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Microvascular Disorders: Vitamin D3 status and disease progression in children with Diabetic Nephropathy

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Background:

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin (Type 1 diabetes, T1D) or when the body cannot effectively use the insulin it produces (Type A diabetes, T2D). Insulin is a hormone that regulates blood sugar.

Type 1 diabetes is mainly a disease of children and young adults. The onset of disease is associated with three classical symptoms - polydipsia, polyphagia, and polyuria. Hyperglycemia is a main and primary metabolic disorder in T1D.

In 2014, 8.5% of adults aged 18 years and older had diabetes. In 2016, diabetes was the direct cause of 1.6 million deaths and in 2012 - 2.2 million deaths.

An increasing incidence of diabetes complications, particularly overt nephropathy and proliferative retinopathy, has been reported in the type 1 diabetes population around the world over the past 15–20 years. Metabolic control including self-monitoring of blood glucose and HbA1c (A1C) testing, blood pressure management are main factors in prevention of the diabetic complications development.

Vascular endothelial cells play a major role in maintaining cardiovascular homeostasis. In addition to providing a physical barrier between the vessel wall and lumen, the endothelium secretes a number of mediators that regulate platelet aggregation, coagulation, fibrinolysis, and vascular tone. Vascular disorders, i.e. hypertension are one of the most important causes of end-stage renal disease and death in patients with T1D. However, it is not clear whether hypertension also contributes to the gradual loss of kidney function. Moreover, it is unclear how these to disorders inter-related in their development and progression do.

There are data about the role of Vitamin D in T1Dand it's complications in adults. However, this issue remains to be open in pediatric practice. It is un-known whether Vitamin D and other players i.e. Endothelin-1 (ET-1) are inter-related in vascular disorders development in diabetic children.

Aim of the study: The aim of the current study was to analyze ET-1, Vitamin D3, hypoxia and their dependence on main clinical parameters (disease course, blood pressure, HbA1c, albuminuria, GFR, cholesterol levels) in children with T1D.

Material and methods: The study involved 42 children with T1D and diabetic nephropathy (aged 3 to 17 years) hospitalized in Endocrinology unit on Children Clinical Hospital №6 (Kyiv, Ukraine) done. Complex examination including conventional methods (physical examination, blood pressure measurement, blood tests, study of urinary sediment, renal ultrasound, etc.) done to all patients. Other than conventional methods i.e. plasma levels of hypoxia, Vitamin D3, ET-1 done. The control group included 16 healthy children. Vitamin D3 levels studied using ELISA assay and commercially available kit (Vitamin D3 (human) ELISA kit (BioVision, USA). Endothelin-1 levels measured using ELISA assay and commercially available Endothelin-1 ELISA kit (Abcam, USA). Material processed using the methods of variation statistics (STATISTICA 6.0) and nonparametric statistical approaches (Mann-Whitney test). Spearman correlation coefficients were used to express associations between parameters. Results are presented as Mean ± SEM, was considered statistically significant level of $P<0.05$.

Results:

Group entitled T1D were children collected after the onset of T1D up to 1 year of the disease course. Group of children with diabetic nephropathy (DN) included patients with disease course at least 1 year and longer. All patients were seen at 3-month intervals and all were on multiple dose flexible insulin treatment. Chronological age, age at diagnosis, diabetes duration, height, weight, body mass index (BMI), and in cases with microvascular complications, date of diagnosis of these complication and diabetes duration at that time, were recorded. The study was approved by the local ethics committee of the hospital.

In our study normal level, insufficiency and deficiency of the Vitamin D defined as - ≥ 30 ng/mL, 21-29 ng/mL and ≤ 20 ng/mL, respectively. All patients included into the study during the period September-May. We show that the most prominent Vitamin D3 deficiency detected in the group of patients with diabetic nephropathy (DN). In control group Vitamin D3 was detected at level 35.68 ± 1.56 ng/mL, in patients with T1D – 32.37 ± 5.1 ng/mL, in patients with DN – 19.39 ± 1.76 ng/mL ($p<0.01$ ascomparedtocontrolgroup).Analysis of the Vitamin D3 levels and the disease course show negative correlation ($R=-0,79$, $p<0,001$). In all children with T1D and DN increased level of ET-1 measured. We show gradually increased level of ET-1 in children with T1D and DN, respectively.

In our study we found that children with T1D and disease course 1 year have increase of GFR up to hyper filtration level. At the same time these patients have normal BP values, increased serum ET-1 level. We hypothesis that hyper filtration might be as a response to metabolic changes that have a case in T1D. In children with DN we found homogeneously enhanced levels of GFR.

Discussion:

The risk of micro vascular and vascular complications in diabetic patients dealing with factors, such as age, sex, blood pressure, dyslipidemia, diabetes duration, smoking and lifestyle habits. Poor metabolic control was identified as an important factor contributing to microvascular complications. In patients with diabetes onset at age 5–14 years, a higher risk for complications (retinopathy, nephropathy, andneuropathy) has been found as compared to patients diagnosed either at a very young age or after puberty, meaning the importance of age when T1D was diagnosed.

With the onset of diabetic nephropathy, a dramatic increase in the risk for microvascular and vascular complications noticed.

It was shown in observational studies that there is a relationship between blood pressure levels and the progression of chronic kidney disease (CKD) and incident end-stage renal disease (ESRD) is direct and progressive in diabetes.

Our data show the prominent deficiency of Vitamin D in T1D patients and

patients with DN, increased ET-1 level (a potent vasoconstrictor peptide). We hypothesize that Vitamin D deficiency is a result of toxic effect of glucose. Increased ET-1 in all patients is a sign of early microvascular changes and resistant vessels damage leading to DN progression and arterial hypertension. All mentioned above changes accompanied by reduced O2-Hb dissociation as a result of increased level of HbA1C and may be a reason of cellular hypoxia. We recommend blood pressure, Vitamin D3, ET-1 and standard metabolic markers measurement at every routine visit in all children with T1D.