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Functional state of the GH/IGF-1 system in adolescents with type 1 diabetes mellitus

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Abstract

Purpose: to study the level of growth hormone (GH) and insulin-like growth factor type 1 (IGF-1) in patients with type 1 diabetes mellitus (DM1) at the stages of puberty.

Material & Methods: 165 children (85 girls (51.5%) and 80 boys (48.5%), aged 8 to 18 years old, suffering from DM1 and staying in the endocrinology department of the State Institution "Institute of Health for Children and Adolescents") of the National Academy of Medical Sciences of Ukraine" (State Institution "IOZGP NAMS"). The criterion for inclusion in the study was the duration of T1DM for more than one year (from 1 to 16 years). The level of GH and IGF-1 was determined in 165 children 8-18 years old (85 girls and 80 boys) with DM1, taking into account gender, the level of sexual development at the time of the survey, the duration of DM1 and the level of glycemic control. Study participants were divided into groups depending on the level of sexual development (T1-T4) at the time of the study, assessed by the Marshall & Tanner scale (Marshall, & Tanner, 1969; Marshall, & Tanner, 1970); duration of DM1 (<5 years, 5 to 10 years, >10 years); level of glycemic control (optimal (HbA1c<7.5%), suboptimal (7.5%≤HbA1c≤9.0%), high-risk (HbA1c>9.0%) according to ISPAD 2018 recommendations (DiMeglio, et al., 2018)

Results: in adolescents with DM1, a physiological type of activation of the GH/IGF-1 system was established with an increase in its activity during the period of puberty proper. Sexual characteristics were determined in the levels of GH and IGF-1 at the stages of puberty. Girls had higher levels of IGF-1 than boys, especially during prepuberty. During prepuberty and puberty proper, GH values were higher in boys, and in late puberty, in girls. It has been established that in girls and boys with an increase in the duration of diabetes, there is an increase in the level of GH and a decrease in IGF-1. The nature of the state of GH/IGF-1 in patients with different experience of DM1 is affected by the level of sexual development at the time of the examination and the sex of adolescents. In boys aged 14-18 years (the period of proper and late puberty), with an increase in the duration of the disease, an increase in the level of GH ($p_{k-w}<0.05$) and a decrease in IGF-1 ($p<0.05$) occur. In girls, an increase in GH ($p_{k-w}<0.05$) and a decrease in IGF-1 ($p_{k-w}<0.05$) with an increase in the duration of DM1 were recorded only in the group of patients aged 16-18 years (late puberty). The relationship between HbA1c and GH and IGF-1 levels has gender specifics: in the state of decompensation, the guys showed a tendency to decrease in GH, and in girls – to increase GH and IGF-1.

Conclusions: the functional state of the GH/IGF-1 system in adolescents with DM1 depends on gender, the level of sexual development, the duration of diabetes and the state of carbohydrate metabolism compensation, which coincides with the data of domestic and foreign studies.

Key words: children, type 1 diabetes mellitus, growth hormone, type 1 insulin-like growth factor.

Анотація

Світлана Турчина, Лариса Нікітіна, Ольга Вародова, Юлія Калмикова , Сергій Калмиков. Функціональний стан системи GH/IGF-1 у підлітків, хворих на цукровий діабет 1 типу. Мета: вивчити рівень гормону роста (GH) та інсуліноподібного фактору росту 1 типу (IGF-1) у хворих на цукровий діабет 1 типу (ЦД1) на етапах статевого дозрівання. **Матеріал і методи:** 165 дітей (85 дівчат (51,5%) і 80 хлопців (48,5%) від 8 до 18 років, які хворіють на ЦД 1 і перебувають в ендокринологічному відділенні ДУ «Інститут охорони здоров'я дітей та підлітків НАМН України» (ДУ "ІОЗДП НАМН"). Критерієм включення в дослідження була тривалість ЦД1 більше одного року (від 1 до 16 років). Визначався рівень GH та IGF-1 у 165 дітей віком 8-18 років (85 дівчат і 80 хлопчиків) з ЦД1 з урахуванням статі, рівня статевого розвитку на момент обстеження, тривалості ЦД1 та рівня глікемічного контролю. Учасники дослідження були розділені на групи залежно від рівня статевого розвитку (Т1-Т4) на момент дослідження, який оцінювався за шкалою Marshall & Tanner (Marshall, & Tanner, 1969; Marshall, & Tanner, 1970); тривалості перебігу ЦД1 (<5 років, від 5 до 10 років, >10 років); рівня глікемічного контролю (оптимальний (HbA1c<7,5%), субоптимальний (7,5%≤HbA1c≤9,0%), з високим ризиком (HbA1c>9,0%) відповідно до рекомендацій ISPAD 2018 (DiMeglio, et al., 2018). **Результати:** у підлітків із ЦД1 встановлено фізіологічний тип активації системи GH/IGF-1 із підвищенням її активності в період власно пубертату. Визначено статеві особливості у рівнях GH та IGF-1 на етапах статевого дозрівання. У дівчат рівень IGF-1 був вище, ніж у хлопців, особливо в період препубертату. В період препубертату та власно пубертату показники GH були вище у хлопців, а в період пізнього пубертату – у дівчат. Встановлено, що у дівчат і хлопців із збільшенням тривалості діабету відбувається збільшення рівня GH та зменшення IGF-1. На характер стану системи GH/IGF-1 у пацієнтів із різним стажем ЦД 1 впливає рівень статевого розвитку на момент обстеження та стать підлітків. У хлопців 14-18 років (період власно та пізнього пубертату) із збільшенням стажу захворювання відбувається збільшення рівня GH (p_{k-w}<0,05) та зменшення IGF-1 (p_{k-w}<0,05). У дівчат збільшення GH (p_{k-w}<0,05) та зменшення IGF-1 (p_{k-w}<0,05) із збільшенням тривалості ЦД1 реєстрували тільки в групі пацієнток 16-18 років (період пізнього пубертату). Взаємозв´язок між показниками HbA1c та рівнями GH і IGF-1 має статеві особливості: у стані декомпенсації у хлопців реєструвалася тенденція до зменшення GH, а у дівчат – до збільшення GH та IGF-1. **Висновки:** функціональний стан системи GH/IGF-1 у підлітків із ЦД1 залежать від статі, рівня статевого розвитку, тривалості діабету та стану компенсації вуглеводного обміну, що збігається з даними вітчизняних та закордонних досліджень.

Ключові слова: діти, цукровий діабет 1 типу, гормон роста, інсуліноподібний фактор росту 1 типу.

Introduction

A special place in the pathogenesis of type 1DM and its complications is occupied by disturbances in the system of regulation of somatotropic hormone (GH), its main mediator of action – insulin-like growth factor-1 (IGF-1) and binding proteins. Hereinafter, this system will be abbreviated as GH/IGF-1.

The exact mechanisms linking type 1 diabetes and poor glycemic control to the growth hormone/insulin-like growth factor-1 and IGF-binding protein-3 (IGFBP-3) axis remain to be elucidated. It has been determined that GH resistance with low IGF-1 levels, which can be observed in patients with 1DM, is often associated with portal hypoinsulification and lack of upregulation of GH receptors. There are conflicting reports on the impact of GH/IGF-1 axis dysregulation on growth in children and adolescents with 1DM, and even on the onset and course of chronic complications. (Nambam, & Schatz, 2018)

It is well known that type 1 diabetes mellitus and other chronic diseases in children have a negative impact on linear growth and sexual development (Turchyna et al., 2022; Turchina et al., 2022). Although prepubertal and postpubertal growth are important phases of growth, puberty and associated hormonal changes are a critical phase for height enhancement and eventual growth, especially in patients with endocrinopathies (Turchyna, 2019). Growth failure observed in patients with diabetes depends on abnormalities in physiological bone growth and is consistent with abnormalities in the growth hormone/insulin-like growth factor-1 axis. These changes may be related to appropriate insulin levels and thus to glycemic control based on the determination of glycated hemoglobin (HbA1c) (Chiarelli et al., 2004).

Assessing concomitant diabetes in the nature of changes in the functional state of the GH/IGF-1 system and its close relationship with the state of metabolic control in children and adolescents, some researchers note that deviations in the work of this hormonal axis can cause physical development disorders (PD).

According to the results of a comprehensive examination of adolescents aged 12-17 years with DM1, it was found that 60,0% of patients had disharmonious PD, mainly due to high growth and underweight. The frequency and structure of physical development disorders were influenced by the de-

gree of compensation of carbohydrate metabolism and the age period in which the manifestation of DM1 occurred. Disharmonious physical development was more often observed in adolescents with a poor level of compensation (76,3%) than with optimal (38,5%, $p_1<0,05$) and suboptimal (52,6%, $p_2<0,05$). Patients with optimal control were most often diagnosed with high growth (26,3%) and underweight (15,8%). In the state of decompensation, the percentage of patients with underweight (18,4%) and overweight (10,5%) significantly increased. Adolescents with disease manifestation during childhood (30,0%) and prepubertal period (21,4%) were significantly more likely to have disharmonious physical development than those with DM1 manifestation during puberty proper (8,6%, $p_1<0,05$ and $p_2<0,05$). It was concluded that adolescents with insufficient compensation of carbohydrate metabolism and patients with the onset of DM1 in childhood and prepuberty are at risk for the formation of disharmonious physical development (Turchina et al., 2019).

Disturbances in the somatotropic function of the pituitary in children with DM1 are reported in the works of domestic and foreign authors, but these data are rather contradictory. So, in the works of A.V. Bolshevoi et al. (2000) noted that an increase in GH production occurs only at the onset of the disease, and then it significantly depends on the state of carbohydrate metabolism compensation and is inhibited when it worsens, which causes growth retardation in children against the background of a long-term decompensated course of DM1. (Bolshova, & Popova, 2000). This is confirmed by the results of other studies (Chiarelli et al., 2004; Zachrisson et al., 1997), in which children with satisfactory glycemic control did not show significant changes in IGF-1 production, and physical development (height and body weight) did not differed from the indicators of healthy peers, while in case of metabolic decompensation of the disease, characteristic disorders were observed in the form of a decrease in IGF-I, which was accompanied by growth retardation (Zachrisson et al., 1997). Some authors indicate that these disorders occurred only in patients of late pubertal and post-pubertal age, possibly due to the longer duration of existing disorders (Cianfarani et al., 2000).

The data indicate the complexity of insular-contrinsular relationships in DM1 under conditions of basal insulin deficiency during puberty. That is why it is important to study the functional state of the GH/IGF-1 system in children and adolescents with DM1, taking into account the degree of puberty, the duration of diabetes, and the level of glycemic control.

Purpose of the study. To study the level of growth hormone and insulin-like growth factor type 1 in patients with type 1 diabetes at the stages of puberty.

Material and methods of research

Participants

165 children (85 girls (51.5%) and 80 boys (48.5%) from 8 to 18 years old with type 1 diabetes and are in the endocrinology department of the State Institution "Institute of Health for Children and Adolescents of the National Academy of Medical Sciences of Ukraine" (SI "IOZDP NAMS"). The criterion for inclusion in the study was the duration of DM1 more than one year (from 1 to 16 years).

The studies were carried out in accordance with the principles of the Helsinki Declaration of Human Rights, the Council of Europe Convention on Human Rights and Biomedicine and the current legislation of Ukraine. The study protocol was approved by the Commission on Medical Ethics of the State Institution "IOZGP NAMS". Parents and patients provided written informed consent to participate in the study.

Methods

Quantitative determination of GH and IGF-1 in blood serum was carried out using enzyme-linked immunosorbent assay (ELISA) on a Rayto RT-2100C photometer using commercial kits from «Granum» (Kharkiv).

Procedure

The analysis of GH and IGF-1 levels was carried out taking into account gender, the level of sexual development at the time of the survey, the duration of DM1 and the level of glycemic control. The study participants were divided into groups based on:

- level of sexual development (T1-T4) at the time of the study, assessed by the Marshal, W.A. and Tanner, J.M. scale (Marshall, & Tanner, 1969; Marshall, & Tanner, 1970);

- duration of DM1 (<5 years, 5 to 10 years, >10 years);

- level of glycemic control (optimal (HbA1c <7.5%), suboptimal (7.5%≤HbA1c≤9.0%), high risk (HbA1c>9.0%) in accordance with ISPAD recommendations 2018 (DiMeglio, et al., 2018).

Statistical analysis

Statistical analysis of the obtained data was carried out using the SPSS 26.0 statistical software package. Number of observations (n), mean standard deviation (M±m) for summing nominal variables. Comparison of data between groups was carried out using one-way analysis of variance (ANOVA). To assess the probability of differences, nonparametric methods were also used – the Wilcoxon-Mann-Whitney test for two independent groups (p_u)

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or the Kruskal-Wallis test (p_{k-w}) for three or more groups. The significance level was set at $p<0.05$.

Results of the study

Given the close relationship between the level of sexual development and the functional state of the GH / IGF-1 system, at the first stage of the study, the indicators of GH and IGF-1 in patients with DM1 were studied, taking into account the level of sexual development according to the Marshal, W.A. and Tanner, J.M. scale. According to the results obtained, the minimum basal GH values were determined in patients of both sexes in the period of pre-puberty (T1) and early puberty (T2). During the period of proper puberty (T3) and late puberty (T4), the GH level was significantly higher in both boys and girls with DM1 (Figure 1).

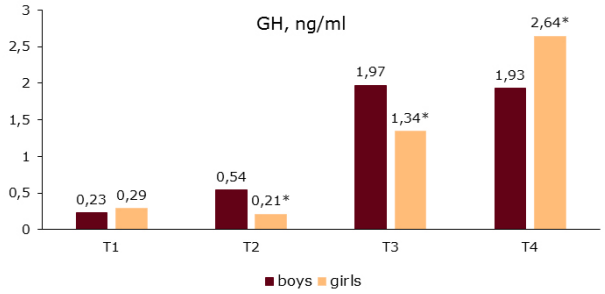

Fig. 1. Level of GH in patients with type 1 diabetes depending on the stage according to Tanner

Note:

** – the significance of the differences between the indicators of the group of boys and the group of girls according to the Wilcoxon-Mann-Whitney test ($p_u<0,05$).*

When determining the IGF-1 indicators, the presence of gender differences in patients with different levels of puberty was established (Figure 2).

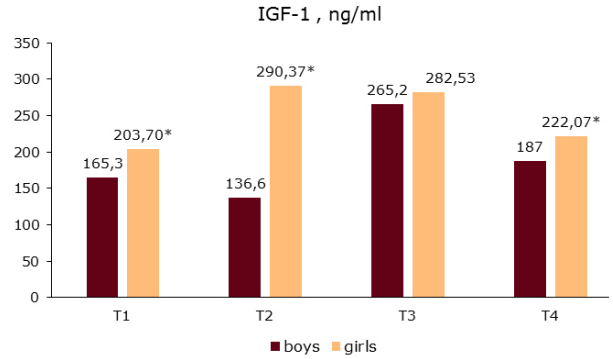

Fig. 2. Level of IGF-1 in patients with type 1 diabetes depending on the stage according to Tanner

Note:

** – the significance of the differences between the indicators of the group of boys and the group of girls according to the Wilcoxon-Mann-Whitney test ($p_u<0,05$).*

First, at all stages of puberty, IGF-1 levels in girls were higher than in men. Secondly, a significant increase in its level in girls occurred earlier – during the prepubertal period (T2), in contrast to boys, in whom IGF-1 production significantly increased only during the period proper (T3) and late (T4) puberty. This may be due to the peculiarities of hormonal regulation during puberty in girls and boys.

Thus, at different stages of puberty in adolescents with DM1, a physiological type of activation of the GH/IGF-1 system was established with the presence of gender characteristics with an increase in the level of GH and IGF-1 in the periods of proper puberty and late puberty. These changes were typical for both girls and boys with DM1.

An analysis of mean GH levels with regard to duration of diabetes noted an increase in its level with an increase in the duration of DM1 with high rates in adolescents with a disease duration of more than 10 years ($p_{k-w}<0,05$). The level of IGF-1 in adolescents of both sexes, on the contrary, tended to decrease against the background of an increase in the duration of diabetes ($p_{k-w}<0,05$). GH and IGF-1 levels in girls who were ill for 1-5 years and more than 10 years were higher than in boys (Figures 3 and 4).

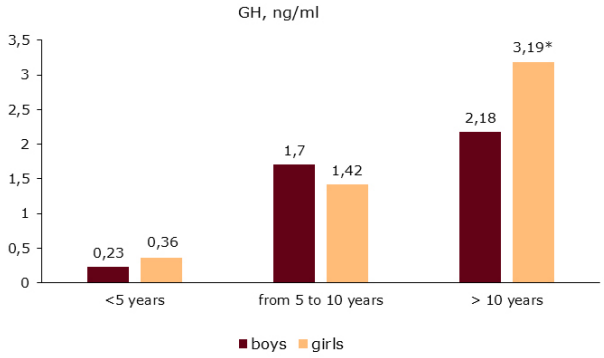

Fig. 3. GH level in patients with type 1 diabetes depending on the duration of the disease

Note:

** – the significance of the differences between the indicators of the group of boys and the group of girls according to the Wilcoxon-Mann-Whitney test ($p_u<0,05$).*

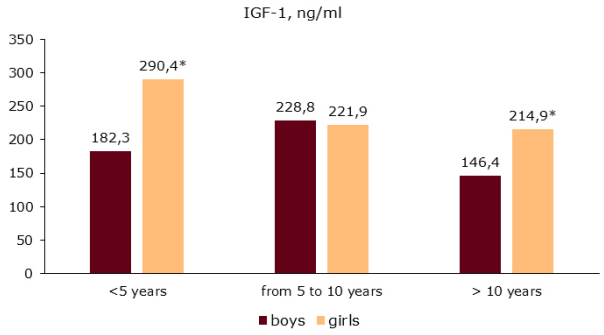

Fig. 4. IGF-1 level in patients with type 1 diabetes depending on the duration of the disease

Note:

** – the significance of the differences between the indicators of the group of boys and the group of girls according to the Wilcoxon-Mann-Whitney test ($p_u<0,05$).*

Analysis of GH taking into account the duration of the disease in patients of all ages showed that an increase in GH was observed with a duration of DM1 more than 10 years in boys aged 14-15 years (actual puberty) and in girls aged 16-18 years (late puberty). During pre- and early puberty (9-13 years), the duration of the disease did not significantly affect the production of GH (Table 1).

IGF-1 parameters also in the prepubertal and early pubertal period, regardless of gender, did not change with an increase in the duration of diabetes and were significantly higher in girls. During the period of proper puberty (14-15 years) and late puberty (16-18 years), in children with an increase in the duration of the disease, there was a decrease in the level of IGF-I (p_{k-w}<0,05). In girls, a significant decrease in IGF-1 (p_{k-w}<0,05) with an increase in the duration of DM1 was recorded only in the group of female patients aged 16-18 years, that is, in the period of late puberty (Table 2).

When studying the state of GH/IGF-1, gender-specific changes in the production of GH and IGF-1 were revealed at various HbA1c levels. In the case of suboptimal glycemic control, boys had higher GH values, while girls, on the contrary, had lower values (p_{k-w}<0,05). In the state of decompensation, the GH level in girls was the highest (p_{k-w}<0,05) and significantly exceeded the indicators in boys.

In boys, the highest GH level, which significantly exceeded its value in girls (p_u<0,05), was determined in the state of subcompensation (p_{k-w}<0,05) (Figure 5.)

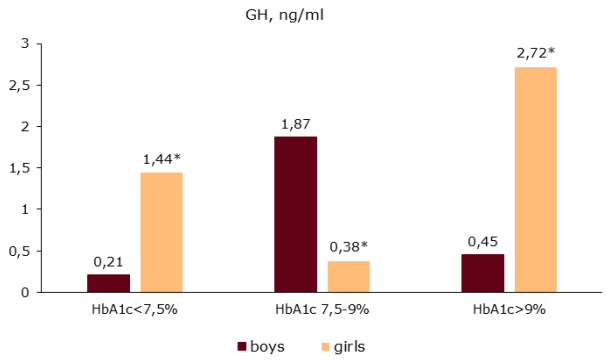

Fig. 5. GH level in patients with type 1 diabetes depending on the level of HbA1c (%)

Note:

** – the significance of the differences between the indicators of the group of boys and the group of girls according to the Wilcoxon-Mann-Whitney test (p_u<0,05).*

The level of IGF-1 in patients with DM1 was not significantly affected by the state of compensation of carbohydrate metabolism in terms of HbA1c. Regardless of the state of carbohydrate metabolism compensation, girls had higher IGF-1 levels than boys (pu<0,05).

Table 1. The content of GH in the blood of DM patients 9-18 years old depending on the duration of the disease (M±m)

Age, years	Duration of the disease					
	From 1 to 5 years		From 5 to 10 years		More than 10 years	
	boys (n=25)	girls (n=32)	boys (n=40)	girls (n=42)	boys (n=15)	girls (n=14)
9-11	0,21±0,03	0,37±0,10	0,24±0,10	0,32±0,19	–	–
12-13	0,29±0,06	0,25±0,06	0,29±0,08	0,93±0,66	–	–
14-15	0,21±0,02*	0,36±0,05	1,06±0,41	0,29±0,18	9,33±8,99	0,22±0,01
16-18	0,25±0,15*	0,98±0,05	3,33±3,21	2,39±2,14	0,14±0,05	5,17±4,27

Note:

** – the significance of the differences between the indicators of the group of boys and the group of girls according to the Wilcoxon-Mann-Whitney test (p_u<0,05).*

Table 2. The content of IGF-1 in the blood of DM patients aged 9-18 years, depending on the duration of the disease (M±m)

Age, years	Duration of the disease					
	From 1 to 5 years		From 5 to 10 years		More than 10 years	
	boys (n=25)	girls (n=32)	boys (n=40)	girls (n=42)	boys (n=15)	girls (n=14)
9-11	172,1±21,6*	212,8±38,8	121,5±22,5*	217,8±37,9	–	–
12-13	144,5±0,1*	325,9±50,3	187,5±24,9*	355,9±100,4	–	–
14-15	216,9±119,1	387,4±7,95	282,3±51,3	176,1±29,8	146,2±14,1*	273,9±16,6
16-18	201,6±8,7*	436,7±60,6	233,9±51,4	209,4±39,4	146,5±20,9	175,6±52,6

Note:

** – the significance of the differences between the indicators of the group of boys and the group of girls according to the Wilcoxon-Mann-Whitney test (p_u<0,05).*

Thus, in the state of decompensation, the guys showed a tendency to a decrease in GH, and in girls, to an increase in GH and IGF-1 (Figures 5 and 6).

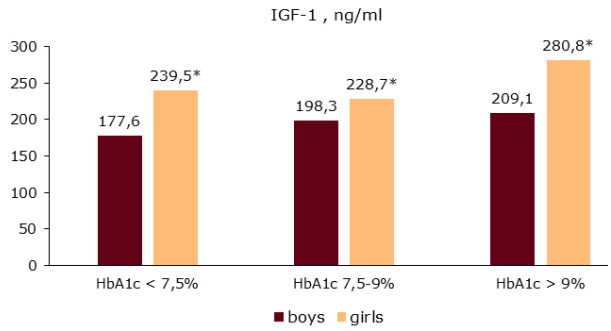

Fig. 6. The level of IGF-1 in patients with type 1 diabetes depending on the level of HbA1c (%)

Note:

** – the significance of the differences between the indicators of the group of boys and the group of girls according to the Wilcoxon-Mann-Whitney test (p_u<0,05).*

These changes may be associated with an insufficient dose of exogenous insulin, which causes decompensation of the disease, and an increase in IGF-1 and GH is a response to hypoinsulinemia. It is noteworthy that changes in GH production were characteristic of boys aged 14-15 years and girls aged 16-18 years, in whom the increase in GH levels was at the level of 4,22±3,1 ng/ml and 5,05±3,04 ng/ml, respectively. An increase in IGF-1 production was recorded in boys with optimal glycemic control at the age of 14-15 (304,0±52,6 ng/ml), and in girls at the age of 12-13 with decompensation of the disease.

Discussion

According to the results obtained, the features of the functional state of the GH/IGF-1 system in adolescents with DM1 depend on gender, the level of sexual development, the duration of diabetes, and the state of carbohydrate metabolism compensation, which coincides with the data of domestic and foreign studies.

Our study demonstrated that, especially during puberty, patients with type 1 diabetes show some changes in the GH/IGF-1 axis, characterized by GH hypersecretion, a decrease in serum IGF-1 levels, consistent with literature data (Massa et al., 1993; Day et al., 1998).

The decrease in serum IGF-1 levels may be associated with low intraportal insulin concentrations: in fact, exogenous subcutaneous insulin therapy is not able to replace pancreatic insulin secretion in the portal circulation (Shishko et al., 1994).

As proven in previous studies, the deployment of manifestations of puberty in healthy adolescents is accompanied by a decrease in insulin sensitivity along with an increase in the activity of the GH/IGF-1 system. The high concentration of GH in the blood serum is one of the most important factors contributing to the development of insulin resistance typical of 1DM at puberty (Radetti et al., 1997; Fowelin et al., 1991). In addition, insufficient intraportal insulin concentration leads to an increase in the production of IGFBP-3, which inhibits the bioactivity of IGF-1 (Radetti et al., 1997; Clark et al., 1998). These processes acquire the greatest intensity at stages III-IV according to Tanner, both in boys and girls (Nambam, & Schatz, 2018).

According to the results of modern scientific studies of changes in the functional state of the GH/IGF-1 system, in patients with DM1, an increase in IGF-1 production similar to healthy peers with an increase in the degree of puberty was revealed, but their indicators were significantly lower than those corresponding to the stage of puberty in the control (Cinaz et al., 2006). As in our study, an increase in IGF-1 levels during puberty was also found in 92 Spanish children (Munoz, et al., 1996).

Some studies have established a certain sexual dimorphism in IGF-1 production. As in our study, significantly lower levels of IGF-1 were determined in children, which was combined with the development of growth retardation, especially in the case of prolonged decompensation (Bizzarri et al., 2014). Girls with DM1 had significantly higher levels of GH and IGF-1, and among them there was a smaller percentage of growth retardation (Turchina et al., 2019).

Along with this, it was found that in adolescents with DM 1, these changes are dependent on the level of HbA1c, especially with regard to the increase in GH levels with excessively low or high levels of HbA1c. At an optimal level of compensation, the increase in GH levels is explained by the authors as possible hypoglycemic conditions and corresponding metabolic disorders (Clark et al., 1998), often observed due to the lability of the disease in childhood and adolescence.

Thus, our data to a certain extent agree with the data of modern literature, but require clarification regarding the factors affecting the functional state of the GH/IGF-1 system in adolescents with DM1. The above indicates the need to continue scientific research in this direction.

Conclusion

1. In adolescents with DM1, a physiological type of activation of the GH/IGF-1 system was established with an increase in its activity during the period of puberty itself.

2. Sexual characteristics were determined in the levels of GH and IGF-1 at the stages of puberty. Girls had higher levels of IGF-1 than boys, espe-

cially during prepuberty. In the period of prepuberty and puberty itself, GH indicators were higher in boys, and in late puberty – in girls.

3. It has been established that in girls and boys with an increase in the duration of diabetes, there is an increase in the level of GH and a decrease in IGF-1. The state of the GH/IGF-1 system in patients with different duration of DM1 is affected by the level of sexual development at the time of the examination and the gender of the child. In children aged 14-18 years (the period of proper and late puberty), with an increase in the duration of the disease, there is an increase in the level of GH (p_{k-w}<0,05) and a decrease in IGF-1 (p_{k-w}<0,05). In girls, an increase in GH (p_{k-w}<0,05) and a decrease in IGF-1 (p_{k-w}<0,05) with an increase in the duration of DM1 were recorded only in the group of patients aged 16-18 years (late puberty).

4. The relationship between HbA1c and GH and IGF-1 levels has gender specifics: in the state of decompensation, the guys showed a tendency to decrease in GH, and in girls – to increase GH and IGF-1.

Author's contribution

Conceptualization, S.T.; methodology, S.T.; check, S.T. and S.K.; formal analysis, L.N.; investigation, S.T.; data curation, L.N. and O.V.; writing – rough preparation, S.T.; writing – review and editing, S.K. and Yu.K.; supervision, S.T.; project administration, S.T. All authors have read and agreed with the published version of the manuscript.

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Conflicts of Interests

The authors declare no conflict of interest.

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