The Pathogenetic Role of Pro- and Anti-Inflammatory Cytokines in Developing of Diabetic Myopathy in Children

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Abstract

The level of interleukin-6 and interleukin-13 was analysed in the blood serum of children with diabetes type 1 from 11 to 17 years old. They divided into three groups: the duration of diabetes less than 1 year (1st group), the duration of diabetes from 1 to 5 years (2nd group) and over 5 years (3rd group). The group of control includes conventionally healthy children. All kids have gone through the detailed clinical examination wich included functional tests to determine the condition of skeletal muscles, such as skeletal muscle strength, muscular tissue loss, functional capability and estimation of the muscular mass.

Pathogeneticic mechanism of diabetic myopathy is a result of dysbalance between pro- and anti-inflammatory interleukins. The first manifestations of diabetic myopathy in children occur after the 5th year of diabetes, but subclinical signs develop over the first years of disease. It appears of muscle strength decrease and violation of its functional capability.

Keywords: diabetic myopathy, interleukin-6, interleukin-13, diabetes mellitus type 1, children

Introduction

Diabetes mellitus type 1 is linked with a wide range of pathologic complications,

including macrovascular diseases, neuropathy, nephropathy, retinopathy, and occurs in conditions of hyperglycaemia [4, 6]. One of the worse complications of hyperglycaemia is protein glycation, which leads to chemical modification of proteins and glycation end products formation (advanced glycation end products (AGE)), including the proteins in skeletal muscles [1]. Thus, fast-acting fibers of myosin II have a greater tendency to be affected by AGE, which results in atrophy and lessening of muscular contraction [17].

Inspite of the fact, that diabetic damage of skeletal muscles or "myopathy" is a widespread clinical case, which is characterized by decreased muscle strength, weakness and general physical activity decreasing; it remains to be insufficiently studied [17]. Decreased muscle function, which includes decreased muscle strength and fatigue, and occurs in young people with diabetes mellitus type 1 contributes to the heightened risk of human performance lack and development of sarkopenia [21, 23, 24].

There was an opinion that diabetic myopathy is a late complication of diabetic peripheral neuropathy [2]. However, the latest investigations have revealed that decreased muscular strength formats earlier and has no link to the neuropathy [27].

Development of diabetic myopathy results not only in weakness and heightened fatigue, but in potential damage to muscle metabolic abilities and the ability to control the glycaemic and lipidemic exertion after each meal. As a result – progressive development of other diabetic complications [23].

Muscle regeneration is mostly influenced by inner program in muscle stem cells, but can be affected by external stimuli. Recently a lot of investigations have shown that different inflammatory cytokines and cells are closely linked to muscular regeneration, including neutrophils, macrophages, transformed growth factor – B (TGF-β), interleukin-10 (IL-10) and interleukin-6 (IL-6), etc [20, 34, 35]. Cytokines are considered to be major mediators in different aspects of healthiness and illness, such as appetite, glucose and lipid metabolism, tolerance to insulin, muscular atrophy of hypertrophy [28]. IL-6 is multifunctional cytokine, which is produced in located areas of tissues and is exuded into blood [16]. Unlike other ones, IL-6 influences anti-inflammatory, regenerative and metabolic processes [10, 33]. Moreover, it has been proved, that muscle tissue is a main resource of IL-6 [19]. Another cytokine produced and excreted by skeletal muscles is IL-3. The mentioned above cytokine has autocrine features due to its influence on the metabolism of glucose, as it increases the amount of glucose consumed by muscle tissue, and glucose production in the liver [12, 36]. The role of IL-3 in the formation of insulin resistance is not eliminated. The experiment with mice has shown the injection of IL-3 to those fed with a greater amount of fats resulted in the activation of macrophages M2 in fatty tissue and assisted for increased sensitivity of tissues to insulin [14].

Objective: to study pathogenetic mechanisms of development and the features of clinical course of diabetic myopathy in children.

Methods

Ones have examined 93 children with diabetes type 1 from 11 to 17 years old. According to the duration of the disease all children were divided into three groups: the duration of diabetes less than 1 year (1st group), the duration of diabetes from 1 to 5 years (2nd group) and over 5 years (3rd group). The first group includes 26 kids (the average age 12,9±0,4 years old). The second group includes 33 patients (average age 13,8±0,4 years old). The third group was formed of 34 kids (average age 14,3±0,4 years old). The group of control includes 30 conventionally healthy children. All groups were representative according to the age, gender and body mass index.

All tested kids have gone through the detailed clinical examination. The clinical examination involved collection of medical anamnesis, medical examination, laboratory and additional methods of examination.

The muscular mass in kids below 14 years old was estimated according to to A.M. Peters formula (2011) [30]. The Boer P. formula was applied for kids above 15 years old and counted the gender [4]. In order to evaluate the condition of muscular system, the skeletal muscle index (SMI) was estimated according to the formula [11]:

SMI = (skeletal muscle mass/body mass)x 100

Skeletal muscle strength was estimated using the wrist spring dynamometr, which was squeezed by the patients' hand. In order to offset the age of a kid when estimating the muscle strength, one has applied the wrist strength index (WSI):

WSI= (wrist strength/body mass (kg)) x 100% [5, 11]

6 points Lovett test was applied to estimate the percentage of muscular tissue loss [25]. In order to identify the strength of muscles of the hip anterior group one used left and right arm flexure. One used arm extensions in order to identify the muscle strength of posterior arm muscle group. To estimate the strength of anterior and posterior leg muscle groups one applied led flexure and extensions. The muscle strength was pinpointed according to the following percentage: 0 points= 0, 1 point = 10%, 2 points = 25%, 3 points = 50%, 4 points = 75%, 5 points = 100%.

The functional capability of skeletal muscles was determined according to the balance tests: "tandem" test modified Romberg position, simple standing positions with different feet positions (eyes opened and closed) [22].

The immunoassay analysis with Human IL-6 High Sensitive (ELISA, Austria) та .Human IL-13 (ELISA Kit, Austria) sets was applied in order to evaluate the amount of IL-6 and IL-3 in the blood serum.

Statistical Analyses

All the results were analyzed using the set of statistic programs «Statistica 13.0» (StatSoftInc. № JPZ8041382130ARCN10-J). Parametrical methods that helped to evaluate simple average, simple square deviation and simple mistake were applied for normally arranged rates. Check of normality was held with test of asymmetry Shapiro-Wilk. The method of correlation analysis was used to calculate the Pearson correlation coefficient in the normal distribution of features and the Spirman

rank correlation coefficient in their absence. The reliability of the differences in the results obtained for different groups in the normal distribution of characteristics was determined by the parametric (Student's criterion) method. In cases where the distribution law was statistically significantly different from the normal one, the non-parametric criterion (U) Mann-Whitney was calculated as a nonparametric analogue of the Student's criterion. Differences were considered to be significant at p <0.05.

Results and discussion
It was revealed that in group of people with diabetes there was a decrease of muscular mass with the increase of the duration of diabetes (h<0,05). The rate of skeletal muscle index of the first and second group didn't vary from the indexes of a control group. However, after 5 years from the disease initiation the rate was reduced in average by 9,1%.

Table 1
Muscular mass index in children with diabetes according to the duration of disease

Rate	I group n=26	2 group n=33	3 group n=34	Control група, n=30
Muscular skeletal index	81,76±1,86	78,8±3,19	74,94±1,91[1][2]	82,22±1,44
Right wrist strength index	37,61±3,02[1]	36,74±2,48[1]	34,55±1,96[1]	48,06±2,52
Left wrist strength index	35,89±2,91[1]	35,03±2,39[1]	34,18±1,99[1]	46,71±2,30
Manual muscle test anterior hip group	91,07±4,23	78,95±2,88[1]	70,83±3,64[1][2]	97,22±1,91
Manual muscle test posterior hip group	85,71±4,32[1]	77,63±3,77[1]	72,22±3,44[1][2]	97,22±1,91

Table 1 (Continued):
Muscular mass index in children with diabetes according to the duration of disease

Manual muscle test anterior shoulder group	89,29±3,43[1]	78,95±3,45[1 2]	73,61±3,18[1 2]	98,61±1,39
Manual muscle test posterior shoulder group	89,29±3,43[1]	77,63±4,64[1 2]	72,22±3,44[1 2]	98,61±1,39

Addition: [1] - a significant (p <0,05) difference compared to the corresponding indicator of the control group; [2] - a significant (p <0,05) difference compared to the corresponding indicator of group 1.

The lowest rates of MMI were observed in patients with glycemic control with the high risk for life (r=-0,34, p<0,05). The decrease of MMI was accompanied by the loss in muscle strength, which was verified by the straight correlation communication in between MMI and WSI in people with diabetes (r=+0,37, p<0,05). The evaluation of left and right wrist strength revealed that in control group the rates didn't exceed the rates in investigated group by ,3-1,4 times; that means that there was a definite wrist strength index decrease starting from the first year of disease (p<0,05).

There was a straight correlation between the WSI amd MMT for upper (r = +0,31, p<0,05), and lower (r = +0,37, p<0,05) limbs. That means that there was an equal decrease of muscle strength in all muscle groups at the same time. The first signs of muscle strength loss in flexor and extensor muscles of upper and lower limbs were noticed by the end of the first year of a disease. All mentioned changes were progressing with the increase of the duration of disease (r = -0,43, p<0,05). If in the control group according to the Lovetta test, normal strength of the limb muscles was determined in 93.3% of children, then among the patients in the first group of such children was 71.4%, while in the second and third groups of patients with diabetes, respectively, in 21.0% and 11.1% of children had normal muscle strength (p <0.05). The most significant decrease in muscle strength was observed in children who did not achieve optimal glycemic control (r = -0.31, p <0.05). Attention was also drawn to the fact that the reduction in muscle strength in patients with diabetes also occurred with an increase in the daily dose of insulin (r = -0.34, p <0.05).

The results of evaluation of functional capability of skeletal muscles have revealed that most of children with diabetes had damages to the balance; they had worsened scores of balance tests compared to the scores of control group (table 2). It was hard to do the "tandem" test and standing on toes with closed/opened eyes for kids with diabetes that lasted one year.

Table 2

The scores of balance tests in children with diabetes according to the duration of the disease

Score	I group n=26	2 group n=33	3 group n=34	Control group, n=30
"tandem" test with yeyes opened, sec.	18,31±1,03	19,37±0,44	19,72±0,28	19,95±0,05
"tandem" test with yeyes closed, sec.	8,46±0,86[1]	9,83±0,86[1]	9,00±0,70[1]	12,89±0,57
Test on toes with eyes opened, sec.	9,5±0,98[1]	10,26±0,71[1]	9,94±0,67[1]	13,39±0,76
Test on toes with eyes closed, sec.	3,08±0,26[1]	3,24±0,26[1]	2,71±0,22[1]	7,63±0,64

Note: [1] - a significant ($p < 0,05$) difference compared to the corresponding indicator of the control group

At the same time there was no difference revealed between the scores of 'tandem' test in both group children with diabetes and control group, that can be explained by the easy techniques of the test.

Taking in account that the muscular system plays an important role in metabolism of glucose and performs regulation integration functions by means of influencing other systems of organs with the aid of cytokines secretion [42]. We have studied the amount of anti-inflammatory interleukin – 6 in the blood serum of children with diabetes according to the duration of the disease (table 3). It was established that according to the duration of disease in children with diabetes the medium level of IL-6 in blood serum was statistically higher that in children from the control group ($p<0,01$). The highest amount of IL-6 was revealed in children from the 1st group, even compared to the rates of the 2nd group.

Table 3.

The amount of interleukin-6 and interleukin-13 in blood serum of children with diabetes according to the duration of the disease

(Me (Q25-Q75))

Score	I group, n=20	2 group, n=20	3 group, n=20	Control group, n=20
IL-6, пг/мл	1,75 (1,28-1,95)[1]	1,2 (1,10-1,75)[12]	1,4 (1,05-2,20)[1]	0,94 (0,63-1,24)
IL-13, пг/мл	21,50 (12,75-25,50)	13,0 (11,50-16,50)[2]	15,0 (11,25-18,25)[2]	15,0 (11,25-18,25)[2]
IL-13/IL-6, con.un.	8,8 (7,4-12,45)[1]	10,8 (8,68-14,12)[1]	10,1 (5,96-11,79)[1]	18,4 (11,19-31,55)

Note: [1] - a significant ($p < 0,01$) difference compared to the corresponding indicator of the control group; [2] - a significant ($p < 0,05$) difference compared to the corresponding indicator of group 1.

The amount of cytokine was influenced by the condition of glycemic control, which was proved by revealed positive correlation analysis between the amount of IL-6 in blood serum and level of hemoglobin glycated ($r=+0,64$, $p<0,05$). The diagram of variation of amount of IL-6 in blood serum in investigated groups is given in fig. 1.
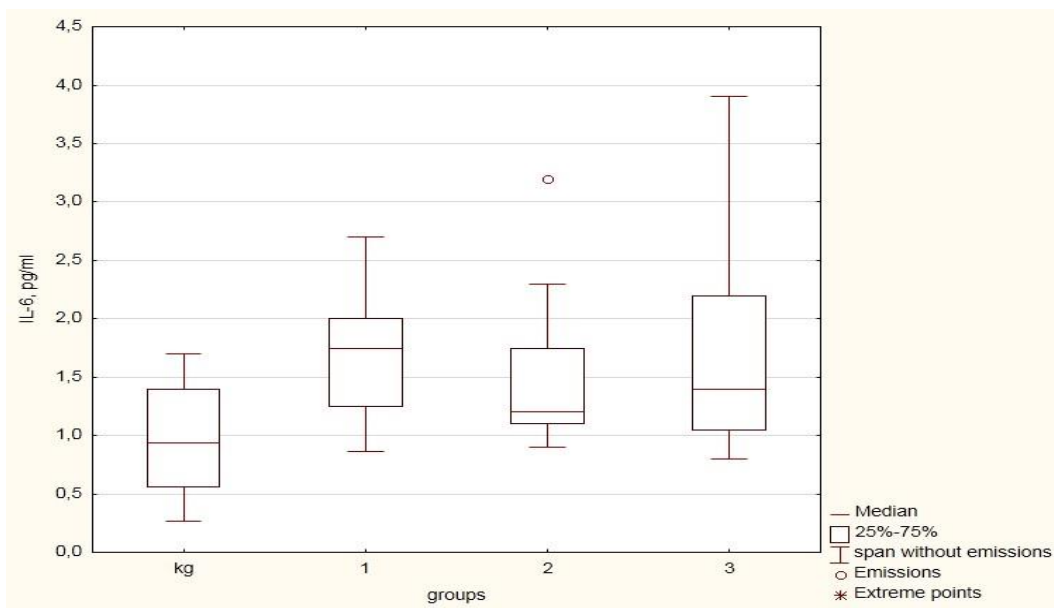

Fig. 1. Diagram of variation of amount of IL-6 in blood serum of kids with diabetes according to the duration of a disease.

As it is shown on pic 1, the widest variation on IL-6 amounts was revealed in children who had diabetes for more than 5 years. In particular, the highest amount of IL-6 was determined in children with low muscle strength in upper ($r=-0,41$, $p<0,05$) and lower ($r=-0,51$, $p<0,05$) limbs.

The next stage of our investigation was to study the amount of anti-inflammatory cytokine interleukin 13 (IL-13) in blood serum of children with diabetes (fig. 2). The analysis of data has shown that the variation of IL-13 in 1st group was higher than the rates of control group and other investigated groups ($p<0,05$).
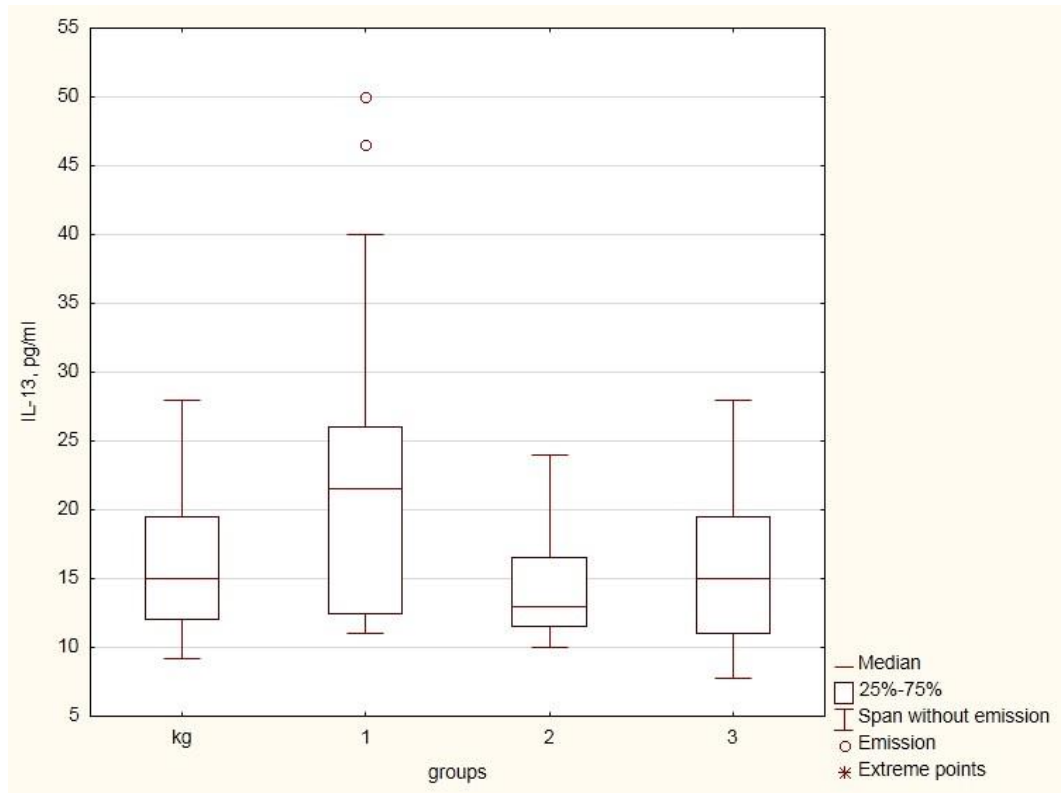
Fig. №2. Diagram of variation of amount of IL-13 in blood serum of kids with
diabetes according to the duration of a disease.

At the same time in patients with higher duration of diabetes amount of IL-13 in
blood serum had no difference among all the investigated groups ($p > 0,05$). All
received data can be an evidence of the fact that there is an activation of IL-13
production is growing during the first year of diabetes in response of the growing
amount of anti-inflammatory IL-6. IL-6 is a cytokine that regulates the process of
inflammatory response formation, which is proved by straight correlation
connection in between mentioned cytokines during the first year of disease
($r = +0,48$, $p < 0,05$) (fig. 3).
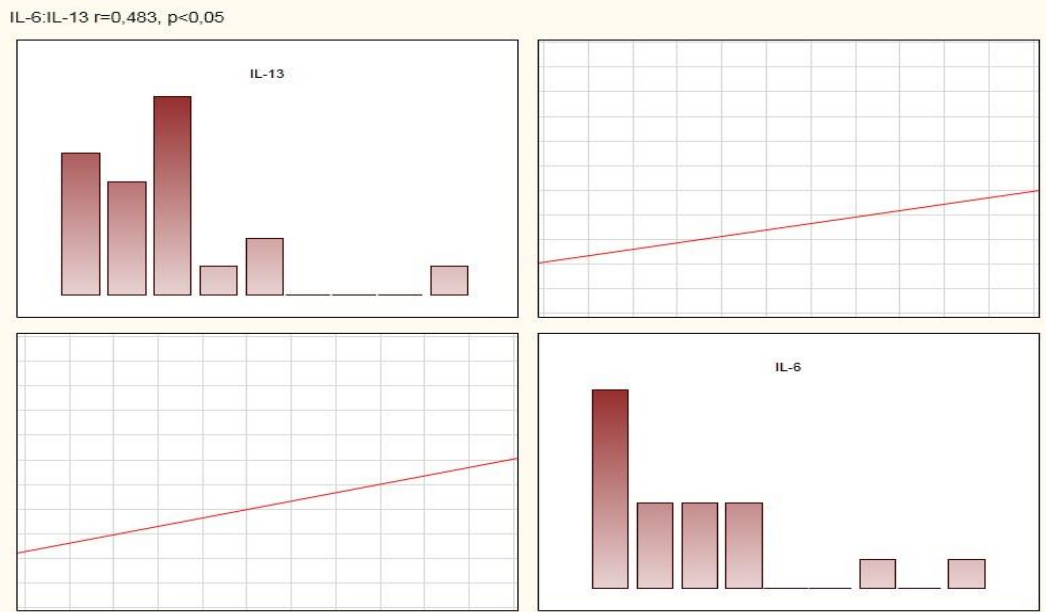
IL-6:IL-13 r=0,483, p<0,05

Fig. №3. Matrix diagram of Spirmen correlation between IL-6 and IL-3 in patients with diabetes with the duration of disease up to 1 year

However, there was a decrease of IL-13 amount and as a result an IL-6 increase in blood serum. The mentioned reverse connection was statistically important in children with the duration of diabetes over 5 years (r=-0,49, p<0,05) (fig. 4).

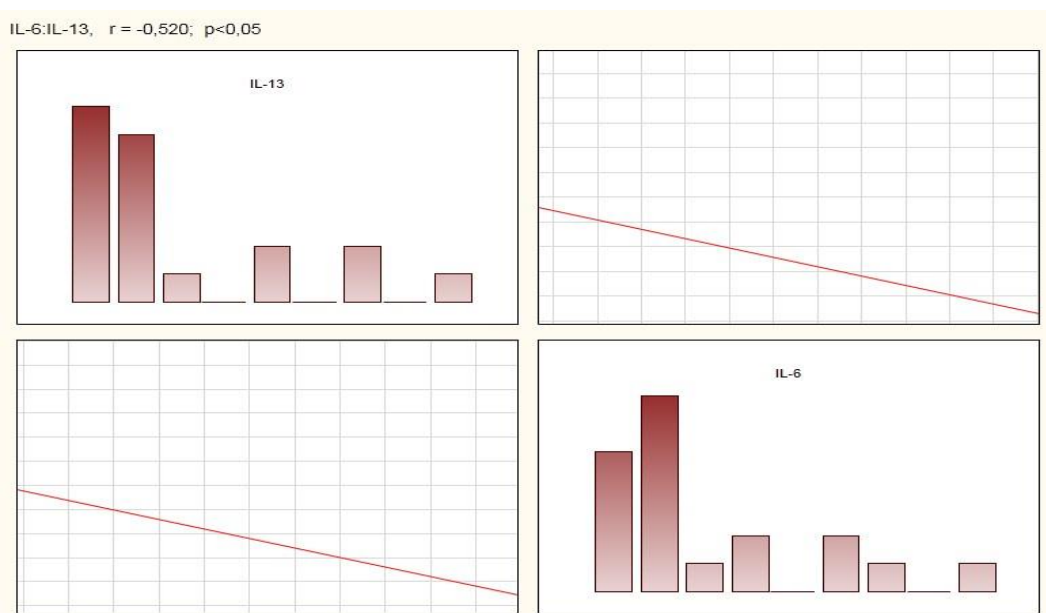IL-6:IL-13, r = -0,520; p<0,05

Fig. № 4. Matrix diagram of Spirmen correlation between IL-6 and IL-13 in patients with diabetes with the duration of the disease over 5 years.

In terms of received data we can assume the violation in between anti- and proinflammatory cytokines amounts in children with prolonged duration of diabetes. Our data matches with other investigations, which have shown the decreased production of IL-13 during diabetes [32, 39]. In order to prove the suspicion about the violation in a balance between anti- and proinflammatory cytokines production, we have revealed the interconnection between IL-6 and IL-13 in investigated groups (table 3, fig. 5).
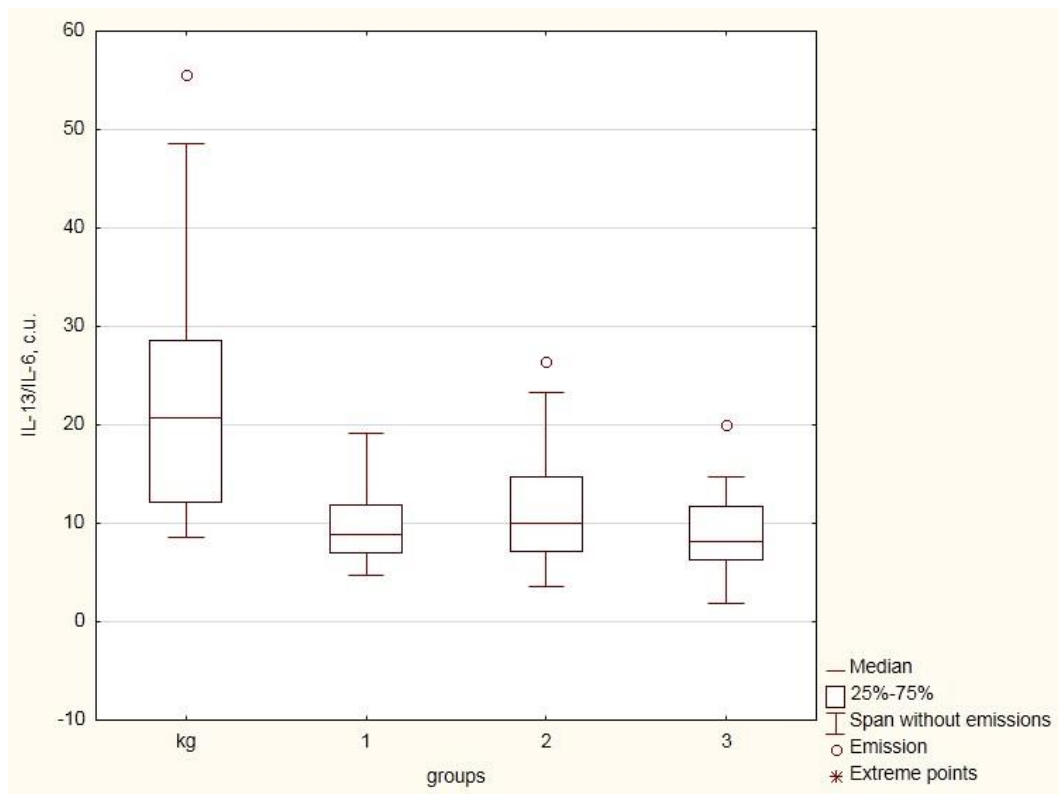

Fig. №5. Diagram of variation of correlation between IL-13/IL-6 in children's blood serum according to the duration of diabetes.

The analysis of received data has shown that the average rates of interconnection between IL-13/IL-6 in control group were higher than in other groups by 1,7-2 times (p<0,01).

The same pattern took place in all groups that were studied. The upper quarter of correlation in all groups didn't get the medium rate in group of control; in children with duration of diabetes over 5 years the upper quarter was on the level of 25th quarter of group of control. Thus, there is a disbalance between the amounts of IL-13 and IL-6 in the side of the last one from the first years of a disease. It turned out that insufficient activation of IL-13 production at the beginning of disease can lead to the progressive autoimmune response [39].

Discussing the received results

All received data has shown a definite decrease of muscle mass in children with diabetes, which led to the decrease of muscle strength and worsening of its functional capability. All revealed violations occurred on the background of increased level of IL-6 and decreased IL-13 level in the blood serum, which implied the chronic inflammatory process in patients with diabetes. It is known that chronic increasing of IL-6 amount causes damages to the skeletal muscles as a result of intercellular signals transferring and leads to loss of myofibrillar protein and muscle atrophy [8, 31]. Moreover, IL-6 reduces the transferring of insulin signals to skeletal muscles, which causes the reduced amount of glucose transported inside [15]. This data was proved by the results of J.P.T. Guimarães, et al. (2019) experimental investigation. He revealed that the higher expression of IL-6 had correlations with lower expression of receptors to insulin in muscles of mice with diabetes WT [8].

The other investigation revealed that IL-13 causes so called "insulin-like" influence on glucose metabolism in human skeletal muscles. IL-13 increases the transport of glucose and exceeds its further metabolism [12]. The experiment demonstrated that mica without IL-13 had hyperglycaemia and hyperinsulinemia, reduced glucose production in liver. Also, there was a violation in glucose absorption to skeletal muscles and white fatty tissue [36]. The investigations of J.E. Heredia et al (2013) revealed that IL-13 plays an essential role in muscle regeneration, at the same time influences proliferation of satellite cells [9].

One of the functions of IL-13 is the inhibition of the synthesis of IL-6 [37]. Insufficient activation of IL-13 synthesis may contribute to the release of proinflammatory cytokines [26], which is one of the causes of the formation of chronic low-level inflammation, which, in turn, leads to a deterioration in the regeneration of skeletal muscle [29]. Due to atrophy of the muscles, glucose-mediated insulin absorption is weakened [3]. At the same time, glucose itself in high concentration is able to change the sensitivity to insulin in the muscles. Hypeglycaemia, caused by increased transport of glucose into skeletal muscles, affects the action of insulin in liver and fatty tissue and initiates the development of insulin resistance [38]. The development of insulin resistance is a result of system chronic slow inflammation, muscle strength and muscle mass decreasing [7, 13, 18]

Conclusions

1. Subclinical signs of diabetic myopathy in children develop over the first years of disease, however the first manifestations occurs after the 5th year of diabetes
2. The major clinical manifestations of diabetic myopathy are muscle strength decrease and violation of its functional capability

3. Pathogenetic mechanism of diabetic myopathy development is the violation of glucose metabolism in skeletal muscles, which is a result of dysbalance between pro- and anti-inflammatory interleukins.

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