The role of bone and fat tissue in glucose metabolism in two different metabolic conditions: obesity and diabetes mellitus type 1 – a pilot study

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Abstract

Background: Recent studies have shown a new link between skeleton, fat tissue, and insulin action. However, clinical data are still limited, especially in children.

Objective: The aim of the presented study was to investigate the relationship between bone and fat hormones and glucose metabolism in children with type 1 diabetes mellitus (T1DM) and obesity.

Methods: Forty-six T1DM children, mean age 12.2±4.6 yrs, mean BMI 20.0±4.7 kg/m^2, 16 obese children, (age 11.3±3.8 yrs, BMI 27.2±7.3 kg/m^2), and 11 control, healthy children, (11.5±5.0 years), BMI 19.0±2.8 kg/m^2) were included into the study. Fasting blood samples for measurement of bone derived 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, HbA1c concentrations were taken at 8.00 AM. Hormones were measured by immunochemistry, vitamin D by HPLC and other parameters by routine chemistry methods. Statistical analysis was performed in all groups using ANOVA with post-hoc Turkey test and multiple regression analysis.

Results: There were significant differences regarding leptin, HbA1c, LDL-cholesterol, HDL-cholesterol/Total Cholesterol levels among groups p<0.001 (Table 1). In T1DM, multiple regression analysis adjusted for age and BMI showed negative correlation between OC and leptin (r=-0.37, p=0.02) and HbA1c (r=-0.4, p=0.01), and positive correlation between OC and HDL/TC (r=0.3, p=0.02). In contrary, serum RANKL correlated positively with adiponectin (r=0.3, p=0.04). Moreover vitamin D correlated negatively with HbA1c (r=-0.3, p=0.03). In obese patients strong correlation between adiponectin and HbA1c (r=-0.8, p=0.02) has been found. In control group only positive correlation between OC and vitamin D (r=0.7, p=0.03) was noted.

Conclusion: It is suggested that cross-talk between bone and fat tissue in pediatric patients depends on insulin action.

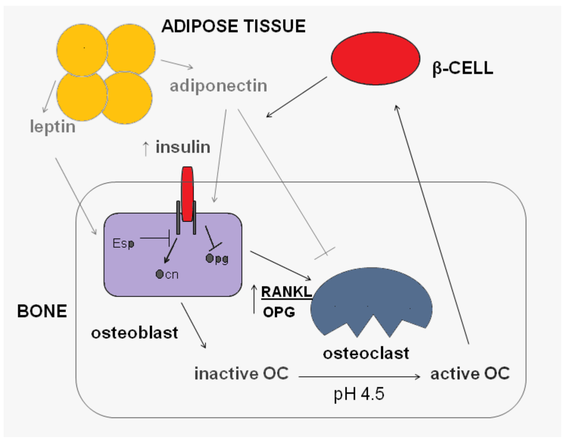
The authors have NOTHING TO DISCLOSE.

Background

The results of experiments on animals indicate that the skeleton is an endocrine organ that affects energy metabolism. Bone-derived osteocalcin is a hormone pharmacologically active on glucose and fat metabolism. There was shown that osteocalcin stimulates insulin secretion and β-cell proliferation. Insulin signaling in osteoblasts integrates bone remodeling and energy metabolism (Figure 1). It was reported that intermittent injections of osteocalcin improve glucose metabolism and prevent type 2 diabetes in mice.

Simultaneously osteocalcin acts on adipocytes to induce adiponectin which secondarily reduce insulin resistance. Adiponectin increases bone mass by suppressing osteoclast and activating osteoblast. Leptin, another hormone exerting a major influence on energy metabolism, is one of them and does so also by modulating *Esp* expression (Figure 1).

Figure 1.
Relationships between bone, adipose tissue and beta cells concerning energy metabolism.



Fasting plasma glucose levels are is elevated in osteoporotic women treated with drugs inhibiting bone resorption and serum undercarboxylated osteocalcin levels are positively correlated with bone resorption in healthy women.

In adults serum osteocalcin was associated with measures of insulin resistance, adipokine levels, and the presence of metabolic syndrome. It has been shown that serum leptin and adiponectin are positively associated with bone mineral density at the distal radius in patients with type 2 diabetes mellitus, so leptin and adiponectin may have a protective effect on bone metabolism..

In children there were found some relationships between osteocalcin, adiponectin and insulin secretion in a weight-dependent manner.

Vitamin D depletion induces RANKL-mediated osteoclastogenesis and bone loss. In obese children vitamin D is related to hyperinsulinemia. It was reported that hypovitaminosis D is a risk factor for developing insulin resistance independent of adiposity .

Objective

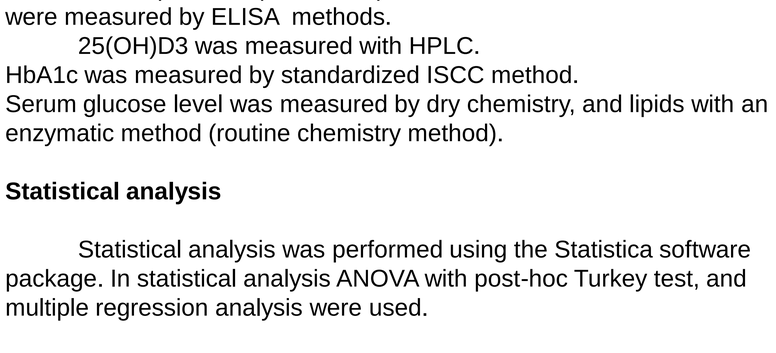
The aim of the study was to investigate the relationship between:
• bone-derived osteocalcin (OC) and Receptor Activator of Nuclear Factor NF-κB ligand (RANKL),
• fat tissue-derived leptin and adiponectin,
• and glucose metabolism in children and adolescents in two different metabolic conditions: type 1 diabetes mellitus (T1DM) and obesity.

Methods

Patients

Forty-six children, 23 girls and 23 boys, mean age 12.2±4.6 yrs with T1DM and 16 obese children, 8 girls and 8 boys, mean age 11.3±3.8 yrs were included into the study. Control groups consist of 11 children, mean age 11.5±5.0 yrs.

Figure 2. Characteristic of the groups included into the study.



Anthropometrical measurements

Height was measured to the nearest centimeter 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 (m^2).

Material

Blood samples were drawn once from the antecubital vein in the fasting state, at 08.00 hours.
HbA1c level was measured at once.
After clotting, blood samples were centrifuged. Serum was stored in -80ºC until the time of measurement of required parameters.

Biochemical methods

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

Statistical analysis

Statistical analysis was performed using the Statistica software package. In statistical analysis ANOVA with post-hoc Turkey test, and multiple regression analysis were used.

Results

There were significant differences regarding leptin, HbA1c, LDL-cholesterol, HDL-cholesterol/Total Cholesterol levels among groups p<0.001 (Table 1 and Table 2).

Table 1.
Mean±SD data of OC, RANKL, leptin, adiponectin, HbA1c, fasting serum glucose, and vitamin D in patietns with T1 DM, obese patients and in controls.

Group	OC [ng/ml]	RANKL [pmol/l]	Leptin [ng/ml]	Adiponectin [ug/ml]	HbA1c [%]	Glu [mmol/l]	25(OH)D$_3$ [ng/ml]
T1 DM	26.3±16.6	24.9±43.8	2.2±3.3	11.6±4.4	7.7±1.6	7.9±2.9	20.4±9.4
obese	28.9±17.4	44.3±51.6	8.1±5.9	6.2±5.3	5.2±0.2	4.4±0.5	17.2±9.2
control	21.7±15.9	28.2±40.7	2.4±0.9	7.7±3.3	5.4±0.1	4.4±0.6	19.2±9
p	NS	NS	<0.001	NS	<0.001	<0.001	NS

Results

Table 2.
Differences in lipid profile (mean±SD data are presented) among the groups of patients with T1 DM, obese patients and controls.

Group	Chol [mmol/l]	TGL [mmol/l]	HDL [mmol/l]	LDL [mmol/l]	HDL/TC [%]
T1 DM	4.43±0.7	1.01±0.7	1.57±0.3	2.36±0.7	35.97±7.8
obese	4.67±1.1	1.5±1.0	1.18±0.3	3.04±0.8	26.0±7.2
control	3.94±0.8	1.02±0.5	1.42±0.3	2.04±0.6	37.3±10.1
p	0.07	0.07	<0.0001	<0.001	<0.001

Type 1 DM patients

Multiple regression analysis adjusted for age and BMI showed that serum OC negatively related to as well leptin as HbA1c levels (p=0.02 and p=0.01)) and positively related to HDL Cholesterol /Total Cholesterol index, HDL/TC (p=0.02) in patients with T1 DM.
In contrary, serum RANKL positively related to adiponectin (p=0.04). Moreover vitamin D negatively related to HbA1c (p=0.03).

Figure 3
The linear association between OC and leptin (r = -0.41, p=0.02) in T1 DM

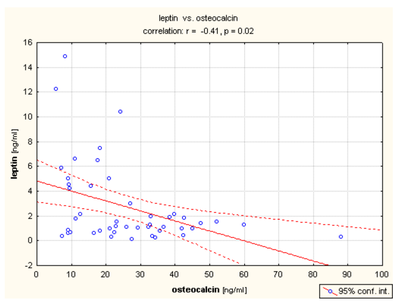


Figure 4
The linear association between OC and HbA1c (r = -0.4, p=0.01) in T1 DM

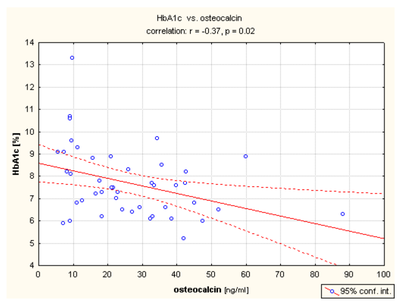


Figure 5
The linear association between OC and HDL/TC (r = -0.3, p=0.02) in T1 DM DM

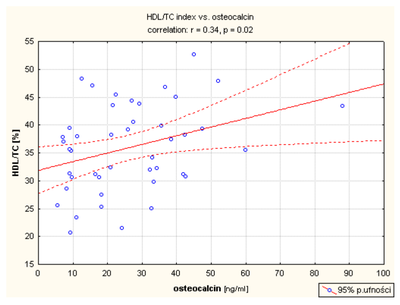
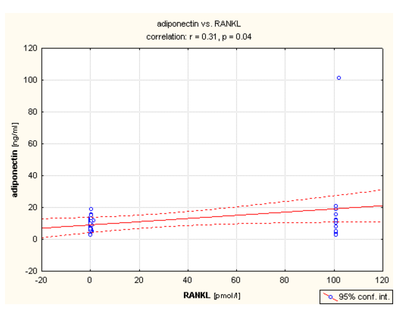


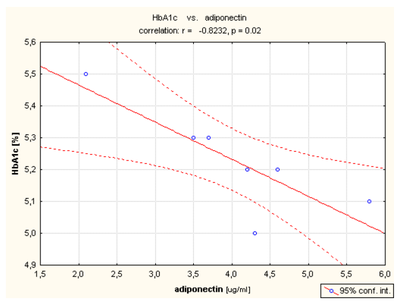
Figure 6
The linear association between RANKL and adiponectin (r = 0.3, p=0.04) in T1



Obese patients

In obese patients adiponectin negatively related to HbA1c (p=0.02).

Figure 7
The linear association between adiponectin and HbA1c (r = 0.8, p=0.02) in obese patients.



In control group only positive correlation between OC and vitamin D (r=0.7, p=0.03) was noted.

Conclusions

Our preliminary data suggest that cross-talk between bone and fat tissue exists in pediatric patients and it could be associated with insulin action. Further studies on larger groups regarding this problem are need.

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