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Hypothyroidism and its role in the development of disorders of carbohydrate and fat metabolism (Literature review)

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Objective: to present the results of some works demonstrating the mechanisms of the action of thyroid-stimulating hormone on the processes of regulation of carbohydrate metabolism, as well as its correlation with weight gain.
Results. A decrease in the level of thyroid hormones has an effect on the liver, thus causing changes in carbohydrate metabolism, for example, as insulin antagonists by increasing the expression of the glucose transporter type 2. An increase in the concentration of thyroid-stimulating hormone is associated with a risk of lipid and carbohydrate metabolism disorders and therefore, increased chances of developing metabolic syndrome, diabetes mellitus and other disorders of carbohydrate metabolism.
Conclusion. All this shows the importance of the problem of combined diabetes mellitus and thyroid diseases, in particular hypothyroidism.

Keywords: stimulating hormone, carbohydrate metabolism, thyroid gland, hypothyroidism, insulin resistance

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In recent years, much attention has been paid to thyroid diseases, in particular, to a condition such as hypothyroidism. The peculiarity of hypothyroidism lies in the prevalence of it as a manifesting form, and subclinical and in a rather long latent period associated with a large number of masks under which it flows. The thyroid gland is regulated by the pituitary gland through thyroid-stimulating hormone (TSH), which rises with primary hypothyroidism. TSH is produced by the anterior pituitary gland (adenohypophysis) and regulates the synthesis and output of thyroid hormones by the type of negative feedback. In addition, TSH can have another effect on the human body.

Purpose: to present the results of some works demonstrating the mechanisms of the action of thyroid-stimulating hormone on the processes of regulation of carbohydrate metabolism, as well as its relationship with an increase in body weight.

Discussion

Numerous epidemiological and experimental studies have shown a relationship between serum TSH and glucose abnormalities [8, 25].

Studies show that fasting plasma glucose levels are supported by gluconeogenesis and glycogenolysis [28].

It should be noted that the liver plays a crucial role in maintaining systemic glucose homeostasis [9, 45], participating in gluconeogenesis [47]. After eating, the liver increases glucose uptake and turns glucose into glycogen and lipids. During periods of short-term fasting, the liver produces and releases glucose, mainly due to glycogenolysis. During prolonged fasting, glycogen is depleted, and hepatocytes synthesize glucose through gluconeogenesis using lactate, pyruvate, glycerol, and amino acids [45]. A large number of studies have shown that thyroid hormones affect gluconeogenesis, glycogen metabolism and the transmission of an insulin signal through exposure to certain genes of hepatocytes. An example of such an effect is gluconeogenesis enzymes: pyruvate carboxylase and phosphoenolpyruvate carboxy kinase.

A key aspect of controlling gluconeogenesis of the liver is the transcriptional regulation of genes encoding enzymes that control the speed of processes, including the catalytic subunit of glucose-6-phosphatase (G6Pase encoded by the G6PC gene) and cytosolic phosphoenolpyruvate carboxykinase (PEPCK encoded PCK1) [34]. In mitochondria, pyruvate under the influence of pyruvate carboxylase is carboxylated with the formation of oxaloacetate [49]. PEPCK promotes decarboxylation of oxaloacetate to phosphoenolpyruvate, which is the target for triiodothyronine (T3). Moreover, T3 causes increased expression of glucose-6-phosphatase mRNA, the final enzyme of gluconeogenesis and glycogenolysis. G6Pase hydrolyzes glucose-6-phosphate into free glucose and inorganic phosphate at the final stage of glucose synthesis and neogluconeogenesis [11, 32].

There is evidence that thyroid hormones reduce the expression of matrix ribonuclein acid (mRNA) of protein kinase B, serine-threonine kinase, a product of the AKT2 gene, a key molecule involved in the transmission of an insulin signal [15]. AKT2 is involved in the synthesis of glycogen in the liver through the inhibition of glycogen synthase kinase-3, which leads to the activation of glycogen synthase.

Thus, a decrease in AKT2 activity, which in turn leads to a decrease in glycogen synthesis, is an example of the effect of thyroid hormones on the liver as antagonists of insulin. Induction of β_2-adrenergic receptor mRNA and suppression RNA of G protein inhibiting (Gi) of adenylate cyclase [15], under the influence of thyroid hormones, leads to potentiation of the glycogenolytic and gluconeogenic effects of adrenaline and glucagon. Another example of the effect of thyroid hormones on the liver as insulin antagonists is an increase in the expression of the glucose transporter type 2 (GLUT2) [48], which leads to an increase in the release of glucose from the liver to the blood. Studies have been conducted in which an increase in blood glucose levels on an empty stomach and glucose production against a background of subclinical hypothyroidism (SH) was observed. SH is a condition in which there is an increase in TSH, but the level of free thyroxine (T4) is in the normal range [17]. Despite the fact that the relationship between hypertension and glucose metabolism is controversial, a number of scientific studies have shown that the coexistence of hypertension and type 2 diabetes is quite common [10, 35, 40]. In addition, it was reported that treatment with L-T4 in patients with hypertension significantly reduces the level of glycated hemoglobin, fasting glucose and after eating, and also increases insulin sensitivity [8, 44].

Studies have also been conducted that indicate that blocking TSH receptors leads to a decrease in glucose [46]. These data indicate that TSH can play an important role in glucose metabolism. However, the molecular mechanism by which TSH affects the level of circulating glucose has not been fully elucidated.

Epidemiological data showed that an increase in TSH is associated with hyperinsulinemia and insulin resistance [6, 16, 26, 36]. Thus, TSH can help increase the level of glucose in the blood using several mechanisms.

TSH acts via the classical pathway cyclic adenosine monophosphate (cAMP) / protein kinase A (PKA), and the cAMP re-

sponse element-binding protein (CREB) coactivator (CREB-regulated transcription coactivator 2 - CRTC2) regulates glucose homeostasis. TSH increases CRTC2 expression through the TSH / cAMP / PKA pathway, which in turn regulates gluconeogenic liver genes. TSH stimulates the dephosphorylation of CRTC2, activating CRTC2 via the TSH / cAMP / PKA pathway and leading to the formation of the CRTC2:CREB complex, as well as increasing hepatic gluconeogenesis.

In addition, the effect of T3 on liver glucose metabolism through the hypothalamus has been described, regardless of the level of plasma hormones that affect carbohydrate metabolism [23]. By exerting a selective effect on the paraventricular nucleus of the hypothalamus, T3 leads to an increase in glucose synthesis and an increase in its release into the blood.

This effect is realized regardless of the concentration of T3, insulin and corticosteroids in the blood. The indicated effects are realized through sympathetic fibers that innervate hepatocytes.

The decrease in free T4 concentration is apparently associated with an increase in insulin resistance and the development of metabolic syndrome, which contributes to an increase in cardiovascular risk [22, 27].

In addition to the above mechanisms, an increase in TSH level can be associated with other characteristics of the patient's condition, such as overweight, which can participate in the development and course of diabetes mellitus. Obesity is one of the manifestations of diabetes mellitus, as well as a predictor of general mortality worldwide [5, 21, 31]. Over the past decades, the prevalence and incidence of it has been steadily growing [20].

Thyroid function also plays an important role in food intake [38]. A number of studies have been conducted that have shown such a relationship. A study by Tiller et al. demonstrated a pronounced positive correlation between the concentration of TSH and the waist circumference and the ratio of the waist circumference to the circumference [42] in a large group of the German population. During a Turkish study, a group of 111 adolescents with increased body weight and 42 healthy subjects presented data showing that obese patients had higher TSH concentrations that positively correlated with total cholesterol, low density lipoprotein cholesterol (LDL), triglycerides and fasting insulin concentrations [39].

Similar findings were made by Norwegian researchers who, having examined the medical records of 30,000 patients without concomitant thyroid disease, showed that, along with an increase in TSH concentration (still within the generally accepted reference range for the population), a statistically significant increase in the concentration of total cholesterol, LDL cholesterol, triglycerides and a decrease in the concentration of high density lipoprotein cholesterol (HDL) [3]. On the other hand, Radetti et al. in a retrospective study of 833 adolescents, it was shown that elevated TSH levels in obese adolescents can negatively affect the heart status of patients due to higher total cholesterol and higher blood pressure [37].

Therefore, most researchers agree that the higher the concentration of thyrotropin, the greater the disruption of carbohydrate metabolism (higher glucose concentration on an empty stomach and after an oral glucose tolerance test), which is accompanied by an increase in cardiovascular risk due to increased concentration total cholesterol, LDL cholesterol and triglycerides.

The above studies show the usefulness of regular monitoring of thyroid function in adults and overweight and obese children [24].

The results [2] of the study also showed that serum TSH within the control range was associated with the size of the waist circumference.

Studies on rats were conducted to study the association of hypothyroidism with impaired carbohydrate metabolism and obesity. It was found that in rats with hypothyroidism, adipocytes and skeletal muscles are less sensitive to insulin [12, 13]. The insulin resistance detected during hypothyroidism can be explained by a violation of translocation of the glucose transporter type 4 (GLUT-4) [48], a decrease in blood flow with respect to tissue glucose extraction [14], and a violation of the effect of lep-

tin on the hypothalamus [7], an increase in the level of circulating free fatty acids [18].

A study was conducted of patients who underwent thyroidectomy for thyroid cancer, they underwent an insulin tolerance test against the background of stopping L-T4 intake, during which insulin resistance was revealed [4]. In addition, in earlier studies, a decrease in glucose utilization revealed by euglycemic hyperinsulinemic clamp was demonstrated [18, 41]. The same was revealed in women with primary hypothyroidism using arteriovenous differences in postprandial glucose obtained from radial artery, veins of subcutaneous tissue of the anterior abdominal wall and deep vein of the forearm [14]. However, in other studies, there was no association between hypothyroidism and insulin resistance, either using the calculated insulin resistance index (Homeostasis Model Assessment of Insulin Resistance - HOMA-IR) [33], which shows sensitivity to fasting insulin, or when assessing blood flow in the muscles of the forearm, nor when using the combination of the latter method with a euglycemic hyperinsulinemic clamp [19].

In hypothyroidism, insulin secretion can be both normal and slightly reduced or increased [29]. Recent data indicate that insulin secretion in hypothyroidism is reduced, because after the start of therapy with L-T4, the concentration of insulin and proinsulin increases significantly [18]. Conversely, in hypothyroidism, an increase in glucose-induced insulin secretion was detected with its subsequent decrease during L-T4 therapy, since beta-cell load decreases with the restoration of euthyroidism [18].

In a small number of studies, the HOMA index was evaluated, during which insulin resistance was detected in case of subclinical hypothyroidism [18, 30], but this was not observed in all studies [1, 43]. In those studies in which insulin resistance was not detected during subclinical hypothyroidism [1, 43], the authors found hyperinsulinemia, which is the first sign of impaired glucose metabolism. E. Maratou et al. [30] found an increase in the HOMA index and a decrease in the Matsuda index in patients with subclinical hypothyroidism, suggesting that insulin resistance is determined both on an empty stomach and after glucose intake. In addition, a decrease in insulin-stimulated glucose transport into monocytes was detected, which is explained by a violation of the GLUT-4 translocation on the plasma membrane.

Conclusion

A decrease in the level of thyroid hormones affects the liver, causing changes in carbohydrate metabolism, for example, as insulin antagonists by increasing the expression of GLUT-2.

An increase in TSH concentration is associated with a risk of lipid and carbohydrate metabolism disorders and, consequently, an increased likelihood of metabolic syndrome, diabetes mellitus, and other disorders of carbohydrate metabolism.

All this shows the importance of the problem of combined diabetes mellitus and diseases of the thyroid gland, in particular hypothyroidism.

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References

1. Al Sayed A, Al Ali N, Bo Abbas Y, Alfadhli E. Subclinical hypothyroidism is associated with early insulin resistance in Kuwaiti women. *Endocrine Journal* 2006;53:653–657.

2. Agger C, Tiller D, Ittermann T, Greiser KH, Meisinger C, Hofman A, Thuesen BH, Linneberg A, Peeters RP, Franco OH, Heier M, Kluttig A, Werdan K, Stricker BH, Schipf S, Markus MRP, Dörr, Völzke H, Haerting J. Association of serum TSH with anthropometric markers of obesity in the general population. *J Thyroid* 26(9):1205-1214.

3. Asvold BO, Vatten LJ, Nilsen TIL, et al. The association between TSH within the refer-

ence range and serum lipid concentrations in a population-based study. The HUNT Study. *Eur J Endocrinol* 2007;156(2):181–186. doi: 10.1530/eje.1.02333, indexed in Pubmed: 17287407.
4. Brenta G, Celi FS, Pisarev M, et al. Acute thyroid hormone withdrawal in athyreotic patients results in a state of insulin resistance. *Thyroid* 2009;19:665-669.
5. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* 2003;348:1625-1638.
6. Celik C, Abali R, Tasdemir N, Guzel S, Yuksel A, Aksu E, Yilmaz M. Is subclinical hypothyroidism contributing dyslipidemia and insulin resistance in women with polycystic ovary syndrome? *Gynecol Endocrinol* 2012;28:615-8.
7. Cettour-Rose P, Theander-Carrillo C, Asensio C, et al. Hypothyroidism in rats decreases peripheral glucose utilization, a defect partially corrected by central leptin infusion. *Diabetologia* 2005;48:624–633.
8. Cheserek MJ, Wu G, Shen L, Shi Y, Le G. Evaluation of the relationship between subclinical hypothyroidism and metabolic syndrome components among workers. *Int J Occup Med Environ Health* 2014;27:175-87.
9. Chichelnitskiy E, Vegiopoulos A, Berriel Diaz M., Ziegler A, Kleiman A, Rauch A, Tuckermann J, Herzig S. In vivo phosphoenolpyruvate carboxykinase promoter mapping identifies disrupted hormonal synergism as a target of inflammation during sepsis in mice. *Hepatology* 2009;50:1963-71.
10. Chubb SA, Davis WA, Inman Z, Davis TM. Prevalence and progression of subclinical hypothyroidism in women with type 2 diabetes: the Fremantle Diabetes Study. *Clin Endocrinol (Oxf)* 2005;62:480-6.
11. Conkright MD, Canettieri G, Screaton R, Guzman E, Miraglia L, Hogenesch JB. and Montminy, M. TORCs: transducers of regulated CREB activity. *Mol Cell* 2003; 668(12):413-23.
12. Czech MP, Malbon CC, Kerman K, et al. Effect of thyroid status on insulin action in rat adipocytes and skeletal muscle. *J Clin Invest* 1980;66:574-582.
13. Dimitriadis GD, Leighton B, Parry-Billings M, et al. Effects of hypothyroidism on the sensitivity of glycolysis and glycogen synthesis to insulin in the soleus muscle of the rat. *Biochem J* 1989;257(2):369-73.
14. Dimitriadis G, Mitrou P, Lambadiari V, et al. Insulin action in adipose tissue and muscle in hypothyroidism. *J Clin Endocrinol Metab* 2006;91:4930- 4937.
15. Feng X, Jiang Y, Meltzer P, Yen PM. Thyroid hormone regulation of hepatic genes in vivo detected by complementary DNA microarray. *Mol Endocrinol* 2000;14(7):947-55.
16. Galofre JC, Pujante P, Abreu C, Santos S, Guillen-Grima F, Fruhbeck G, Salvador J. Relationship between thyroid-stimulating hormone and insulin in euthyroid obese men, *Ann Nutr Metab* 2008;53:188-94.
17. Gencer B, Collet TH, Virgini V, Auer R, Rodondi N. Subclinical thyroid dysfunction and 686 cardiovascular outcomes among prospective cohort studies. *Endocr Metab Immune Disord Drug Targets* 2013;13:4-12.
18. Handisurya A, Pacini G, Tura A, et al. Effects of thyroxine replacement therapy on glucose metabolism in subjects with subclinical and overt hypothyroidism. *Clin Endocrinol (Oxf)* 2008;69(6):963-9.
19. Harris PE, Walker M, Clark F, et al. Forearm muscle metabolism in primary hypothyroidism. *Eur J of Clin Invest* 1993;23:585–588.
20. Haslam DW, James WPT Obesity. *Lancet* 2005;366:1197-1209.
21. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation* 1983;67:968-977.
22. Januszek-Trzciakowska A, Malecka-Tendera E. Subkliniczna niedoczynność tarczycy u otyłych dzieci [Subclinical hypothyroidism in obese children]. *Postepy Hig Med Dosw (Online)* 2013;67:770–774, doi: 10.5604/17322693.1061415, indexed in Pubmed: 24018443.
23. Klieverik LP, Janssen SF, van Riel A, et al. Thyroid hormone modulates glucose production via a sympathetic pathway from the hypothalamic paraventricular nucleus to the liver. *Proc Natl Acad Sci USA* 2009;106:5966–5971.
24. Korzeniowska KA, Brzezinski M, Szarejko K, Radziwiłł M., Anyszek T, Czupryniak L, Soszyński P, Berggren PO, Mysliwiec M. The association of thyroid-stimulating hormone (TSH) and free thyroxine (fT4) concentration levels with carbohydrate and lipid metabolism in obese and overweight teenagers. *Endokrynologia Polska* 2019;70(2):172-178. DOI: 10.5603/EP.a2018.0090.·
25. Kota SK, Meher LK, Krishna S. and Modi K. Hypothyroidism in metabolic syndrome, Indian. *J Endocrinol Metab* 2012;16:332-3.
26. Kouidhi S, Berhouma R, Ammar, M, Rouissi, K., Jarboui, S, Clerget-Froidevaux,

MS, Seugnet I, Abid, H, Bchir F, Demeneix B, Guissouma H, Elgaaied AB. Relationship of thyroid function with obesity and type 2 diabetes in euthyroid Tunisian subjects. *Endocr Res* 2013;38:15-23.
27. Kulaga Z, Litwin M, Tkaczyk M, et al. The height-, weight-, and BMI-for-age of Polish school-aged children and adolescents relative to international and local growth references. *BMC Public Health* 2010;10:109. doi: 10.1186/1471-2458-10-109.
28. Lai G, Wu J, Liu X, Zhao Y. 20-HETE induces hyperglycemia through the cAMP/PKA-PhK-GP pathway. *Mol Endocrinol* 2012; 26:1907-16.
29. Lenzen S, Bailey CJ. Thyroid hormones, gonadal and adrenocortical steroids and the function of the islets of Langerhans. *Endocr Rev* 1984;5:411-434.
30. Maratou E, Hadjidakis DJ, Peppa M, et al. Studies of insulin resistance in patients with clinical and subclinical hyperthyroidism. *Eur J Endocrinol* 2010;163:625-630.
31. Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS, Marks JS Prevalence of obesity, diabetes, and obesity-related health risk factors. *JAMA* 2001; 289:76-79.
32. Nordlie RC, Foster JD and Lange AJ. Regulation of glucose production by the liver, *Annu Rev Nutr* 1999;19:379-406.
33. Owecki M, Nikisch E, Sowiński J. Hypothyroidism has no impact on insulin sensitivity assessed with HOMA-IR in totally thyroidectomized patients. *Acta Clin Belg* 2006;61:69-73.
34. Patel K, Foretz M, Marion A, et al. The LKB1-salt-inducible kinase pathway functions as a key gluconeogenic suppressor in the liver, *Nat Commun* 2014;5:4535.
35. Perros P, McCrimmon RJ, Shaw G. and Frier BM. Frequency of thyroid dysfunction in diabetic patients: value of annual screening. *Diabet Med* 1995;12:622-7.
36. Proces S, Delgrange E, Vander Borght TV, Jamart J and Donckier JE. Minor alterations in thyroid-function tests associated with diabetes mellitus and obesity in outpatients without known thyroid illness. *Acta Clin Belg* 2001;56:86-90.
37. Radetti G, Grugni G, Lupi F, et al. The relationship between hyperthyrotropinemia and metabolic and cardiovascular risk factors in a large group of overweight and obese children and adolescents. *J Endocrinol Invest* 2017;40(12):1311–1319. doi: 10.1007/s40618-017-0705-z.
38. Rotondi M, Leporati P, La Manna A, Pirali B, Mondello T, Fonte R, Magri F, Chiovato L. Raised serum TSH levels in patients with morbid obesity: is it enough to diagnose subclinical hypothyroidism? *Eur J Endocrinol* 2009;160: 403-408.
39. Sert A, Pirgon O, Aypar E, et al. Subclinical Hypothyroidism as a Risk Factor for the Development of Cardiovascular Disease in Obese Adolescents With Nonalcoholic Fatty Liver Disease. *Pediatric Cardiology* 2013;34(5): 1166–1174, doi: 10.1007/s00246-013-0638-z.
40. Smithson MJ. Screening for thyroid dysfunction in a community population of diabetic patients. *Diabet 771 Med* 1998;15:148-50.
41. Stanická S, Vondra K, Pelikánová T, et al. Insulin sensitivity and counter-regulatory hormones in hypothyroidism and during thyroid hormone replacement therapy. *Clin Chem Lab Med* 2005;43:715-720.
42. Tiller D, Ittermann T, Greiser KH, et al. Association of Serum Thyrotropin with Anthropometric Markers of Obesity in the General Population. *Thyroid* 2016;26(9):1205–1214. doi: 10.1089/thy.2015.0410, indexed in Pubmed: 27393002.
43. Tuzcu A, Bahceci M, Gokalp D, et al. Subclinical hypothyroidism may be associated with elevated high- sensitive c-reactive protein (low grade inflammation) and fasting hyperinsulinemia. *Endocr J* 2005;52(1):89-94.
44. Velija-Asimi Z. and Karamehic J. The effects of treatment of subclinical hypothyroidism on metabolic control and hyperinsulinemia. *Med Arh* 2007;61:20-1.
45. Wahren J and Ekberg K. Splanchnic regulation of glucose production. *Annu Rev Nutr* 2007;27:329-45.
46. Wang T, Xu J, Bo T, Zhou X, Jiang X, Gao L and Zhao J. Decreased fasting blood glucose is 784 associated with impaired hepatic glucose production in thyroid-stimulating hormone receptor knockout mice, *785 Endocr J* 2013;60:941-50.
47. Weinstein SP, O'Boyle E, Fisher M, Haber RS. Regulation of GLUT2 glucose transporter expression in liver by thyroid hormone: evidence for hormonal regulation of the hepatic glucose transport system. *Endocrinology* 1994;135(2):649- 54.
48. Weinstein SP, O'Boyle E, Haber RS. Thyroid hormone increases basal and insulin-stimulated glucose transport in skeletal muscle. The role of GLUT4 glucose transporter expression. *Diabetes* 1994;43(10):1185-9.

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