Sclerostin and its associations with energy metabolism in children and adolescents

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Background

The recent evidence has shown that the skeleton can in turn affect carbohydrate metabolism. Bone-derived osteocalcin, which is a specific marker of bone formation, predominately, is produced by osteoblasts, is pharmacologically active on glucose and fat metabolism [Convareux, 2009]. The results of studies on animals revealed that mice lacking the osteoblast-secreted molecule osteocalcin display decreased β-cell proliferation, glucose intolerance and insulin resistance. Removing one Osteocalcin allele from the TGF-β-deficient mice corrects their metabolic phenotype. Ex vivo, osteocalcin can stimulate CycloD1 and Insulin expression in β-cells and Adiponectin, an insulin-sensitizing adipokine, in adipocytes; in vivo osteocalcin can improve glucose tolerance. By revealing that the skeleton extends an endocrine regulation of sugar homeostasis this study expands the biological importance of this organ and our understanding of energy metabolism [Lee, 2007].

Another osteoblast-secreted molecule – sclerostin is a potent inhibitor, in the Wnt pathway, which is a major regulator of bone mass. Increased bone formation through this pathway results from both the expansion of osteoprogenitor cells as well as reduced apoptosis of mature osteoblasts [Baron 2007, Kirshan 2006]. Its biological importance is underlined by clinical observations in subjects with sclerosteosis and van Buchem disease, two genetic disorders associated with impaired sclerostin production and markedly increased bone mass [Staehling-Hampton 2002, Bateman 2002]. A neutralizing antibody to sclerostin has recently shown to increase bone formation and to also reduce bone resorption both in mice [Lit 2009] and humans [Paski, 2011].

Fascinatingly, attenuation of Wnt-mediated transcription, resulting from an autosomal-dominant missense mutation in LRPS, a co-receptor for the Wnt-signaling pathway, has been linked recently genetically not only to premature osteoporosis, but also to coronary artery disease as well as several features of the metabolic syndrome including hyperlipidemia, hypertension and diabetes. It was hypothesized that antagonism of Wnt signaling by oxidative stress with increasing age may be a common molecular mechanism contributing to the development not only of involutional osteoporosis but also of diabetes, hypertension, hyperlipidemia and insulin resistance. [Manolagas, 2007]. An increased sclerostin levels were found in adult patients with type 2 diabetes mellitus (DM) and atherosclerotic diseases [Morales-Santana S, 2013].

Objective

The aim of the study was to to analyze associations between serum level of sclerostin and as well other bone-related molecules as adipokines and some markers of glucose and lipid metabolism in children and adolescents.

Methods

Fifty-seven patients, 40 with type 1 diabetes mellitus (T1DM) and 17 with obesity, treated in the Department of Pediatric and Adolescent Endocrinology and diabetes in 11 control, healthy age- and BMI-matched children were included in the study between years 2013–2014. The Local Ethical Committee approved the study. All participants and their parents gave their written, informed consents.

Patients with T1DM, 19 girls and 21 boys, mean age 12.4±2.7 yrs, body mass index (BMI) 20.2±3.8 kg/m² were treated with an intensive insulin therapy method. In 32 patients insulin analogs were administered, which in 17 patients were treated with CSII. In 8 patients, regular and NPH insulin were administered. The mean daily insulin dose of the entire group of patients reached 0.77±0.57 U/kg b.w. The mean diabetes duration was 4.2±2.9 years.

Seventeen obese children, 9 girls and 8 boys, mean age 11.3±3.8 yrs, BMI 27.2±7.3 kg/m² were included into the study. Obesity was defined as at or above the 95th percentile of the sex-specific BMI for age growth charts

Control group consisted of eleven, healthy children, mean age 11.5±0.5 yrs, BMI 19.0±2.8 kg/m².

Anthropometrical measurements

Height was measured to the nearest millimeter using a rigid stadiometer. Weight was measured unclothed to the nearest 0.1 kg using a calibrated balance scale. Reference data for Polish Children were used [Palczewska, 1999]. Body mass index (BMI) will be calculated as weight in kilograms (kg) divided by the square of height in meters (m²).

Material

Fasting blood samples for measurement of bone derived sclerostin, osteocalcin (OC) and Receptor Activator of Nuclear Factor NF-κB ligand (RANKL), fat tissue-derived leptin and adiponectin, as well as vitamin D, lipid profile, glucose, C-peptide, insulin, and HbA1c concentrations were taken from the antecubital vein at 8.00 AM. HbA1c, glucose, and lipid levels were measured at once. After clotting, blood samples were centrifuged. Serum was stored in -80°C until the time of measurement of the rest parameters.

Biochemical methods

Serum levels of sclerostin (Biomedica), osteocalcin (DiaSource), RANKL (Biomedica), leptin (DiaSource), adiponectin (DiaSource), insulin (DiaSource), and C-peptide (Diagroups) were measured by ELISA methods. 25(OH)D3 was measured with HPLC HbA1c was measured by standardized ICSC method. Serum glucose level was measured by dry chemistry, and lipids with an enzymatic method (routine chemistry method).

Results

Serum levels of sclerostin, OC, RANKL, and adiponectin did not differ among three groups: patients with T1DM, obese patients, and healthy ones. There were significant differences regarding leptin, C-peptide, fasting serum glucose (FG), HbA1c, LDL-cholesterol levels, and HDL-cholesterol/Total Cholesterol ratio among the examined groups. Leptin and C-peptide concentrations were significantly higher in obese children than in patients with T1DM and in controls (p<0.001, p<0.0001, respectively). FG and HbA1c were significantly higher in patients with T1DM than obese and healthy ones (p<0.001) (Table 1). HDL-cholesterol level, and HDL-cholesterol/Total Cholesterol ratio were the highest in highest one (p<0.001, p<0.001, respectively) and LDL-cholesterol level was the highest in obese patients (p<0.001) (Table 2).

Conclusions

The results of our study suggest that sclerostin could play an important role in the energy metabolism in children and adolescents. Its action seems to be associated with other bone-derived molecules as osteocalcin, but also fat-derived leptin. Moreover their relationships could be modified in different metabolic stages.

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The authors have NOTHING TO DISCLOSE.