Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2024.234154.2873 Volume 30, Issue 4, July 2024
Manuscript ID ZUMJ-2311-3008 (R1)
DOI 10.21608/ZUMJ.2023.249581.3008

Review Article

Is There an Association between Thyroid Disease and Metabolic Syndrome

Ahmed Khamees Saeid[1*], Hatem Mahmoud Salem[1], Moanes Mohamed Arafa[2], Nermin Saad Ghanem[1]

1-Internal Medicine Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt
2-Radiodiagnosis Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt

Corresponding author:
Ahmed Khamees Saeid

Email:
ahmadkhamissaeed@gmail.com

Submit Date 18-11-2023
Revise Date 25-11-2023
Accept Date 01-12-2023

ABSTRACT:

Background: The metabolic syndrome and thyroid dysfunctions are the two most prevalent endocrine illnesses, and they significantly overlap. Due to their strong associations with morbidity and mortality, both have a huge global influence on health care. Insulin resistance (IR) is a primary component of metabolic syndrome (MetS) which is a collection of disorders related to metabolism. The management and maintenance of cellular energy balance depend on thyroid hormones (TH). Both the central nervous system and TH's direct connection with peripheral target organs serve as mediating mechanisms for these activities. Recently, there has been discussion on the potential link between MetS and its constituent parts , changes in the morphology and function of the thyroid gland. Studies concentrating on TNs' risk factors are required because of the disease's significant morbidity.

Aim: To summarize recent developments in the association of thyroid function with metabolic syndrome (MetS).

Conclusions: Thyroid stimulating hormone, free T3, free T4, and metabolic parameters have a complex relationship that may be influenced by inflammatory markers, age, sex, BMI, insulin resistance, smoking, iodine intake, and other factors.

Keywords: Thyroid; Hypothyroidism; Hyperthyroidism; Metabolic Syndrome

INTRODUCTION

The corpus of research suggests that thyroid function abnormalities impact blood pressure (BP), body weight, and the metabolism of lipids and glucose. These factors are linked to a number of metabolic markers, which could consequently result in the onset or exacerbation of MetS components. Thyroid hormones have an impact on both insulin resistance and obesity, which are strongly related to the pathophysiology of Metabolic Syndrome (MetS) [1].

The co-occurrence of thyroid insufficiency and MetS may exacerbate their shared metabolic characteristics, particularly in overt hypothyroid states, which has a significant influence on population health in terms of metabolic and cardiovascular risk factors, particularly in the elderly. Proof of low normal thyroid function or subclinical thyroid function is highly disputed. The relationship between MetS/insulin resistance and thyroid autoimmunity is also not well established at this time because there is insufficient data, especially in obese people [2].

One of the hypothesized reasons for MetS is inflammation; however, there is no proof that thyroid function directly affects inflammatory markers, such as IL-6 and high-sensitivity C-reactive protein (hsCRP), or that thyroid

https://doi.org/10.21608/zumj.2024.234154.2873 Volume 30, Issue 4, July 2024

antibodies are associated with inflammatory markers [3].

Metabolic syndrome and low normal thyroid function:

Regarding the relationship between thyroid hormones and MetS in euthyroid people, a number of researches present contradictory findings, most evaluate the syndrome's constituent parts rather than the condition as a whole. The majority of papers first discuss how serum levels of thyroid stimulating hormone (TSH) are related to MetS components, and then they concentrate on free thyroxine, or freeT4 (FT4). Studies examining the FT3/FT4 ratio or free triiodothyronine levels (free T3 (FT3)) have been relatively modest in number. However, the majority of researches use a cross-sectional methodology, and longitudinal studies are required to clarify causation and determine how variations in thyroid hormones affect the incidence of MetS [1].

Sex impact:

Sex has a significant impact on MetS, thyroid function, and the relationships between these variables. Whether sex-split analysis or a straightforward correction for sex is employed may explain the notable variations in the findings of various research. The various ways that sex hormones affect thyroid metabolism, including how estrogen affects women's lipid profiles and TSH levels as well as postmenopausal effects and low testosterone levels on MetS parameters in men, may be the cause of the gender gap. It has also been suggested that sex differences have a genetic foundation [4, 5].

Age impact:

In older adults, the relationship between serum TSH and MetS may be different. It has been observed that FT3 levels gradually decreased with advancing age, although TSH and FT4 levels remained rather stable. FT3/FT4 ratios have been shown to rise in tandem with TSH levels up to the age of 40. After that point, though, the influence of TSH on T3 production is said to be muted, which could be because of decreased deiodinase activity, the aging-related development of TSH resistance, or a combination of these factors. Aging rats showed a similar discrepancy in the TSH-FT3 relationship [6].

BMI impact:

Although the relationship between obesity and thyroid function is still unknown, interventional research have supported both theories. Obesity may affect thyroid function, while thyroid function alterations may affect body weight. In contrast, insulin resistance in obese people may cause compensatory hyperinsulemia, which may lower DIO2 activity and mimic a hypothyroid state. Obese people may have reduced gene expression of TSH and FT3 receptors in their visceral and subcutaneous fat as a compensatory mechanism to deal with peripheral resistance that results from hypertrophic alterations in adipocytes, which raises TSH and FT3 levels [7, 8].

According to research using direct measurements of body composition (computed tomography scan) and insulin resistance (euglycemic clamp), obese people have a significantly higher TSH but no variations in FT3 or FT4. This finding points to a possible connection between the rise in visceral fat and the subsequent development of insulin resistance. Because BMI is not a reliable indicator of the distribution of fat mass and because different people have different body compositions, not all obese or overweight people will necessarily be insulin resistant, controversial findings from previous studies may have been pertaining to the estimation of insulin resistance and adipose tissue via indirect approaches [9].

The influence of additional variables Even though they have a big impact on MetS components, alcohol use and smoking have received less attention in this research. For instance, alcohol intake may have a negative effect on high density lipoprotein (HDL) cholesterol (HDL-C), blood pressure, and waist circumference. Smoking also may have a deleterious effect on HDL-C levels. A reduced iodine pool, which has not been taken into account in most researches, may be another reason explaining the greater ratios of FT3/FT4 and TSH in those with less ideal metabolic profiles [10].

https://doi.org/10.21608/zumj.2024.234154.2873 Volume 30, Issue 4, July 2024

Hypothyroidism and metabolic syndrome:

Subclinical hypothyroidism (SCH) has been linked in numerous studies to obesity, worsening lipid profiles, elevated blood pressure, and systemic inflammatory markers that are similar to those seen in meta-Syndrome (MetS). Most of these studies don't evaluate MetS as a whole and have a cross-sectional design. MetS patients had a significantly higher chance of developing SCH over a 4-year follow-up compared to non-MetS participants, according to a single cohort study involving 66,822 Taiwanese individuals [11].

Regarding glycemia and insulin resistance in thyroid dysfunction individuals, there are disagreements. It has been documented that overt hypothyroidism (OH) is associated with decreased insulin sensitivity, SCH and OH both exhibit insulin resistance, a feature that may reach subclinical or even physiological levels. This suggests that the lower the thyroid hormone levels, the less sensitive tissues are to insulin [12].

There have been reports of fasting hyperinsulinemia in SCH patients with reduced or normal homeostatic model assessment for insulin resistance (HOMA-IR). On the other hand, poor glycemic control in individuals with type 2 diabetes may be a sign of thyroid dysfunction. This may be due to decreased glucose oxidation, decreased glycogen synthesis, downregulation of glucose transporters, and decreased intracellular glucose consumption. This suggests that diseases associated with insulin resistance are linked to thyroid hypofunction like MetS and cardiovascular disease (CVD), and that these links are more pronounced in cases of overt hypothyroidism than in cases of subclinical or thyroid function that is below normal. However, the conclusions regarding MetS are more debatable [13].

Levothyroxine's positive effects on body weight in obese persons with SCH who had TSH levels less than 10 mU/l are not supported by any research. The relationship between BMI and thyroid hormones is well known, and vice versa. Following weight loss, there are studies showing that thyroid hormone levels can be returned to normal [14].

Even in cases of moderate SCH, observational studies also show a correlation between SCH and elevated triglycerides, low density lipoprotein (LDL-C), or low-density lipoprotein, and total cholesterol (TC). Levothyroxine dramatically increased LDL-C levels in SCH patients in a meta-analysis, despite having no discernible effect on TC, triglycerides, or HDL-C levels. Few SCH patients reported a significant improvement in their lipid profile, and the results on the effects of levothyroxine medication on lipid profiles were inconsistent [15].

There have been reports of improvements in the metabolic abnormalities in SCH patients after receiving LT4 therapy; however, more clinical research is needed to assess the impact of LT4 therapy over time on cardiovascular and metabolic risks in individuals with SCH, suggesting that mild thyroid hypofunction screening and treatment may be necessary. Overall, there is disagreement over the risks, advantages, and clinical significance of treatment for people with TSH levels less than 10 mU/l, particularly in relation to metabolic abnormalities, even though there is evidence of a decreased CVD risk after levothyroxine therapy in SCH. This heterogeneity in the reports may be partially explained by the inclusion of different TSH levels [16].

Thyroid autoimmunity and metabolic syndrome:

It is unclear how thyroid autoimmunity contributes to insulin resistance and MetS. Similar to the frequency of autoimmune thyroid disease (AITD), several researches suggest a female dominance in MetS. Furthermore, increased TSH and IL-6 levels have been found in MetS and AIT, indicating a potential connection between AITD and MetS. There is contradictory data on the metabolic and cardiovascular risks associated with Hashimoto's thyroiditis [17].

While other studies revealed no correlation between thyroid antibody levels and coronary heart disease, Waring et al. reported a higher

https://doi.org/10.21608/zumj.2024.234154.2873 Volume 30, Issue 4, July 2024

frequency of MetS in Hashimoto's thyroiditis [18, 19].

AITD has been positively correlated specifically in women, with hemoglobin A1c, HOMA-IR, obesity, central obesity, hyperlipidemia, and MetS, as demonstrated by a study on 9082 Chinese euthyroid persons [20].

Another study on postmenopausal euthyroid women found no difference in the prevalence of MetS between the thyroid peroxidase antibody (TPOAb)-positive and negative groups, despite the fact that obese subclinical hypothyroid women with Hashimoto's thyroiditis had a higher prevalence of the condition. This was in contrast to the study on obese people, which refuted the idea that TPOAb contributed to the development of MetS [21].

TPOAb was linked to HOMA-IR and hsCRP levels regardless of thyroid function, 5608 nonobese euthyroid individuals participated in the study. This research implies a connection between insulin resistance, chronic inflammation, and minor variations in thyroid hormone levels, thyroid autoimmunity, and metabolic problems in the nonobese population. To ascertain if levothyroxine medication could be beneficial in reducing the incidence of MetS for TPO or CVD even in cases of euthyroidism or ab positive individuals, more clinical trials are required [22].

Hyperthyroidism and metabolic syndrome:

While it is common to find insulin resistance the likelihood of MetS in hyperthyroidism is lower in this condition because excess thyroid hormones have catabolic effects that can affect body mass and lipid composition. Numerous investigations have revealed insulin resistance in hyperthyroidism, even in its preclinical form, and hyperglycemia, a dysmetabolic condition, in subclinical forms of the disease [22].

In keeping with the findings of Yavuz et al. indicating lower insulin sensitivity in a group with subclinical hyperthyroidism, Maratou et al. postulated the occurrence of insulin resistance in both fasting and post-glucose stages [12, 23].

This equilibrium can be disrupted and glucose intolerance brought on by excess (or even deficiency) thyroid hormone, especially after hepatic insulin resistance because of increased hepatic output of glucose through increased rates of gluconeogenesis and glycogenolysis. In certain organs, thyroid hormones can have an antagonistic (liver) or agonistic (muscles) effect on insulin. Crucially, earlier studies have shown that the insulin resistance index and even slight decreases in thyroid hormone levels within the normal range are negatively correlated [24].

Thyroid nodules and metabolic syndrome:

According to certain research, individuals with several MetS components had a higher risk of thyroid nodules than those with one or no MetS component. Thyroid nodules are also more common in people with poorly treated MetS, particularly in those with uncontrolled aberrant glucose metabolism [25].

Research has indicated a favorable correlation between the incidence of thyroid nodules and insulin resistance. Through insulin or insulin-like growth factor 1, insulin resistance may directly activate the proliferation pathway, controlling thyroid gene expression as well as the proliferation and differentiation of thyroid cells [26].

Moreover, there is a chance that insulin resistance is related to the thyroid's vascular structure, which would promote the growth of thyroid nodules. To find out whether variations in other metabolic markers can promote thyroid nodule formation in certain ways, more investigations are still required [27].

A recent meta-analysis revealed that because TNs were more common in men, women, and children, the increased prevalence of MetS in TN patients was not correlated with sex and combination groups when MetS patients were studied based on sex. These differences were not statistically significant. Since the differences in the age-based subgroup analysis were not statistically significant, it cannot be concluded that there are differences in the prevalence of MetS among TN patients under 40, between 40 and 50, between 50 and 60, and above 60 years of age. However, the

https://doi.org/10.21608/zumj.2024.234154.2873 Volume 30, Issue 4, July 2024

researchers were unable to show a connection between TNs and MetS in the population with low iodine levels [28].

Everyone is aware of the important role iodine plays in the onset and progression of thyroid disorders. The onset of TNs may potentially be caused by the body consuming too much or too little iodine. In cases of iodine excess, thyroid nodules are more common to be multiple, but in cases of iodine deficit, thyroid nodules are more common to be solitary [29].

MetS occurrence is also linked to iodine nutrition in addition to TN. Iodine deficiency was linked to elevated blood pressure and cholesterol, and a cross-sectional investigation found a correlation between urine iodine concentration (UIC) and problems connected to metabolism, which showed up as a U-shaped curve [30].

Iodine's physiological role in the human body is mostly determined by its properties as a halogen element. Iodine is prone to free radical reactions and is quite reactive. Since iodine is an antioxidant, it can directly function as an electron donor to reduce reactive oxygen species (ROS). It can also be used as a free radical to iodinate unsaturated fatty acids and tyrosine on cell membranes, reducing their reactivity with free radicals, in order to accomplish the anti-oxidation purpose. Iodine's lowering qualities can aid in the thyroid's regular function, aid in the synthesis of thyroid hormones, and potentially help with long-term metabolic disorders linked to free radical damage [31].

CONCLUSIONS

Although the danger of MetS is still debatable, according to the review, people who already have thyroid hypofunction especially when it is at low normal levels run the risk of developing several metabolic disorders. The intricate link between TSH, FT3, FT4, and metabolic parameters can be impacted by inflammatory indicators, age, sex, BMI, insulin resistance, smoking, alcohol consumption, iodine intake, and other factors. The same conclusion cannot be drawn for general populations because these factors' distributions vary significantly amongst populations. Furthermore, the majority of researches employ indirect methods to estimate BMI and insulin resistance, which may not accurately reflect the distribution of fat mass and may cause misunderstandings. Because minor thyroid hypofunction has negative effects on the metabolism and cardiovascular system, screening and treatment may be necessary, especially in light of the possibility of side effects from replacement therapy, such as osteoporosis and atrial fibrillation. The only two conditions that may be linked to hyperthyroidism are insulin resistance and dysglycemia. Even in patients with low normal TSH values, AITD may represent a possible risk factor for metabolic disorders. Before we can make any firm judgments about the usefulness of thyroid hormone treatment for people with SCH or low normal thyroid function, there is still a great deal of information that has to be gathered.

Declaration of interest

The authors report no conflicts of interest.

Funding information

None declared

REFERENCES

1. **Mehran L, Amouzegar A, Azizi F.** Thyroid disease and the metabolic syndrome. Curr Opin Endocrinol., *Diabetes Obes Metab*, 2019; *26*(5), 256-65.
2. **Agbaht K, Mercan Y, Kutlu S, Alpdemir MF, Sezgin T.** Obesity with and without metabolic syndrome: do vitamin D and thyroid autoimmunity have a role? Diabetes Res. Clin. Pract., 2014; 106(1), 27-34.
3. **Raposo L, Martins S, Ferreira D, Guimarães T, Santos C.** Metabolic syndrome, thyroid function and autoimmunity-the PORMETS study. Endocr Metab Immune Disord Drug, 2019; 19(1), 75-83.
4. **Fröhlich E and Wahl R.** Insight into potential interactions of thyroid hormones, sex hormones and their stimulating hormones in the development of non-alcoholic fatty liver disease. Metabolites, 2022, 12(8), 718.
5. **Rawal R, Teumer A, Völzke H, Wallaschofski H, Ittermann T, Åsvold O, et al.** Meta-analysis of two genome-wide association studies identifies four genetic loci associated with thyroid function. Hum. Mol. Genet., 2012; 21(14), 3275-82.
6. **Xu F, Cohen A, Lofgren E, Greene W, Delmonico J, Greaney L.** The association between physical activity and metabolic syndrome in older adults with obesity. J. frailty and aging. 2019, 8, 27-32.
7. **Nannipieri M, Cecchetti F, Anselmino M, Camastra S, Niccolini P, Lamacchia M, et al.** Expression of thyrotropin and thyroid hormone receptors in adipose

https://doi.org/10.21608/zumj.2024.234154.2873 Volume 30, Issue 4, July 2024

tissue of patients with morbid obesity and/or type 2 diabetes: effects of weight loss. *IJO*, 2009; 33(9), 1001-6.

8. **Emiroğlu C, Özdemir Ç, Görpelioğlu S, Aypak C.** The Relationship between thyroid hormones, metabolic syndrome and HOMA-IR in people with obesity or overweight. Clin. Diabetol., 2022, 11(5), 333-9.
9. **Muscogiuri G, Sorice P, Mezza T, Prioletta A, Lassandro P, Pirronti T, et al**. High‐normal tsh values in obesity: Is it insulin resistance or adipose tissue's guilt? Obes., 2013; 21(1), 101-6.
10. **Slagter N, van Waateringe P, van Beek P, van der Klauw M, Wolffenbuttel H, van Vliet-Ostaptchouk V.** Sex, BMI and age differences in metabolic syndrome: the Dutch lifelines cohort study. Endocr. Connect., 2017; 6(4), 278.
11. **Chang H, Yeh C, Caffrey L, Shih R, Chuang M, Tu K.** Metabolic syndrome is associated with an increased incidence of subclinical hypothyroidism–A cohort study. Sci. Rep., 2017; 7(1), 1-8.
12. **Ding X, Zhao Y, Zhu Y, Wu P, Wang Y, Peng Y, et al.** The association between subclinical hypothyroidism and metabolic syndrome: an update meta-analysis of observational studies. Endocr. J., 2021, 68(9), 1043-56.
13. **Iwen A, Oelkrug R, Kalscheuer H, Brabant G.** Metabolic syndrome in thyroid disease. Endocr Metab Disord., 2018; 49, 48-66.
14. **Pearce H, Brabant G, Duntas H, Monzani F, Peeters P, Razvi S, et al.** 2013 ETA guideline: management of subclinical hypothyroidism. Eur. Thyroid J., 2013; 2(4), 215-28.
15. **Li X, Meng Z, Jia Q, Ren X.** Effect of L-thyroxine treatment versus a placebo on serum lipid levels in patients with sub-clinical hypothyroidism. Biomed. Rep., 2016; 5(4), 443-49.
16. **Chen S, Wohlford F, Vecchie A, Carbone S, Yavuz S, Van Tassell B et al.** Acute effects of liothyronine administration on cardiovascular system and energy metabolism in healthy volunteers. Front. Endocrinol., 2022, 13, 843539.
17. **Merrill J, Mu Y.** Thyroid autoimmunity as a window to autoimmunity: an explanation for sex differences in the prevalence of thyroid autoimmunity. J. Theor. Biol., 2015; 375, 95-100.
18. **Corona G, Croce L, Sparano C, Petrone L, Sforza A, Maggi M et al.** Thyroid and heart, a clinically relevant relationship. J Endocrinol Invest, 2021, 44(12), 2535-44.
19. **Collet H, Bauer C, Cappola R, Åsvold O, Weiler S, Vittinghoff E, et al.** Thyroid antibody status, subclinical hypothyroidism, and the risk of coronary heart disease: an individual participant data analysis. J. Clin. Endocrinol. Metab., 2014; 99(9), 3353-62.
20. **Chen Y, Zhu C, Chen Y, Wang N, Li Q, Han B, et al**. Are thyroid autoimmune diseases associated with cardiometabolic risks in a population with normal thyroid-stimulating hormone? *Mediators* Inflame., *2018*.
21. **Siemińska L, Wojciechowska C, Walczak K, Borowski A, Marek B, Nowak M, et al.** Associations between metabolic syndrome, serum thyrotropin, and thyroid antibodies status in postmenopausal women, and the role of interleukin-6. Endokrynol Pol, 2015; 66(5), 394-403.
22. **Liu J, Duan Y, Fu J, Wang G.** Association between thyroid hormones, thyroid antibodies, and cardiometabolic factors in non-obese individuals with normal thyroid function. Front. Endocrinol., 2018, 9, 130.
23. **Yavuz G, Toprak A, Deyneli O, Aydın H, Yüksel M, Akalın S.** Exogenous subclinical hyperthyroidism impairs endothelial function in nodular goiter patients. Thyroid, 2008; 18(4), 395-400.
24. **Brenta G.** Why can insulin resistance be a natural consequence of thyroid dysfunction? J. Thyroid Res., 2011.
25. **Shin J, Kim H, Yoon H, Kang I, Cha Y, Lim J.** Relationship between metabolic syndrome and thyroid nodules in healthy Koreans. Korean J. Intern. Med., 2016; 31(1), 98.
26. **Badia X, Valassi E, Roset M, Webb M.** Disease-specific quality of life evaluation and its determinants in Cushing's syndrome: what have we learnt?. Pituitary, 2014; 17(2), 187-95.
27. **Eggo C.** Molecular regulation of thyroid gland function. *Current opinion in endocrinology,* Diabetes Obes Metab, 2010; 17(5), 396-401.
28. **Zhang C, Gao X, Han Y, Teng W, Shan Z.** Correlation between thyroid nodules and metabolic syndrome: a systematic review and meta-analysis. Front. Endocrinol., 2021; 12, 730279.
29. **Shan Z, Chen L, Lian X, Liu C, Shi B, Shi L, et al.** Iodine status and prevalence of thyroid disorders after introduction of mandatory universal salt iodization for 16 years in China: a cross-sectional study in 10 cities. Thyroid, 2016; 26(8), 1125-30.
30. **Jin M, Zhang Z, Li Y, Teng D, Shi X, Ba J, et al.** U-shaped associations between urinary iodine concentration and the prevalence of metabolic disorders: a cross-sectional study. Thyroid, 2020; 30(7), 1053-65.
31. **Zbigniew S.** Role of iodine in metabolism. Recent Pat Endocr Metab Immune Drug Discov, 2016; 10(2), 123-6.

Citation:

SAEID, A., Salem, H., Enaba, M., Ghanem, N. Is There an Association between Thyroid Disease and Metabolic Syndrome. *Zagazig University Medical Journal*, 2024; (2021-2026): -. doi: 10.21608/zumj.2023.249581.3008