LIPIDIC PROFILE AND METABOLIC CONTROL IN TYPE 1 DIABETIC CHILDREN

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Abstract

Introduction. *Type 1 diabetes mellitus is a progressive autoimmune disease characterized by destruction of β cells in the pancreatic islets. The concept of „metabolic memory", i.e. diabetic vascular stress persists after glucose normalization, suggests the need for a good metabolic control. Dyslipidemia also plays a key role in inducing endothelial dysfunction, oxidative stress, inflammation and tissue remodeling in the diabetic patient.*

The aims *of this study were as follows: 1 - to determine the lipidic profile in DM children and healthy subjects; 2 - to investigate the correlation between C-peptide and years of evolution, to establish the metabolic control in DM patients; 3 - to establish the autoimmune pattern in DM patients who other other autoimmune diseases.*

Methods and results. *A control group of 36 healthy subjects with the mean age of 10.68±4.46, without any evidence of diabetes and 51 patients mean age of 11.65±4.10 diagnosed with type 1 DM were included in the study. We determined the metabolic parametrs such as lipidic profile, hemoglobin A_{1c}, C-peptide. The specific autoimmune antibodies were determined in 13 diabetic children who also had other autoimmune diseases. The lipidic profile showed a diabetic dyslipidemia ($p<0.05$). The level of the C-peptide in the diabetic group was 0.42±0.64, with a significat correlation coefficient between C-peptide and the years of evolution ($p=0.002$). The HbA_{1c} showed a poor metabolic control in the DM group, with a mean value of 9.51±1.87.*

Conclusions. *Metabolic control seems to be a pivotal pathway not only for the diabetic complications but also for the metabolic memory, therefore the possibility of „switching off" the metabolic memory could be an important strategy for the prevention of diabetic complications, in addition to a therapeutical intervention for diabetic dyslipidemia.*

Keywords: diabetes, lipidic profile, hemoglobin A_{1c}, C-peptide.

PROFILUL LIPIDIC ŞI CONTROLUL METABOLIC LA PACIENŢII PEDIATRICI CU DIABET ZAHARAT TIP I

Rezumat

Introducere. *Diabetul zaharat tip I este o boală autoimună cu caracter progresiv, ce se caracterizează prin distrugerea insulelor β pancreatice. Conceptul de "memorie metabolică", dat de persistenţa stresului oxidativ după normalizarea valorilor glicemice, sugerează necesitatea unui control metabolic eficient. Dislipidemia joacă un rol important în disfuncţia endotelială, stresul oxidativ, inflamaţia și remodelarea tisulară la pacienţii cu diabet zaharat tip I.*

Obiectivele *acestui studiu sunt: 1 - determinarea profilului lipidic la pacienţii pediatrici cu diabet zaharat tip I și lotul de control; 2 - analizarea corelaţiei între valoarea peptidului C și vechimea bolii la pacienţii cu diabet; 3 - stabilirea unui profil al autoimunităţii pancreatice la pacienţii cu diabet zaharat tip I și alte boli autoimune asociate.*

Material și metodă. *S-au introdus în studiu un număr de 36 copii sănătoși cu vârsta medie de 10,68±4,46 ani, servind ca și lot martor și 51 pacienţi cu vârsta medie de 11,65±4,10 ani, diagnosticaţi cu diabet zaharat tip I ca și lot de studiu. Am determinat parametri metabolici precum profil lipidic, hemoglobina glicozilată și peptidul C. Autoanticorpii specifici au fost determinaţi la 13 pacienţi diabetici care asociază și alte boli autoimune. Profilul lipidic a arătat prezenţa dislipidemiei (p<0,05) la pacienţii pediatrici cu diabet zaharat tip I, faţă de lotul martor. Valoarea medie a peptidului C a fost de 0,42±0,64, cu un coeficient de corelaţie semnificativ statistic între peptidul C și vechimea diabetului (p=0,002). Valoarea medie a hemoglobinei glicozilate a arătat un control metabolic deficitar în rândul pacienţilor cu diabet zaharat tip I (9,51±1,87).*

Concluzii. *Controlul metabolic pare să deţină rolul crucial atât în apariţia complicaţiilor diabetice, cât și în memoria metabolică. Astfel, posibilitatea închiderii cercului vicios al memoriei hiperglicemice pare să fie strategia esenţială de prevenire a complicaţiilor diabetice, în asociere cu controlul dislipidemiei.*

Cuvinte cheie: diabet, profil lipidic, hemoglobina glicozilată, peptid C.

INTRODUCTION

Type 1 diabetes mellitus (DM) is a progressive autoimmune disease characterized by the destruction of β cells in pancreatic islets [1]. DM is characterized by long-term hyperglycemic status which can induce oxidative stress reactions, and therefore increase production of reactive oxygen species (ROS). Under diabetic conditions ROS are produced through the glycation reaction [2], which appears in different tissues [3], including pancreatic islets, and leads to β cell destruction and diabetes development [4]. Even in healthy individuals, glucose alteration is known to increase formation of cellular oxidative stress [5]. Despite significant advances in hyperglycemia treatment, blood glucose monitoring and markers of glycemic control, debilitating complications persist in most diabetic patients. The concept of „metabolic memory", i.e. diabetic vascular stress, persists after glucose normalization and suggests the need for early aggressive treatment, metabolic control and agents which reduce cellular reactive species and glycation in order to minimaze long-term diabetic complications [6].

The aims of this study were as follows: 1 - to determine the lipidic profile in DM children and healthy subjects; 2 - to investigate the correlation between C-peptide and years of evolution, to establish the metabolic control in DM patients; 3 - to establish the autoimmune pattern in DM patients who also had other autoimmune diseases associated.

MATERIAL AND METHODS

Study groups

In this study, a control group of 36 healthy subjects (16 males and 20 females), with the mean age of 10.68±4.46, without any evidence of diabetes, and 51 patients (31 males and 20 females), mean age of 11.65±4.10 diagnosed with type 1 DM were included as study groups. Patients were selected from the 2nd Clinic of Pediatrics in Cluj-Napoca, Romania. DM was diagnosed according to the criteria of the World Health Organization.

Metabolic parameters

Cholesterol, HDL-cholesterol and triglyceride levels were measured using conventional methods (Abbott Spectrum Auto Analyzer). LDL-cholesterol was estimated by the Friedewald's formula. HbA_{1c} was measured using a microparticle agglutination inhibitor method.

Statistical analysis

Clinical laboratory parameters were expressed as means ± standard deviation. Mean values were compared between children with type 1 DM and healthy subjects by the unpaired Student's t-test. The Spearman correlation coefficient was used to test the relationship between the variables. A $p<0.05$ was considered statistically significant.

RESULTS

Clinical characteristics of the patient groups are summarized in Table I.

Table I. Demographic and biochemical parameters in study groups. Data are presented as mean±SD.

	DM (n=51)	Control (n=36)	p
Sex (female/male)	20/31	20/16	-
AGE	11.65±4.10	10.68±4.46	-
HbA_{1C}	9.51±1.87	-	-
CST	158.72±25.03	130.17±15.88	0.0000009
HDL	53.17±9.74	60.41±11.25	0.0019
LDL	105.43±23.41	87.25±10.45	0.00004

The lipidic profile showed a significant difference between diabetic patients and control group regarding the cholesterol (CST), HDL-cholesterol and LDL-cholesterol values ($p<0.05$) (Figure 1, 2, 3).

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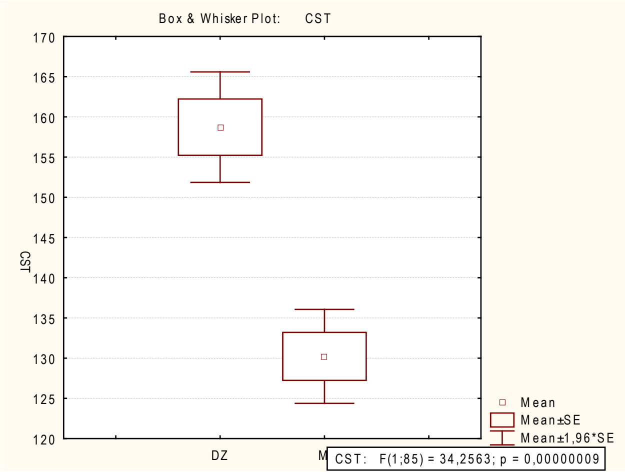

Figure 1. Box-plot showing the cholesterol values in diabetic type 1 study group and healthy subjects; p<0.05 with a statistical significance.

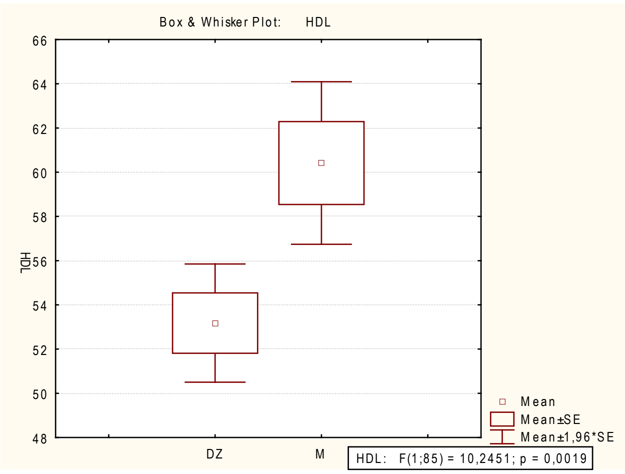

Figure 2. Box-plot showing the mean values±SD for HDL-cholesterol in diabetic type 1 children and the control group.

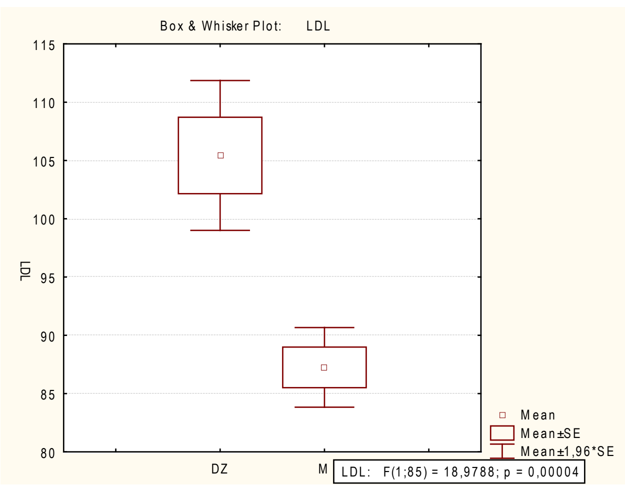

Figure 3. Box-plot showing the statistical difference in LDL-cholesterol values in diabetic children versus the control group.

The level of the C-peptide in the diabetic group was 0.42±0.64, with a significat coefficient of correlation between C-peptide and the years of evolution (r=-0.40, p=0.002). The HbA_{1c} showed a poor metabolic control in the DM group, with a mean value of 9.51±1.87.

The DM study group was divided into two subgroups: (1) patients with DM type 1 (n=38) and patients having DM + other autoimmune diseases (n=13). In patients associating DM and other autoimmunities we determined insulin antibodies (IAA), protein tyrosine phosphatase-like protein antibodies (IA2) and glutamic acid decarboxylase 65 antibodies (GAD65). The pancreatic autoimmunity pattern is summarized in Table II.

Table II. Mean Value±SD for IAA, IA2 and GAD65 in diabetic patients associated autoimmune diseases.

	Autoimmune Thyroiditis (n=9)	Celiac Disease (n=3)	Idiopathic Juvenile Arthritis (n=1)
IAA	0.45±0.85	1.66±0.44	1.26
IA2	247.87±189.72	93.33±161.65	411
GAD65	0.66±0.74	1.70±0.66	1.1

DISCUSSION

DM type 1 is known to be a relapsing disease, with a honeymoon period as a last response before the total destruction of the residual β cells [7]. Therefore, the decline of the C-peptide level is in strong correlation with the disease status [8]. The C-peptide level is a valuable tool in assessing the remnant β cell function. This raises the possibility that C-peptide could be the therapeutical target, by improving the β cell secretory function.

Endothelial dysfunction is the critical pathway in the pathogenesis of vascular disease associated with type 1 diabetes. Dyslipidemia plays a key role in inducing endothelial dysfunction, oxidative stress, inflammation and tissue remodeling in the diabetic patient [9]. It is known that dyslipidemia accentuates the development of both macro- and microvascular disease in diabetic patients [10]. In our study, the low HDL-cholesterol level with high levels of LDL-cholesterol in diabetic children can suggest the predisposition of these patients in developing early diabetic complications.

HbA_{1c} is a good indicator for metabolic control and non-enzymatic glycation in DM. Hyperglicemia leaves a very early imprint on the development of vascular implications, and has an important therapeutic implication: it seems mandatory to begin an aggressive treatment right from the onset of diabetes type 1. Tight control of glycemia is the key strategy and especially concerning the postprandial hyperglicemia which is accompanied by high levels of reactive species [11], not only in plasma but also intracellularly [12]. Additionally, evidence suggests that the "metabolic memory" may appear even when good glycemic control is achieved. If we can determine the critical steps that are involved in the hyperglycemic memory, it might be possible to interrupt the pathways that determine this vicious circle in the natural history of diabetes mellitus type 1. In DM patients the progressive loss of beta cells is due to the attack by the patients' own immune system [13,14]. DM has a prodromal stage of islet autoimmunity and it has been estimated that although an individual may be positive for islet autoantibodies for months to years, the clinical onset does not occur until 80–90% of the beta cells have been killed [15], thus DM occurs because of the selective autoimmune destruction of the pancreatic beta cells [16]. The current classification of diabetes endorsed by both the American Diabetes Association and the World Health Organization is based on etiopathogenesis. Lately, DM type 1 has been characterized by a state of β-cell destruction [17]. Evidence that type 1 diabetes is an autoimmune process is most commonly based on the presence of specific antibodies such as ICAs, GAD65, IA2 or IAAs.

The diagnostic sensitivity of GAD 65, IA2 or IAA can vary with age or sex. GAD65 are present in 80% at the onset of type 1 diabetes [18]. GAD65 levels are higher and prevalent in patients with other associated autoimmune diseases, such as thyroiditis [19]. IA2 have been reported in 32–75% of subjects with newly diagnosed type 1 diabetes and decreases in frequency with increasing age at onset [20]. Diagnostic sensitivity varies the most with age in IAA and it is known that they often may precede other autoimmune markers [21], which has led to the hypothesis that insulin may be an autoantigen in type 1 diabetes that plays a role early in the pathogenic process.

CONCLUSION

Therapeutic intervention to correct both the quantitative and qualitative changes characteristic of diabetic dyslipidemia should be viewed as a priority for reducing both macrovascular and microvascular risk. Metabolic control seems to play a crucial role not only in the diabetic complications but also in metabolic memory, therefore the possibility of „switching off" the metabolic memory could be an important strategy for the prevention of diabetic complications.

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