ABSTRACT

Type 1 diabetes is currently one of the most common chronic diseases in the population of children and adolescents. In recent years, there has been a very dynamic increase in the incidence of this disease in Poland. Accurate understanding of the pathogenesis of type 1 diabetes and its complications is currently the greatest challenge in diabetology. Adipose tissue and the digestive tract are an important part of the endocrine system, producing the largest amount of regulatory peptides. The increasing knowledge about the function of gastric peptides and adipocytokines in the body allows us to conclude that they are an essential element connecting the process of food consumption, the nutritional status of the body and its growth, e.g. by regulating carbohydrate metabolism and insulin resistance. They modulate insulin sensitivity both in a healthy body and in an organism with impaired pancreatic function, exerting long-term effects on energy homeostasis. Available works prove that adipocytokines and gastrointestinal peptides play an important role in the pathogenesis of not only many metabolic diseases, but also autoimmune diseases. There are reports on the role of these peptides in the pathogenesis of type 1 diabetes and the impact on its course, including e.g. development of late vascular complications.

The basic type of adipose tissue in the adult human body is white adipose tissue consisting of fat cells (adipocytes) that produce proteins that cause metabolic effects by affecting other cells. These peptides, referred to as adipokines (adipocytokines), can act both locally (autoand paracrine) and systemically (endocrine), similarly to typical hormones. More than a hundred compounds produced by adipocytes have been described, and their number is stil growing. These include, among others, apelin and omentin. The function of omentin is most likely to increase insulin sensitivity and stimulate glucose metabolism, and this effect is observed both locally and systemically. In vitro studies have shown that omentin increases insulin response by stimulating insulin-dependent glucose uptake in both subcutaneous and visceral adipocytes, but does not affect basal glucose transport. Omentin is also a useful biomarker of vascular endothelial function because the level of circulating omentin is an independent factor responsible for the presence of atherosclerotic plaques in patients with type 2 diabetes. Only omentin-1 is detected in the circulation. Apelin is another adipokine. It has also been shown that it improves the sensitivity of cells to insulin and can delay the development of metabolic disorders, largely through strong positive inotropic and hypotensive effects.

Currently, many peptide compounds are known, which can be described as gastrointestinal hormones. The role of some of them is not fully understood. Some of the gastric and intestinal

peptides are secreted into the bloodstream, i.e. they act in the endocrine way, some are released into the intercellular fluid affecting the neighboring cells, so they act in the paracrine way, while others act in the neuroendocrine way, i.e. they are released from the nerve endings. Ghrelin and obestatin are one of the main gastric peptides involved in the feedback loop between signals from the circuit and the central nervous system. They are hormones secreted mainly by the parietal cells of the fundus of the stomach. They have a common source - preproghrelin and opposing action. Although some works cast doubt on their antagonistic effect. Ghrelin, called the hunger hormone- its expression and secretion are increased in a situation of negative energy balance. It remains an independent predictor of insulin resistance. Obestatin, on the other hand, is considered a satiety hormone.

Most of the studies evaluating the relationship between gastrointestinal peptides, adipocytokines and carbohydrate metabolism are based on data obtained from studies conducted on animals and in adults with type 2 diabetes. However, there are few reports defining these relationships in a group of young patients with type 1 diabetes.

Aim of the study

The aim of our study was to assess the concentration of selected gastric peptides and adipocytokines in the blood serum of children with type 1 diabetes, taking into account the duration of the disease, and to search for the relationship between these gastric peptides and adipocytokines and selected clinical and biochemical parameters.

Material and methods

80 children aged 4-18 (M/F- 37/43) were qualified for the study, under the care of the Department of Paediatrics, Endocrinology, Diabetology with the Cardiology Subdepartment and the Diabetology Clinic of the UDSK in Białystok. A group of 46 children [mean patient age 13.4 ± 3.3 years (4-18 years), mean duration of the disease 5.0 ± 2.3 years (0-14 years)] with type 1 diabetes (diagnosed according to ISPAD criteria) with a control group of 34 healthy children [mean age 13.4 ± 3.0 years (4-17.5 years)] with a negative history of inflammatory, autoimmune and neoplastic diseases. For the purposes of the study, the group of children with diabetes was divided into 4 subgroups: subgroup I - patients with newly diagnosed type 1 diabetes, after recovering from ketoacidosis (n=10), II - suffering from DM t.1 up to 5 years

(n=9), III - patients suffering from 5-10 years (n=20), IV- patients suffering from more than 10 years (n=7). Data from the medical history and medical documentation (age of onset, duration of the disease, insulin demand, metabolic control), blood pressure values, anthropometric parameters such as age, height, weight, BMI, BMI-SDS, laboratory tests (HbA1c, lipids, TSH, fT3, fT4, ATG, ATPO, creatinine, ALT, AST, albuminuria) determined by standard methods and the concentration of ghrelin, apelin, omentin-1 and obestatin in blood serum determined by ELISA. Additionally, children with type 1 diabetes underwent ophthalmological and neurological examinations.

Statistical analysis was performed using Statistica 13.1. Comparing quantitative variables without normal distribution, the non-parametric Student's t-test was used and confirmed by the Mann-Whitney U test. In the presented study, the level of statistical significance was $p<0.05$. The Person and Spearman linear correlation coefficients and ROC curves were used to estimate the strength of the correlation between the individual parameters.

Results

The obtained results showed that in all subgroups of patients the concentrations of the tested gastric peptides and adipocytokines were lower than their level in the control group. The mean concentration of omentin-1 in the group of children with type 1 diabetes ranged from 122.4-124.8 ng/ml vs 157.1 ng/ml in the control group, the concentration of obestatin 119- 122.9 ng/ml vs 155.4 ng/ml, apelin concentration 120.7-124.1 pg/ml vs 151.3 pg/ml, ghrelin concentration 122.7-125.2 pg/ml vs 164.5 pg/ml. The differences between the individual subgroups and the control group were statistically significant ($p<0.0001$). In addition, it was observed that the lowest level of all tested regulatory peptides was found in the subgroup of children suffering the longest, but without statistical significance.

The level of glycated hemoglobin was the highest in subgroup I and amounted to 10.1%. This is due to the fact that these were newly diagnosed cases of type 1 diabetes. Mean values of HbA1c in children in subgroups II and III were comparable (6.9% vs 7.6%). We observed a higher HbA1c value (8.7%) in the subgroup of children suffering from the longest illness, and thus in the subgroup with the lowest level of the tested peptides.

Children suffering from type 1 diabetes were of comparable age to the control group (p=ns). Similarly, as demonstrated by the statistical analysis, the basic biometric parameters (height,

weight, BMI) between the study group and the control group did not show statistically significant differences. A significantly higher standardized BMI-SDS index was observed in the group of children with type 1 diabetes (p=0.025). When analyzing the anthropometric parameters in the group of children with type 1 diabetes, it was observed that the individual subgroups did not differ statistically significantly in terms of height, only children with newly diagnosed diabetes were significantly younger (p=0.029) and had statistically significantly lower body weight (p=0.028) compared to the control group, while patients with the longest duration of the disease and the lowest concentration of the tested substances showed a higher BMI compared to healthy children (p=0.027). Significantly higher standardized SDS-BMI indices were observed in subgroups of children older than 5 years (subgroup III and IV, p=0.009 and p=0.011).

In addition, a statistically significant negative correlation was found between BMI and the concentration of all tested regulatory substances, as well as body weight and the level of obestatin, ghrelin and apelin in the subgroup of children suffering the longest, as well as between BMI and the concentration of obestatin and apelin in the subgroup of children suffering from 5-10 years.

Conclusions

1. The concentration of gastric peptides (ghrelin, obestatin) and adipocytokines (apelin, omentin) in the blood serum is lower in patients with type 1 diabetes compared to the healthy group.

2. Regulatory peptide concentrations may change with the duration of type 1 diabetes.

3. Body weight and BMI affect the level of regulatory peptides in the body.