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IRIZIN AS A MARKER OF DIABETIC MYOPATHY IN CHILDREN WITH DIABETES TYPE 1*

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The development of acute and chronic complications of diabetes caused by hyperglycemia remains to be an essential problem due to the fact that there is no way to obtain constant normoglycemia. The main cause of lack of stable optimal glycemic control in terms of insulin-dependent diabetes is impoverishment of energy resources and mitochondrial dysfunction which leads to faster muscle protein loss [1]. The main manifestations are lack of muscle mass, strength and activity. One applies a term «diabetic myopathy» in order to describe such condition in children and young patients. It is considered to be a yet unexplored chronic complication [2].

There is an obvious link between muscle tissue condition and general health condition. Development of diabetic myopathy causes not only fragility and fatigue, but also potential damage of metabolic abilities of skeletal mus-

cles, which influences the tolerance to insulin, an ability to control the glycemic and lipid exertion during each meal and causes progress of other diabetic chronic complications [3]. However, molecular mechanisms of such metabolic damages are still unexplored.

It was revealed that the gene fibronectin type III domain containing 5 (FNDC5) codes the pro-hormone, which is a transmembrane protein, that in terms of muscle work goes through the post-translation modification — limited proteolysis, and turns into regulatory peptide irizin, which was established in 2012 [4]. The latest investigations showed the greater expression of gene peroxisome proliferator-activator receptor coactivator (PGC) 1 and FNDC5 with the further formation of irizin in muscle tissue in terms of physical exertion, and that implies the muscle tissue to be a main resource of irizin. A number of experiments proved the

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suggestion of autocrine function of irizin as a regulator of glucose metabolism [5].

Irizin is synthesized not only by skeletal tissue, but also by adipose tissue. It was shown that some location of brown adipose tissue had a functional activity in elder people and there is a negative correlation with body mass index (BMI) [6].

There is plenty of data studying the correlation between the amount of irizin and the development of diabetes type 2 and metabolic syndrome. There is much less information about the amount of irisin in blood serum of

people with Type 1 diabetes (T1D) [7]. So the understanding of processes occurred in muscle tissue of those with diabetes type and revealing the factors that influence the development of diabetic myopathy has a great importance for the further establishing of clinical strategy that would aid the condition of muscle tissue.

The purpose of the study: to study the amount of irizin in blood serum of children with type 1 diabetes counting the duration of clinical course and determine the role of irizin in diagnosing the diabetic myopathy.

MATERIALS AND METHODS

There were 90 children with T1D from 11 to 17 years old. According to the duration of the disease all children were divided into three groups. The first group included 26 kids with the duration of diabetes less than 1 year (the average age $13,0 \pm 0,4$ years old). The second group includes 27 patients with the duration of diabetes from 1 to 5 years (average age $13,7 \pm 0,4$ years old). The third group was formed of 37 kids with the duration of diabetes over 5 years (average age $14,3 \pm 0,4$ years old). The group of control includes 25 conventionally healthy children. All groups were representative according to the age, gender and body mass index.

All tested kids has gone through the detailed clinical examination included measuring the height and weight with BMI calculation. The muscle mass in kids up to 15 years old was evaluated using the A. M. Peters formula (2011) [8]. The muscle mass in kids over 15 years old was evaluated using the Boer P. Formula (1984), that also count the gender [9]. In order to evaluate the condition of muscular system, the skeletal muscle index (SMI) was estimated according to the formula [10]:

$$\text{SMI} = \\ = (\text{skeletal muscle mass/body mass}) \times 100.$$

The percentage of adipose tissue in children under 15 years old was evaluated using the following formula [11]:

$$\text{BFP} = (1.51 \times \text{BMI}) - (0.70 \times \text{Age}) - \\ - (3.6 \times \text{S}) + 1.4,$$

where: S — 1 for male and 0 for female;
BMI — Body Mass Index;
Age — Age in years.

The percentage of adipose tissue in children over 15 years old was evaluated using the following formula [11]:

$$\text{BFP} = (1.20 \times \text{BMI}) + (0.23 \times \text{Age}) - \\ - (10.8 \times \text{S}) - 5.4,$$

where: S — 1 for male and 0 for female;
BMI — Body Mass Index;
Age — Age in years.

The adipose mass was evaluated using Gurruci et al. formula (2007) [12].

$$\text{BFM} = (\text{BFP} / 100) \times \text{Weight},$$

where: BFP — percentage of adipose tissue;
Weight — in kg.

One also evaluated the coefficient of correlation between the muscle and adipose tissue mass.

The ultrasonic examination was held on «SA 8000 Live» US equipment with the linear sensor with the 7-13 MGz frequency. The front femoral muscle group and the posterior shin muscle group were examined.

Thigh muscles were investigated at the level of the upper and middle third of the front surface, and the thickness of the muscles was measured in a strictly transverse section. The leg muscles were evaluated at the level of the middle third with a measurement of their thickness perpendicular to the surface of the small tibia.

Also, the thickness of muscle fibers, the thickness of the transition and epimize were estimated, the muscle-connective tissue coefficient (MSC) was calculated as the ratio of thickness of the muscle to the total thickness of the connective tissue layer and a visual assess-

ment of the structure of the muscles (striation and homogeneity) was performed.

The enzyme-linked immunosorbent assay of «Irizin» (ELISA, Czech Republic) sets was applied in order to evaluate the amount of irizin in the blood serum.

All the results were analyzed using the set of statistic programs «Statistica 13.0» (Stat-

SoftInc. № JPZ8041382130ARCN10-J). Parametrical methods that helped to evaluate simple average, simple square deviation and simple mistake were applied for normally arranged rates. The method of correlation analysis was used to calculate the Pearson correlation coefficient in the normal distribution of. Differences were considered to be significant at $p < 0.05$.

RESULTS AND THEIR DISCUSSION

It was revealed that the BMI in all examined groups had no statistic difference and was appropriate to the age average indexes (table 1). At the same time, the examination of muscle mass in children with diabetes type 1 has shown, that there was a gradual decreasing of relative age normal indicators, as the disease had been progressing, which was proved by credible SMI decrease ($p < 0,05$) in group of children with the duration of diabetes over 5 years relatively to the rates of group of control and 1st group (table 1).

The lowering of muscle mass in children with T1D caused the further increase of adipose tissue, which was proved by higher percentage of adipose mass with the growing of duration of disease.

There was a statistically important ($p < 0,05$) decreasing of correlation between muscle and adipose tissues in children with T1D, counting the duration of disease, which implied the redistribution of component body content. There was a reducing of muscle mass proportion at the background of relative increasing of adipose component.

Counting that the analysis of skeletal muscle architecture also has an important, the next stage was to perform the US scanning.

There was no damages revealed in muscles, membranes and fascia of children from the group of control (fig. 1).

All the muscles that were examined had approximately the same echo structure. Muscle fibers were visualized as hypoechoic homogeneous in structure of formation, which are separated from each other and from surrounding tissues by thin hyperechogenic lines (fascia). Perimizium shared muscle fibers with each other and was defined as a homogeneous hyperhegenetic linear structure with a clear contour. The epimizium was visualized as a hyperheric linear homogeneous structure with a clear, equal contour that covers the muscle from all sides.

Children with diabetes type 1 had structure damages in muscle tissue, revealed during US examination.

Moreover, the degree of manifestation correlated to the duration of disease. It was established that the first damages in muscle tissue

Table 1

The rates of skeletal muscle index and the percentage of adipose tissue in children with T1D according to the duration of disease, $M \pm m$

Indicators	1 group n = 26	2 group n = 27	3 group n = 37	Group of control, n = 25
Body mass index, kg/m ²	18,82 ± 0,65	20,24 ± 0,53	20,46 ± 0,55	19,79 ± 0,65
Skeletal muscle index, % SMI	81,77 ± 1,28	77,91 ± 2,19	77,51 ± 1,27 * †	81,62 ± 1,15
% body fat (BFP), %	16,94 ± 1,05	20,14 ± 1,22*	20,42 ± 0,97 * †	16,62 ± 1,12
Muscle mass/adipose mass, LBM/BFM	5,51 ± 0,50	4,42 ± 0,48	4,22 ± 0,24 * †	5,54 ± 0,45

Note:

* a significant ($p < 0,05$) difference compared to the corresponding indicator of the control group;

† a significant ($p < 0,05$) difference compared to the corresponding indicator of group 1.

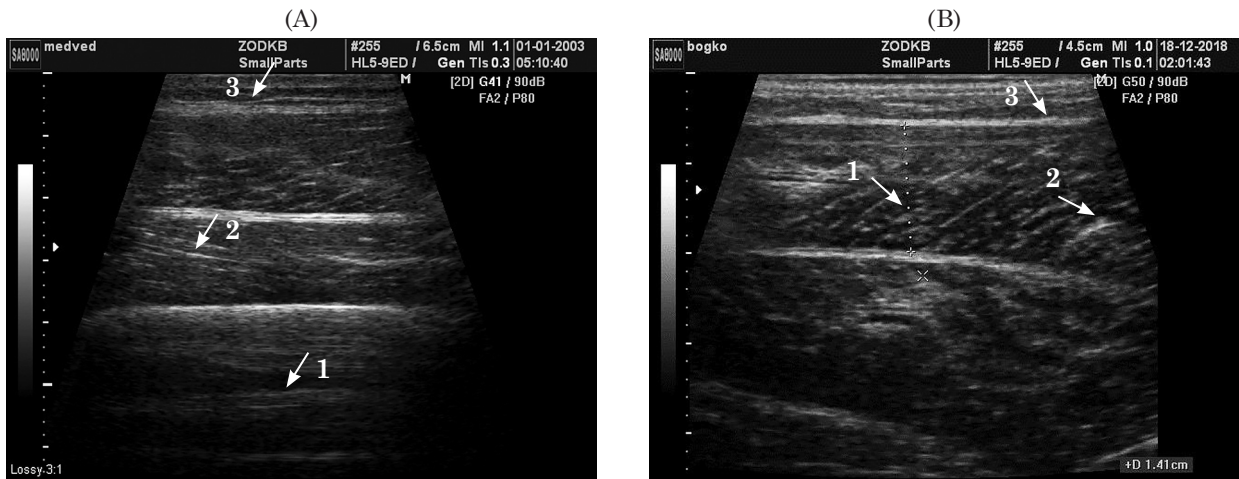


Fig. 1. Sonogram of the front femoral muscles (A) and m.gastrocnemicus (B) in children from the group of control.

Note: 1 — muscle tissues, 2 — perimysium, 3 — epimysium.

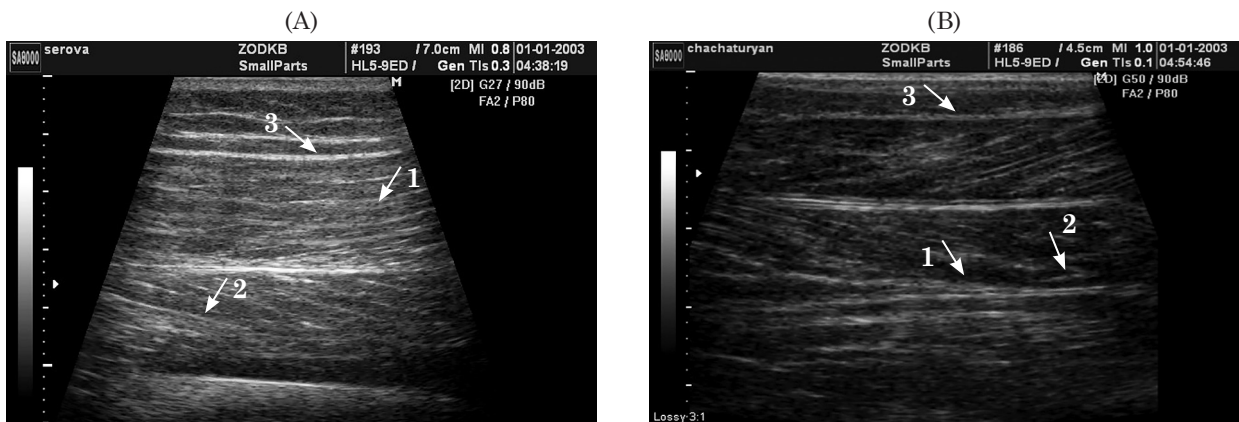


Fig. 2. Sonogram of the front femoral muscles (A) and m.gastrocnemicus (B) in children from the group of with the duration of diabetes less than 1 year.

Note: 1 — muscle tissues, 2 — perimysium, 3 — epimysium.

architecture were observed from the first year of disease (fig. 2).

Thus, the patients from the 2st group had the increased echogenicity of separate muscle fibers, which suggested the higher muscular density. The higher amount of perimysium membranes has led to the general higher muscular echogenicity. However, there was no damage of perimysium.

Despite the high muscular echogenicity, the patients from the 2nd group had the reduced muscular homogeneity and thickened connective tissue fibers. Epimysium visualized as hyperechogenic linear structure with sharp and thickened contour (fig. 3).

The most significant structure changes were noticed in patients with the duration of

diabetes over 5 years. In addition to all mentioned violations of muscle structure, they also had disorderly arrangement of inter-muscular connective tissue layers, which attested the presence destructure (fig. 4).

The comparison of muscle parameters held between children from the group of control and children with diabetes type 1 has shown the credible thinning of front femoral muscle group in the dynamics of disease (table 2). The thickness of the front femoral muscle group in children from the 1st and 2nd group didn't diverge much from the rates, get in the group of control. Meanwhile, the patients with the duration of diabetes over 5 years had thinner muscular fibers and front femoral muscle group in general ($p < 0,05$). Due to the reduce of muscular

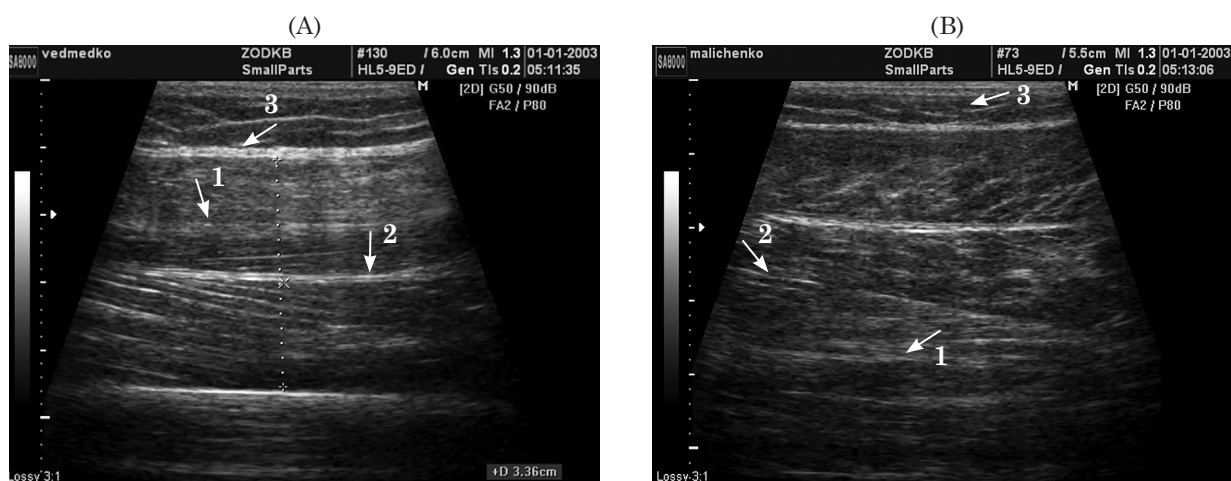


Fig. 3. Sonogram of the front femoral muscles (A) and m.gastrocnemicus (B) in children from the group of with the duration of diabetes from 1 to 5 years.

Note: 1 — muscle tissues, 2 — perimysium, 3 — epimysium.

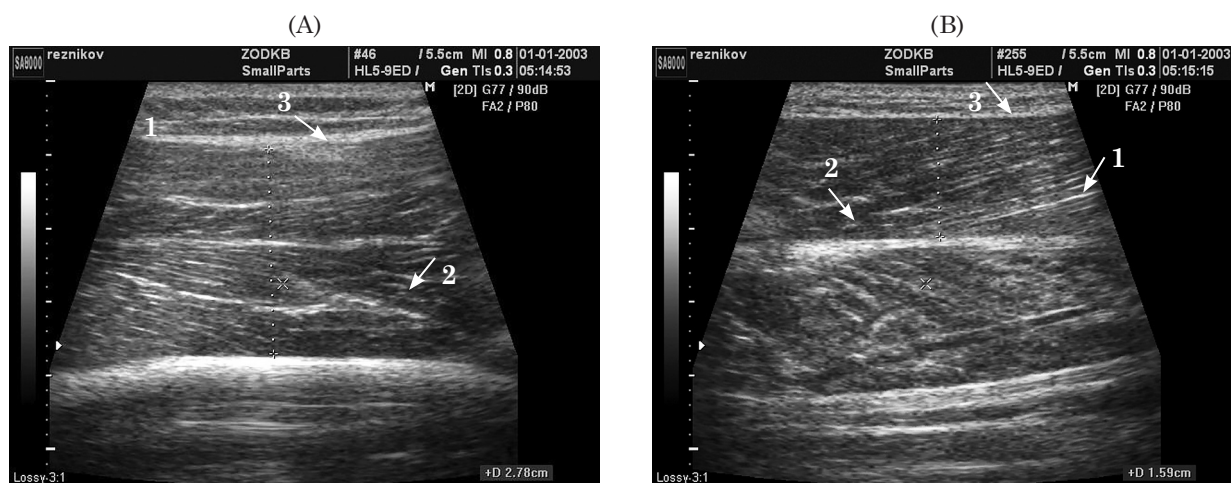


Fig. 4. Sonogram of the front femoral muscles (A) and m.gastrocnemicus (B) in children from the group of with the duration of diabetes over 5 years.

Note: 1 — muscle tissues, 2 — perimysium, 3 — epimysium.

thickness, the patients from the 3rd group had lower coefficients of correlation between the thickness of muscle fiber and general thickness of connective tissue ($p < 0,05$).

Similar changes in patients in the 3rd group occurred on the part of the muscles of the back of the shin, which was characterized by a decrease in muscle fiber and a decrease in the ratio of muscle fibers / connective tissues. At the same time, the total thickness of the muscles of the posterior group of the leg in children of the 3rd group, did not differ statistically from the parameters of the control group (table 2).

It might be assumed, that preservation of general muscular thickness of given muscle group accompanied by reduced muscle fiber

thickness and higher general echogenicity of muscles in patients with prolonged duration of T1D is linked to the replacement of muscular tissue by connective tissue septa.

Taking into account the data on the relationship between the muscle state and the levels of circulating irisin [5], we investigated the content of the latter in the observation groups (Fig. 5). According to the results of the study, it was found that the level of irisin in blood serum in children with T1D, differed depending on the duration of the disease.

In patients from groups 1 and 2, the amount of irisin was 1.3 times lower than in the control group and was 1.51 ± 0.14 ng/ml, 1.50 ± 0.13 ng/ml versus 1.98 ± 0.16 ng/ml, respectively ($p < 0.05$);

Table 2

**Ultrasonic indicators of examination of skeletal muscles of lower limbs
in children with T1D according to the duration of disease, M ± m**

Indicator	I group n = 26	2 group n = 27	3 group n = 37	Group of control, n = 25
Front femoral muscle group				
Muscle thickness (sm)	2,75 ± 0,12	2,80 ± 0,09	2,55 ± 0,10*	2,83 ± 0,17
Muscle fiber thickness (sm)	0,16 ± 0,007	0,16 ± 0,009	0,15 ± 0,007*	0,17 ± 0,005
MCK,	1,20 ± 0,07	1,23 ± 0,08	1,05 ± 0,07*	1,26 ± 0,05
Posterior shin muscle group				
Muscle thickness (sm)	1,46 ± 0,04	1,50 ± 0,04	1,51 ± 0,03	1,54 ± 0,05
Muscle fiber thickness (sm)	0,15 ± 0,007	0,16 ± 0,007	0,14 ± 0,006*	0,16 ± 0,006
MCK	1,23 ± 0,08	1,23 ± 0,06	1,06 ± 0,07*	1,29 ± 0,05

Note:

* a significant ($p < 0,05$) difference compared to the corresponding indicator of the control group.

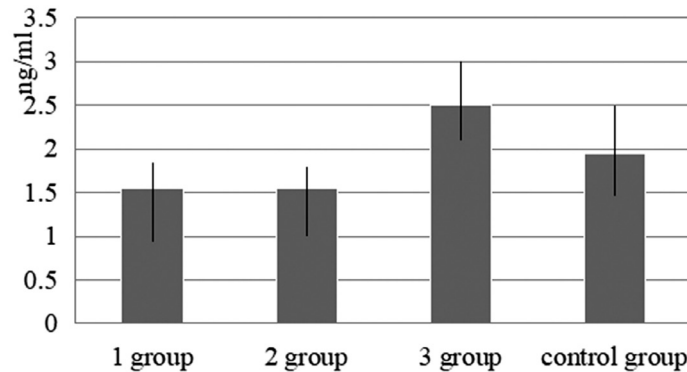


Fig 5. The amount of irizin in blood serum of children with T1D according to the duration of disease.

at the same time there was a statistically significant increase in the serum of the amount of the indicated myokine in patients from group 3, which was 2.54 ± 0.18 ng/ml, which exceeded the corresponding indexes in both patients with shorter duration of the disease and in the control group ($p < 0,05$).

Counting the data of correlation analysis it was noticed that the amount of irizin was influenced by muscle mass starting from the second year of disease. We had a positive correlation between SMI and amount of irizin in patients from the 2nd group ($r = + 0,64$, $p < 0,05$). The mentioned above correlation was applied for patients from the 3rd group, but had weaker connections ($r = + 0,37$, $p < 0,05$). Thus, the lowest amount of irizin was indicated in patients with low SMI. At the same time, the amount of irizin in blood serum was not influenced by muscle mass index in group of con-

trol, as well as in patients from the 1st group. It was also revealed that, there was a multidirectional correlation between the amount of irizin in blood serum and US rates of skeletal muscles in patients with T1D. If in patients from groups 1 and 2 one received a positive correlation between the amount irizin and muscle thickness ($r = + 0.38$ and $r = + 0.38$, respectively, $p < 0.05$), and also, between amount irizin and MSC ($r = + 0.34$ and $r = + 0.38$, respectively, $p < 0.05$), then in patients of the 3rd group one observed an inverse relationship between both irizin and muscle thickness rates ($r = - 0.43$, $p < 0.05$), and between irisin and MSC ($r = - 0.58$, $p < 0.05$). It could be expected, that all revealed changes of irizin amount in children with prolonged T1D, accompanied by muscle mass loss and damages of the inner muscular architecture, could be compensatory and directed to the increased glucose inflow to the

muscles, in terms of its deficiency. At the same time, the increasing of irisin amount in blood serum accompanied by muscle mass loss and muscle thinning can be due to the secretion of irisin by adipose tissue [13], which has higher content in patients with prolonged T1D, from the one side, and increased expression of gene FNDC5 as a compensatory mechanism to the response of adipose tissue amount growing [14, 15]. Taking into account the association between the content of irisin in blood serum and loss of muscle mass, as well as changes in the skeletal musculoskeletal architecture, the level of this myokine may be used as a diagnostic criterion for the development of diabetic myopathy in children T1D. At the same time, the lower level Irizin in the first 5 years of diabetes may be associated with lower expression and activity of PGC-1 α in myocytes [16]. However, these studies were conducted in patients with type 2 diabetes mellitus. Therefore, the data we receive need further study.

In a study by D. Espes et al. (2015) a negative correlation was determined between the level of irisin and the age of manifestation of type 1 diabetes in adult female patients [17]. We have not obtained a significant difference

between the levels of irisin in children depending on sex. Given the same average age in all study groups, it can be concluded that children with a diabetes mellitus duration of more than 5 years had an earlier age of manifestation of diabetes mellitus. It is not ruled out that an increase in the level of irisin during the course of T1D may be associated with the development of resistance to irisin, but this question leaves much to be desired for further study [18]. At the same time, we established a positive correlation between the irisin content and the daily dose of exogenous insulin ($r = + 0.40$, $p < 0.05$). It is known that loss of muscle mass is accompanied by the development of insulin resistance, including in T1D, therefore, an increase in the level of irisin in the blood serum during the long course of T1D may be compensatory character, taking the ability of this myokine to increase glucose tolerance and reduce insulin resistance [4, 19]. This assumption was confirmed in Li M. et al. (2015) and Qiu S. et al. (2016) researches, which showed a positive correlation of serum irisin levels with the development of insulin resistance regardless of age and BMI [20, 21].

CONCLUSIONS

1. There is a redistribution of component constitution of body as a reduced muscle mass and increased percentage of adipose tissue in children with type 1 diabetes in dynamics of disease.
2. There is a change in sonogram of skeletal muscles in dynamics of disease, such as reduced muscle fiber thickness, muscle architecture damage and increased echogenicity of muscle fibers due to the growth of connective tissue fibers.
3. In children with type 1 diabetes mellitus with a disease duration of more than 5 years, a decrease in muscle mass and impaired skeletal muscle architectonics is accompanied by an increase in serum irisin content. Determining the serum level above the indicated myokine can be used as an additional marker for the development of diabetic myopathy in children.

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ІРИЗИН ЯК МАРКЕР ДІАБЕТИЧНОЇ МІОПАТІЇ У ДІТЕЙ, ХВОРИХ НА ЦУКРОВИЙ ДІАБЕТ 1 ТИПУ

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Мета дослідження: визначити рівень іризину у сироватці крові дітей, хворих на цукровий діабет 1 типу, в залежності від тривалості захворювання та його роль в діагностиці діабетичної міопатії. Було обстежено 90 дітей, хворих на цукровий діабет 1 типу (ЦД1) (середній вік $13,7 \pm 0,3$ років). В залежності від тривалості перебігу захворювання було сформовано 3 групи: 1 група — 26 дітей до 1 року захворювання на ЦД1; 2 група — 27 дітей — тривалість ЦД1 від 1–5 років; 3 група — 37 дітей з тривалістю ЦД1 більше 5 років. Групу контролю склали 25 умовно здорових дітей репрезентативних за віком та статтю. Всім дітям проводилась оцінка м'язової та жирової маси та їх індексів, ультразвукове обстеження скелетних м'язів та визначення рівня іризину у сироватці крові методом ІФА. Встановлено, що зі збільшенням тривалості ЦД1 відбувався перерозподіл компонентного складу тіла у вигляді зменшення питомої ваги м'язової та збільшення відсотку жирової маси, а також зміни ультразвукової картини скелетних м'язів, які характеризувались зменшенням товщини м'язового волокна, порушенням нормальної архітекτονіки м'язу та підвищенням ехогенності м'язових пучків. Встановлено, що в перші роки захворювання зниження м'язової маси супроводжувалося зменшенням рівня іризину, натомість при тривалому перебігу ЦД1 відбувалося його підвищення, що супроводжувалося втратою м'язової маси та порушенням архітекτονіки скелетної мускулатури. Таким чином, підвищення рівня іризину може використовуватись в якості додаткового маркера розвитку діабетичної міопатії.

Ключові слова: міопатія, іризин, цукровий діабет 1 типу, діти.

ІРИЗИН КАК МАРКЕР ДИАБЕТИЧЕСКОЙ МИОПАТИИ У ДЕТЕЙ, БОЛЬНЫХ САХАРНЫМ ДИАБЕТОМ 1 ТИПА

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Цель исследования: определить уровень иризина в сыворотке крови детей, больных сахарным диабетом 1 типа, в зависимости от длительности заболевания и его роль в диагностике диабетической миопатии. Было обследовано 90 детей, больных сахарным диабетом 1 типа (СД1) (средний возраст $13,7 \pm 0,3$ лет). В зависимости от длительности течения заболевания было сформировано 3 группы: 1 группа — 26 детей до 1 года заболевания СД1; 2 группа — 27 детей, продолжительность СД1 от 1–5 лет; 3 группа — 37 детей с продолжительностью СД1 более 5 лет. Группу контроля составили 25 условно здоровых детей репрезентативных по возрасту и полу. Всем детям проводилась оценка мышечной и жировой массы и их индексов, ультразвуковое исследование скелетных мышц и определения уровня иризина в сыворотке крови методом ИФА. Установлено, что с увеличением продолжительности СД1 происходило перераспределение компонентного состава тела с уменьшением удельного веса мышечной и увеличения процента жировой массы, а также изменения ультразвуковой картины

скелетных мышц, которые характеризовались уменьшением толщины мышечного волокна, нарушением нормальной архитектоники мышцы и повышением экзогенности мышечных пучков. Установлено, что в первые годы заболевания снижение мышечной массы сопровождалось уменьшением уровня иризина, в то время как при длительном течении СД1 происходило его повышение, которое сопровождалось потерей мышечной массы и нарушением архитектоники скелетной мускулатуры. Таким образом, повышение уровня иризина может использоваться в качестве дополнительного маркера развития диабетической миопатии.

Ключевые слова: миопатия, иризин, сахарный диабет 1 типа, дети.

IRIZIN AS A MARKER OF DIABETIC MYOPATHY IN CHILDREN WITH DIABETES TYPE 1*

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The purpose of the study: to study the amount of irisin in the blood serum of children with Type 1 diabetes considering the duration of clinical course and determine the role of irisin in diagnosing the diabetic myopathy. The study included 90 children with Type 1 diabetes (T1D) (average age 13,7±0,4 years old). Depending on the duration of the disease, 3 groups were formed: 1 group — 26 children under 1 year with T1D; group 2 — 27 children — duration of T1D from 1–5 years; group 3 — 37 children with T1D duration more than 5 years. The control group included of 25 conditionally healthy children of a representative age and gender. All children were evaluated for their muscle and fat mass and their indices, ultrasound examination of skeletal muscles, and determination of irisin levels in the blood serum by ELISA. It was established that with increasing durations of T1D there was a redistribution of the component body composition in the form of a decrease in the specific the muscle mass and an increase in the percentage of fat mass, as well as changes in the ultrasound pattern of skeletal muscles characterized by a decrease in the thickness of the muscle fibers, a infraction of the normal architecture of muscle and increased echogenicity of muscle bundles. It was established that in the first years of the disease, the decrease in muscle mass was accompanied by a decrease in the level of irisin, whereas with the prolonged course of T1D there was an increase in it, which was accompanied by loss of muscle mass and infraction of the architecture of skeletal muscles. Thus, increasing the level of irisin can be used as an additional marker for the development of diabetic myopathy.

Key words: myopathy, irisin, Type 1 diabetes, children.