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# CONTENTS

## MEDICINE

# RISK FACTORS FOR DEVELOPING DIABETIC MYOPATHY IN CHILDREN WITH TYPE 1 DIABETES MELLITUS

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**ABSTRACT**

Aim of study: to determine the pathogenetic factors that have an impact on the development of diabetic myopathy in children with DM1, to investigate the structure of the factors. The observation group included 136 children 14.3 ± 0.3 years old who have been suffering from DM1 for 1 to 10 years. Diagnosed diabetic myopathy in 45 (33.1%) patients (19 (24.4%) boys and 25 (44.8%) girls). By factor analysis, 5 factors were identified that are of leading importance in the pathogenesis of the development of diabetic myopathy in children with DM1. These factors accounted for 73.33% of the total dispersion. The first rank place was represented by the group factor (nitrotyrosine and homocysteine), which accounted for 19.54% of the total dispersion; interpreted as a factor of "oxidative stress". The second rank place was represented by the content of triglyceride in the blood serum and the level of the triglyceride-glucose complex, which amounted to 16.69% of the total dispersion; interpreted as "insulin resistance factor". The third rank place was interpreted as "the state of peripheral blood supply", which accounted for 13.93% of the total variance, and included the indicators of the ankle-brachial index before and after exercise stress. The fourth rank place was interpreted as an "anamnestic factor", which accounted for 12.04% of the total dispersion, and included three risk factors: age, sex of the patient, and duration of DM1. The fifth factor ("inflammation factor") included the indicators of glycosylated hemoglobin and interleukin-6, and demonstrates the development of chronic low-level inflammation against the background of hyperglycemia. Thus, using factor analysis, we determined that oxidative stress, insulin resistance, impaired peripheral circulation, duration of diabetes mellitus, female sex, chronic hyperglycemia, increased activity of proinflammatory cytokines had a priority effect on the pathogenesis of diabetic myopathy. We have formed a factorial model that will optimize the diagnosis of diabetic myopathy, improve approaches to its therapy and prevention, identifying among children with DM1 the risk group for the development and progression of this complication.

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It is known that skeletal muscle is the main site of metabolic fuel use in the body, and the organ for insulin-mediated glucose utilization. Thus, cellular dysfunction of skeletal muscles is one of the most important pathophysiological signs of diabetes [1]. The importance of the role of skeletal muscle in controlling the metabolism of the whole body is understood, but research on the mechanisms of development of diabetic myopathy is negligible.

For the study of complex systems, it is effective to use factor analysis with the allocation of principal components (factors). This is a set of pathogenetic influences that are of the greatest importance in the development of the pathological process.

**Aim of study:** to determine the pathogenetic factors that determine the development of diabetic myopathy in children with type 1 diabetes mellitus, and to investigate the factor structure.

**Research materials and methods.**

The main group included 136 children aged 11 to 17 years (mean age 14.3 ± 0.3 years) with type 1 diabetes mellitus. The duration of the disease ranged from 1 to 10 years. The development of diabetic myopathy was observed in 45 (33.1%) children. This complication was diagnosed in 19 (24.4%) boys and 26 (44.8%) girls. Diabetic myopathy was diagnosed with a decrease in skeletal muscle strength and skeletal muscle mass index in comparison with the normative indicators [2]. We analyzed the data of the anamnesis of the disease, including data on the duration of the course of diabetes mellitus, sex, and age of children who were examined, the state of glycemic control, the presence of chronic complications, signs of insulin resistance. To assess insulin resistance, the content of triglycerides in the blood serum was studied, and the triglyceride-glucose index (TyG) was determined [3]. To assess the state of the peripheral circulation, the ankle-brachial index (ABI) was determined before and after physical activity [4]. Investigated the content in blood serum of nitrotyrosine, homocysteine, and interleukin-6 using enzyme-linked immunosorbent assay. Commercial kits «Nitrotyrosine» (ELISA, The Netherlands) «Homocysteine» (EIA, United Kingdom), «Human IL-6 High Sensitive» (ELISA, Austria) were used for the study.

Factor analysis was performed to identify the minimum number of hidden common factors that had the greatest influence on the development of diabetic myopathy. For the selection of factor complexes, the Spearman correlation matrix was used. At the next stage, the factorial influence of the studied indicators was determined. We chose the method of principal component analysis as a method for factorizing the correlation matrix. We used the Kaiser criterion to determine the number of common factors in the model (eigenvalues of each factor must exceed 1); common factors explain the overall share, which is over 70%. We used Rotation Mathod: Varimax for indicators with factor loadings of more than 0.7 Factor analysis was performed using Rotation Mathod: Varimax, taking into account the results of the initial analysis, and was also used to describe the dispersion of the principal component data set [5].

At the planning stage of the study, we received permission from the regional commission on bioethics of Zaporizhzhya State Medical University. All procedures in which the supervised children participated were in line with the ethical standards of the institutional and national research committee and the 1964 Declaration of Helsinki, as further amended or compared with ethical standards. Received informed consent from each patient who was under examination, as well as their official guardians.

**Results.** As a result of factor analysis, 5 factors were identified that determined the development of diabetic myopathy in children with type 1 diabetes mellitus. These factors accounted for 73.33% of the total dispersion (tab. 1), while the first 3 factors accounted for 50.16% of the dispersion.

Table 1. Eigenvalues of factors and percentage of total dispersion

| Factors | Eigenvalues of factors | Percentage of total dispersion (%) | Accumulated eigenvalues | Accumulated percentage of total dispersion (%) |
|---|---|---|---|---|
| 1 | 2,15 | 19,54 | 2,15 | 19,54 |
| 2 | 1,84 | 16,69 | 3,98 | 36,23 |
| 3 | 1,53 | 13,93 | 5,52 | 50,16 |
| 4 | 1,32 | 12,04 | 6,84 | 62,19 |
| 5 | 1,22 | 11,14 | 8,07 | 73,33 |

Based on the analysis, a matrix of factor loads was formed (tab. 2).

Table 2. Factor load matrix

| | Factor 1 | Factor 2 | Factor 3 | Factor 4 | Factor 5 |
|---|---|---|---|---|---|
| Duration of type 1 diabetes mellitus | | | | 0,605 | |
| Glycosylated hemoglobin (HbA1) | | | | | 0,773 |
| ABI before load | | | 0,747 | | |
| ABI after load | | | 0,858 | | |
| Triglycerides | | 0,900 | | | |
| TyG index | | 0,927 | | | |
| Nitrotyrosine | 0,871 | | | | |
| Homocysteine | 0,763 | | | | |
| IL-6 | | | | | 0,758 |
| Age | | | | 0,780 | |
| Sex | | | | 0,776 | |

Analysis of the identified factors in the group of children with diabetic myopathy showed that the first factor determined 19.54% of dispersion and consisted of two potential risk factors: 1) the level of nitrotyrosine (factor load 0.871); 2) homocysteine level (0.763). Interpreted this factor as a factor of "oxidative stress".

The second most important factor was the group factor, which had 16.69% of the total proportion of dispersion, which combined two initial potential risk factors: 1) the content of triglycerides in blood serum; 2) the level of the triglyceride-glucose index. Interpreted this factor as "insulin resistance factor".

The third most significant factor contained 13.93% of the total proportion of dispersion, and included factors that we interpreted as the "state of peripheral blood supply", which included indicators of the ankle-brachial index before and after exercise stress.

The fourth factor in the matrix contained 12.04% of the total dispersion. Interpreted this factor as an "anamnestic factor" and included three initial risk factors that had the highest factor load: 1) the patient's age (factor load 0.780); 2) the sex of the child (factor load 0.776); 3) the duration of the course of diabetes mellitus (factor load 0.605).

The fifth factor included indicators of glycosylated hemoglobin (factor loading 0.773) and interleukin-6 (factor loading 0.758). We assume that this factor demonstrates the development of chronic low-level inflammation against the background of hyperglycemia. Interpreted as "inflammation factor".

**Discussion.** Modern ideas about the pathogenetic mechanisms of complications of diabetes mellitus, including diabetic myopathy, indicate the leading role of oxidative stress in the pathogenesis of their development [6, 7]. The increased activity of oxidative processes leads to the progression of pathological changes in the microvascular blood flow and the gradual depletion of the capillary network in skeletal muscles. This pathological process leads to the redistribution of muscle fibers, their atrophy, dysfunction of skeletal muscles, and the development of diabetic myopathy [8, 9, 10]. Experimental studies have shown that the use of the antioxidant properties of alpha-lipoic acid reduces the severity of morphological changes in the skeletal muscles of rats, which are caused by diabetes mellitus. Also, treating the muscles with alpha-lipoic acid prevents atrophy. These observations support the important role of oxidative stress and antioxidant defenses in the development of diabetic myopathy again [11].

Another reason for the development of diabetic myopathy is a decrease in insulin sensitivity. Elevated blood triglyceride and fatty acid levels and increased intracellular lipid storage are the distinctive of insulin resistance [12].

Richardson et al. (2005) the earliest scientists to demonstrate increased levels of free fatty acids leading to intracellular matrix remodeling due to increased collagen deposition in human skeletal muscle [13]. Similar changes are found in insulin-resistant skeletal muscle [14]. At the same time, under conditions of insulin resistance, protein synthesis in muscle tissue decreases and there is no sufficient synthesis of ATP in mitochondria, which is necessary for muscle contraction [15]. Nomura T. et al. (2007) described a close relationship between skeletal muscle health and decreased

insulin sensitivity. This study demonstrated that insulin resistance is an independent risk factor for decreased muscle strength [16]. In addition, it is known that in persons who have insulin resistance, reduced oxidative capacity is characteristic of skeletal muscle [17].

It is known that diabetes mellitus is one of the main risk factors that affect the early development and rapid progression of diabetic angiopathy [18]. It has been proven that a decrease in blood supply to skeletal muscles leads to the prevalence of catabolism over anabolism in muscle tissue, and, as a result, increases skeletal muscle fatigue, and causes a decrease in muscle strength and a decrease in exercise stress tolerance [19].

It is known that both the duration of the course of diabetes mellitus and sex affect the development of complications. Sex dimorphic has so far been described in the regulation of skeletal muscle protein depending on insulin resistance, muscle fiber strength and distribution, mitochondrial function, oxidative metabolism, and fatigue in mammalian [1]. Known clinical and experimental, which describe the "female advantage" in the progression of diabetic myopathy, which is explained by differences in the regulation of skeletal muscle proteins. Experimental animals were used to demonstrate sex-dimorphic expression of some skeletal muscle proteins: a decrease in the expression of the myosin heavy chain, which is associated with the rate of muscle contraction; decrease in the expression of tropomyosins, which have a key role in the structure and regulation of muscle contraction. The above changes were more pronounced in female rats compared to male rats with diabetes mellitus [1].

One of the main risk factors for the development and progression of myopathy in diabetes mellitus is chronic hyperglycemia, when the amount of end products of glycation increases. Hyperglycemia accelerates the decline in muscle mass, and an increase in the concentration of advanced glycation end products contributes to a decrease in muscle strength [20]. Skeletal muscle satellite cells can turn into adipocytes in the presence of hyperglycemia. This can lead to fatty infiltration of muscles, an increase in fat mass and, consequently, to a decrease in muscle mass and dysfunction of skeletal muscles [21].

Increased activity of proinflammatory cytokines increases the risk of developing diabetic myopathy [22]. It was investigated that a chronic increase in the concentration of circulating IL-6 has a harmful effect on skeletal muscles. This can be explained by the fact that intracellular signaling is inhibited, which leads to the loss of myofibrillar protein and muscle atrophy, and, as a consequence, to a decrease in muscle strength and muscle mass [23, 24].

Thus, the factor analysis made it possible to determine the leading pathogenetic mechanisms of the development and progression of diabetic myopathy in children with type 1 diabetes mellitus.

**Conclusions.**

1. Factor analysis made it possible to determine the leading pathogenetic mechanisms of the development of diabetic myopathy in children with type 1 diabetes mellitus. Oxidative stress, insulin resistance, impaired peripheral circulation, duration of type 1 diabetes mellitus, female sex, chronic hyperglycemia, and increased activity of proinflammatory cytokines are the factors that most influenced the pathogenesis of the development of diabetic myopathy.

2. The factor model that we have obtained allows us to optimize the diagnosis of diabetic myopathy, improve therapeutic tactics, and improve prevention by differentiating the developmental groups and progression of diabetic myopathy among children with type 1 diabetes mellitus.

**Conflict of interests:** The authors confirm that there are no conflicts of interest.

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