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ORIGINAL ARTICLE

Fetuin A and Interleukin 8 in Children with Clinical Remission of Type 1 Diabetes

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ABSTRACT

Background: Shortly after clinical diagnosis of type 1 diabetes (T1D), clinical partial remission (CPR) in most patients is observed. Increasing body weight and impaired insulin sensitivity may play a role in the pathogenesis of CPR. Several cytokines can also participate in the development of insulin resistance. **Objective:** To evaluate a relationship between birth weight and body mass index of children at the T1D onset, besides the concentrations of IL-8 and fetuin-A and the presence of clinical partial remission in the course of T1D. **Methods:** The study group consisted of 134 children with a newly diagnosed T1D in whom the presence of CPR in a further 2-year course of diabetes was evaluated. The control group included 47 children without glucose tolerance disorders. The concentrations of IL-8 and fetuin-A were determined by the ELISA method. **Results:** CPR occurred in 75.34% of T1D patients. At T1D onset, higher values of BMI SDS in the remitters as compared to the patients without remission were observed. At the T1D onset, the concentrations of fetuin-A (p=0.031) and IL-8 (p=0.042) were significantly higher in patients with compared to those without CPR. **Conclusion:** Evaluation of fetuin-A and IL-8 concentrations in patients with a newly diagnosed T1D can differentiate between patients with or without CPR. Maintenance of proper body weight in children with a newly diagnosed T1D may be the most important factor determining the incidence of clinical partial remission.

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Keywords: BMI, Diabetes Type 1, Fetuin A, Interleukin 8, Remission

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INTRODUCTION

In children and adolescents with type 1 diabetes (T1D), an autoimmune process begins many months or even years before the clinical diagnosis of the disease, leading to a loss of function and apoptosis of β cells (1). This results in insulin deficiency that causes characteristic T1D symptoms (2) Due to the beginning of intensive insulin therapy after clinical T1D onset, a reduction of β cells apoptosis, improvement of residual insulin secretion, and peripheral tissue insulin sensitivity are observed. This results in a clinical partial remission (CPR) (1). The presence of CPR is associated with a lower incidence of acute complications, chronic vascular complications in a further course of T1D, and a better long-term metabolic control in the patients (3). Thus, the researchers aim at extending the CPR duration and finding its prognostic markers. The research focuses on significant changes in immunological parameters in early stages of T1D in children, which may serve as potential biomarkers of T1D progression (4). On the other hand, increasing obesity in the pediatric population also encourages the possible impact of the patients' body weight and insulin resistance in the pathogenesis of T1D (5). CPR occurs more frequently in children with higher BMI SDS (6). Further, it is worth noting that high birth weight and rapid weight gain in the first two years of children's life is associated with a progression to clinical T1D (7). Due to an oxidative β cells stress and increased antigens presentation, rapid weight gain may raise insulin intake. Moreover, an increased oxidative β cells stress is observed in patients with physical inactivity and overweight (8). Also, physiological changes observed during puberty may additionally contribute to the development of insulin resistance (9). Influence of insulin resistance and body weight on the CPR occurrence are widely discussed (10,11). In the assessment of insulin resistance in T1D patients, a euglycemic metabolic clamp is still used, remaining a helpful diagnostic standard but also an expensive and time-consuming method (12). Fetuin-A is considered as a new biochemical indicator of insulin resistance in peripheral tissues in patients with type 2 diabetes and healthy subjects (13). Insulin affects the target cells by binding to a specific receptor on the surface of the cell membrane. The activated insulin receptor becomes an active tyrosine kinase and causes phosphorylation of proteins, which transfer insulin signals to other cellular proteins (14). Fetuin-A is a glycoprotein inhibitor of the tyrosine kinase insulin receptor (15). The chronic inflammation characteristic for obesity is also considered an independent predictor of insulin resistance development in adolescents (16). Cytokines mediating in inflammatory insulin resistance directly influence insulin signaling in adipocytes and skeletal muscles. Among pro-inflammatory cytokines, the interleukin-8 (I-8) is considered a marker of adipose tissue inflammation in diabetic patients (17). According to *in vitro* studies, IL-8 can induce the insulin resistance by inhibiting kinase phosphorylation in human adipocytes (18). This study aims at evaluating a relationship between birth weight and body mass index of children at the T1D clinical onset, as well as the concentrations of fetuin-A and I-8 and the presence of clinical partial remission.

MATERIALS AND METHODS

Ethic. The study protocol was approved by the Bioethics Committee of the Medical University in Lodz. Poland (RNN/20/15/KE and RNNN/362/17/KE). Patients and/or their parents gave written informed consent for participation in the study. All

procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and the Helsinki Declaration of 1975, as revised in 2008.

Patients. The study group consisted of 134 patients with a newly diagnosed T1D, treated with subcutaneous insulin therapy according to the WHO definition. The detailed characteristics of the study group are presented in Table 1. The CPR presence within 2-years follow-up was defined as the value of glycated hemoglobin (HbA1c) corrected by an insulin dose of <9 according to the formula: HbA1c (%) +4 x daily insulin dose (U/kg of body weight), estimated in accordance with the ISPAD Clinical Practice Consensus Guidelines 2014 (19). HbA1c was determined by high-performance liquid chromatography (HPLC) using the Bio-Rad VARIANTTM Hemoglobin A1c Program (Bio-Rad Laboratories, Inc. Hercules, CA, USA). Compliance with the clinical remission criteria was assessed at five time points, 3, 6, 12, 18, and 24 months after the diagnosis. The remitters group included patients who met the criteria of the presence of remission in at least one-time point. The criterion for exclusion from the study group was the lack of clinical data and laboratory results, not allowing the assessment of the clinical remission occurrence during the two-year observation. The control group for the cytokines levels evaluation consisted of 47 patients without glucose tolerance disorders and other metabolic disorders; it included 18 boys and 29 girls aged 2-18 years (Me 12.17 years; 25%-75% 8.19-16.15).

ELISA. In both groups, a retrospective analysis was performed to evaluate the concentrations of fetuin-A and IL-8. In sera of venous blood of the patients from the time of T1D clinical diagnosis, the levels of IL-8 and fetuin-A by the immunoenzymatic (ELISA) (respectively: DFTA00, the R&D company, USA; DLB50 kit, the R&D company, USA; D8000C, the R&D company, USA) were determined. The sensitivity level was 0.62 ng/mL and - 3.5 pg/mL for fetuin-A and IL-8, respectively.

Data Gathering: The analysis also included the individual and clinical parameters, such as age, sex, BMI SDS (body mass index standard deviation score), birth weight, GADA (glutamic acid decarboxylase antibodies), ICA (islet cell antibodies), and ZnT8 (zinc transporter 8) antibodies levels.

Using the Children's Hospital of Philadelphia website https://zscore.research.chop.edu, the BMI SDS was evaluated based on the data of age, gender, weight, and height. This website makes it possible to calculate the BMI (kg/m2) and BMI SDS (body mass index standard deviation) according to data from the Disease Control Center. Based on BMI SDS values, patients were qualified to the group with normal body weight or the group with overweight and obesity. Overweight was diagnosed when BMI SDS exceeded +1SD and obesity when it exceeded +2SD. The birth weight data were taken from the Children's Health Books. Based on WHO percentile charts, patients were qualified to the following subgroups: born with a weight appropriate for gestational age (AGA), small for gestational age (SGA), or large for gestational age (LGA).

GADA and ZnT8 antibodies levels were evaluated by the immunoenzymatic method (respectively: ELISA RSR GADAb, RSR, UK and ELISA RSR ZnT8Ab, RSR, UK). The reference values were <10 U/ml and <15 U/ml for GADA antibodies and ZnT8 antibodies, respectively. The ICA antibodies levels were determined by an indirect immunofluorescence method using a human pancreas.

Statistical Analysis. Categorical variables were presented as numbers with appropriate percentages and continuous variables as medians with interquartile range (25%-75%). Verification of the distribution normality was carried out using the Kolmogorov-

Smirnov test. In order to compare the concentration of cytokines in the studied groups, the Mann-Whitney test was performed. Receiver Operating Characteristics (ROC) curves were evaluated for the CPR occurrence model with calculating the area under the ROC curve (AUC). 95% Confidence Intervals (95%CI) were computed for AUCs. A logistic regression analysis was used to assess the total influence of the analyzed parameters on the CPR occurrence at the time of T1D diagnosis. The strength of the combined effect of these parameters was determined by the odds ratio (OR) with confidence limits (95%Cl). Changes in BMI SDS values at particular time points in the course of the disease were assessed using a non-parametric ANOVA test. Results with p-values <0.05 were considered as statistically significant. Analyses were performed using Statistica 13.1 PL software (Statsoft, Tulsa, OK, USA).

RESULTS

CPR occurred in 101 of the 134 T1D patients (75.34%) with similar frequency in both sexes (76% vs. 74%; p=0.845). At T1D diagnosis, normal body weight was found in 153/186 (82%) patients, while overweight or obesity was observed in 18% of patients. The percentage of obese individuals in the group of patients with and without remission is presented in Table 1.

Table 1. Characteristics of the study group. LGA –weight large for gestational age, AGA - weight appropriate for gestational age, SGA – weight small for gestational age.

Parameter	Remitters group Percentages or Median (25%-75%)	Non-remitters group Percentages or Median (25%-75%)	p-value
Sex, n (%)			
Boys	47 (47%)	16 (48%)	0.845
Girls	54 (53%)	17 (52%)	
Age (years)	8.43 (5.73-12.09)	11.71 (5.63 -13.57)	0.052
Daily insulin intake (IU/kg)	0.531 (0.367 – 0.700)	0.769 (0.601 – 0.978)	0.001
HbA1c (%)	11.65 (10.40- 12.90)	12.5 (11.10-14.40)	0.010
BMI SDS	0.489 (0.431 – 1.157)	0.030 (1.032- 0.574)	0.030
Overweight and obesity. n (%)	25 (26%)	1 (3%)	0.010
Birth weight (g)	3400 (3070-3700)	3375 (3000-3700)	0.677
LGA. n (%)	11 (16%)	1 (6%)	
AGA. n (%)	13 (18%)	4 (22%)	0.470
SGA. n (%)	46 (66%)	13 (72%)	

At T1D onset, higher values of BMI SDS in the group with CPR compared to the group without (Me 0.489 ((25%-75% -0.431 – 1.157) vs. Me -0.030 (25%-75% -1.032-0.574); p=0.030) were observed. In Figure 1, differences between the values of BMI SDS in subgroups with and without remission during a two-year follow-up (p=0.002) are shown. In children born with LGA, the CPR of T1D was present in 11/12 (92%), and they had a higher level of GADA antibodies (Me 288 U/ml (25%-75% 140-510) vs.

76 U/ml (25%-75% 17-328); p=0.048)) as compared to those born with AGA. At the time of T1D diagnosis, all patients born with LGA had positive GADA antibodies.

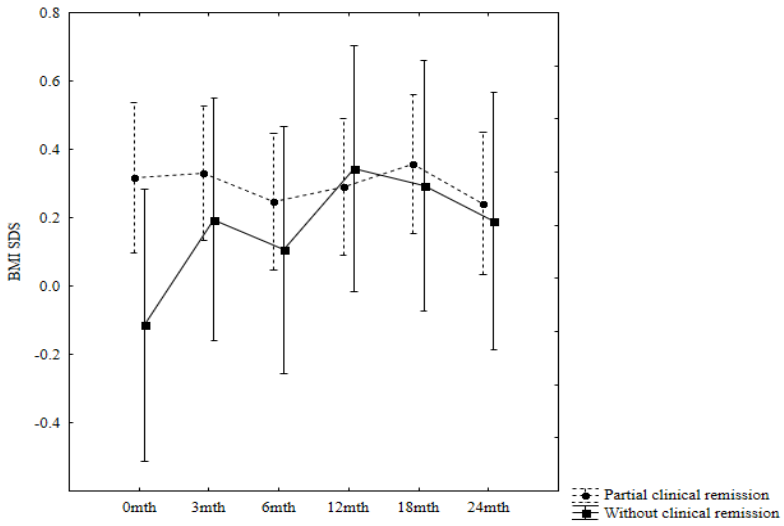

Figure 1. Changes in BMI SDS values in subgroups of type 1 diabetic patients with and without remission during two-year follow-up; p=0.002.

Patients born with SGA were older at T1D diagnosis (Me 9.920 years (25%-75% 7.123-11.450)) than those born with LGA (Me 5.778 years (25%-75%, 4.643-8.852); p=0.011). However, GADA antibodies at T1D diagnosis were less frequently present in the subgroup of patients born with SGA (66.67% vs. 100%; p=0.027), and the levels of ZnT8 antibodies were significantly lower (1111 U/ml (25%-75% 1085-1166) vs. Me 76 U/ml (25%-75% 5-231); (p=0.014) as compared to the patients born with LGA. Concentrations of fetuin-A in the study group did not differ significantly from the control group (p=0.428). However, evaluating the concentrations between the remitters and non-remitters, the significantly higher fetuin-A concentrations in the remitters were observed as compared to the patients without remission (Me 1.409 mg/dl (25%-75% 1.200-1.957) vs. Me 1.205 mg/dl (25%-75% 1.040-1.532); p=0.031). Fetuin-A levels were also significantly higher in the patients without GADA autoantibodies (p=0.009) and ICA antibodies at T1D diagnosis (p=0.007) (Table 2).

Table 2. Relationship of fetuin-A concentration with the presence of ICA. GADA and ZnT8 antibodies. ICA – islet cell antibodies. GADA – glutamic acid decarboxylase antibodies. ZnT8 - Zinc transporter 8 antibodies.

Antibodies	Concentration of fetuin A in absence of antibodies	Concentration of fetin A in presence of antibodies	p-value
	Median (25%-75%)	Median (25%-75%)	
GADA	1.559 (1.342 – 2.151)	1.358 (1.096 – 1.647)	**0.007**
ICA	1.542 (1.196 – 2.103)	1.344 (1.080 – 1.538)	**0.009**
ZnT8	1.357 (0.985 – 1.521)	1.363 (1.064 – 1.779)	0.585

The IL-8 concentration in T1D patients did not differ significantly from healthy children (p=0.176), however, the significantly higher IL-8 levels were observed in patients with CPR compared to those without (Me 9.284 mg/dl (25%-75% 7.146 – 13.488) vs. Me 7.600 mg/dl (25%-75% 6.000-11.377) p=0.042). Interestingly, in patients born with LGA, a higher level of IL-8 (Me 12.941 mg/dl (25%-75% 9.287 – 29.290) vs. 8.360 (25%-75% 7.141- 12.780); (p=0.016)) compared to those born with AGA, and a tendency to higher IL-8 level as compared to those born with SGA (Me 12.941 mg/dl (25%-75% 9.287 – 29.290) vs. Me 9.91 mg/dl (25%-75% 7.141 – 13.760; p=0.095) were observed. In a multivariate analysis, including variables of birth weight, BMI SDS values, and fetuin-A or IL-8 concentrations at T1D onset, a statistically significant relationship between BMI SDS value and the presence of CPR was observed (Table 3). With the rise of BMI SDS by 1 SD, the probability of disease remission increased 2.3 times (OR=2.305 (95% CI 1.301-4.084)).

Table 3. Parameters included in the logistic regression assessing the probability of disease remission.

Parameter	OR	Cl +95%	Cl -95%	p-value
IL-8 [pg/ml]	1.003	0.951	1.058	0.922
Fetuin A [mg/ml]	2.745	0.866	8.698	0.086
Birth weight [g]	0.999	0.999	1.001	0.701
BMI SDS	2.305	1.301	4.084	**0.004**

Furthermore, the ROC curves with AUCs for optimal values of fetuin-A and IL-8 for the CPR presence were calculated. Predicting value of fetuin-A was 1.139 mg/dl (AUC 0.626; 95%Cl 0.518-0.734) with 81.2% of sensitivity and 45.5% of specificity (p=0.022) (Figure 2).

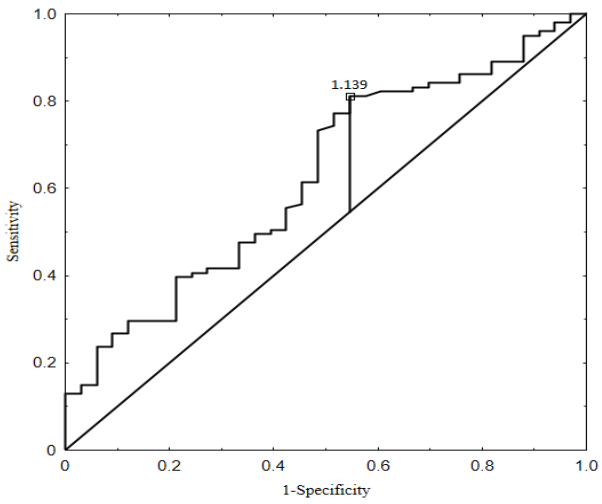

Figure 2. ROC curve for the fetuin-A value predicting the clinical partial remission (AUC 0.626; 95%Cl 0.518-0.734).

For IL-8 concentration, a cut-off point in the model was 7.45 ng/dl (AUC 0.620; 95%Cl 0.507-0.733). The model's sensitivity and specificity equaled 74.0% and 50.0%, respectively (p=0.038) (Figure 3).

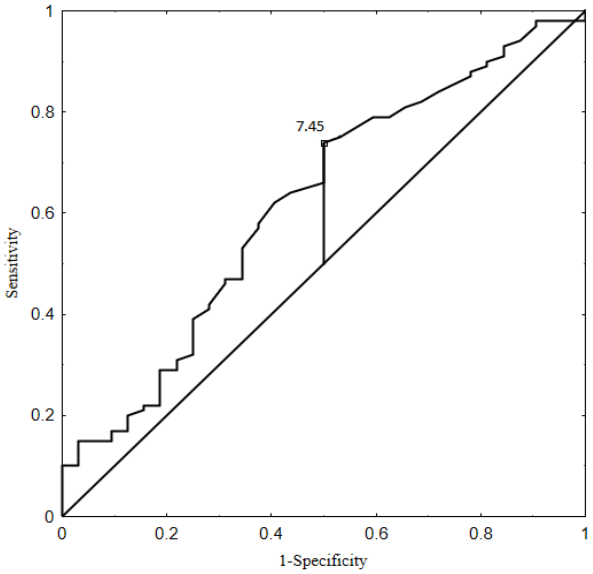

Figure 3. ROC curve for the interleukin-8 value predicting the clinical partial remission (AUC 0.620; 95%Cl 0.507-0.733).

DISCUSSION

The present study confirmed the strongest effect of body mass on clinical partial remission presence in the course of T1D, irrespective of the remission definition applied (11). Scholin *et al.* also observed the relationship between normal body weight and the incidence of clinical remission (10). Rydzewska *et al.* suggested that obesity/overweight or lower weight loss in patients at T1D diagnosis may predispose CPR to develop, which was observed even in the youngest children under 5 years of age (20). Higher body weight at the time of T1D diagnosis in remitters may be a result of lower intensity of weight loss or no weight loss before clinical T1D diagnosis; on the other hand, it may reflect increasing overweight or obesity both in the general pediatric and type 1 diabetic population (21). It should be emphasized that in the study group, changes in BMI SDS values at subsequent time points were observed. Moreover, the BMI SDS values in remitters were more stable in two-year observation, whereas in patients without CPR, the BMI SDS were lower at the disease onset and reached higher values thereafter. Factors influencing body weight of the patients are related to the metabolic control of diabetes and insulin resistance (22). Our results indirectly indicated the role of insulin resistance in the occurrence of CPR in children with T1D. The present study also showed dysregulation of key inflammation and insulin resistance-related cytokines with potential functional implications. By comparing patients with a new-onset T1D depending on the presence of future CPR, a predictive tool was proposed to stratify such individuals and identify those with the highest probability of remission, making them

prime candidates for clinical trials on beta-cell preservation or immunomodulation. Considering the main marker of insulin resistance, fetuin-A concentration, its significantly higher level was found in the study group in the patients with partial clinical remission as compared to those without. In several studies, the positive correlations between fetuin-A concentration and disease duration, BMI, WHR, besides waist and hip circumference in patients with T1D were observed (23). In the study group, the concentrations of IL-8 at the time of T1D clinical diagnosis were significantly higher in the remitters. Besides its role in the inflammatory process of adipose tissue and insulin resistance, IL-8 increases both the expression of IL-8 mRNA (in human adipocytes) and the IL8 receptor, acting in an autocrine way.17 Furthermore, a significant increase in circulating IL-8 level has been noted in relation to poor T1D metabolic control (24). The observed relationships of the above cytokines with the presence of ICA and GADA autoantibodies may also additionally suggest the association of insulin resistance with the severity of the autoimmune process in T1D patients. An overlap of insulin resistance on the already initiated but still clinically silent process of autoimmune destruction of β-cells may result in earlier hyperglycemia with a lower intensity of β-cells destruction (25). A better preserved residual function of β-cells may promote their temporary regeneration after beginning insulin therapy, thus enabling the CPR occurrence of the disease. This hypothesis seems to be indirectly confirmed by higher levels of fetuin-A and IL8, observed at the onset of disease in patients with CPR. Moreover, an assessment of the ROC curves for these parameters made it possible to determine the cut-off points for their values, beyond which a clinical partial remission in patients with T1D is likely to occur. Although the regression analysis has identified BMI SDS as the most significant marker affecting the occurrence of CPR in T1D in children, as described previously, (11) the potential impacts of selected cytokines have also been shown. It is also worth noting that not only the weight of patients at the clinical onset of T1D can be important for the presence of clinical partial remission of the disease. Interestingly, in our study group, more than 90% of patients born with LGA had clinical partial remission and higher IL-8 levels compared to children born with AGA, regardless of the presence of GADA antibodies at the time of T1D diagnosis. Chronic fetal hyperglycemia and hyperinsulinemia may result in higher birth weight and over-stimulated β cells (26). On the other hand, the patients born with SGA have been characterized by a younger age at T1D onset and lower levels of antibodies. Some previous studies have suggested that sub-optimal birth weight can be related to insulin resistance of tissues and increased activity of pancreatic β cells already in fetal life, leading to dysregulation in the immune system (27).

The limitation of this study is the relatively low number of patients with a newly diagnosed T1D. For this reason, the study has only a preliminary character, and further studies are needed to confirm the results. To sum up, it seems that lower intensity of weight loss or even no weight loss of children with a newly diagnosed type 1 diabetes is the main factor determining the occurrence of remission in the course of this disease. However, the obtained values of IL-8 and fetuin-A may be useful in identifying patients with or without CPR in the course of T1D in children. Therefore, an evaluation of fetuin-A and IL-8 concentrations in patients with a newly diagnosed T1D may be useful in predicting the occurrence of remission in the future.

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