Abstract

Type 1 diabetes mellitus (T1DM) is one of the most common chronic diseases in children and young adults, leading to decreased life quality and lifespan, with obesity being recently recognised as a major contributing factor to these health problems.

For the past years the prevalence of obesity is growing in general population of children, but also among diabetic patients, resulting in increased risk of cardiovascular complications. It is estimated that up to 35% of young patients with type 1 diabetes are overweight. Furthermore, the prevalence of insulin resistance, associated with being overweight and obese, was previously linked with type 2 diabetes, is increased in children with T1DM and contributes to earlier development of microangiopathy as well as macroangiopathy, which was confirmed in DCCT study.

The coexistence of obesity in patients with type 1 diabetes is associated with additional risk factors for the development of macroangiopathy. In addition, based on data obtained from studies conducted in the population of adult patients, insulin resistance, metabolic syndrome, polycystic ovary syndrome and non-alcoholic fatty liver disease (NAFLD) are also found in obese type 1 diabetic patients. In addition, excessive body weight has a negative impact on the managing of type 1 diabetes, causes fluctuations in blood glucose levels and higher daily requirement of the insulin. The risk of developing microvascular complications also increases. Patients with a higher BMI present a more atherogenic lipid profile, an increase in the thickness of the intima-media complex, and thus a higher risk of developing cardiovascular diseases. NAFLD is also considered an additional risk factor for the development of atherosclerosis, contributing to the severity of cardiovascular complications, but there are also publications associating with a higher risk of diabetic retinopathy and nephropathy. The obesity epidemic caused increased interested in factors released by adipose tissue, such as inflammatory cytokines, fatty acids and adipocytokines. In addition to well described adipocytokines and markers of the inflammatory process, new prognostic indicators of an increased risk of developing cardiovascular diseases are still being sought. Among them are: irisin, osteoprotegerin, fetuin A and E-selectin.

Objectives:

The aim of this study was to analyze and compare selected new markers of metabolic complications of excessive body weight and classical cardiovascular risk factors between children, adolescents and young adults with type 1 diabetes, patients with type 1 diabetes and excessive body weight, obese patients without diabetes compared to healthy people.

Specific objectives:

1. Analysis of the occurrence of classical cardiovascular risk factors in the population of lean type 1 diabetic patients, type 1 diabetic patients with excessive body weight, and obese non-diabetic patients compared to healthy individuals.

2. Analysis of the severity of insulin resistance in the study groups.

3. Vascular structure analysis – measurement of the middle and inner layers of common carotid arteries (cIMT) in the study groups.

4. Assessment of the occurrence of NAFLD in the study groups.

5. Analysis of selected new markers of metabolic complications of excessive body weight

(adiponectin, E-selectin, irisin, osteoprotegerin, fetuin A) in the studied groups of patients.

Patients:

Hundred and four patients, aged between 10 and 24 years, 31 with T1DM and obesity, 41 with obesity, 32 with T1DM and normal weight were enrolled in the study. The onset of T1DM must have been at least 2 years prior. The control group consisted of 32 aged-matched healthy peers.

The study was performed in the Pediatric Endocrinology and Diabetology Division, Department of Clinical Pediatrics as well as Outpatient's Clinics of Provincial Specialist Children's Hospital in Olsztyn.

Methods:

The following parameters were analyzed in the study groups: age, sex, height, body weight, BMI, BMI SDS, waist circumference, waist – SDS, blood pressure, additionally in patients withy type 1 diabetes: duration of the disease, daily insulin dosage, treatment method, estimated glucose disposal rate (eGDR 1, eGDR2), visceral adiposity index (VAI).

Biochemical research: lipids, vitamin D3, fasting glucose, fasting insulin, HbA1C, adiponectin, irisn, osteoprotegerin, fetuin A, E-selectin concentration; AST, ALT, GGTP activity.

In obese patients OGTT was pedformed. Ultrasound examination: ultrasonographic evaluation of the thickness of the middle and inner layers od common carotid arteries; ultrasound of the abdomen to asses NAFLD occurrence.

Statistical analysis were performed using STATISTICA v.13.3 software. Quantitative variables were expressed as mean and standard deviation (SD).

For quantitative data, the results are described using the following parameters: numer of cases (N), mean value, $\pm$ 95% confidence interval, median (Me), minimum (Min), maximum (Max), Q1 first quartile and Q3 quartile third, and the standard deviation (SD). Qualitative (categorical) variable data were described by comparing the number of cases (N) and their percentage ratio (%) in the study group. In order to check the significance of the distribution of results of qualitative variables (e.g. sex and prediabetes) in the study groups, the chi-square test (c2) was used.

The Shapiro-Wilk test was used to check the normality of the distribution. In the case of parametric distributions (the distribution of results was normal), the Student's t-test and ANOVA (F) for multiple groups were used to compare the means in the two groups.

A post-hoc NIR test was used to compare means between the four groups. For non-parametric distributions, the Mann-Whitney U test (U) was used. In order to find the relationship between the variables and the new markers, non-parametric R-Spearmann correlation analysis was used.

Results:

Patients with type 1 diabetes mellitus and excessive body weight compared to non-diabetic obese youth had similar values of systolic blood pressure, diastolic blood pressure, cholesterol, LDL, triglyceride levels, all values higher compared to non-obese T1DM and healthy controls. HbA1C, eGDR1, eGDR2, triglycerides concentrations, systolic blood pressure were higher in the group of patients with type 1 diabetes mellitus than in non-obese diabetic patients.

In my study, the concentration of adiponectin was similar in the group of patients with T1DM, T1DM and excessive body weight, but slightly lower compared to the control group, but without statistical significance. The lowest concentration was found in non – obese diabetic patients compared to the control group. There was no statistical significance in adiponectin concentrations between the patients with T1DM and excessive body weight and non – obese.

In the non – diabetic obese group, a significantly positive correlation was found between adiponectin concentration and HDL, and a negative between VAI, TG, LDL concentrations and GGTP activity. In the group of patients with T1DM, positive correlation of adiponectin with HDL concentration as well as with eGDR1, eGDR2 was also obtained, while negative correlation with VAI and systolic blood pressure was obtained.

Irisin concentration was lower in all study groups compared to the control group. There was no correlation between irisin concentration and BMI, insulin resistance, LDL and triglyceride concentrations, however negative correlation with HDL was noted in the group of patients with T1DM, where the irisin level was the lowest.

In the study, fetuin A concentrations were higher in the non-diabetic obese patients and those with T1DM and excessive body weight, compared to the control group, and the highest concentration was found in the non – diabetic obese. However, no significant difference was found between the groups of the T1DM and T1DM and excessive body weight. Positive correlation of fetuin A with HDL concentration was established in the group of patients with T1DM and excessive body weight.

The concentration of E-selectin was higher in diabetic and obese patients without diabetes compared to the control group. Despite of the absence of the statistical significance, it was noticeable that patients with T1DM and excessive body weight had slightly higher values than the T1DM group, but lower compared to non – diabetic obese patients. The conducted analysis showed no correlation between the classical risk factors of cardiovascular complications and the concentration of E-selectin.

There were no differences in the concentration of OPG between non – diabetic obese patients, those with T1DM and T1DM and excessive body weight, however the values were higher compared to the control group. A positive correlation between OPG concentration and SDS waist circumference was found only in the non-diabetic obese patients.

There were no statistical differences in intima media thickness between patients with type 1 diabetes with normal weight, excessive weight, and with non-diabetic obese children, however cIMT values were higher compared to reference group.

In patients with typ1 diabetes there was no correlation between cIMT and BMI, HbA1C, daily insulin dosage, eGDR1 and eGDR2. In the non – diabetic obese group, were the highest BMI was noted, there was negative correlation between adiponectin concentration and cIMT. There was no correlation between concentration of E-selectin, irisin, fetuin A, OPG and cIMT.

In my study, NAFLD was present in 24% of non – diabetic obese patients and in 13% with T1DM and excessive body weight. It was not found in patients with T1DM or in the control group. As for the activity of liver enzymes, the highest values of ALT, GGTP were found in the group of obese patients, compared to the patients with diabetes and the control group. There were no significant differences between patients with T1DM and T1DM and excessive body weight. However in the group with T1DM and excessive body weight, the concentration of osteoprotegerin positively correlated with AST, ALT, and in the group of non – diabetic obese patients – GGTP negatively with the concentration of adiponectin. There was no correlation with other tested biomarkers (irisin, E-selectin, fetuin A) in any of the studied groups.

Additionally, in the group of non-diabetic obese patients with NAFLD, significantly higher values of BMI, BMI-SDS, waist SDS, fasting insulin, HOMA IR, AST, ALT and osteoprotegerin concentration were found than in the group without NAFLD. Patients with T1DM and excessive body weight, diagnosed with NAFLD had significantly higher results of: cholesterol, TG, LDL, VAI, AST, ALT, GGTP than in the those without NAFLD. No correlation was found between NAFLD and HbA1C, daily insulin dose, eGDR1, eGDR2. In the group of diabetic patients, NAFLD was associated with the presence of an atherogenic lipid profile.

Conclusions:

Children and young adults with type 1 diabetes show numerous abnormalities in terms of classical cardiovascular risk factors, new markers and early structural (increase in the thickness of the intima-media of the common carotid arteries) changes in the cardiovascular system than healthy children.

Overweight/obesity in children and adolescents with type 1 diabetes is associated with worse metabolic control, insulin resistance, atherogenic lipid profile, higher systolic blood pressure, and typical components of the metabolic syndrome.

Lower adiponectin concentration is associated with higher body weight, insulin resistance and negatively correlates with cIMT. The assessment of irisin concentration as a marker of the atherosclerosis may be difficult to interpret due to the high impact of physical activity on its production and seems to be of little use in clinical practice. Higher concentrations of fetuin A may be used in the future to assess the risk of insulin resistance and cardiovascular complications, but it is necessary to establish age norms and correlations with body weight and HbA1C.

Patients with type 1 diabetes have higher values of E-selectin compared to the control group. Obesity is an additional factor affecting its concentration. It seems to be a good marker of early atherosclerotic changes. Determination of osteoprotegerin may be a marker of early atherosclerotic changes, however, it is necessary to conduct further studies and establish the correlation with body weight, glycemic control, and insulin resistance among patients with type 1 diabetes.

Overweight and obesity are the risk factors for the development of NAFLD in patients with type 1 diabetes. The occurrence of NAFLD is associated with the severity of metabolic disorders and higher cIMT, therefore it is important to perform regular ultrasound examinations in patients with type 1 diabetes and obesity. Medical care for patients with type 1 diabetes should also include preventive measures aimed at reducing the risk of developing vascular complications in the future. Particular attention should be paid to maintaining a normal body weight among children and adolescents with type 1 diabetes.