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Diagnosis and treatment of thyroid disorders in obese patients — what do we know?

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Abstract

Obesity-related changes in the composition of the body interfere with the proper functioning of the thyrotropic axis, leading to its disturbances and changes in the structure of the thyroid gland. Distinguishing what is related to obesity and what constitutes pathological changes is crucial for the proper treatment of patients.

In this paper authors present a case of a patient with a diet-induced obesity, whose only abnormalities in thyroid assessment included an elevated level of thyroid stimulating hormone (TSH) and hypoechoic thyroid gland on ultrasound. Based on this clinical situation, we reviewed literature in order to establish rules regarding management of thyroid disorders in obese individuals.

The most common obesity-related thyroid abnormality is an isolated increase of TSH, without clinical symptoms of hypothyroidism, defined as hyperthyrotropinaemia. In obese adults, autoimmune thyroid disease is found equally often as in the normal-weight population. Thyroid enlargement, increased risk of nodules, and decreased echogenicity, not related to autoimmunity, is frequent among obese individuals. Weight loss leads to the normalisation of TSH levels and thyroid echogenicity.

Excessive weight can influence both the TSH level and ultrasound image of the thyroid gland; however, these findings can be reversed by weight reduction. Therefore, in asymptomatic obese patients elevated TSH should not be treated with thyroid hormone replacement.
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Key words: *obesity; hyperthyrotropinaemia; thyroid ultrasound; autoimmune thyroid disease; bariatric surgery; weight reduction*

Introduction

Lifestyle and dietary changes over the past decades have led to the currently prevailing pandemic of obesity. According to the WHO reports from 2016, around 39% of the world's population are overweight (body mass index [BMI] > 25) and 13% are obese (BMI > 30). The growing number of obese individuals is a serious problem for the health care system because obesity contributes to increased mortality and disability, directly and indirectly, due to the number of associated complications affecting practically every organ and system in the human body.

Obesity-related changes in the composition of the body, hormonal activity, and cytokine profile interfere with proper functioning of the thyrotropic axis, leading to its disturbances and changes in the structure of the thyroid gland [2]. However, data published so far do not allow us to state clearly whether these changes are permanent or temporary and disappear after weight reduction. Given the increasing prevalence of obesity, an interpretation of the thyroid function tests in obese patients is nowadays an everyday challenge in clinical practice. Distinguishing what is related to obesity and what constitutes pathological changes is crucial for the proper treatment of patients. Recently, an excellent review regarding the pathophysiology of obesity-associated changes in thyroid function has been published [2]. In this paper, we intend to focus on more clinical aspects of this problem that may be useful in daily practice.

Clinical situation

A 51-year-old woman presented with a 30-year-long history of difficulties with maintaining proper body weight despite being physically active and eating a healthy diet. Her medical history revealed type 2 diabetes (diagnosed 10 years before and treated with metformin), hypertriglyceridaemia, and hypercholesterolaemia treated with a statin. Her family history was remarkable for metabolic diseases (obesity and diabetes). Her physical examination, apart from obesity (body mass index, BMI = 36), did not show other abnormal find-

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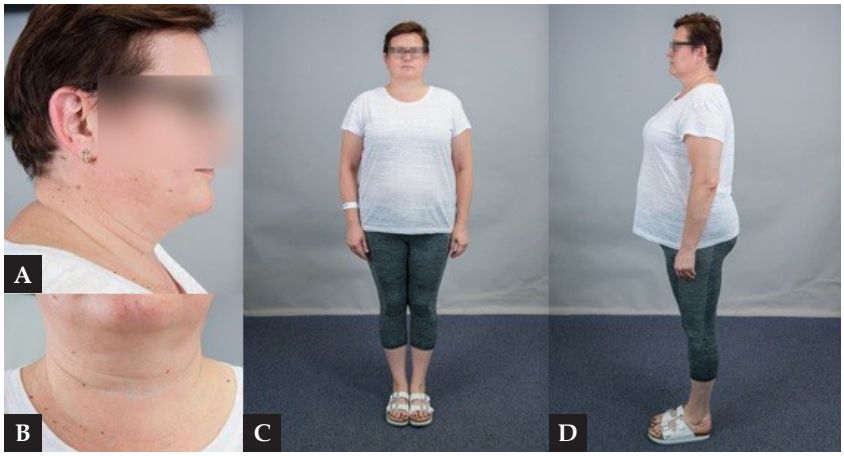

Figure 1. *Clinical presentation of the patient*

Table I. ***Laboratory findings***

Parameter	Normal range	Results
White blood count [10^3/uL]	4–11	6.24
Red blood count [10^3/uL]	3.8–5.2	4.62
Hemoglobin [g/dL]	12.0–16.0	12.4
Platelets [10^3/uL]	150–400	263
Thyroid stimulating hormone [ulU/mL]	0.23–4.2	4.8
Free triiodothyronine [pmol/L]	3.1–6.8	3.93
Free thyroxine [pmol/L]	11–22	18.7
Thyroperoxidase antibodies [ulU/mL]	< 34	< 0.9
Thyroglobulin antibodies [ulU/mL]	< 115	33.9
Cortisol after 1 mg of dexamethasone [ug/dL]	< 1.8	0.52
Sodium [mmol/L]	137–145	135.4
Potassium [mmol/L]	3.6–5.0	4.38
Alanine transaminase [U/L]	7–56	12
Glucose [mg%]	70–99	**115**
Insulin [ulU/mL]	2.6–24.9	**15.0**
HOMA-IR	< 2	**4.26**
HbA_{1c} (%)	< 7.0	**7.2**
Triglycerides [mg/dL]	50–150	**342**
Total cholesterol [mg/dL]	120–190	131

HOMA-IR — HOmeostatic Model Assesment-Insulin Resistance

ings including features of hypercortisolaemia, hyperandrogenism, or hypothyroidism (Fig. 1A–D).

Her laboratory findings are summarised in Table I (abnormal results are in bold). The only abnormality found in the endocrinological tests was a slightly elevated level of thyroid stimulating hormone (TSH), while levels of the free thyroid hormones were within the normal range and her anti-thyroid autoantibodies concentrations were within the normal range.

Her thyroid ultrasound revealed diffusely, mildly hypoechoic gland without distinctive nodules. Right lobe measurements in mm: 16 × 13 × 45 and left lobe 16 × 12 × 14. No pathological lymph nodes were found (Fig. 2A, B).

Clinical question: *How should the patient's thyroid function tests and thyroid ultrasound be further enhanced?*

How often can we expect thyroid dysfunction in obese individuals?

According to available epidemiological studies, the majority of obese patients without diagnosed thyroid disease remain euthyroid [3]. However, numerous studies showed a direct proportional relationship between TSH concentration and BMI, and subsequently it was found that up to 20% of obese patients present with subclinical hypothyroidism (SH, characterised by elevated TSH level, while free thyroid hormone concentrations are within normal limits) [3–5]. To compare, subclinical hypothyroidism affects approximately 4–9% of patients with normal body weight [6]. The prevalence of subclinical hypothyroidism in different populations of obese individuals is summarised in Table II.

The pathogenesis of obesity-related changes in thyroid hormone levels has recently been explained in detail by Garcia-Solis et al. [2]. In short, an increase in TSH level in obese individuals is believed to result from the central resistance to locally-produced triiodothyronine (fT3) and represents an adaptive process aimed at increasing basal energy expenditure.

Another possible explanation is the effect of high concentrations of leptin (adipokine produced by adipose tissue), the levels of which correlate positively with TSH, regardless of BMI [7]. Experimental data showed

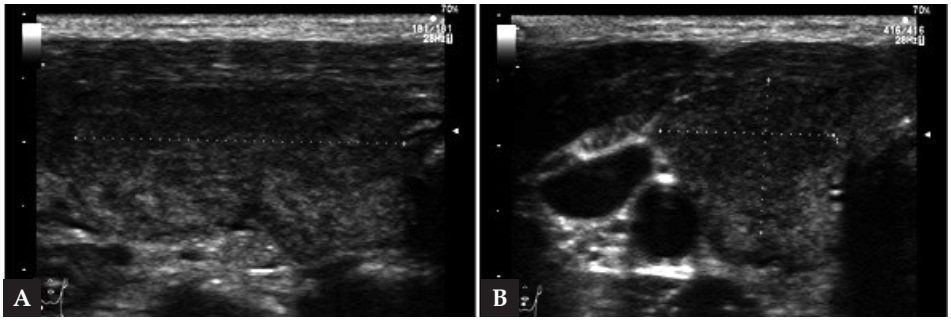

Figure 2. *Thyroid USG images: longitudinal (A) and transverse (B) view*

Table II. *Prevalence of subclinical hypothyroidism in different populations of obese individuals*

Study [ref.]	Number of study participants	Prevalence of SH (%)	Mean TSH [uIU/mL]	Mean fT3 [pmol/L]	Mean fT4 [pmol/L]	Positive aTPO (%)	Positive aTG (%)
Chikunguwo S et al. [5]	86	10.5	4.5				
Bétry C et al. [7]	800	20	2.8				
Janssen IMC et al. [10]	503	14.1	5.8 (among SH)		15.2 (among SH)		
Rotondi M et al. [14]	350	13.7	5.95 (among SH)	3.06 (among SH)	11.41 (among SH)	10	5.1
Rotondi M et al [15]	55		5.4	3.2	11.4	27.3	18.2
García-García E et al. [16]	129		3.12		16.3		
Bhowmick SK et al. [17]	308	11.7	2.51		17.8		
Marzullo P et al. [20]	165	10.3	2.7	2.8	11.7	17	15.2
Moulin de Moraes CM et al. [24]	72	18	3.03		13.4		
Abu-Ghanem Y et al. [25]	38		2.45		13.27		

SH — subclinical hypothyroidism; TSH — thyroid stimulating hormone; fT3 — free triiodothyronine; fT4 — free thyroxine; aTPO — thyroperoxidase antibodies; aTG — thyroglobulin antibodies

that leptin could directly stimulate thyrotropin-releasing hormone (TRH) and TSH secretion [8]. Furthermore, leptin is responsible for the increase in fT4 to fT3 conversion, by activation of deiodinases, which is believed to constitute another mechanism that increases the basic metabolic rate and energy expenditure [9]. Both leptin and TSH levels decrease after calorie restriction, which may suggest that energy-balance status more than adiposity itself affect thyrotropic hormone release. Hypothetically, positive energy-balance might increase TSH, which leads to thyroid hormone elevation and therefore thermogenesis along with energy expenditure, so further weight gain is limited [3, 7].

Jansen et al. suggest that hyperthyrotropinaemia is a more adequate name than subclinical hypothyroidism to describe obesity-related TSH elevation [10]. The increase of TSH observed in obese patients represents the central axis activation in order to boost energy expenditure to prevent weight gain. In true SH free thyroid hormone levels are usually low/normal, while among obese they are found to be in normal and high/normal range, which reflects central hypothalamus and pituitary resistance [10]. Indeed, experimental studies suggest that obesity is associated with lower expression of thyroid hormone receptors (TR) as well as deiodinases both in the central nervous system and in peripheral tissues [2, 11, 12].

Central and peripheral resistance to thyroid hormones observed in obese subjects can also be explained by the theory of metabolic inflammation ("metaflammation"). This term describes a chronic inflammatory state that occurs among obese patients and affects many tissues. According to this theory, excess lipid accumulation in adipose tissue leads to increased expression of genes encoding chemokines, cytokines, and adhesion molecules in adipocytes, which draws immune cells, which in turn leads to the production of inflammatory mediators [2, 13].

Although hyperthyrotropinaemia is more common, obesity does not exclude a diagnosis of hyperthyroidism. One should also remember that decreased TSH level in an obese subject may suggest hypothalamic dysfunction. However, detailed data on those phenomena are sparse.

In summary, most obese individuals are euthyroid. The most common obesity-associated thyroid hormone abnormality is hyperthyrotropinaemia, which can be distinguished from SH by normal and/or high/normal concentrations of thyroid hormones.

Does obesity increase the risk of AITD?

Epidemiological studies show that adult obese patients with elevated levels of TSH have significantly (up to 50%) lower rates of antithyroid antibodies (thyroperoxidase antibodies — aTPO and thyroglobulin antibodies — aTG) compared to patients with normal body weight with similarly elevated levels of TSH. In one study, untreated obese patients with TSH levels above the normal range had half the rate of antithyroid antibodies incidence when compared to normal-weight individuals (32% *vs.* 66%) [15]. Antibodies in euthyroid individuals in obese and non-obese patient groups were found similarly often (in about 11% of people). These data suggest that the autoimmune process is not the main cause of elevated levels of TSH among adult obese patients [15].

In turn, in a paediatric population, Garcia et al. showed that thyroid autoimmunity occurred more often (6.3% *vs.* 2.9%) in overweight children and adolescents in comparison to normal weight paediatric patients [16]. A similar observation was found among 308 obese children in a study conducted by Bhowmick et al. [17].

There are a number of theories regarding immune system dysfunction that may lead to autoimmunity in obese subjects. That includes vitamin D deficiency associated with obesity [18]. Similarly, metabolic inflammation may occur because high levels of pro-inflammatory cytokines correlate positively with higher concentrations of antithyroid antibodies [19]. Finally, high leptin levels may affect the occurrence of autoimmune thyroid disease both directly and by promoting pro-inflammatory state [20].

In summary, in adult obese individuals the prevalence of thyroid autoimmunity (assessed by the presence of antithyroid antibodies) does not differ from the normal-weight population even in those with elevated TSH levels. In contrast, in a study performed in paediatric obese patients, antithyroid autoantibodies were found significantly more often than in normal-weight peers [21]. The prevalence of elevated aTPO and aTG levels in obese subjects in different populations is summarised in Table II.

Does obesity influence ultrasound imaging of the thyroid gland?

Literature data indicate that patients with obesity are more likely to present hypoechoic images of thyroid parenchyma in ultrasound study (US), which is considered a characteristic marker of autoimmune thyroiditis (AITD). However, the presence of antithyroid antibodies in different populations of obese individuals does not correlate with the presence of changes in the echogenicity of the thyroid gland. In one of the few studies, correlation of the ultrasound image with autoimmune thyroiditis was observed in only 20.9% of obese people *vs.* 85.7% of people in the normal-weight group [15]. A hypoechogenic thyroid on US with absence of antithyroid antibodies was observed in only 1.9% of non-obese individuals, compared to 64.8% of obese patients [15]. This indicates that the hypoechoic nature of the thyroid parenchyma in obese patients must be due to other reasons than the autoimmune process.

Metabolic inflammation is again believed to be a possible explanation of this US phenomenon. The cytokines released by adipose tissue lead to vasodilation and more permeable blood vessels in the thyroid. As a result, plasma exudation and imbibition of parenchyma occur. This situation differs from the autoimmune thyroiditis that was confirmed by a fine-needle biopsy, which did not show lymphocyte infiltrations, ruling out Hashimoto's disease as a cause of parenchyma derangement [21]. It is also suggested that the hypoechogenic image of the thyroid gland in obese subjects may result from the accumulation of adipose tissue [15].

Because TSH levels increase in parallel with BMI value, and TSH is the main tropic factor for the thyreocytes, one should also remember that obesity is associated with increased thyroid volume and an increased risk of thyroid nodules [3, 22].

To sum up: obesity is associated with several changes in thyroid US, including its enlargement, increased risk of nodules and decreased echogenicity, which does not mirror the presence of autoimmune thyroid disease.

Does weight loss have an influence on thyroid function and US imaging?

Weight loss can be achieved by lifestyle interventions, pharmacological treatment, bariatric procedures, or a combination of them all. In studies based on lifestyle intervention (diet combined with increased physical activity), a decrease of fat mass was associated with a decrease in TSH level (from the mean 2.8 mU/L to 2.2 mU/L) [23]. In this study, the number of individuals with TSH level above the normal range decreased significantly after the intervention from 17.2% to 6.2%. Available results indicate that bariatric surgery, regardless of the method, also results in a reduction of TSH to the normal range in nearly all patients. One study showed a mean reduction of TSH level from 4.5 to 1.9 U/mL after the bariatric procedure (gastric bypass or

Table III. *The influence of weight loss on thyroid function*

Study [ref.]	Number of study participants	Mean TSH [uIU/mL]		Mean fT4 [pmol/L]		BMI	
		Before	After	Before	After	Before	After
Radetti G et al. [23]	72	2.8	2.2*	10.8	10.07	NS	NS
Chikunguwo S et al. [5]	86	4.5	1.9*	15.2	13.9	49	32
Janssen IMC et al. [10]	61	5.8	2.8			47	33
Abu-Ghanem Y et al. [25]	38	2.45	1.82*	13.27	12.96	42.4	32.5*
Moulin de Moraes CM et al. [24]	72	3.03	1.97*	1.04	1.07	53	33.7*
Zendel A et al. [39]	72	3.9	3*	13.7	14.9	43.7	29.8*

TSH — thyroid stimulating hormone; fT4 — free thyroxine; BMI — body mass index; NS — not significant; *statistically significant difference

adjustable gastric banding), and all patients diagnosed with subclinical hypothyroidism before the procedure (10.5% of the studied group) experienced a normalisation of TSH levels. It is worth mentioning that fT4 level was independent of BMI, and bariatric surgery did not affect this parameter [5]. Similar results were obtained Moraes et al. — in his group also all patients with subclinical hypothyroidism before the operation (25% of the group) experienced a normalisation of TSH after Roux-en-Y gastric bypass surgery [24]. In other studies the percentage of obese subjects whose TSH levels normalised after the procedure (laparoscopic sleeve gastrectomy) was as much as 90% [10, 25]. These findings strongly suggest that obesity-associated hyperthyrotropinaemia is transient and resolves after weight loss. The influence of surgery-induced weight loss on thyroid function in different studies is summarised in Table III.

In a study carried out in just 10 patients, which assessed the influence of bariatric surgery on thyroid US, loss of weight was associated with a parallel increase in the thyroid echogenicity, suggesting that also morphological changes of the thyroid in obesity are reversible with weight loss [26].

In summary: available data strongly indicate that loss of weight leads to the normalisation of TSH levels. So far, no large-scale study has shown how the echogenicity of the thyroid parenchyma changes after weight loss and whether there is a correlation with the ultrasound image and the incidence of autoimmune thyroid disease before and after weight loss.

Should we treat thyroid dysfunction in obesity?

Administration of thyroid hormones to obese individuals to induce weight lost has been considered for a long time, and the first attempts were made in the 1940s and 1950s [27]. This concept was based on the observation of hyperthyroid patients who, in the course of the disease, decrease their body weight by 15% on average, which is related to the thermogenic and lipolytic activity of thyroid hormones in adipose tissue. Thyroid hormones, in supraphysiological doses, has been administered to euthyroid obese subjects during caloric deprivation to enhance weight loss [28]. However, such therapy resulted in muscle wasting and weakness and adverse cardiac effects due to subclinical or overt hyperthyroidism [29]. In contrast, physiological doses of thyroid hormones (5–20 μg of T3) as supplementation to a very low-calorie diet did not seem to be erosive for the muscle tissue and had a beneficial effect on lipid profile, without a significant influence on body weight [30, 31]. In his review from 2001 Krotkiewski listed clinical indications for the administration of thyroid hormones in obese individuals. The main indication for the use of LT4 was subclinical hypothyroidism with hyperlipidaemia. Addition of T3 could have been considered in the case of patients with adequately substituted hypothyroidism (regardless of its aetiology) with obesity resistant to a lifestyle intervention or suspected of thyroid hormone conversion disorders [27]. However, in a meta-analysis from 2009, Kaptein found that available data were insufficient to assess how thyroid hormone administration influences fat and muscle loss in obese subjects during caloric deprivation, and considering the risk of hyperthyroidism he discourages such therapy in euthyroid patients [29].

Because the lipid-lowering effect of thyroid hormone is mediated mainly by the thyroid hormone receptor (TR) β in the liver (while the effect on bone and heart mainly by TRα isoforms), selective TRβ agonists may be effective for obesity-associated hyperlipidaemia [32]. However, weight loss with thyroid hormone analogue treatment has not yet been reported in clinical trials, and animal studies suggest that the regulation of basal metabolic rate is more dependent on TRα. Moreover, basic studies have demonstrated that adipose tissues of obese individuals are characterised by lower expression of genes encoding TR, which may limit the thermogenic

and lipolytic potential of thyroid hormones and their derivates [11].

While there are no data justifying the administration of thyroid hormones to obese individuals with normal serum TSH levels, treatment of obese patients with elevated TSH requires an individual approach. If elevated TSH is the only abnormality, it can be defined as obesity-associated hyperthyrotropinaemia. This clinical condition is defined as an isolated increase of TSH (above the upper range but < 10 mIU/L) without clinical symptoms, thyroid antibodies, goitre, or associated thyroidal illness. As was described above, in obese individuals hyperthyrotropinaemia represents an adaptive process aimed at increasing basal energy expenditure, and it may normalise after weight loss. Moreover, until now, no randomised, controlled trial evaluating the effectiveness of thyroid hormone treatment in obese adult individuals with hyperthyrotropinaemia or systematic review has been performed. The only trials regarding LT4 treatment of obese individuals with hyperthyrotropinaemia were performed in children. This concept was based on epidemiological data showing that in children increasing TSH is associated with impaired glucose metabolism and dyslipidaemia [33].

However, in children with the addition of thyroxine 1–2 ug/kg for up to six months, lifestyle intervention did not cause a significant change in body weight, BMI, linear growth, or lipid profile [34, 35]. In obese children with hyperthyrotropinaemia dietary-behavioural intervention contributed to a reduction of body mass index, irrespective of levothyroxine use. This finding suggests that moderately elevated levels of TSH are a consequence rather than a cause of overweight and pharmacological treatment should be avoided. Given the fact that there is no evidence for a favourable effect of LT4 treatment on body weight in obese subjects with TSH < 10 mU/L and normal fT4 level, the American Thyroid Association guidelines do not recommend such treatment [36].

However, some obese individuals with increased TSH level < 10 mIU/L may meet the diagnostic criteria for mild subclinical hypothyroidism (e.g. showing symptoms of hypothyroidism, with thyroid hormone levels in the low-normal range or present antithyroid antibodies), and then some indications for LT4 supplementation occur. A typical situation is the procreation period in women and pregnancy [37]. Other indications for SH treatment refer to metabolic risk. There are data confirming that LT4 treatment in normal-weight patients with SH can reduce the levels of total and LDL cholesterol [36]. However, this effect is more pronounced in patients with TSH > 10 mU/L. What is important, while in euthyroid normal-weight patients FT4 levels are negatively correlated with TG, and TSH levels are correlated positively to total cholesterol levels, in overweight subjects such a correlation does not exist. This finding indicates that body weight might interfere with the effect of thyroid hormone on lipid profile and LT4 treatment of obese patients with SH, and hyperlipidaemia may not be beneficial [38]. Moreover, levothyroxine replacement therapy for subclinical hypothyroidism did not result in improved survival or decreased cardiovascular morbidity. Data on health-related quality of life and symptoms did not demonstrate significant differences between intervention groups [6].

In summary: patients with isolated hyperthyrotropinaemia should not be treated with thyroid hormone replacement unless there are symptoms or other signs of thyroid disease.

Final remarks and conclusions

The lack of prospective, case-control studies regarding the treatment of obesity-associated thyroid abnormalities makes it impossible to formulate definite guidelines regarding their management in everyday practice. However, based on the available data, we can conclude that most obese patients are euthyroid, even though their TSH levels usually exceed those observed in normal-weight individuals. The most common thyroid hormone abnormality associated with obesity is hyperthyrotropinaemia, which can be distinguished from the SH by the normal and/or high/normal concentrations of thyroid hormones. Obesity is also associated with thyroid enlargement, increased risk of nodules, and decreased echogenicity in US imaging. However, the prevalence of antithyroid antibodies in adult obese patients is no higher than in the normal-weight population.

Indications for LT4 treatment in obese individuals are limited to overt hypothyroidism and some selected cases of its subclinical form. Patients with isolated hyperthyrotropinaemia (such as the one presented in this paper) should not be treated with thyroid hormone replacement unless there are symptoms or other signs of thyroid disease. Administration of thyroid hormones to obese individuals without thyroid disease in order to induce weight reduction or improve metabolic profile is not justified and may lead to hyperthyroidism and its complications.

Author contributions

The first authorship of S.N.G and A.K. is of equal rank.

Conflicts of interest

The authors declare none.

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REVIEW