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PREVENTION AND CORRECTION OF THYROID DYSFUNCTION IN ADOLESCENTS WITH TYPE 1 DIABETES AT PUBERTY STAGES*

S. I. Turchina, T. P. Kostenko, L. D. Nikitina, O. V. Varodova, G. V. Kosovtsova, S. O. Chumak, O. V. Shushliapina, N. V. Filipova, L. P. Levchuk, O. I. Yudchenko

SI «Institute for Children and Adolescents Health Care of the National Academy of Medical Sciences of Ukraine», Kharkiv, Ukraine
svetlanaturchina00@gmail.com

The study of the thyroid gland (TG) function during puberty period is of special interest due to the important role of its hormones in the development of the reproductive system [1]. In the period of pre-, and especially, early puberty, even in practically healthy adolescents, the thyrotropin (TSH) levels increase and signs of thyroid insufficiency of varying degrees may develop due to hormonal changes during puberty [2]. In the background of the increased need for thyroid hormones and increased iodine uptake by the thyroid gland, the urinary iodine excretion increases leading to the formation of relative iodine deficiency even under conditions of normal iodine intake. In the case of iodine deficiency in the environment, its obvious lack during puberty only worsens and can contribute to dysfunction of the pituitary-thyroid system with subsequent onset of thyropathies [3], which negatively affects somato-sexual development [4–6].

It should be noted that thyroid dysfunction is common not only in the presence of thyroid pathology, but also in metabolic disorders, in particular in type 1 diabetes mellitus (T1DM) [7]. It is proved that only one third of the subjects (33.3 ± 3.8)% have the physiological type of regulation of the thyroid system with normal levels of TSH, free T_3 and T_4. [8]. The relationship between the thyroid system function and the course of T1DM in children and adolescents has been identified [9].

In subclinical hypothyroidism (scHT), patients with T1DM may have deteriorating glycemic control, changes in the blood lipid spectrum towards atherosclerotic changes, which increases the risk of cardiovascular complications.

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The most common cause of hypothyroidism in children and adolescents with T1DM is autoimmune thyroiditis (AIT), the incidence of which increases during puberty due to increased antithyroid autoimmunity stress, which may lead to worsening of glycemic control caused by frequent hypoglycemia and reduced need for exogenous insulin [8, 10].

Based on epidemiological studies data, AIT and diffuse nontoxic goiter (DNTG) are most commonly detected in patients with T1DM, the frequency of which is significantly higher than in the general population [8, 11]. According to previously obtained data, 41.2% of adolescents with T1DM had thyroid pathology. Diffuse nontoxic goiter of grade I or II and AIT were most often diagnosed (17% of patients). It has been proven that the frequency of these thyropathies depended on gender, the nature of physical development and the course of puberty, the age of onset of T1DM and the compensation of diabetes. Thyropathies were most often diagnosed in adolescents with T1DM manifestation in early puberty (80.0%) with a diabetes duration of 5 to 10 years, with insufficient compensation of carbohydrate metabolism and disharmonious physical development [11, 12].

Thus, the development of dysthyroidism in patients with T1DM negatively affects not only the course of diabetes but can also contribute to impaired physical and sexual development due to the direct involvement of thyroid hormones in the processes of growth and puberty.

Aim of the study is to improve the methods of prevention and treatment of disorders of the functional state of the pituitary-thyroid system in adolescents with type 1 diabetes mellitus.

MATERIALS AND METHODS

114 patients with T1DM aged 9-16 years were examined in the clinic of SI «ICAH NAMSU». The comparison group consisted of 149 practically healthy peers with harmonious physical and sexual development. Taking into account the level of sexual development (SD) at the time of examination, adolescents of both groups were divided into subgroups:

a) prepubertal;

b) early puberty;

c) puberty.

In all adolescents, the levels of thyrotropin (TSH), free fractions of thyroid hormones (fT_4 and fT_3) were determined by the enzyme-linked immunosorbent assay and ratios (fT_3/fT_4 and TSH/fT_4) were calculated. When assessing the functional state of the thyroid gland, attention was paid to both the level of hormones and the value of their ratios, which allowed to objectify the diagnosis of thyroid dysfunction in adolescence. Euthyroidism was diagnosed at optimal TSH levels (1.2-2.5 mIU/mL) and TSH/fT_4 ratio up to 0.19 CU. Minimal thyroid insufficiency (MTI): TSH/fT_4 0.19 to 0.29 CU. Subclinical hypothyroidism (scHT): at TSH/fT_4 more than 0.29 CU. Manifest hypothyroidism with elevated TSH more than 10 mIU/mL and decreased fT_4 [5].

The studies were conducted in compliance 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. Protocol of the study was approved by the Medical Ethics Committee of the SI «ICAH NAMSU». Parents and patients provided written informed consent to participate in the study.

The results of the examination of adolescents were combined into an electronic data bank, the mathematical processing of which was carried out using the «SPSS Statistics 17.0» and «Microsoft Excel-2007» software. The median and interquartile range (Me [Lq; Uq]) were determined. To assess the significance of differences, non-parametric methods were used, such as Wilcoxon-Mann-Whitney (P_U) tests. The significance of the percentage discrepancies was assessed using the Fisher's angular transformation (Pφ). The critical significance level for testing statistical hypotheses when comparing groups was assumed to be 0.05.

RESULTS AND THEIR DISCUSSION

The analysis of the thyroid profile in patients with T1DM (main group) and in practically healthy peers (control group) with different degrees of sexual development revealed

Table 1

Thyroid status in adolescents with type 1 diabetes mellitus (main group) and healthy peers (control group) in the stages of sexual development (Me [Lq; Uq])

Parameter	Puberty period					
	prepubertal (n = 59)		early puberty (n = 83)		puberty (n = 121)	
	control group (n = 34)	patients with T1DM (n = 25)	control group (n = 49)	patients with T1DM (n = 34)	control group (n = 66)	patients with T1DM (n = 55)
TSH, mIU/mL	2.10 [1.45; 3.20]	2.20 [1.60; 3.10]	2.68 [1.60; 3.55]	2.7 [1.70; 3.75]	2.15 [1.40; 2.85]	2.20 [1.30; 3.10]
P_U		> 0.05		>0.05		>0.05
fT_4, pmol/L	16.75 [13.70; 18.30]	14.00 [12.70; 16.00]	15.10 [12.50; 17.50]	14.05 [11.90; 17.10]	14.90 [13.20; 17.00]	14.90 [12.30; 16.40]
P_U		>0.05		>0.05		> 0.05
fT_3, pmol/L	4.05 [3.20; 5.40]	7.65 [7.00; 9.30]	4.20 [3.40; 5.10]	8.15 [7.20; 8.80]	4.15 [3.40; 5.00]	7.05 [5.60; 7.60]
P_U		< 0.05		< 0.05		< 0.05
fT_3/fT_4, CU	0.27 [0.21; 0.35]	0.58 [0.40; 0.70]	0.27 [0.23; 0.34]	0.59 [0.51; 0.67]	0.27 [0.23; 0.32]	0.51 [0.42; 0.61]
P_U		< 0.05		< 0.05		< 0.05
TSH/fT_4, CU	0.11 [0.08; 0.22]	0.20 [0.11; 0.20]	0.15 [0.09; 0.20]	0.28 [0.13; 0.34]	0.14 [0.09; 0.20]	0.18 [0.10; 0.19]
P_U		< 0.1		< 0.05		> 0.05

Note.
P_U is a significance of differences in groups with the same level of sexual development.

similar trend of change of group averages during puberty (Table 1).

The highest TSH values in adolescents of both groups were recorded during early puberty, which occurred in the background of a decrease in fT_4 and an increase in the TSH/fT_4 ratio However, in patients with T1DM the levels of fT_3 and TSH/fT_4 or fT_3/fT_4 ratios were significantly higher compared to control group. Especially during early puberty. These changes indicate the stress of the thyroid system at the beginning of puberty, which is the basis not only for increasing the risk of thyroid pathology during this period of puberty, but also for the disturbances of physical and sexual development.

In the individual analysis of thyroid profile parameters using previously developed criteria [5], it was found that the optimal TSH levels were observed in 57.8% of patients with T1DM, 32.5% of patients with T1DM had MTI, 6.6% — scHT, and 3.1% — manifest hypothyroidism. The most frequent increase in TSH levels in both groups was diagnosed during early puberty (Fig. 1). However, in contrast to practically healthy peers with a similar level of puberty, in adolescents with T1DM, an increase in the TSH level above 4 mIU/mL was also found more frequently during the prepubertal period ($P\varphi < 0.05$) and during the puberty ($P\varphi < 0.05$).

In order to objectively assess the functional state of the pituitary-thyroid system, an individual analysis of the TSH/fT_4 ratio was performed. This parameter reflects not only the activation of pituitary hormones during puberty, but also the functional state of the thyroid system as a whole. That is, thyroid responses to pubertal changes. Individual analysis of TSH/fT_4 ratios showed presence of MTI in 23.8% and scHT in 12.2% of patients with T1DM. Every second adolescent with T1DM was diagnosed with signs of thyroid insufficiency during early puberty. It was during this period that the proportion of patients with the TSH/fT_4 ratio of more than 0.29 CU (23.5%) was the highest,

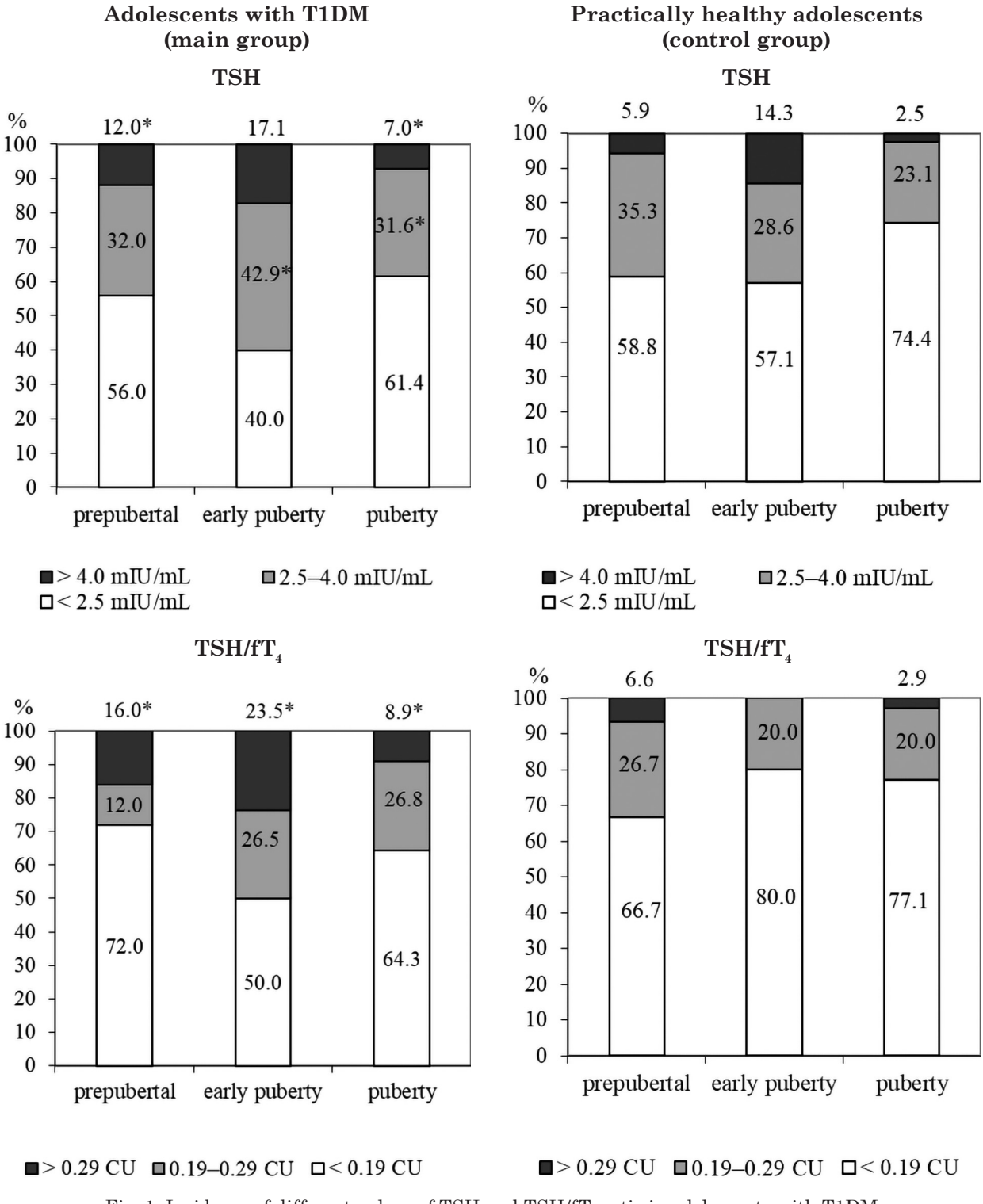

Fig. 1. Incidence of different values of TSH and TSH/fT_4 ratio in adolescents with T1DM and in adolescents of control group at the stages of sexual development.
* $p < 0.05$ significance of differences in groups with the same level of sexual development.

among whom 11.4% were diagnosed with manifest hypothyroidism. Thus, among adolescents with T1DM at the beginning of puberty, every second child had signs of MTI or scHT. This is significantly more often than in the group of practically healthy peers.

Also, noteworthy is the fact that 95% of T1DM patients had an increased fT_3/fT_4 ratio and 100% — during early puberty. It is the increase in fT_3 and fT_3/fT_4 ratio that may indicate an iodine deficiency condition with a high risk of iodine deficiency disease. Especially in

the absence of group and individual prophylaxis in iodine-deficient regions.

The obtained results confirm the current data on changes in the functional state of the pituitary-thyroid system in patients with T1DM during pubertal hormonal changes with development of dysthyroidism [8], which to some extent may be not only a consequence of metabolic changes in T1DM, but also a manifestation of absolute and relative iodine deficiency with increasing need during periods of active growth and puberty.

Thus, prevention of disorders of the pituitary-thyroid system in adolescents with T1DM in puberty involves not only achieving optimal glycemic control, but also prevention of iodine deficiency, diagnostics and correction of thyroid dysfunction.

According to the WHO guidelines, iodine deficiency prevention can be general, for population groups and individual [13]. However, in the context of wartime in Ukraine, attention should be focused on individual prophylaxis with the use of potassium iodide preparations not only in risk groups but also in the entire population of Ukraine. This is due not only to medical reasons, but also to the social aspect in wartime, when the risk of radiation threat increases. Euthyroid, iodine-adequate thyroid states are the best health protection.

General recommendations include prevention of iodine deficiency before the birth of child and at all stages of ontogeny. The daily prophylactic dose for infants is 90 μg, for children 6–12 years — 120 μg, for adolescents from 12 years — 150 μg, pregnant and lactating women receive 250 μg of potassium iodide per day [14]. Particular attention should be paid to children and adolescents with T1DM, among whom there is a significant increase in the incidence of thyropathies with signs of thyroid insufficiency. Despite some peculiarities of examination and treatment of patients with comorbid thyroid disease, there are general principles of prevention and correction of thyroid dysfunction during puberty.

The first is the individual prevention of iodine deficiency in age-appropriate prophylactic doses with the use of pharmacological preparations of potassium iodide, which are safe and effective. Iodomarin® 100 or Iodomarin® 200 can be used in different age categories, is prescribed to pregnant women and newborns, is well tolerated, and once daily intake meets the daily iodine requirement. The use of dietary supplements in patients is contraindicated, as it may have negative consequences.

Secondly, according to previously developed guidelines, examination and treatment of adolescents with suspected thyroid pathology should be performed after the achievement of carbohydrate metabolism compensation [8]. Regarding the correction of thyroid dysfunction, in case of AIT exclusion, monotherapy with potassium iodide drugs in therapeutic doses (Iodomarin® 200) or combination therapy with potassium iodide (Iodomarin® 100 or Iodomarin® 200) and levothyroxine (L-Thyroxine Berlin-Chemie) are prescribed. After achieving the euthyroid state, it is recommended to prescribe potassium iodide or Iodomarin® as monotherapy for 6 months or more (as indicated). After compensation of carbohydrate metabolism is achieved in patients with T1DM and AIT, the hypothyroidism therapy shall be started with L-Thyroxin Berlin-Chemie in adequate doses. L-thyroxin Berlin-Chemie is produced using Snap Tab technology, which ensures stable dose repeatability, is lactose-free, has different dosages and can be prescribed to patients of any age, and its packaging provides protection against sunlight and destruction of the active ingredient.

Thus, summarizing all the above, it is possible to draw the following conclusions:

- almost every third adolescent (36.0 %) with T1DM has signs of thyroid insufficiency of varying degrees;
- almost all adolescents with T1DM (95.0 %) are diagnosed with increased fT_3, which may be a manifestation of iodine deficiency during puberty;
- most often, disorders of the pituitary-thyroid system are diagnosed during early puberty, when the number of patients with signs of hypothyroidism significantly increases (23.5 %);
- prevention and correction of thyroid dysfunction is a mandatory part of the rehabilitation program for children and adolescents with T1DM.

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SI «Institute of Child and Adolescent Health of the NAMS of Ukraine», Kharkiv, Ukraine

svetlanaturchina00@gmail.com

Aim of the study is to improve the methods of prevention and treatment of disorders of the functional state of the pituitary-thyroid system in adolescents with type 1 diabetes mellitus (T1DM).

Materials and methods. 114 patients with T1DM aged 9–16 years (main group) and 149 healthy peers (control group) were examined. In all adolescents, the levels of thyrotropin (TSH), free fractions of thyroid hormones (fT_4 and fT_3) were determined by the enzyme-linked immunosorbent assay and ratios (fT_3/fT_4 and TSH/fT_4) were calculated. Analysis of the obtained values is carried out taking into account the level of sexual development of adolescents.

The results of the examination of adolescents were combined into an electronic data bank, the mathematical processing of which was carried out using the «SPSS Statistics 17.0» and «Microsoft Excel–2007» software. The critical significance level for testing statistical hypotheses was assumed to be 0.05.

Results. At the onset of puberty, adolescents in both groups experience an increase in TSH levels in the background of a decrease in fT_4 levels and an increase in the TSH/fT_4 ratio. The TSH/fT_4 and fT_3/fT_4 ratios were significantly higher in patients with T1DM than in the control group.

In the case of an individual analysis, it was found that the signs of thyroid insufficiency were most often diagnosed during early puberty among adolescents of both groups (60.0% in patients with T1DM and 43.9% in the control group, $p < 0.05$). At all stages of puberty, the incidence of patients with hypothyroidism was significantly higher among adolescents with T1DM than in the control group (prepubertal: 16.0% vs. 6.6%, $p < 0.05$, early puberty: 23.5% vs. 0%, $p < 0.05$, puberty: 8.9% vs. 2.9%, $p < 0.05$). The inclusion of potassium iodide (Iodomarin® 100 or Iodomarin® 200) and levothyroxine (L-Thyroxin Berlin-Chemie) in the treatment regimen for the prevention and treatment of thyroid dysfunction is justified.

Conclusions. In adolescents with T1DM, the proportion of patients with signs of thyroid dysfunction significantly increases due to an increase in TSH levels in the background of a decrease in fT_4 and an increase in fT_3. Most often, signs of thyroid insufficiency are diagnosed during early puberty. Prevention and correction of thyroid dysfunction is a mandatory part of the rehabilitation program for children and adolescents with T1DM.

Keywords: type 1 diabetes mellitus, adolescents, thyroid dysfunction.

ПРОФІЛАКТИКА ТА КОРЕКЦІЯ ТИРЕОЇДНОЇ ДИСФУНКЦІЇ У ПІДЛІТКІВ ІЗ ЦУКРОВИМ ДІАБЕТОМ 1 ТИПУ НА ЕТАПАХ СТАТЕВОГО ДОЗРІВАННЯ

Турчина С. І., Костенко Т. П., Нікітіна Л. Д., Вародова О. В., Косовцова Г. В., Чумак С. О., Шушляпіна О. В., Філіпова Н. В., Левчук Л. П., Юдченко О. І.

ДУ «Інститут охорони здоров'я дітей та підлітків НАМН України», м. Харків, Україна
svetlanaturchina00@gmail.com

Мета дослідження — удосконалити методи профілактики та лікування порушень функціонального стану гіпофізарно-тиреоїдної системи у підлітків, хворих на цукровий діабет 1 типу (ЦД1).

Матеріали та методи. Обстежено 114 пацієнтів із ЦД1 у віці 9-16 років (основна група) та 149 практично здорових однолітків (група порівняння). У всіх підлітків у сироватці крові імуноферментним методом визначено рівень тиреотропіну (ТТГ), вільних фракцій тиреоїдних гормонів (fT_4 і fT_3) та розраховано їх співвідношення (fT_3/fT_4 та ТТГ/fT_4). Аналіз отриманих показників проведено з урахуванням рівня статевого розвитку підлітків.

Результати обстеження об'єднано в електронний банк даних, математична обробка яких була проведена за допомогою пакетів програм «SPSS Statistics 17,0», «Microsoft Excel–2007». Критичний рівень значущості для перевірки статистичних гіпотез приймався рівним 0,05.

Результати. У підлітків обох груп на початку статевого дозрівання відбувається збільшення рівня ТТГ на тлі зменшення рівня fT_4 та збільшення співвідношення ТТГ/fT_4. Показники співвідношень ТТГ/fT_4 та fT_3/fT_4 були вірогідно більшими у хворих на ЦД1, ніж в групі порівняння.

При індивідуальному аналізі встановлено, що ознаки тиреоїдной недостатності найчастіше визначали в період раннього пубертату серед підлітків обох груп (60,0% серед хворих на ЦД1 та 43,9% — в групі порівняння, $p < 0,05$). На всіх етапах статевого дозрівання частота пацієнтів із гіпотиреозом була вірогідно більшою серед підлітків із ЦД1, ніж в групі порівняння (препубертат: 16,0% проти 6,6%, $p < 0,05$, ранній пубертат: 23,5% проти 0%, $p < 0,05$, власно пубертат: 8,9% проти 2,9%, $p < 0,05$). Обґрунтовано включення до схеми лікування препаратів калію йодиду (препарат Йодомарин® 100 або препарат Йодомарин® 200) та левотироксину (L-Тироксин Берлін-Хемі) при профілактики та лікуванні тиреоїдної дисфункції.

Висновки. У підлітків із ЦД1 вірогідно збільшується відсоток хворих, які мають ознаки тиреоїдної дисфункції завдяки підвищенню рівня ТТГ на тлі зменшення показників fT_4 та збільшення fT_3. Найчастіше ознаки тиреоїдної недостатності діагностують в період раннього пубертату. Профілактика та корекція тиреоїдної дисфункції є обов'язковою складовою реабілітаційної програми дітей та підлітків із цукровим діабетом 1 типу.

Ключові слова: цукровий діабет 1 типу, підлітки, тиреоїдна дисфункція.