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Antibodies To Insulin In Children With Diabetes Mellitus

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Annotation. The levels of antibodies to insulin analysed in 58 children with diabetes mellitus with the help of enzyme immunoassay were found to be increasing with the disease duration and insulin dependence in the patients. The concentration of antibodies was found correlating with the frequency of viral infections in the anamnestic data of the children, and with the presence of microangiopathic, lipodystrophic and immunopathologic conditions.
Key words: children, insulin, diabetes mellitus, antibodies, microangiopathy, lipodystrophy, enzyme immunoassay.

Introduction. The need for a quantitative assessment of the level of antibodies to insulin is due, on the one hand, to the development of allergic reactions to exogenous insulin, insulin resistance, and the duration of insulin therapy in patients, and on the other hand, to the emergence of data on the possible role of autoantibodies in the etiology and pathogenesis of type I diabetes mellitus. [1-5, 7].

The frequency of detection of insulin antibodies in patients with diabetes mellitus ranges from 48 to 91%. Most often, insulin antibodies appear 3-6 months after the beginning of diabetes correction, and the peak intensity of their formation occurs in the period from 1 year to 5 years [12-17]. The formation of insulin antibodies with repeated administrations has been shown in animal experiments [10]. Most researchers have found a correlation between the dose of insulin administered and the titer of antibodies to it [6, 8, 11, 12]. Prolonged insulin preparations most often had pronounced immunogenicity. The level of anti-insulin antibodies in patients decreased significantly when the drug was changed, and, as a rule, it was possible to simultaneously reduce the dose of insulin administered [10, 13]. In a number of studies, high levels of antibodies were detected in patients with diabetes with microangiopathy and lipodystrophies; other authors did not find such a relationship [7, 9].

Our goal was to analyze the results of a study of the level of antibodies to exogenous and endogenous insulin in children with diabetes mellitus, depending on the duration of the disease, daily insulin requirements, and the combination of diabetes mellitus with autoimmune diseases.

Material and methods of the study. The quantitative determination of insulin antibodies was carried out using the solid-phase enzyme immunoassay [1]. Polyvinyl chloride microtiter plates were used as a solid phase. The binding agent was insulin "monopeaque" of the purification stage of the Kaunas Endocrine Preparations Plant. When comparing the results of the study of anti-insulin antibodies, a concentration of over 50×10^{-3} g/l obtained from adult donors was taken as the diagnostic level.

We examined 58 children with diabetes, aged from 1 to 14 years. The disease duration ranged from several months to 10 years.

Results of the study and their discussion. Anti-insulin antibodies were detected in all patients with diabetes mellitus. In 39 out of 58 children, the antibody titer exceeded the norm. To compare the intensity of

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insulin antibody formation with the duration of diabetes mellitus, all patients were divided into three groups. Group 1 included children with newly diagnosed diabetes, Group 2 - with a disease duration of 1 to 3 years, and Group 3 - children who had diabetes for more than 3 years. Table 1 shows that with increasing duration of the disease, the number of children with a high titer of anti-insulin antibodies increases. ($p<0,01$).

When comparing the concentration of antibodies to insulin in patients with the daily requirement for insulin (per 1 kg of body weight), it turned out that with a high daily requirement for it, higher concentrations of antibodies are determined (Table 2).

Table 1

The level of anti-insulin antibodies in the blood serum of children with diabetes mellitus depending on the duration of the disease

Group of children	Number of children with elevated antibody levels		Average antibody level, x 10^{-3} g/l
	Absolutely	%	
1 st (*n* = 14)	9	64,2	62,3
2 st (n = 20)	12	59,3	74,9
3 st (n = 24)	18	77,8	79,1 .

It should be noted that in the group of children with insulin requirements from 0,5 to 1 U/kg, the average level of insulin antibodies was slightly lower than in groups 1 and 3. In group 1, the percentage of children with high levels of insulin antibodies was higher than in group 3. This indicates a more intensive synthesis of antibodies in patients with long-term diabetes mellitus.

Table 2

The level of anti-insulin antibodies in the blood serum of children with diabetes mellitus depending on the daily insulin requirement

Group of patients	Daily insulin requirement, U/kg	Number of children with elevated antibody levels		Average antibody level, x 10^{-3} g/l
		Absolutely	%	
1 st (n = 12)	Up to 0,5	9	75,0	80,7
2 st (n = 34)	0,5-1,0	22	64,7	65,9
3 st (n = 12)	More than 1,0	8	66,6	93,9

To determine the dependence of the level of anti-insulin antibodies on the presence of certain viral infections, autoimmune diseases, angiopathies and lipodystrophies in patients, we identified two subgroups: with normal and high levels of antibodies, respectively.

Table 3 shows that patients with high levels of antibodies to insulin had a history of viral infections more often (measles, rubella, mumps, viral hepatitis, acute respiratory viral infections) than patients with normal serum antibody concentrations.

In the case of diabetes mellitus combined with immunopathological diseases (drug allergy, neurodermatitis, bronchial asthma, rheumatoid arthritis, Hashimoto's goiter), high concentrations of insulin antibodies were detected in 35.8% of cases, normal titers - in 21,1%. A similar trend is found when comparing the intensity of antibody formation in children depending on the presence of autoimmune diseases in close relatives. Two children had an allergic reaction to insulin in the form of urticaria; in both, the level of insulin antibodies was moderately higher than normal.

In a combination of diabetes mellitus and bronchial asthma, the average level of antibodies to insulin in children was 65,8 x 10^{-3} g/l, i.e. moderately exceeded the norm, while in 1 patient with diabetes with concomitant rheumatism it was three times higher than the norm, amounting to 154,3 x 10^{-3} g/l.

Table 3

Frequency of detection of some concomitant diseases and complications of diabetes depending on the concentration of anti-insulin antibodies in the blood

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Number of children										
Antibody level	with viral infections		with immune diseases		having relatives with autoimmune diseases		with angiopathies		with lipodystrophies	
	qua.	%	qua.	%	qua.	%	qua.	%	qua.	%
Normal	19	68,4	4	21,1	3	15,8	10	52,6	12	63,2
Increased	39	92,3	14	35,8	6	20,5	30	76,9	29	74,3

The data we have obtained allow us to consider that an autoimmune mechanism plays a certain role in the pathogenesis of insulin-dependent diabetes mellitus. This is evidenced by the frequent occurrence of viral infections and autoimmune diseases in the anamnesis of children with diabetes mellitus, and this corresponds to a fairly high level of antibodies to insulin.

However, assessments of the role of insulin antibodies in the pathogenesis of diabetes mellitus in the literature are contradictory. Some researchers believe that insulin antibodies do not play a decisive role in the occurrence of autoimmune processes, while others attach great importance to them in insulin resistance and insulitis (2, 12]. We found that in the group of children with microangiopathies, the normal level of anti-insulin antibodies was observed in 52,6% of cases, and elevated in 76,9%, i.e., it differed significantly in comparable groups (Table 3). Lipodystrophies (in a total of 41 children) were detected 2.5-3 years after the onset of the disease (insulin therapy), and they were more common in the group of children with a high concentration of antibodies to insulin than in children with normal levels.

In 6 patients, diabetes mellitus was complicated by purulent infection (streptoderma, staphylococcal lacunar tonsillitis, abscess on the hip). The average level of insulin antibodies in them was 75,2 x 10-3 g/l, while in 2 children it was within the normal range.

Conclusion. The results of our studies indicate an increase in the level of antibodies to insulin in patients with diabetes mellitus in the initial period of the disease. With an increase in the duration of the disease, the initial concentration of antibodies to insulin almost doubles. A dependence of the level of antibodies to insulin on the amount of insulin administered was revealed. Multiple lipodystrophies and generalized microangiopathies were combined with a high level of antibodies to insulin.

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