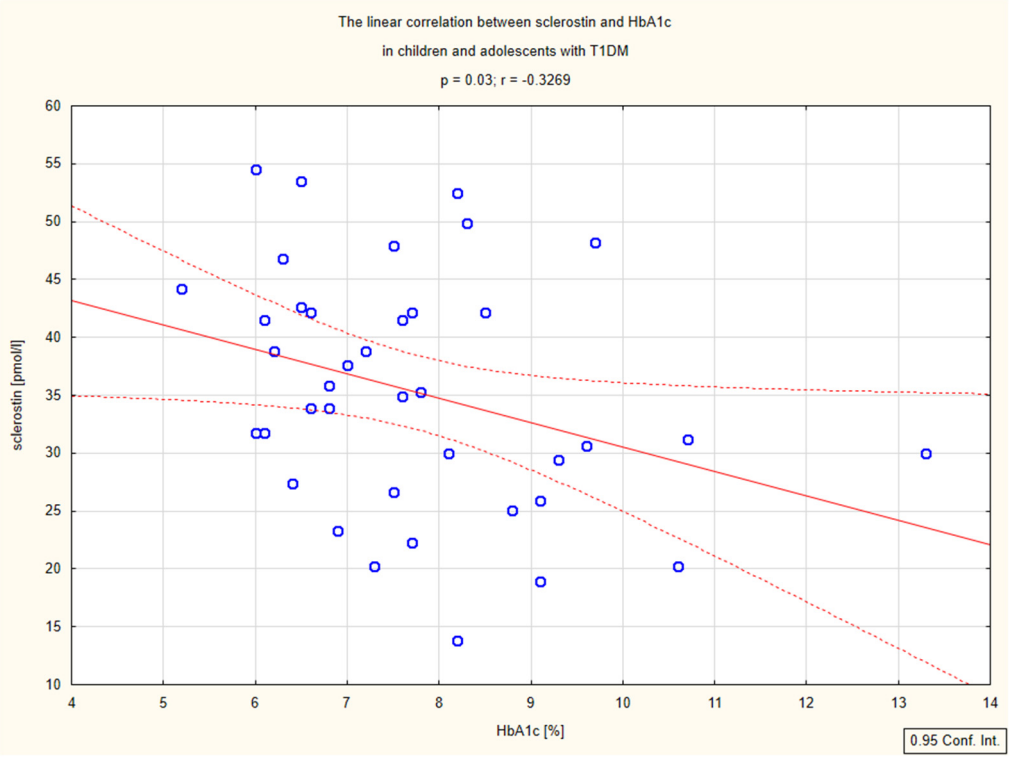

Fig. 1. The linear positive correlation between sclerostin and osteocalcin in children and adolescents with type 1 diabetes mellitus (Pearson correlation coefficients).

leptin promotes weight loss, which, in turn, has a beneficial effect on diabetes control [34]. The latest data indicates that leptin can play a role in diabetes pathophysiology, which is not associated with its action on appetite control. Leptin could play a major role in the growth of pancreatic islet cells and insulin secretion. It is known that leptin can stimulate osteoblasts to produce osteocalcin, a protein that stimulates insulin release [35,36]. In non-obese mice with uncontrolled T1D, leptin therapy alone or combined with low-dose insulin reverses the catabolic state by suppressing hyperglucagonemia. Additionally, leptin mimics the anabolic actions of insulin and normalizes the HbA1c levels with far less glucose variability [37,38]. In contrast to insulin, leptin inhibits lipogenic and cholesterolgenic transcription factors and

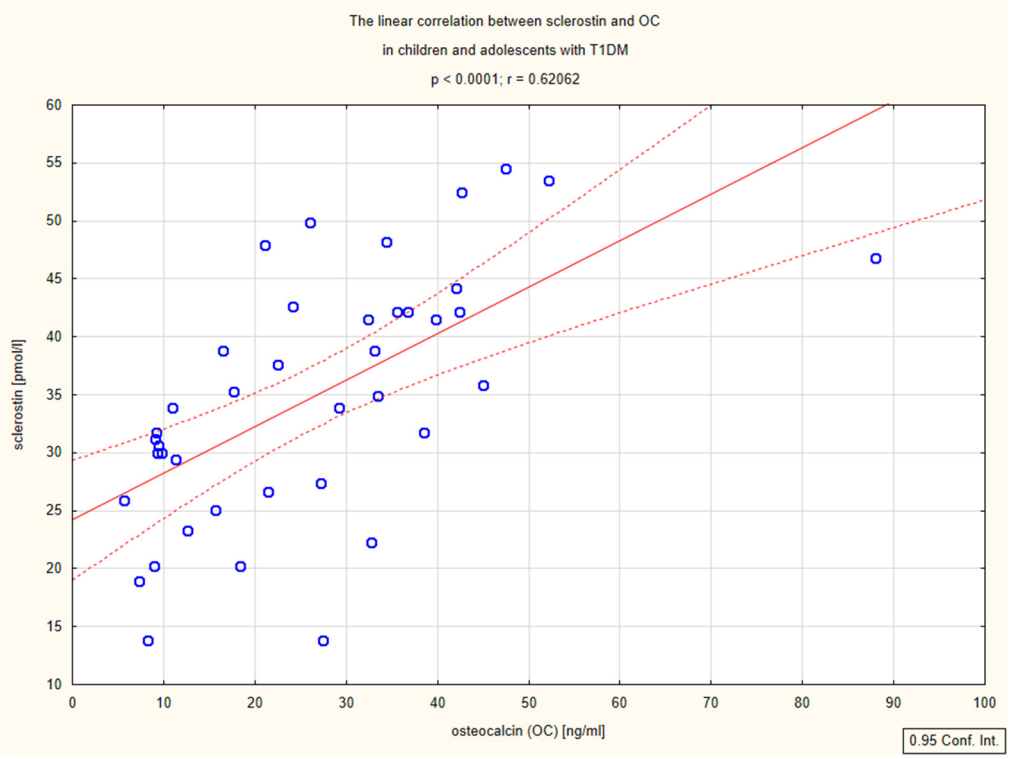

Fig. 2. The linear associations between sclerostin and HbA1c level in children and adolescents with type 1 diabetes mellitus (Pearson correlation coefficients).

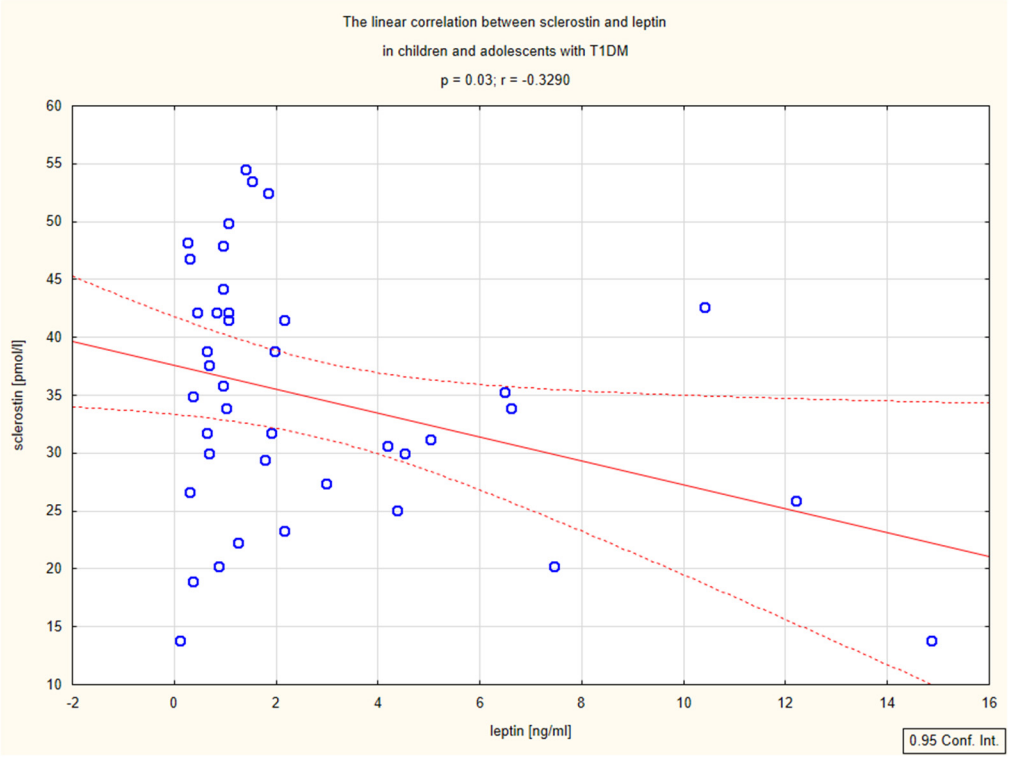

Fig. 3. The linear associations between sclerostin and leptin level in children and adolescents with type 1 diabetes mellitus (Pearson correlation coefficients).

enzymes, additionally also reduces the plasma lipid concentrations and tissue lipid contents [38]. We found negative correlation between sclerostin and leptin. In our previous study we reported that leptin could be significant for good metabolic control of diabetes, so it is seems not be astonishing that the relationship between sclerostin and HbA1c is also negative, as is the relationship between sclerostin and leptin.

In summary, the bone-derived OC and sclerostin could play an important role in the regulation of glucose metabolism in children and adolescents. In young patients with T1D the crosstalk between bone-derived sclerostin and fat-derived leptin could potentially influence the results of metabolic control of the disease. It could have an important implication in regards to the risk of cardiovascular diseases in the future.

The strength of our study includes the presentation of sclerostin distribution in healthy and T1D Caucasian children. The cohort was homogeneous therefore representing the pediatric population of Central Europe. The study presents new data suggesting a possible role of sclerostin in the regulation of carbohydrate metabolism in children and adolescents with T1D. For first time the study presents associations between sclerostin and other bone- and fat-derived molecules in regards to glucose metabolism in T1DM.

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. The serious limitation is the lack of data of bone mineral density (BMD) in the participants of the study. Therefore, our suggestions about the potential role of sclerostin on bone formation are only speculations. We did not consider a possible influence of physical activity on the results of serum sclerostin levels. Our patients with T1DM did not have any physical activity limitations and therefore we posited that both groups are similar regarding this issue.

5. Conclusions

The results of our study could suggest a relationship between sclerostin and glucose metabolism in children and adolescents with T1D. Further investigation is required to determine if an increase in sclerostin levels could present as a potential cause of the reduction of bone formation in T1D. Both bone-derived OC and fat-derived leptin seem to possibly modulate the regulation of metabolic control together with sclerostin in young patients with T1D.

Declaration of conflicts of interest

None of the authors have a conflict of interest.

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Author contribution statement

A.W. designed the study, researched and analyzed data, wrote and edited the manuscript. K.S. and J.S. reviewed the manuscript.

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