sciendo

Review • DOI: 10.2478/ahem-2023-0015 • AHEM • Vol. 77 Issue 1/2023 • 107–117

Advances in Hygiene and Experimental Medicine
Postępy Higieny i Medycyny Doświadczalnej

Is there a link between obesity phenotype and thyroid diseases? A mini-review of current concepts

Review

Ewa Malwina Milewska- Kobos*, Ewelina Szczepanek- Parulska, Marek Ruchala

Department of Endocrinology, Metabolism and Internal Medicine, University of Medical Sciences, Poznan, Poland

Received 5 May, 2023, Accepted 3 August, 2023

Abstract

Obesity is a chronic, relapsing, and progressive disease that leads to negative health consequences. Excessive adiposity frequently coexists with metabolic and nonmetabolic complications, deteriorating health and reducing quality of life and life span. Individuals with obesity are not a homogenous group and can present different obesity phenotypes. The most common obesity phenotypes include: metabolically healthy obese (MHO) and metabolically unhealthy obese (MUO). The latter category involves those with developed metabolic syndrome (MetS) and non-fully-developed metabolic syndrome (pre-MetS). The fundamental factor leading to obesity is imbalance between energy uptake and expenditure. From this perspective the thyroid gland plays the pivotal role in metabolism regulation and obesity development. The thyroid regulates thermogenesis, appetite, and lipids turnover. Clinically, hypothyroid patients have decreased metabolic rate and subsequently experience increase of BMI and excess adiposity. The interaction between the thyroid gland and obesity is bidirectional. Several mechanisms of alteration of the hypothalamus-pituitary-thyroid axis in obesity are proposed. Excessive adiposity and dysfunction of adipose tissue may contribute to the development of thyroid functional and structural impairment, such as autoimmunity, thyroid nodules, and thyroid cancer. The prevalence of certain thyroid disorders in obese individuals is higher than in nonobese subjects and this trend is more pronounced in unhealthy obesity phenotypes. The aim of this mini-review is to present the current knowledge on the interaction between thyroid gland disorders and obesity, with special focus on obesity phenotypes.

Keywords

thyroid disease • obesity • obesity phenotypes • metabolic syndrome • metabolically healthy obese

1. Introduction

Obesity is a chronic, progressive and relapsing disease, characterized by excessive and dysfunctional adiposity. In the adult population it is defined as body mass index (BMI) >30 kg/m2 (in Caucasian population) or increased percentage of adipose tissue [1].

Although there is an agreement for the BMI values defining obesity, there is no clear consensus for the cut-off values for normal and excessive body fat percentage. Most commonly these are held to be >25% for men and >30-35% for women [2,3]. The global prevalence of obese people has tripled over the last 3 decades [4], being an emerging health problem in most developed countries. Recently BMI has been considered a screening tool, but to establish full diagnosis, a more detailed examination should be performed, including assessment of obesity-related complications, to adequately stratify the health risk [5,6]. Thus, obese individuals are not a homogenous group and may represent different obesity phenotypes, according to metabolic status. The most common obesity phenotypes presented in the literature are: metabolically healthy obese (MHO) and metabolically unhealthy obese (MUO), which can be further categorized into those with developed metabolic syndrome (MetS) and non-fully developed metabolic syndrome (pre-MetS) [7].

The most recent criteria of MetS are based on the measurement of blood pressure, triglycerides (TG), HDL-cholesterol, fasting glucose (FG), and waist circumference (WC). To diagnose MetS, 3 out of 5 abnormal findings should be confirmed [8]. On the opposite pole, there are metabolically healthy obese individuals (MHO phenotype). These patients, despite being classified as obese, do not present components of MetS. Moreover, MHO should have no antihypertensive, glucose-lowering, or hypolipemic treatment [9]. Although this phenotype does not present any metabolic complications of obesity, it cannot be considered as healthy as the non-obese population. In long-term observational studies the individuals classified as MHO eventually develop metabolic alterations, progressing to the category of MUO [10-12], and may have other obesity-related complications.

Pathogenesis of obesity is complex and involves psychological, behavioral, neuroendocrine, and environmental factors. However, the fundamental element leading to obesity is imbalance between

* *E-mail: ewamalwina.milewska@gmail.com*

© 2023 Ewa Malwina Milewska- Kobos *et al*.. This work is licensed under the CreAtive Commons Attribution-NonCommercial-NoDerivs 4.0 License.

energy uptake and energy expenditure. From this perspective the pivotal role in metabolism regulation and obesity development is played by the thyroid gland. Indeed, the interaction between thyroid hormones and obesity is bidirectional. Excessive adiposity and dysfunction of adipose tissue may be related to the development of thyroid functional and structural impairment such as hypothyroidism [13-15], autoimmunity [14,16], thyroid nodules [17-19], and thyroid cancer [20,21]. In most cases the hormonal imbalance can be reversed by weight loss, no matter the method (bariatric surgery, dietary intervention, or pharmacotherapy) [22]. The prevalence of thyroid disorders in the obese population is higher than in normal weight individuals [23], and the European guidelines recommend the assessment of thyroid function in all obese patients [24].

There is much evidence in the literature on the relation between obesity and thyroid diseases, both at functional and morphological levels; however, still there is scarce data on the prevalence of particular disorders according to obesity phenotypes. The aim of this mini-review is to present the current knowledge on the interaction between thyroid gland disorders and obesity, with special focus on obesity phenotypes.

2. Thyroid and metabolism regulation

The thyroid gland plays a fundamental role in metabolism regulation and energy expenditure. In the physiological mechanism, triiodothyronine (T3) serum concentration exerts negative feedback on thyrotropin releasing hormone (TRH) and thyroid stimulating hormone (TSH) production, regulating the activity of tissue-specific deiodinases (D1, D2, D3) and therefore conversion of thyroxine (T4) to triiodothyronine (T3). Thyroid hormones (TH) act in genomic and non-genomic mechanisms, either binding to nuclear thyroid receptors (TR, tissue-specific isoforms alpha 1, 2 and beta 1,2,3) or non-nuclear receptors located in mitochondria, cytoplasm, and cell membrane. They control thermogenesis, set the basic metabolic rate, regulate hepatic lipid metabolism and lipids turnover [25]. Thyroid hormones, specifically T3, also regulate food intake at the central level, by modulating the release of orexigenic peptides in hypothalamus—agouti-related peptide (AgRP) and neuropeptide Y (NPY) [26,27].

Recently, it has also been suggested that TH may stimulate white adipose tissue (WAT) browning and indeed augment brown adipose tissue (BAT)— the main site of facultative thermogenesis [28].

3. Patomechanisms of thyroid diseases in obesity

Several mechanisms of hypothalamus-pituitary-thyroid (HPT) axis alterations in obesity have been proposed, including low-grade inflammation, insulin resistance (IR), disturbed adipokines production, altered deiodinases activity, and TR expression as well as relative resistance to TH.

Obesity is often characterized by a low-grade inflammatory status. The impairment of oxygen and blood supply in hypertrophic adipocytes leads to hypoxia and ischemia that in turn stimulate infiltration of macrophages [29]. Dysfunctional tissue overproduces immunomodulating adipose tissue–derived compounds (adipokines) such as leptin, adiponectin, visfatin, and resistin, which have immunomodulating properties. In combination with increased oxidative stress, overproduction of reactive oxygen species (ROS), and overexpression of cyclooxygenase 2, it provokes endothelial damage and further changes in immunity [30-33]. Overproduction of cytokines may also have inhibitory effect on sodium/iodide transporter [34,35] and deiodinases activity [36]. Moreover, cytokine-induced increased permeability of blood vessels contributes to the altered morphology of thyroid gland [34].

Insulin resistance can be defined as resistance to the insulin stimulation of the target organs: mainly adipose tissue, skeletal muscles, and liver. This condition is usually acquired, and related to excessive body fat [37]. Dysfunctional adipose tissue with hypertrophic adipocytes account for the release of proinflammatory cytokines that, together with accompanying lipolysis and overproduction of free fatty acids (FFA), aggravates inflammation, facilitates ectopic deposition of fat, and impairs insulin signaling in WAT [38-40]. On the systemic level, the lipotoxic effect of accumulation of FFA on skeletal muscles and liver also impairs insulin signaling and induces such proinflammatory responses as macrophage infiltration, ROS production, steatosis, and fibrosis with all its negative metabolic consequences [41-44]. A correlation between insulin and TH concentration as well as the stimulatory effect of insulin on deiodinases activity has been observed [45-47]. In addition, an association between high fT3/fT4 ratio and IR has also been documented [48]. Moreover, IR and hyperinsulinemia may contribute to thyroid morphological changes and carcinogenesis [49], acting synergistically with TSH and growth factors [50,51] and having an impact on angiogenesis [52].

In most obese patients we can commonly observe normal or increased TSH concentration, normal or slightly decreased fT4 concentration, and fT3 within reference range. These findings can be linked with leptin, which is an important effector in the postulated "hypothalamus-pituitary-adipose tissue-axis" [26, 53-55]. In the study of Betry et al. [54] a strong correlation between leptin level and TSH concentration has been demonstrated, independently from BMI, in the group of 800 obese patients. In a recent study by Karpuzoglu et al. it was revealed that maternal serum leptin was positively correlated with TSH in newborns, being a risk indicator of hypothyroidism [56]. Leptin is exclusively secreted by adipose tissue and it regulates energy homeostasis and food intake. It crosses the blood-brain barrier and plays an important role in synthesis and regulation of TH production. Leptin stimulates D1 and conversion of T4 to T3 in liver and kidneys [57,58] as well as in white adipose tissue [59].

Through a central mechanism it regulates TRH secretion and in turn TSH production. It is observed that after weight loss and reduction of amount of circulating leptin, there is a reduced stimulation of TRH and TSH [53]. Physiologically, leptin induces TRH expression in the paraventricular nucleus (PVN) and production of anorexigenic peptides in the arcuate nucleus (AN). In AN leptin activates proopiomelanocortin (POMC) neurons and downregulates the synthesis of AgRP and NPY, which subsequently results in a decreased food intake [60]. However, due to leptin resistance, in obesity the impact of circulating leptin on synthesis of anorexigenic peptides is minimal.

As mentioned before, obese patients, even if in euthyroid state, have relatively higher TSH, fT3 and fT3/fT4 ratio in comparison to non-obese individuals [45]. It can be interpreted as a compensatory mechanism preventing further weight gain. However, despite the rise of fT3 and TSH, in individuals with obesity no spontaneous weight loss is observed, probably due to reduced expression of thyroid and beta-adrenergic receptors and altered function of deiodinase in adipose tissue [61,62]. It may cause relative resistance to TH at both peripherical and central levels. It was demonstrated that one of the reasons for increased TSH production in obesity may be pituitary resistance to fT3 [63-65]. D1 is overexpressed in white adipose tissue of obese individuals and the expression of TSH receptors and TR alfa 1 is decreased. This state is reversible: after weight loss (surgical or non-surgical) the expression of D1 deiodinase, expression of TSH receptor, and TR alfa1 is restored to normal. In these patients TSH and fT3/fT4 ratio also declines [22,61,66]. In euthyroid obese patients TH treatment is not advised for weight loss, as there is no evidence for its efficacy or safety [67,68]. American and European guidelines strongly recommended against such a therapy [24,69].

BAT is involved in the process of non-shivering thermogenesis [70]. Physiologically, BAT activity depends on the sympathetic nervous system; this process can be regulated centrally (via the hypothalamus), but also may be regulated by TH [71]. Moreover, BAT is an important site of T4 to T3 conversion. Sympathetic stimulation enhances local T3 production via increased activity of BAT-specific D2 [72,73]. Obesity is characterized by catecholamine resistance [74]. Downregulation of adrenergic receptors in BAT may affect the activity of D2, that contributes to lowering thermogenesis and energy consumption [75-79]. The possible mechanism can be linked with inflammatory state and macrophage infiltration of BAT and hyperleptinemia [80]. It has been shown that leptin may influence the activity of deiodinases: it may increase activity of D1 and decrease activity of D2 in BAT, contributing to lowering the metabolic rate and thermogenesis [13, 81]. Importantly, in obese individuals also the quantity of BAT is reduced in comparison to the lean population [74,82,83]. Impaired differentiation of preadipocytes into BAT is plausibly the consequence of the catecholamine resistance mentioned before [74, 79] and concomitant oxidative stress and low grade inflammation [84, 85].

4. Obesity and thyroid disorders

Most euthyroid obese individuals present a typical constellation of TSH and free thyroid hormones; however, the prevalence of hypothyroidism is 10 times higher than in the normal-weight population [23,86,87]. The relationship between autoimmune thyroid disease (AITD) and obesity is not well established and the data from different studies are conflicting. The prevalence of anti-thyroid peroxidase antibodies (TPOAb) positivity in the adult population with severe obesity ranges between 11–17% [84,88], which is similar to the general, non-obese population. Interestingly, the presence of anti-thyroid antibodies in individuals with elevated TSH is lower than in the non-obese subjects. This phenomenon may be explained by dominant non-immune causes of TSH increase. In the meta-analysis from 2019 [14], obesity was correlated with positive TPOAb (RR 1.93, 95% CI 1.31-2.85, $p = 0.001$), but not with positive anti-thyroglobulin antibodies (TGAb). Obese patients had increased risk of hypothyroidism (RR 1.86, 95% CI 1.63-2.11, $p < 0.001$) and slightly (at the border of statistical significance) elevated risk of Hashimoto's thyroiditis ($p = 0.077$). Contrarily, in the novel study by Guo et al. [89] hyperthyretropinemia has not been associated with the BMI category; however, in the presence of positive anti-thyroid antibodies, the risk of developing hypothyroidism in obese individuals was significantly increased and correlated with BMI. The obesity may facilitate the development of autoimmunity including AITD, but in obesity autoimmune etiology of hyperthyreotropinemia or hypothyroidism does not play the dominant role.

Obesity is also associated with thyroid hypoechogenicity on ultrasound examination, but contrarily to the general population, it is not related to AITD, but rather to the accumulation of fat in the neck area and increased permeability of small thyroid vessels associated with obesity [90,91].

The morphological changes of the thyroid gland in obese individuals are often found. The proposed mechanisms are linked to the higher concentration of TSH, insulin, and growth factors that stimulate development of goiter and thyroid nodules [17].

Insulin exerts both metabolic and mitogenic effects on the thyroid cells, while insulin lowering agents exhibit anti-goitrogenic effects [92]. The insulin receptor (IRec) belongs to the tyrosine kinase family and is represented in two isoforms—A (IRec-A) and B (IRec-B)—which differ in their tissue distribution, affinity to other than insulin ligands (proinsulin, insulin- growth factors), and therefore activation of the specific molecular pathways [93]. IRec-A is predominantly present in less-differentiated cells, has a higher affinity to IGF, and its activation triggers mitogenic pathways. IRec-B is expressed mostly in well-differentiated cells and is responsible for metabolic activity of insulin [94,

95]. Moreover, the needed insulin concentration for metabolic pathway activation is much lower than for mitogenic pathway activation. However, under persistent insulin stimulation, the proportions of IRec-A to IRec-B in different tissues may change, causing upregulation of IRec- A [96]. Such a situation is observed in obese individuals [20, 97] and can partially explain why obesity is also a well-established risk factor of carcinogenesis [98,99]. Obese individuals exhibit 55% increased risk of TC development in comparison to lean individuals. Interestingly, this increased incidence is specific for papillary (PTC), follicular (FC), and anaplastic (ATC) variants, while the risk for medullary thyroid cancer (MTC) is reduced. The differences in the risk of tumor type may be associated with their different histological origin (follicular cells for PTC, FTC, and ATC vs. parafollicular cells for MTC) [21].

5. Thyroid diseases and obesity phenotypes

5.1. Hypothyroidism

The risk of thyroid dysfunction can be even more prominent in certain obesity phenotypes. In the study by Wang et al. [100] males with an unhealthy obesity phenotype had the highest risk of hypothyroidism in comparison to MHO and metabolically healthy nonobese (MHNO); 19.88 vs. 14.52 and 12.19 per 1000 person-years, respectively. Interestingly, in this study neither the presence of obesity nor metabolic alterations were independent risk factors for hypothyroidism in the female group [100]. It is in line with the observations from the recently performed study by our group, in which we have evaluated metabolic and endocrine complications according to different obesity phenotypes [7]. We did not observe a statistically significant relationship between the prevalence of hypothyroidism and BMI category. However, it was significantly associated with the metabolic category ($p = 0.04$), with the lowest prevalence among the MHO population (22%) in comparison to pre-MetS (57%) and MetS group (47%) [7]. In another cohort study [101] evaluating the relationship between fT3, fT4, and fT3/fT4 ratio in over 1000 euthyroid subjects, the obese patients (both MHO and MUO) had significantly higher fT3 and fT3/fT4 ratio. MUO phenotype was characterized by significantly lower fT4 levels. Elevated TSH was not associated with any obesity phenotype, however it was correlated positively with non-obese but metabolically unhealthy phenotype (MUNO), ($p < 0.01$). A similar conclusion came from the previous cohort study by Kim et al. [102] evaluating over 13,000 Korean euthyroid patients, who were subdivided according to metabolic category. No significant differences were observed between TSH or fT4 concentration and obesity phenotypes. The population-based study by Amouzegar et al. also investigated association of TH levels with obesity phenotypes [103]. The highest fT4 levels, though still within reference range, were detected in metabolically healthy normal weight (MHNW) individuals. Moreover, during a 9-year follow-up period, each 1 ng/ml increase in fT4 level was associated with the increased chance of developing or maintaining the MHNW, and decreased by 50% the risk of transgression into MHO phenotype. In a population-based study by Shin et al., performed in a non-diabetic euthyroid healthy population, fT4 was negatively associated with BMI and homeostatic model assessment of insulin resistance (HOMA-IR) in both genders; the subjects in the lowest fT4 quartile had an odds ratio (OR) for IR equal to 1.99 (95% CI 1.61-2.46), as compared to those in the highest quartile [104]. In addition, low normal fT4 was independently related to IR in normal weight subjects and to obesity.

5.2. Autoimmunity

Although an association between thyroid autoimmunity and obesity has been suggested by some studies, data on the risk of AITD in relation to different obesity phenotypes is scarce. In a recent population-based study by Amouzegar et al. [105] the risk of developing thyroid autoimmunity in the period of 9-year follow-up was the highest among metabolically unhealthy, but non-abdominally obese [8.78 (7.31-10.55) per 1000 person-years of follow-up], and the risk was doubled in women. However, there was no significant association between other obesity phenotypes and development of TPOAb positivity during a 9-year follow-up period.

The gender-specificity in relation to autoimmune thyroiditis and obesity phenotype was identified in the recent study of Yang et al. [106]. Increasing BMI categories and WC quartiles were positively correlated with Hashimoto's thyroiditis (HT) risk (p for the trend < 0.05). In females, an unhealthy obesity phenotype was a risk factor for autoimmune thyroiditis, while metabolically healthy non-abdominally obese women were not at higher risk of developing autoimmune thyroiditis. In males, obesity (independently from metabolic category) was a significant risk factor for HT, including MHO category ($p = 0.032$). Abdominal obesity, regardless of metabolic status, was an independent risk factor for the development of HT in males ($p < 0.001$), but not in females.

5.3. Thyroid nodules

Although obesity is strongly associated with goiter and thyroid nodules (TN), to the best of our knowledge there was no study examining the incidence of the disease according to obesity phenotypes. However, there are many studies evaluating the relationship between MetS and thyroid nodular disease. It is therefore possible that the conclusions drawn can be extrapolated to the discussion on obesity phenotypes; those accompanied by the presence of MetS may be at higher risk. In the study of Ayturk et al. for the first time is has been shown that IR is an independent risk factor for nodule formation [17]. Patients with MetS were significantly more frequently diagnosed with TN (50.4 vs 14.6%, p

< 0.0001), and the thyroid volume (TV) was significantly higher in MetS group (17.5 ± 5.5 vs 12.2 ± 4.2 ml, p < 0.0001). Importantly, IR, but not TSH, correlated with the risk of TN.

The meta-analysis performed by Zhang et al. revealed an unequivocally positive correlation between MetS and TN (p < 0.0001), independently from age and sex [107]. The pooled TN prevalence in MetS patients was 45% (95% CI 36-54%).

Another recent meta-analysis by Zhang et al. also showed that risk of TN was higher in case of MetS (OR 1.87, 95% CI 1.44-2.45) and such components of MetS as central obesity (OR 1.41, 95% CI 1.15-1.72), hypertriglyceridemia (OR 1.13, 95% CI 1.10-1.15), low high-density lipoprotein cholesterolemia (OR 1.11, 95% CI 1.02-1.20), abnormal blood pressure (OR 1.68, 95% CI 1.62-1.75), and hyperglycemia (OR 1.59, 95% CI 1.46-1.74) [108]. Interestingly, in this study central obesity displayed sex-related differences, being a risk factor in males (OR 1.38, 95% CI 1.02-1.86), but not in females (OR 1.47, 95% CI 0.97-2.23). Similar gender differences were reported in another study, where MetS was associated with higher prevalence of TN in males (OR 1.38, 95% CI 1.05-1.81) compared with females (OR 1.02, 95% CI: 0.75-1.39). However, these differences were not statistically significant [109]. In the study by Siqueira et al. the occurrence of TN in severely obese patients was significantly (p = 0.017) higher than in a control group (30% vs 13%) [18]. Among the factors associated with higher incidence were components of MetS: higher fasting glycemia (p = 0.009), fasting insulin (p = 0.001), HOMA-IR (p = 0.045), and TG (p = 0.009), but lower high-density lipoprotein cholesterol (p = 0.041). Similarly, an Italian population study by Buscemi et al. demonstrated that impaired glucose metabolism and type 2 diabetes were significantly associated with TN [19].

The conclusions from a large community-based study performed by Xu et al. are in line with previous observations: components of MetS such as central obesity, hypertension, and diabetes are independent risk factors for TN [110]. In another community-based cross-sectional study performed in China by Song et al., individuals with central adiposity had greater risk of TN (OR 1.62, 95% CI 1.14-2.28), while obesity defined on the basis of BMI measurement was not associated with elevated risk [111]. Higher BMI was associated with TN (OR 5.59, 95% CI 1.39-22.51 and 5.15, 95% CI 1.30-20.37) only in a subgroup with TSH > 4.2 mIU/L. They concluded that the assessment of central obesity was superior to BMI in terms of evaluating TN risk.

The conclusions from several studies investigating the association between TV and MetS are also consistent. The previously cited study by Guo et al. showed that individuals with MetS are at higher risk of both thyroid nodules and increased TV (p = 0.0037) [109]. Similarly, in another study central obesity expressed as WC was related to TN (OR 1.04, 95% CI 1.02-1.06, p = 0.0036), while increased WC was an independent risk factor for increased TV [112].

5.4. Thyroid cancer

Obesity is a risk factor for developing numerous types of cancers, including TC. However, the studies investigating correlation between BMI and TC are not fully consistent. Though many suggest positive correlation [113-116], there are a few showing no relationship [117,118]. The recent study by Ahmadi et al. concluded that there is no correlation between BMI and incidence of TC [119]. Authors observed that BMI measurement does not provide relevant information on TC risk. Recently, a meta-analysis published by Zheng et al. suggested for the first time the reduced risk of cancer in MHO individuals in comparison to MUO [120]. The study indicates that cancer incidence is approximately 30% lower in the MHO group than in MUO individuals (OR 0.71; 95% CI 0.61-0.84).

Importantly, in another study by Lin et al. it was revealed that even age, ethnicity, or smoking status do not significantly influence the risk of cancer in MHO patients [121]. However, regarding the TC risk, the incidence is higher in the female group. Gender differences regarding the consequences of adiposity per se and metabolic complications are also reported by other studies. In the cohort study by Kwon et al. including over 250,000 individuals, free of TC at baseline, and divided according to BMI and metabolic health status [122], during the 5-year follow-up they observed that increase in waist circumference was positively associated with the risk of TC in metabolically unhealthy men and women (p for trend < 0.005). There were also some gender-specific differences. Men with obesity (regardless of metabolic status) had increased risk of TC. In women only MUO women, but not MHO, had increased risk of TC. The gender differences were revealed also in the study by Dung et al., where women with central obesity and MUO phenotype were exposed to higher risk of TC [18, 123].

6. Discussion

Concomitant thyroid diseases are common findings in individuals with obesity. The relationship between obesity and thyroid is complex and bidirectional. Hypothyroidism may promote development of obesity, but also obesity may be the underlying cause of thyroid dysfunction and morphological changes. Although thyroid dysfunction is not mentioned among obesity-related disease, taking into consideration its high prevalence in comparison to non-obese population, in our opinion thyroid evaluation should be recommended for all individuals with obesity. Although a recommendation to measure TSH concentration in every obese patient is mentioned in the latest European consensus, other guidelines suggest performing thyroid diagnostics only in case of clinical suspicion of thyroid disorder [5,6,24].

Regulation of TH production is complex, influenced by environmental, physiological, and genetic factors. In the context of obesity, thyroid dysfunction, most commonly hypothyroidism,

may contribute to decreased thermogenesis and metabolic rate. This in turn facilitates weight gain [15, 124] and may result in unfavorable body composition [125-127]. Moreover, lower fT4 levels are associated with adverse changes in lipid profile, muscular and liver accumulation of fatty acids, IR and, in consequence, the development of MetS [48,124,128,129]. It was observed that even small TSH rise (even within reference ranges) is associated with higher BMI [130,131]. However, hypothyroidism rarely causes the development of severe obesity. Higher fT3 and fT3/fT4 ratio that are typically found in obese individuals can be interpreted as a compensatory mechanism preventing even more weight gain [45]. In many studies it was confirmed that normal thyroid function can be restored after weight loss [22,61,66,132-134]. The alterations in thyroid function can rather be the consequence of obesity than its only cause and may reflect an adaptational change in HPT axis, playing its role as a metabolic regulator.

Recently the concept of Adiposity Based Chronic Disease (ABCD) has emerged [135]. Indeed, the spectrum of metabolic consequences expressed by the different obesity phenotypes is a manifestation of different grades of adipose tissue sickness. From this point of view it is more likely that unhealthy metabolic status puts the obese individuals at higher risk of thyroid related diseases, rather than obesity per se. As fat tissue can be considered a separate endocrine organ, importantly not only the amount of adipose tissue but its altered distribution and function may lead to health deterioration. As highlighted before, dysfunctional adipose tissue with hypertrophic adipocytes is characterized by inflammation and an altered profile of produced cytokines and adipokines that contribute to metabolic dysregulation and putatively to autoimmunity [136].The study of Marzullo et al. showed that higher leptin levels in obese subjects were associated with the presence of thyroid antibodies and thyroid autoimmunity [16]. Furthermore, recent research revealed that another adipokine—visfatin—correlates with TPOAbs in hypothyroid patients both in adults and children [137, 138]. In the report by Belligoli et al. the omental and subcutaneous adipose tissue of the patients with obesity and impaired glucose metabolism was characterized by impaired vascularization, increased adipocyte size, and significant reduction in adipocyte stem cells, contributing to hypoxia, inflammation, and reduced capacity for TG storage [139]. Thus, persistent low-grade inflammatory status provokes endothelial damage, changes in immunity, development of IR that in the long term may lead to the alteration of thyroid morphology and function [31-33,129]. In conclusion, although patients with hypothyroidism are at higher risk of gain weight, also individuals with unhealthy obesity phenotypes are at higher risk of hypothyroidism, development of thyroid autoimmunity, thyroid nodules, and thyroid cancer. The higher risk may be particularly attributed to altered glucose metabolism and IR. Indeed, not excessive adiposity per se measured by BMI, but particularly dysfunction and central distribution of adipose tissue with concomitant metabolic complications may contribute most to the risk of autoimmunity, morphological changes, and malignant transformation, which incidence might be dependent on obesity phenotype. Importantly, there are also gender differences indicating other genetic, environmental, and hormonal factors. Typically, in men excessive adiposity per se (regardless of metabolic status) was an independent risk factor for thyroid cancer and thyroid autoimmunity, while in women the risk was higher only in those presenting an unhealthy obesity phenotype. Gender differences regarding the consequences of adiposity and metabolic complications may be explained with different hormonal status and gender-specific fat distribution. These conclusions drawn from the review are in agreement with the current approach to obesity diagnosis and treatment; they should also direct the attention of clinicians to the assessment of body composition, body fat distribution, and obesity complications, rather than focussing on BMI itself.

Abbreviations

AgRP agouti-related peptide
AITD autoimmune thyroid disease
ATC anaplastic thyroid cancer
BAT brown adipose tissue
BMI body- mass index
FC follicular thyroid cancer
FFA free fatty acids
FG fasting glucose
fT3 free tri-iodothyronine
fT4 free thyroxine
HOMA-IR homeostatic model assessment of insulin resistance
HPT hypothalamus-pituitary-thyroid
HT Hashimoto's thyroiditis
IR insulin resistance
IRec insulin receptor
MetS metabolic syndrome
MHNW metabolically healthy normal weight
MHNO metabolically healthy non-obese
MHO metabolically healthy obese
MTC medullary thyroid cancer
MUO metabolically unhealthy obese
NPYneuropeptide Y
OR odds ratio
POMC proopiomelanocortin
pre-MetS pre-metabolic syndrome
PTC papillary thyroid cancer
PVN paraventricular nucleus
ROS reactive oxygen species
T3 tri-iodothyronine
T4 thyroxine
TC thyroid cancer
TG triglycerides

TGAb anti-thyroglobulin antibodies
TN thyroid nodules
TPOAb anti-thyroid peroxidase antibodies
TRH thyrotropin releasing hormone
TSH thyroid stimulating hormone
TV thyroid volume
WAT white adipose tissue
WC waist circumference

Authors' contribution

Conceptualization: Ewa Malwina Milewska and Ewelina Szczepanek- Parulska; validation: Ewelina Szczepanek- Parulska and Marek Ruchala; writing - original draft preparation: Ewa Malwina Milewska; writing - review and editing: Ewa Malwina Milewska and Ewelina Szczepanek- Parulska. All authors have read and agreed to the version of the manuscript.

ORCID

Ewa Malwina Milewska https://orcid.org/0009-0008-5145-6098
Ewelina Szczepanek- Parulska https://orcid.org/0000-0003-3661-3274
Marek Ruchala https://orcid.org/0000-0001-9743-2405

Conflict of interest

The authors have no potential conflicts of interest to declare.

References

[1] [Anonymous]. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. World Health Organ Tech Rep Ser 1995; 854: 1-452

[2] [Anonymous]. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. Obes Res 1998; 6 Suppl 2: 51S-209S

[3] Snitker S. Use of body fatness cutoff points. Mayo Clin Proc 2010; 85: 1057; author reply 1057-1058

[4] Collaboration NCDRF. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. Lancet 2017; 390: 2627-2642

[5] Garvey WT, Mechanick JI, Brett EM et al. American Association of Clinical Endocrinologists and American College of Endocrinology Comprehensive Clinical Practice Guidelines for Medical Care of Patients with Obesity. Endocr Pract 2016; 22 Suppl 3: 1-203

[6] Wharton S, Lau DCW, Vallis M et al. Obesity in adults: a clinical practice guideline. CMAJ 2020; 192: E875-E891

[7] Milewska EM, Szczepanek-Parulska E, Marciniak M et al. Selected organ and endocrine complications according to BMI and the metabolic category of obesity: A single Endocrine Center Study. Nutrients 2022; 14:

[8] Alberti KG, Eckel RH, Grundy SM et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009; 120: 1640-1645

[9] Lavie CJ, Laddu D, Arena R et al. Healthy Weight and Obesity Prevention: JACC Health Promotion Series. Journal of the American College of Cardiology 2018; 72: 1506-1531

[10] Mongraw-Chaffin M, Foster MC, Anderson CAM et al. Metabolically Healthy Obesity, Transition to Metabolic Syndrome, and Cardiovascular Risk. Journal of the American College of Cardiology 2018; 71: 1857-1865

[11] Lin H, Zhang L, Zheng R et al. The prevalence, metabolic risk and effects of lifestyle intervention for metabolically healthy obesity: a systematic review and meta-analysis: A PRISMA-compliant article. Medicine (Baltimore) 2017; 96: e8838

[12] Kramer CK, Zinman B, Retnakaran R. Are metabolically healthy overweight and obesity benign conditions?: A systematic review and meta-analysis. Annals of internal medicine 2013; 159: 758-769

[13] Fontenelle LC, Feitosa MM, Severo JS et al. Thyroid Function in Human Obesity: Underlying Mechanisms. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme 2016; 48: 787-794

[14] Song RH, Wang B, Yao QM et al. The Impact of Obesity on Thyroid Autoimmunity and Dysfunction: A Systematic Review and Meta-Analysis. Front Immunol 2019; 10: 2349

[15] Santini F, Marzullo P, Rotondi M et al. Mechanisms in endocrinology: the crosstalk between thyroid gland and adipose tissue: signal integration in health and disease. Eur J Endocrinol 2014; 171: R137-152

[16] Marzullo P, Minocci A, Tagliaferri MA et al. Investigations of thyroid hormones and antibodies in obesity: leptin levels are associated with thyroid autoimmunity independent of bioanthropometric, hormonal, and weight-related determinants. J Clin Endocrinol Metab 2010; 95: 3965-3972

[17] Ayturk S, Gursoy A, Kut A et al. Metabolic syndrome and its components are associated with increased thyroid volume and

nodule prevalence in a mild-to-moderate iodine-deficient area. Eur J Endocrinol 2009; 161: 599-605

[18] Siqueira RA, Noll M, Rodrigues APS et al. Factors Associated with the Occurrence of Thyroid Nodules in Severely Obese Patients: A Case-Control Study. Asian Pac J Cancer Prev 2019; 20: 693-697

[19] Buscemi S, Massenti FM, Vasto S et al. Association of obesity and diabetes with thyroid nodules. Endocrine 2018; 60: 339-347

[20] Harikrishna A, Ishak A, Ellinides A et al. The impact of obesity and insulin resistance on thyroid cancer: A systematic review. Maturitas 2019; 125: 45-49

[21] Schmid D, Ricci C, Behrens G et al. Adiposity and risk of thyroid cancer: a systematic review and meta-analysis. Obes Rev 2015; 16: 1042-1054

[22] Lautenbach A, Wernecke M, Mann O et al. Thyroid-stimulating hormone levels in euthyroid patients 8 years following bariatric surgery. Int J Obes (Lond) 2022; 46: 825-830

[23] van Hulsteijn LT, Pasquali R, Casanueva F et al. Prevalence of endocrine disorders in obese patients: systematic review and meta-analysis. Eur J Endocrinol 2020; 182: 11-21

[24] Pasquali R, Casanueva F, Haluzik M et al. European Society of Endocrinology Clinical Practice Guideline: Endocrine work-up in obesity. Eur J Endocrinol 2020; 182: G1-G32

[25] Szczepanek-Parulska E, Sokolowski J, Dmowska D et al. Lipid profile abnormalities associated with endocrine disorders. Endokrynol Pol 2022; DOI: 10.5603/EP.a2022.0059:

[26] Lopez M, Alvarez CV, Nogueiras R et al. Energy balance regulation by thyroid hormones at central level. Trends Mol Med 2013; 19: 418-427

[27] Coppola A, Liu ZW, Andrews ZB et al. A central thermogenic-like mechanism in feeding regulation: an interplay between arcuate nucleus T3 and UCP2. Cell Metab 2007; 5: 21-33

[28] Weiner J, Kranz M, Kloting N et al. Thyroid hormone status defines brown adipose tissue activity and browning of white adipose tissues in mice. Sci Rep 2016; 6: 38124

[29] Guzik TJ, Skiba DS, Touyz RM et al. The role of infiltrating immune cells in dysfunctional adipose tissue. Cardiovasc Res 2017; 113: 1009-1023

[30] Maurizi G, Della Guardia L, Maurizi A et al. Adipocytes properties and crosstalk with immune system in obesity-related inflammation. J Cell Physiol 2018; 233: 88-97

[31] Cao H. Adipocytokines in obesity and metabolic disease. J Endocrinol 2014; 220: T47-59

[32] Haider DG, Schaller G, Kapiotis S et al. The release of the adipocytokine visfatin is regulated by glucose and insulin. Diabetologia 2006; 49: 1909-1914

[33] Silswal N, Singh AK, Aruna B et al. Human resistin stimulates the pro-inflammatory cytokines TNF-alpha and IL-12 in macrophages by NF-kappaB-dependent pathway. Biochem Biophys Res Commun 2005; 334: 1092-1101

[34] Longhi S, Radetti G. Thyroid function and obesity. J Clin Res Pediatr Endocrinol 2013; 5 Suppl 1: 40-44

[35] Pekary AE, Levin SR, Johnson DG et al. Tumor necrosis factor-alpha (TNF-alpha) and transforming growth factor-beta 1 (TGF-beta 1) inhibit the expression and activity of Na+/K(+)-ATPase in FRTL-5 rat thyroid cells. J Interferon Cytokine Res 1997; 17: 185-195

[36] Kwakkel J, Surovtseva OV, de Vries EM et al. A novel role for the thyroid hormone-activating enzyme type 2 deiodinase in the inflammatory response of macrophages. Endocrinology 2014; 155: 2725-2734

[37] Kissebah AH, Vydelingum N, Murray R, et al. Relation of body fat distribution to metabolic complications of obesity. J Clin Endocrinol Metab. 1982; 54: 254-260.

[38] Chen YC, Jiao Y, Cui Y et al. Aberrant brain functional connectivity related to insulin resistance in type 2 diabetes: a resting-state fMRI study. Diabetes Care 2014; 37: 1689-1696

[39] Zeyda M, Stulnig TM. Obesity, inflammation, and insulin resistance--a mini-review. Gerontology 2009; 55: 379-386

[40] Griffin ME, Marcucci MJ, Cline GW et al. Free fatty acid-induced insulin resistance is associated with activation of protein kinase C theta and alterations in the insulin signaling cascade. Diabetes 1999; 48: 1270-1274

[41] Matulewicz N, Karczewska-Kupczewska M. Insulin resistance and chronic inflammation. Postepy Hig Med Dosw (Online). 2016; 70: 1245-1258.

[42] Petersen MC, Shulman GI. Mechanisms of Insulin Action and Insulin Resistance. Physiol Rev. 2018; 98: 2133-2223

[43] Jornayvaz FR, Samuel VT, Shulman GI. The role of muscle insulin resistance in the pathogenesis of atherogenic dyslipidemia and nonalcoholic fatty liver disease associated with the metabolic syndrome. Annu Rev Nutr. 2010; 30: 273-290.

[44] Sakurai Y, Kubota N, Yamauchi T, Kadowaki T. Role of insulin resistance in MAFLD. Int J Mol Sci. 2021; 22: 4156. Published 2021 Apr 16. doi:10.3390/ijms22084156

[45] Michalaki MA, Vagenakis AG, Leonardou AS et al. Thyroid function in humans with morbid obesity. Thyroid 2006; 16: 73-78

[46] Galofre JC, Pujante P, Abreu C et al. Relationship between thyroid-stimulating hormone and insulin in euthyroid obese men. Ann Nutr Metab 2008; 53: 188-194

[47] Martinez-deMena R, Obregon MJ. Insulin increases the adrenergic stimulation of 5′ deiodinase activity and mRNA expression in rat brown adipocytes; role of MAPK and PI3K. J Mol Endocrinol 2005; 34: 139-151

[48] Stepanek L, Horakova D, Stepanek L et al. Free triiodothyronine/free thyroxine (FT3/FT4) ratio is strongly associated with insulin resistance in euthyroid and hypothyroid adults: a cross-sectional study. Endokrynol Pol 2021; 72: 8-13

[49] Malaguarnera R, Vella V, Nicolosi ML et al. Insulin Resistance: Any Role in the Changing Epidemiology of Thyroid Cancer? Front Endocrinol (Lausanne) 2017; 8: 314

[50] Kimura T, Van Keymeulen A, Golstein J et al. Regulation of thyroid cell proliferation by TSH and other factors: a critical evaluation of in vitro models. Endocr Rev 2001; 22: 631-656

[51] Vella V, Pandini G, Sciacca L et al. A novel autocrine loop involving IGF-II and the insulin receptor isoform-A stimulates growth of thyroid cancer. J Clin Endocrinol Metab 2002; 87: 245-254
[52] Wang K, Yang Y, Wu Y et al. The association between insulin resistance and vascularization of thyroid nodules. J Clin Endocrinol Metab 2015; 100: 184-192
[53] Yu H, Li Q, Zhang M et al. Decreased leptin is associated with alterations in thyroid-stimulating hormone levels after Roux-en-Y gastric bypass surgery in obese euthyroid patients with Type 2 diabetes. Obes Facts 2019; 12: 272-280
[54] Betry C, Challan-Belval MA, Bernard A et al. Increased TSH in obesity: Evidence for a BMI-independent association with leptin. Diabetes Metab 2015; 41: 248-251
[55] Schaffler A, Binart N, Scholmerich J et al. Hypothesis paper Brain talks with fat--evidence for a hypothalamic-pituitary-adipose axis? Neuropeptides 2005; 39: 363-367
[56] Karpuzoglu H, Ucal Y, Kumru P et al. Increased maternal leptin levels may be an indicator of subclinical hypothyroidism in a newborn. J Med Biochem 2022; 41: 156-161
[57] Araujo RL, Andrade BM, Padron AS et al. High-fat diet increases thyrotropin and oxygen consumption without altering circulating 3,5,3′-triiodothyronine (T3) and thyroxine in rats: the role of iodothyronine deiodinases, reverse T3 production, and whole-body fat oxidation. Endocrinology 2010; 151: 3460-3469
[58] Araujo RL, Andrade BM, da Silva ML et al. Tissue-specific deiodinase regulation during food restriction and low replacement dose of leptin in rats. Am J Physiol Endocrinol Metab 2009; 296: E1157-1163
[59] Macek Jilkova Z, Pavelka S, Flachs P et al. Modulation of type I iodothyronine 5′-deiodinase activity in white adipose tissue by nutrition: possible involvement of leptin. Physiol Res 2010; 59: 561-569
[60] Ghamari-Langroudi M, Vella KR, Srisai D et al. Regulation of thyrotropin-releasing hormone-expressing neurons in paraventricular nucleus of the hypothalamus by signals of adiposity. Mol Endocrinol 2010; 24: 2366-2381
[61] Nannipieri M, Cecchetti F, Anselmino M et al. Expression of thyrotropin and thyroid hormone receptors in adipose tissue of patients with morbid obesity and/or type 2 diabetes: effects of weight loss. Int J Obes (Lond) 2009; 33: 1001-1006
[62] Kurylowicz A, Jonas M, Lisik W et al. Obesity is associated with a decrease in expression but not with the hypermethylation of thermogenesis-related genes in adipose tissues. J Transl Med 2015; 13: 31
[63] Juiz-Valina P, Cordido M, Outeirino-Blanco E et al. Central resistance to thyroid hormones in morbidly obese subjects is reversed after bariatric surgery-induced weight loss. J Clin Med 2020; 9.
[64] Tjorve E, Tjorve KM, Olsen JO et al. On commonness and rarity of thyroid hormone resistance: a discussion based on mechanisms of reduced sensitivity in peripheral tissues. Med Hypotheses 2007; 69: 913-921
[65] Laclaustra M, Moreno-Franco B, Lou-Bonafonte JM et al. Impaired sensitivity to thyroid hormones is associated with diabetes and metabolic syndrome. Diabetes Care 2019; 42: 303-310
[66] Moulin de Moraes CM, Mancini MC, de Melo ME et al. Prevalence of subclinical hypothyroidism in a morbidly obese population and improvement after weight loss induced by Roux-en-Y gastric bypass. Obes Surg 2005; 15: 1287-1291
[67] Moreira-Andrés MN, Del Cañizo-Gómez FJ, Black EG, Hoffenberg R. Long-term evaluation of thyroidal response to partial calorie restriction in obesity. Clin Endocrinol (Oxf). 1981;15: 621-626.
[68] Kaptein EM, Beale E, Chan LS. Thyroid hormone therapy for obesity and nonthyroidal illnesses: a systematic review. J Clin Endocrinol Metab. 2009; 94: 3663-3675.
[69] Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: prepared by the american thyroid association task force on thyroid hormone replacement. Thyroid. 2014; 24: 1670-1751.
[70] Villarroya F, Cereijo R, Villarroya J et al. Brown adipose tissue as a secretory organ. Nat Rev Endocrinol 2017; 13: 26-35
[71] Bianco AC, Sheng XY, Silva JE. Triiodothyronine amplifies norepinephrine stimulation of uncoupling protein gene transcription by a mechanism not requiring protein synthesis. J Biol Chem 1988; 263: 18168-18175
[72] Branco M, Ribeiro M, Negrao N et al. 3,5,3′-Triiodothyronine actively stimulates UCP in brown fat under minimal sympathetic activity. Am J Physiol 1999; 276: E179-187
[73] Silva JE, Larsen PR. Potential of brown adipose tissue type II thyroxine 5′-deiodinase as a local and systemic source of triiodothyronine in rats. J Clin Invest 1985; 76: 2296-2305
[74] Wang Q, Zhang M, Ning G et al. Brown adipose tissue in humans is activated by elevated plasma catecholamines levels and is inversely related to central obesity. PLoS One 2011; 6: e21006
[75] Reynisdottir S, Wahrenberg H, Carlstrom K et al. Catecholamine resistance in fat cells of women with upper-body obesity due to decreased expression of beta 2-adrenoceptors. Diabetologia 1994; 37: 428-435
[76] Chamberlain PD, Jennings KH, Paul F et al. The tissue distribution of the human beta3-adrenoceptor studied using a monoclonal antibody: direct evidence of the beta3-adrenoceptor in human adipose tissue, atrium and skeletal muscle. Int J Obes Relat Metab Disord 1999; 23: 1057-1065
[77] Valentine JM, Ahmadian M, Keinan O et al. beta3-Adrenergic receptor downregulation leads to adipocyte catecholamine resistance in obesity. J Clin Invest 2022; 132:
[78] Guo T, Marmol P, Moliner A et al. Adipocyte ALK7 links nutrient overload to catecholamine resistance in obesity. Elife 2014; 3: e03245
[79] Alcala M, Calderon-Dominguez M, Serra D et al. Mechanisms of Impaired Brown Adipose Tissue Recruitment in Obesity. Front Physiol 2019; 10: 94
[80] Villarroya F, Cereijo R, Villarroya J et al. Toward an Understanding of How Immune Cells Control Brown and Beige Adipobiology. Cell Metab 2018; 27: 954-961
[81] Araujo RL, Carvalho DP. Bioenergetic impact of tissue-specific regulation of iodothyronine deiodinases during nutritional imbalance. J Bioenerg Biomembr 2011; 43: 59-65

[82] de Heredia FP, Gómez-Martínez S, Marcos A. Obesity, inflammation and the immune system. Proc Nutr Soc. 2012; 71: 332-338.

[83] Deng J, Neff LM, Rubert NC, et al. MRI characterization of brown adipose tissue under thermal challenges in normal weight, overweight, and obese young men. J Magn Reson Imaging. 2018; 47: 936-947. doi:10.1002/jmri.25836

[84] Kang S, Bajnok L, Longo KA, et al. Effects of Wnt signaling on brown adipocyte differentiation and metabolism mediated by PGC-1alpha. Mol Cell Biol. 2005; 25: 1272-1282. doi:10.1128/MCB.25.4.1272-1282.2005

[85] Villarroya F, Cereijo R, Gavaldà-Navarro A, Villarroya J, Giralt M. Inflammation of brown/beige adipose tissues in obesity and metabolic disease. J Intern Med. 2018; 284: 492-504.

[86] Hollowell JG, Staehling NW, Flanders WD et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 2002; 87: 489-499

[87] Garmendia Madariaga A, Santos Palacios S, Guillen-Grima F et al. The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. J Clin Endocrinol Metab 2014; 99: 923-931

[88] Fierabracci P, Pinchera A, Martinelli S et al. Prevalence of endocrine diseases in morbidly obese patients scheduled for bariatric surgery: beyond diabetes. Obes Surg 2011; 21: 54-60

[89] Guo X, He Z, Shao S et al. Interaction effect of obesity and thyroid autoimmunity on the prevalence of hyperthyrotropinaemia. Endocrine 2020; 68: 573-583

[90] Radetti G, Kleon W, Buzi F et al. Thyroid function and structure are affected in childhood obesity. J Clin Endocrinol Metab 2008; 93: 4749-4754

[91] Rotondi M, Cappelli C, Leporati P et al. A hypoechoic pattern of the thyroid at ultrasound does not indicate autoimmune thyroid diseases in patients with morbid obesity. Eur J Endocrinol 2010; 163: 105-109

[92] Ittermann T, Markus MR, Schipf S et al. Metformin inhibits goitrogenous effects of type 2 diabetes. Eur J Endocrinol 2013; 169: 9-15

[93] Belfiore A, Malaguarnera R, Vella V, et al. Insulin receptor isoforms in physiology and disease: An updated view. Endocr Rev. 2017; 38: 379-431. doi:10.1210/er.2017-00073

[94] Moruzzi N, Lazzeri-Barcelo F. Insulin Receptor Isoforms in Physiology and Metabolic Disease [Internet]. Evolving Concepts in Insulin Resistance. IntechOpen; 2022.

[95] Leibiger B, Leibiger IB, Moede T, et al. Selective insulin signaling through A and B insulin receptors regulates transcription of insulin and glucokinase genes in pancreatic beta cells. Mol Cell. 2001; 7: 559-570.

[96] Kaminska D, Hämäläinen M, Cederberg H, et al. Adipose tissue INSR splicing in humans associates with fasting insulin level and is regulated by weight loss. Diabetologia. 2014; 57: 347-351.

[97] Rezzonico JN, Rezzonico M, Pusiol E et al. Increased prevalence of insulin resistance in patients with differentiated thyroid carcinoma. Metab Syndr Relat Disord 2009; 7: 375-380

[98] Avgerinos KI, Spyrou N, Mantzoros CS et al. Obesity and cancer risk: Emerging biological mechanisms and perspectives. Metabolism 2019; 92: 121-135

[99] Lauby-Secretan B, Scoccianti C, Loomis D et al. Body fatness and cancer--Viewpoint of the IARC Working Group. N Engl J Med 2016; 375: 794-798

[100] Wang Y, Lin H, Li Q et al. Association between different obesity phenotypes and hypothyroidism: a study based on a longitudinal health management cohort. Endocrine 2021; 72: 688-698

[101] Nie X, Ma X, Xu Y et al. Characteristics of Serum Thyroid Hormones in Different Metabolic Phenotypes of Obesity. Front Endocrinol (Lausanne) 2020; 11: 68

[102] Kim JM, Kim BH, Lee H et al. The relationship between thyroid function and different obesity phenotypes in Korean euthyroid adults. Diabetes Metab J 2019; 43: 867-878

[103] Amouzegar A, Kazemian E, Abdi H et al. Association between thyroid function and development of different obesity phenotypes in euthyroid adults: A nine-year follow-up. Thyroid 2018; 28: 458-464

[104] Shin JA, Mo EY, Kim ES et al. Association between lower normal free thyroxine concentrations and obesity phenotype in healthy euthyroid subjects. Int J Endocrinol 2014; 2014: 104318

[105] Amouzegar A, Kazemian E, Abdi H et al. Abdominal Obesity Phenotypes and Incidence of Thyroid Autoimmunity: A 9-Year Follow-up. Endocr Res 2020; 45: 202-209

[106] Yang H, Xia Q, Shen Y et al. Gender-specific impact of metabolic obesity phenotypes on the risk of Hashimoto's Thyroiditis: A retrospective data analysis using a health check-up database. J Inflamm Res 2022; 15: 827-837

[107] Zhang C, Gao X, Han Y et al. Correlation Between Thyroid Nodules and Metabolic Syndrome: A Systematic Review and Meta-Analysis. Front Endocrinol (Lausanne) 2021; 12: 730279

[108] Zhang F, Li Y, Yu X et al. The Relationship and Gender Disparity Between Thyroid Nodules and Metabolic Syndrome Components Based on a Recent Nationwide Cross-Sectional Study and Meta-Analysis. Front Endocrinol (Lausanne) 2021; 12: 736972

[109] Guo W, Tan L, Chen W et al. Relationship between metabolic syndrome and thyroid nodules and thyroid volume in an adult population. Endocrine 2019; 65: 357-364

[110] Xu L, Zeng F, Wang Y et al. Prevalence and associated metabolic factors for thyroid nodules: a cross-sectional study in Southwest of China with more than 120 thousand populations. BMC Endocr Disord 2021; 21: 175

[111] Song B, Zuo Z, Tan J et al. Association of thyroid nodules with adiposity: a community-based cross-sectional study in China. BMC Endocr Disord 2018; 18: 3

[112] Su Y, Zhang YL, Zhao M et al. Association between thyroid nodules and volume and metabolic syndrome in an iodine-adequate area: A large community-based population study. Metab Syndr Relat Disord 2019; 17: 217-222

[113] Son H, Lee H, Kang K et al. The risk of thyroid cancer and obesity: A nationwide population-based study using the Korea National

Health Insurance Corporation cohort database. Surg Oncol 2018; 27: 166-171

[114] Youssef MR, Reisner ASC, Attia AS et al. Obesity and the prevention of thyroid cancer: Impact of body mass index and weight change on developing thyroid cancer - Pooled results of 24 million cohorts. Oral Oncol 2021; 112: 105085

[115] He Q, Sun H, Li F et al. Obesity and risk of differentiated thyroid cancer: A large-scale case-control study. Clin Endocrinol (Oxf) 2019; 91: 869-878

[116] Kitahara CM, Pfeiffer RM, Sosa JA et al. Impact of Overweight and Obesity on US Papillary Thyroid Cancer Incidence Trends (1995-2015). J Natl Cancer Inst 2020; 112: 810-817

[117] Fussey JM, Beaumont RN, Wood AR et al. Does obesity cause thyroid cancer? A Mendelian randomization study. J Clin Endocrinol Metab 2020; 105:

[118] Rotondi M, Castagna MG, Cappelli C et al. Obesity does not modify the risk of differentiated thyroid cancer in a cytological series of thyroid nodules. Eur Thyroid J 2016; 5: 125-131

[119] Ahmadi S, Pappa T, Kang AS et al. Point of care measurement of Body Mass Index and thyroid nodule malignancy risk sssessment. Front Endocrinol (Lausanne) 2022; 13: 824226

[120] Zheng X, Peng R, Xu H et al. The association between metabolic status and risk of cancer among patients with obesity: Metabolically Healthy Obesity vs. Metabolically Unhealthy Obesity. Front Nutr 2022; 9: 783660

[121] Lin CJ, Chang YC, Cheng TY et al. The association between metabolically healthy obesity and risk of cancer: A systematic review and meta-analysis of prospective cohort studies. Obes Rev 2020; 21: e13049

[122] Kwon H, Chang Y, Cho A et al. Metabolic obesity phenotypes and thyroid cancer risk: A cohort study. Thyroid 2019; 29: 349-358

[123] Nguyen DN, Kim JH, Kim MK. Association of metabolic health and central obesity with the risk of thyroid cancer: Data from the Korean Genome and Epidemiology Study. Cancer Epidemiol Biomarkers Prev 2022; 31: 543-553

[124] Biondi B, Kahaly GJ, Robertson RP. Thyroid dysfunction and diabetes mellitus: Two closely associated disorders. Endocr Rev 2019; 40: 789-824

[125] Sawicka-Gutaj N, Zybek-Kocik A, Kloska M et al. Effect of restoration of euthyroidism on visfatin concentrations and body composition in women. Endocr Connect 2021; 10: 462-470

[126] Stangierski A, Ruchala M, Krauze T et al. Treatment of severe thyroid function disorders and changes in body composition. Endokrynol Pol 2016; 67: 359-366

[127] Jacobsen R, Lundsgaard C, Lorenzen J et al. Subnormal energy expenditure: a putative causal factor in the weight gain induced by treatment of hyperthyroidism. Diabetes Obes Metab 2006; 8: 220-227

[128] Roef GL, Rietzschel ER, Van Daele CM et al. Triiodothyronine and free thyroxine levels are differentially associated with metabolic profile and adiposity-related cardiovascular risk markers in euthyroid middle-aged subjects. Thyroid 2014; 24: 223-231

[129] Teixeira P, Dos Santos PB, Pazos-Moura CC. The role of thyroid hormone in metabolism and metabolic syndrome. Ther Adv Endocrinol Metab 2020; 11: 2042018820917869

[130] Bjergved L, Jorgensen T, Perrild H et al. Thyroid function and body weight: a community-based longitudinal study. PLoS One 2014; 9: e93515

[131] Soriguer F, Valdes S, Morcillo S et al. Thyroid hormone levels predict the change in body weight: a prospective study. Eur J Clin Invest 2011; 41: 1202-1209

[132] Olszanecka-Glinianowicz M, Chudek J, Szromek A et al. Changes of systemic microinflammation after weight loss and regain - a five-year follow up study. Endokrynol Pol 2012; 63: 432-438

[133] Khan WF, Singla V, Aggarwal S et al. Outcome of bariatric surgery on hypothyroidism: experience from a tertiary care center in India. Surg Obes Relat Dis 2020; 16: 1297-1301

[134] Ostrowska L, Gier D, Zysk B. The influence of reducing diets on changes in thyroid parameters in women suffering from obesity and Hashimoto's Disease. Nutrients 2021; 13:

[135] Fruhbeck G, Busetto L, Dicker D et al. The ABCD of Obesity: An EASO Position Statement on a Diagnostic Term with Clinical and Scientific Implications. Obes Facts 2019; 12: 131-136

[136] Duntas LH, Biondi B. The interconnections between obesity, thyroid function, and autoimmunity: the multifold role of leptin. Thyroid 2013; 23: 646-653

[137] Farghaly HS, Metwalley KA, Ahmed FA et al. Visfatin level in children and adolescents with autoimmune thyroiditis. Ther Adv Endocrinol Metab 2017; 8: 119-125

[138] Sawicka-Gutaj N, Zybek-Kocik A, Klimowicz A et al. Circulating visfatin in hypothyroidism is associated with free thyroid hormones and antithyroperoxidase antibodies. Int J Endocrinol 2016; 2016: 7402469

[139] Belligoli A, Compagnin C, Sanna M et al. Characterization of subcutaneous and omental adipose tissue in patients with obesity and with different degrees of glucose impairment. Sci Rep 2019; 9: 11333