

Thyroid dysfunction and the state of the GH/IGF-1 system in adolescents with type 1 diabetes mellitus

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Abstract

Purpose: to determine the relationship between the functional state of the pituitary-thyroid system and the growth hormone/insulin-like growth factor type 1 (GH/IGF-1) system in adolescents with type 1 diabetes mellitus (DM1) during puberty.

Material & Methods: 165 children (85 girls (51,5%) and 80 boys (48,5%) aged 8 to 18 years old who have DM1 and are in the endocrinology department of the State Institution "Institute for Children and Adolescents Health Care at the National Academy of Medical Sciences of Ukraine" (SI "ICAHC NAMS"). The criterion for inclusion in the study was the duration of DM1 for more than one year (from 1 to 16 years). The level of thyrotropin (TSH), free fractions of thyroxine (fT₄) and triiodothyronine (fT₃), GH and IGF-1 was determined and the ratio (fT₃/fT₄ and TSH/fT₄) was calculated. 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); functional state of the pituitary-thyroid system: (euthyroidism (TSH/fT₄ < 0,19 c.u.), minimal thyroid insufficiency (0,19 c.u. ≤ TSH/fT₄ ≤ 0,29 c.u.), with subclinical hypothyroidism (TSH/fT₄ > 0,29 c.u.) (Turchina et al., 2016).

Results: it was found that among adolescents with DM1, almost every child has signs of thyroid dysfunction. An increase in the fT₃ level and the fT₃/fT₄ ratio were more often diagnosed. The frequency of increase in the level of TSH and the ratio of TSH/fT₄ fluctuated widely and depended on the sexual development of the child. More often, signs of SGH were determined during early puberty (23,5%), which probably exceeded those in prepubertal (16%, Pφ < 0,05), proper (8,9%, Pφ < 0,05) and late puberty (6,1%, Pφ < 0,05). These changes indicate the tension of the thyroid system at the beginning of puberty, which is the basis not only for an increase in the risk of thyroid pathology in this period of puberty, but also for violations of physical and sexual development.

Conclusions: almost a third of adolescents with DM1 had signs of thyroid insufficiency of varying degrees, which was most often determined during early puberty. The progression of thyroid insufficiency was accompanied by a decrease in the level of GH and IGF-1.

Key words: adolescents, type 1 diabetes mellitus, growth hormone, insulin-like growth factor type 1, pituitary-thyroid system.

Анотація

Тиреоїдна дисфункція та стан системи GH/IGF-1 у підлітків, хворих на цукровий діабет 1 типу. Мета: визначити взаємозв'язок між функціональним станом гіпофізарно-тиреоїдної системи та системи гормону росту/інсуліноподібного фактору росту 1 типу (GH/IGF-1) у підлітків, хворих на цукровий діабет 1 типу



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(ЦД1) в період пубертату. **Матеріал і методи:** 165 дітей (85 дівчат (51,5%) і 80 хлопців (48,5%) від 8 до 18 років, які хворіють на ЦД1 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 тиреотропіну (TSH), вільних фракцій тироксину (fT_4) та трийодтироніну (fT_3), GH та IGF-1 та розраховано співвідношення (fT_3/fT_4 та TSH/fT_4). Учасники дослідження були розділені на групи залежно від рівня статевого розвитку (T1-T4) на момент дослідження, який оцінювався за шкалою Marshall & Tanner (Marshall & Tanner, 1969; Marshall & Tanner, 1970); функціонального стану гіпофізарно-тиреоїдної системи: (еутиреоз ($TSH/fT_4 < 0,19$ ум. од.), мінімальна тиреоїдна недостатність ($0,19 \text{ с.у.} \leq TSH/fT_4 \leq 0,29 \text{ с.у.}$), з субклінічний гіпотиреоз ($TSH/fT_4 > 0,29 \text{ с.у.}$) (Turchina et al., 2016). **Результати:** встановлено, що серед підлітків із ЦД1 майже кожна дитина має ознаки тиреоїдної дисфункції. Найчастіше діагностували збільшення рівня рівню fT_3 та співвідношення fT_3/fT_4 . Частота збільшення рівня TSH та співвідношення TSH/fT_4 коливалась в широких межах та залежала від статевого розвитку підлітка. Найчастіше ознаки SGH визначали в період раннього пубертату (23,5%), що вірогідно перевищувало показники в препубертаті (16%, $P < 0,05$), власно (8,9%, $P < 0,05$) та пізньому пубертаті (6,1%, $P < 0,05$). Зазначені зміни свідчать про напруження тиреоїдної системи на початку пубертату, що є підґрунтям не тільки для збільшення ризику формування тиреоїдної патології саме в цьому періоді пубертату, але й порушення фізичного та статевого розвитку. **Висновки:** майже третина підлітків із ЦД1 мала ознаки тиреоїдної недостатності різного ступеню, яку найчастіше визначали в період раннього пубертату. Прогресування тиреоїдної недостатності супроводжувалось зменшенням рівня GH та IGF-1.

Ключові слова: підлітки, цукровий діабет 1 типу, гормон роста, інсуліноподібний фактор росту 1 типу, гіпофізарно-тиреоїдна система

Introduction

Growth is a multifactorial process influenced by a significant number of medical and social factors (Murray & Clayton, 2013; Sotnikova-Meleshkina et al., 2022), among which thyroid hormones (TH) occupy a special place. TH regulates vital body processes from fetal cell agglomeration after conception (Murray & Clayton, 2013) to maintenance of cellular energy and metabolism in adulthood (Forhead & Fowden, 2014).

TH synthesis is stimulated by the secretion of thyrotropin-releasing hormone from the hypothalamus, which in turn stimulates the anterior pituitary

gland to synthesize and secrete thyrotropin or thyroid-stimulating hormone (TSH). TSH acts directly on the thyroid gland to stimulate TH synthesis, completing the so-called hypothalamic-pituitary-thyroid axis (Feldt-Rasmussen et al., 2021).

For optimal thyroid function, it is necessary to supply not only iodine, but also other nutrients, among which selenium occupies a special place. Selenium is critical for the selenoprotein-iodothyronine deiodinase enzymes, which catalyze the removal of iodide from T4 in the conversion of T4 to T3. Selenoproteins also play an important antioxidant role in the thyroid gland (Ventura et al., 2017; Turchyna et al., 2022a).

It has now been proven that TH act on almost every cell of the body, affecting growth processes during the life cycle, both directly affecting the development of bones and skeleton (Laron, Z., 2003; Sellitti & Suzuki, 2014), and indirectly, affecting to the GH/IGF system. Growth hormone (GH) and insulin-like growth factors (IGF) promote growth by acting on organs associated with key metabolic effects, including the liver, skeletal muscle, and bones (Ipsa et al., 2019).

Through the GH/IGF somatotropic axis, GH promotes the synthesis and secretion of IGFs, which are proteins normally produced in the liver in response to GH stimulation (Silva et al., 2009). IGFs, in turn, enhance cell proliferation and differentiation (Hellström et al., 2016).

GH also stimulates the production of various growth factors (epidermal growth factor, nerve growth factor and erythropoietin). The physiological mechanisms that ensure the growth of the child arise through important and complex relationships between TH, GH and IGF. TH influences GH expression and action (Robson et al., 2002; Zimmermann, 2011), and GH secretion is dependent on normal thyroid function (Laron, Z., 2003; Cabello & Wrutniak, 1989).

In addition, TH synthesis requires the presence of IGF-1 (Sellitti & Suzuki, 2014), and IGF-1 itself is required for the anabolic effect of T3 (Laron, Z., 2003). In addition, GH accelerates the peripheral conversion of T_4 to T_3 (Sato et al., 1977).

During childhood, from six months and three years until puberty, the GH/IGF-1 and TH axis become more influential on growth, and during puberty, GH and IGF-1 concentrations increase significantly in both male and female bodies (Murray & Clayton, 2013).

Among the leading factors that can disrupt the hormonal support of the somato-sexual development of a child, there are endocrine diseases, among which DM1 occupies a special place. A comprehensive examination of children and adolescents with DM1 identified a violation of the course of puberty and the formation of menstrual function in girls. In 2/3 of the surveyed there was a formation of disharmonic development (Turchina et al., 2019).

When studying the functional state of the GH/IGF-1 system, it was found that in adolescents with DM1 during the period of puberty proper, an increase in the level of GH and IGF-1 occurred, but their indicators were lower than in healthy peers. It has also been proven that 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 (Turchina et al., 2022b).

At the same time, convincing data were obtained on the high incidence of thyroid pathology in adolescents with DM1, the frequency of which depended on gender, the nature of physical development and the course of puberty, the age of manifestation of DM1, and compensation for diabetes. Thyropathies were more often detected in adolescents with DM1 manifestation in early puberty (80.0%) with a duration of diabetes from 5 to 10 years, with insufficient compensation for carbohydrate metabolism and disharmonious physical development (Turchina et al., 2022c; Kostenko, 2022).

That is why it is important to conduct scientific research aimed at determining the relationship between the functional state of the thyroid system and the GH/IGF-1 system in adolescents with DM1.

Purpose of the study. To determine the relationship between the functional state of the pituitary-thyroid system and the growth hormone/insulin-like growth factor type 1 (GH/IGF-1) system in adolescents with type 1 diabetes mellitus (DM1) during puberty

Material and methods of research

Participants

165 children (85 girls (51.5%) and 80 boys (48.5%) from 8 to 18 years old who have DM 1 and are in the endocrinology department of the State Institution "Institute for Children and Adolescents Health Care at the National Academy of Medical Sciences of Ukraine" (SI "ICAHC NAMS"). The criterion for inclusion in the study was the duration of T1DM for more than one year (from 1 to 16 years). Parents and patients provided written informed consent to participate in the study.

Procedure

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 SI "ICAHC NAMS".

The analysis of the level of TSH, fT_4 , fT_3 , GH and IGF-1, the ratio of fT_3/fT_4 and TSH/fT_4 . GH and IGF-1 was performed taking into account the level of sexual development at the time of the examination and the functional state of the pituitary-thyroid system. The study participants were divided

into groups based on:

- the level of sexual development (T1-T4) at the time of the study, assessed by the scale of Marshal, W.A. and Tanner, J.M. (Marshall & Tanner, 1969; Marshall & Tanner, 1970);
- functional state of the pituitary-thyroid system: (euthyroidism ($TSH/fT_4 < 0,19$ c.u. – conditional units – c.u.), minimal thyroid insufficiency ($0,19 \text{ c.u.} \leq TSH/fT_4 \leq 0,29$ c.u.), subclinical hypothyroidism ($TSH/fT_4 > 0,29$ c.u.) (Turchina et al., 2016).

Methods

Blood serum test. Quantitative determination of TSH, fT_4 , fT_3 , GH and IGF-1 in blood serum was performed using enzyme immunoassay (ELISA) on a Rayto RT-2100C photometer using commercial kits from Granum (Kharkiv).

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 (SD) for summation of 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) or the Kruskal-Wallis test (p_{k-w}) for three or more groups. The significance of percentage differences was assessed using the Fisher angular transform (Pφ). The significance level was set at $p < 0,05$.

Results of the study

Accordingly, according to the previously obtained data, it was found that at the stages of puberty, changes in the functional state of the pituitary-thyroid system occur both in healthy adolescents and in patients with endocrine pathology. It has been proven that during puberty, the percentage of adolescents with signs of thyroid dysfunction and thyroid hormone deficiency of varying degrees probably increases (Turchina et al., 2010), which can affect the hormonal supply of puberty. Especially in adolescents with such a severe pathology as DM1.

Taking into account the close relationship between the level of sexual development and the functional state of the thyroid system, the parameters of the thyroid profile in patients with DM1 were determined, taking into account the level of sexual development according to the scale of Marshal, W.A. and Tanner, J.M.

According to the results obtained, the highest TSH levels were recorded during early puberty (T2), which occurred against the background of a decrease in the fT_4 level, an increase in its conversion to T3, and an increase in the TSH/fT_4 ratio (Figure 1).

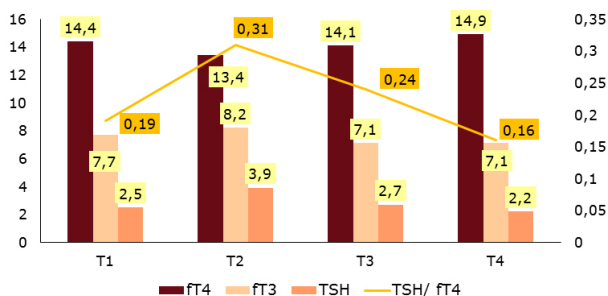


Figure 1. Indicators of the thyroid profile in patients with type 1 diabetes depending on the stage according to Tanner

In the individual analysis of the thyroid profile indicators, we used the evaluation criteria developed during the examination of healthy children and adolescents with harmonious physical and sexual development. According to the specified criteria, the ranges of optimal, increased or decreased values were allocated (Turchina et al., 2016).

According to the results of individual analysis, only half of the examined patients with DM1 had optimal TSH values. In a third, the TSH level was moderately increased, and in 10% of patients it was more than 4 μ IU/ml.

More often, an increase in the level of TSH was diagnosed during early puberty (Figure 2).

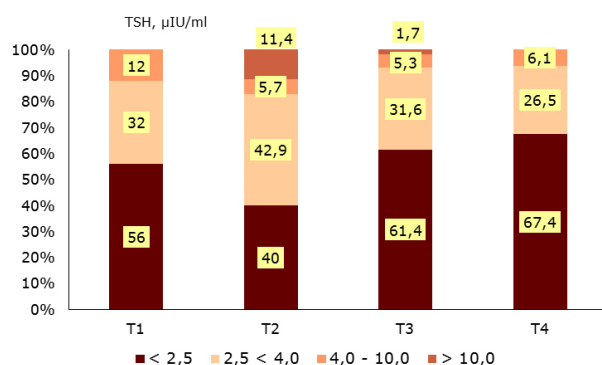


Figure 2. The frequency of TSH indicators of different levels in patients with type 1 diabetes depending on the stage according to Tanner

A more objective assessment of the state of the pituitary-thyroid system is an assessment using the TSH/ft₄ ratio. This indicator reflects not only the activation of pituitary hormones during puberty, but also the functional state of the thyroid system as a whole. That is, the responses of the thyroid gland to pubertal restructuring. An individual analysis of the TSH/ft₄ ratio indicators indicated the presence of minimal thyroid insufficiency (MTI) in 23,8% of patients and SCH in 12,2%. In early puberty (T2), signs of thyroid insufficiency were determined in every second adolescent with DM1. It is during this period that the largest percentage of patients with subclinical hypothyroidism (SCH) is observed. Thus, among adolescents with DM1 at the onset of puberty, every second child had signs

of MTI or SCH (Figure 3).

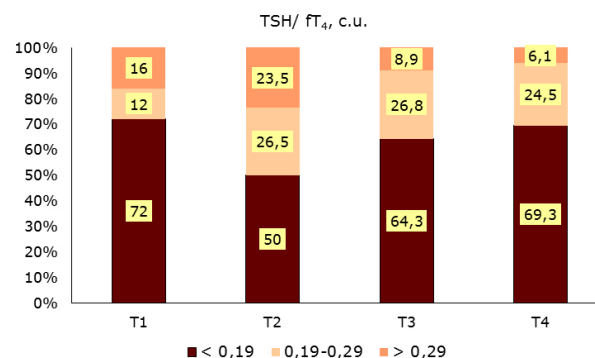


Figure 3. The frequency of TSH/ft₄ indicators of different levels in patients with type 1 diabetes depending on the stage according to Tanner

It is also noteworthy that 95% of modern patients with DM1 had increased ft₃/ft₄ ratios and 100% during early puberty. It is the increase in the ft₃ level and the ft₃/ft₄ ratio that may indicate a state of iodine deficiency with a high risk of developing iodine deficiency diseases. Especially in the absence of group and individual prophylaxis in iodine-deficient regions.

In order to determine the relationship between thyroid profile indicators and the GH/IGF-1 system, an analysis of the level of GH and IGF-1 was carried out, taking into account TSH indicators. The results obtained indicate an inverse relationship between GH and TSH levels. That is, the lowest GH values were recorded in the group of adolescents with overt hypothyroidism. As for IGF-1, the situation is rather ambiguous. It should be noted that in this case we did not take into account the level of TH and the appointment of replacement therapy with levothyroxine drugs. It is TH that influence the state of the GH/IGF-1 system and stimulate the production of IGF-1 (Figure 4).

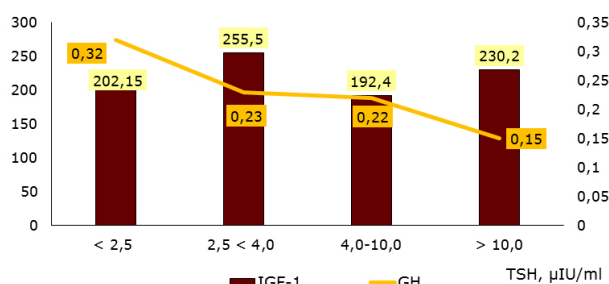


Figure 4. Indicators of GH and IGF-1 in patients with type 1 diabetes depending on the level of TSH

Analysis of the level of GH and IGF-1 in the groups of adolescents with euthyroidism, MTI and SCH determined a significant decrease in the level of IGF-1 in the case of progression of thyroid insufficiency, which may contribute to the formation of disharmonious physical development in patients with diabetes mellitus (Figure 5).

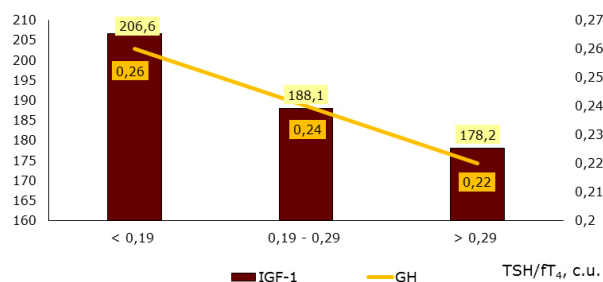


Figure 5. Indicators of GH and IGF-1 in patients with type 1 diabetes depending on the level of TSH/ft₄, c.u.

Discussion

When performing a scientific study, it was found that among adolescents with DM1, almost every child has signs of thyroid dysfunction. An increase in the ft₃ level and the ft₃/ft₄ ratio were more often diagnosed. The frequency of increase in the level of TSH and the ratio of TSH/ft₄ fluctuated widely and depended on the sexual development of the adolescent. More often signs of SGH were determined during early puberty (23,5%), which probably exceeded the indicators in prepuberty (16%, Pp<0,05), puberty proper (8,9%, Pp<0,05) and late puberty (6,1%, Pp<0,05). These changes indicate tension in the thyroid system at the beginning of puberty, which is the basis not only for an increased risk of thyroid pathology in this period of puberty (Turchyna et al., 2022d), but also for physical and sexual development disorders (Turchina et al., 2019).

The obtained results confirm the current data on changes in the functional state of the pituitary-thyroid system in patients with DM1 during pubertal hormonal changes with the formation of a state of dythyroidism (Biondi et al., 2019; Fatourechi et al., 2017).

Previous studies conducted at the SI "ICAHC NAMS" indicate that the vast majority of patients have multivariate dythyroidism associated with a complex of negative factors with varying degrees of significance, but, of course, the determining factor in the formation of thyroid dysfunction in DM1 is the state of carbohydrate metabolism compensation (Budrejko, 2011).

Among the mechanisms for the development of dysthyroidism in type DM1 in children and adolescents, a violation of thyroxin deiodination can be distinguished, a mediocre sign is a significant frequency of its elevated level along with a frequent decrease in free and, especially, reverse T₃ levels. Disturbances in the transport of thyroid hormones against the background of diabetes in children and adolescents play an insignificant role in the formation of dythyroidism.

Obviously, such disorders are the basis for the frequent formation of thyroid pathology in patients with DM1, which, according to previous studies, was detected in the majority (75%) of sick children

and adolescents, including 23.6% – autoimmune thyroiditis, that requires mandatory screening of thyroid pathology in this group of patients. At the same time, the evaluation of ultrasound data and the thyroid hormone profile should be carried out taking into account certain features inherent in patients of childhood and adolescence. So, the study of the functional state of the thyroid gland is advisable only when compensating for carbohydrate metabolism with the obligatory determination of not only TSH, but also the levels of free T₃ and T₄. It should also be taken into account that in a significant part of children and adolescents with diabetes, even without thyroid pathology, signs of dystyrosis are detected, the most common variants of which are an increase in the content of TSH against the background of normal thyroid hormones, an isolated decrease in the level of ft₃ and an increase in the level of ft₄, which was stated earlier (Budrejko, 2011).

According to our data, it was confirmed that almost every third adolescent (36.0%) with DM1 has signs of thyroid insufficiency of varying degrees. However, in modern adolescents with DM1, an increased level of ft₃ is probably more often diagnosed, which may be a manifestation of iodine deficiency during puberty. It may be a consequence of the cessation of mass and individual prevention of iodine deficiency, which was negatively affected by such social factors as the Covid-19 pandemic and military operations on the territory of Ukraine. All this contributes to an increase in the frequency of adolescents with disorders of the pituitary-thyroid system, especially during puberty. It is also noteworthy that the percentage of DM1 patients during puberty not only outweighs population indicators, but is also probably higher than in patients with DM1 in previous years. Especially during early puberty, when active hormonal changes occur and the need for thyroid hormones increases significantly.

Our results confirm the relationship between the pituitary-thyroid system and the level of GH/IGF-1 and the impact of thyroid dysfunction on the state of GH/IGF-1 (Robson et al., 2002; Laron, 2003).

It has been proven that during the formation of thyroid insufficiency, there is a change in the production of GH and IGF-1, which affects not only the physical development of a child with DM1, but also the formation of complications of diabetes (Nambam & Schatz, 2018).

The results obtained are the basis for continuing the study of the impact of disorders in the state of the thyroid system and the GH/IGF-1 system in the formation of disharmonious physical development in adolescents with DM1.

Conclusions

1. Almost every third adolescent (36.0%) with DM1 has signs of thyroid insufficiency of varying degrees.

2. Almost all adolescents with DM1 (95.0%) are diagnosed with an increased level of fT_3 , which may be a manifestation of iodine deficiency during puberty.

3. More often, disorders of the pituitary-thyroid system are diagnosed during early puberty, when the number of patients with signs of hypothyroidism is likely to increase (23,5%).

4. The progression of thyroid insufficiency is accompanied by a decrease in the level of GH and IGF-1, which may be the basis for the formation of disharmonious physical development.

Author's contribution

Conceptualization, S.T.; methodology, S.T.; check, S.T.; formal analysis, L.N.; investigation, S.T.; data curation, L.N., T.K. and O.V.; writing – rough preparation, S.T.; writing – review and editing, S.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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