The role of thyroid hormone in metabolism and metabolic syndrome

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Abstract: Metabolic syndrome (MetS) and thyroid dysfunction are common in clinical practice. The objectives of this review are to discuss some proposed mechanisms by which thyroid dysfunctions may lead to MetS, to describe the bidirectional relationship between thyroid hormones (THs) and adiposity and finally, to resume a list of recent studies in humans that evaluated possible associations between thyroid hormone status and MetS or its clinical components. Not solely THs, but also its metabolites regulate metabolic rate, influencing adiposity. The mechanisms enrolled are related to its direct effect on adenosine triphosphate (ATP) utilization, uncoupling synthesis of ATP, mitochondrial biogenesis, and its inotropic and chronotropic effects. THs also act controlling core body temperature, appetite, and sympathetic activity. In a bidirectional way, thyroid function is affected by adiposity. Leptin is one of the hallmarks, but the pro-inflammatory cytokines and also insulin resistance impact thyroid function and perhaps its structure. MetS development and weight gain have been positively associated with thyroid-stimulating hormone (TSH) in several studies. Adverse glucose metabolism may be related to hyperthyroidism, but also to reduction of thyroid function or higher serum TSH, as do abnormal serum triglyceride levels. Hypo- and hyperthyroidism have been related to higher blood pressure (BP), that may be consequence of genomic or nongenomic action of THs on the vasculature and in the heart. In summary, the interaction between THs and components of MetS is complex and not fully understood. More longitudinal studies controlling each of all confounding variables that interact with endpoints or exposure factors are still necessary.

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Introduction

Patients with both thyroid dysfunction and metabolic syndrome (MetS) are frequently observed in clinical practice. It is estimated that more than 20% of adult people fulfill criteria for MetS in different population studies.[1–4]

MetS is most often associated with obesity and consists of different metabolic risk factors that are associated with higher risk for cardiovascular disease, type 2 diabetes, and mortality.[2–4] In clinical practice, there are different criteria to define MetS, but the two most common adopted for its diagnosis are based mainly on four main characteristics, as shown in Table 1.[2–4] The two criteria are those recommended by the IDF (International Diabetes Federation) and by the National Cholesterol Education Program (NCEPT)–Adult Treatment Panel III (ATPIII; NCEPT–ATPIII).[2–4] The four features present in both criteria are also usually reported in other defining criteria, irrespective of the adopted standard recommendations.[2–4] Those four major components of MetS consist of different physiological characteristics: (a) body adiposity, especially central adiposity measured by waist circumference; (b) serum glucose levels that reflect diabetes diagnosis or the risk for its

Table 1. Criteria defining metabolic syndrome (MetS)*.

	IDF	NCEPT–ATPIII
Waist circumference (⇧adiposity)	>94 cm ♂ (European) >90 cm ♂ (Asiatic) >80 cm ♀	≥102 cm ♂ ≥88 cm ♀
Serum glucose	≥100 mg/dl or diabetes diagnoses	≥110 mg/dl
Triglycerides	≥150 mg/dl	≥150 mg/dl
HDL-c	<40 mg/dl ♂ <45 mg/dl ♀	<40 mg/dl ♂ <50 mg/dl ♀
Blood pressure	Systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg or HBP treatment	Systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg

*Three or more elements are necessary for MetS diagnosis.
BP, blood pressure; HBP, high blood pressure, HDL-c, high-density lipoprotein cholesterol; IDF, International Diabetes Federation; NCEPT–ATPIII, National Cholesterol Education Program–Adult Treatment Panel III.

development; (c) lipid abnormalities related to metabolic risk [high serum triglycerides or low, high-density lipoprotein cholesterol (HDL-c)]; and (d) increased blood pressure (BP) levels. The presence of three or more abnormalities, concerning any of the described elements, is needed to define MetS. Additionally, some authors define MetS by the presence of abnormal serum levels of insulin or markers of insulin resistance (IR).[2–4]

At the same time, the prevalence of hypothyroidism in different population surveys has been reported to be just around 8–15%.[5–7] Additionally, this prevalence increases with age, reaching almost 20% of elderly subjects.[7] The interest in studying possible associations between these two common disorders has increased. The knowledge that MetS may not necessarily be a consequence of thyroid dysfunction but also that thyroid dysfunction may arise from the effects of MetS has gained attention.[8–14] Sectional studies have shown that the overlap between both diagnoses is common, justifying a high association between them, as shown in Table 2.[14,15–105] However, as highly prevalent entities, the cause–consequence effect may not be established in these types of studies. We also observed that some studies applied a predefined criterion to establish the presence or absence of MetS and its associations with thyroid function,[14,16,19,20,24–26,29,30,33,34,38,42,45,47–49,52,54, 55,57,62,66–68,73,75–77,79,82,84,92–94,96–98,100–103,106,108] but the majority just evaluated the presence of one or more specific features related to MetS and not necessarily its diagnosis.

Cohort studies also do not seem to be capable of showing that a unidirectional pathway justifies this association,[17,18,28,34,68,74,76,82,95,99,106–117] and the hypotheses that both thyroid dysfunction leads to MetS and that this condition also influences thyroid function has gained credibility.[9–13] THs, and also some of their metabolites, regulate metabolic rate, leading to variations in weight gain and adiposity.[9–11,13] Additionally, THs also act on central regulation of appetite control and sympathetic activity. In the opposite direction, thyroid function is affected by adiposity, with leptin having important modulatory effects.[9–11,13] Also, pro-inflammatory cytokines related to obesity and IR may impact thyroid function and perhaps its structure.[9,11–13] Table 3 summarizes the results of longitudinal studies done over the past decade regarding the association between thyroid function and MetS diagnosis, or even different MetS components. For this purpose, we did not include a detailed analysis of studies focusing on the effect of bariatric surgery on thyroid, even though a recent meta-analysis found that patients who underwent bariatric surgery exhibited a reduction of TSH, free triidothyronine (FT3) and triidothyronine (T3) levels after surgery.[12]

In this review, we will discuss some proposed mechanisms by which thyroid dysfunctions may

Table 2. Sectional studies evaluating the associations between MetS and thyroid function (From 2009 to July 2019).

Author (region)	Study population	Sample size	Results
Rotondi *et al.*[15] (Italy)	Class III obese and non-obese (EU, SCH, OH)	466	**A** = obese had higher TSH and lower FT4 and FT3
Alevizaki *et al.*[16] (Greece)	EU subjects	303	**A** = FT4 negatively correlated with SCF and SCF/PPF; TSH and T3 positively correlated with SCF and PPF (not in multivariate analysis) **G** = TSH positively correlated with HOMA-IR **L** = NA **BP** = NA
Teixeira *et al.*[17] (Brazil)	SCH, OH and controls from ambulatory setting of a tertiary hospital	103	**A** = NA **G** = SCH with higher FPG then OH **L** = TG higher in SCH and OH **BP** = NE
Volzke *et al.*[18] (Germany)	Population survey (including EU and subclinical dysfunctions)	2910	**BP** = NA with TH or subclinical thyroid function
Park *et al.*[19] (Korea)	Euthyroid post-menopausal women	2205	MetS positively associated with TSH **A** = NA **G** = NA **L** = TG positively associated with TSH **BP** = DBP positively associated with TSH
Kim *et al.*[20] (Korea)	EU subjects	44,196	**A** = BMI higher in the lowest quintiles (women); WC negatively correlated with FT4 (Men); **G** = FPG higher in the highest quintiles of FT4 **L** = HDL-c higher in the highest quintile of FT4 **BP** = higher SBP and DBP in the highest quintiles of FT4
Asvold *et al.*[21] (Norway)	No previous known thyroid disease	32,781	**A** = low thyroid function positively associated with BMI
Nam *et al.*[22] (Korea)	Euthyroid obese and overweight pre-menopausal women	177	**A** = T3 positively correlated with VAT, SCF and total fat, WC and BMI **G** = T4L positively correlated with glucose and HOMA-IR (women) **L** = T4L negatively correlated with HDL **BP** = T4L positively correlated with DBP (men)
Friedrich *et al.*[23] (Pomerania)	Population survey (excluding those with known thyroid diseases)	3348	**A** = TSH positively associated with BMI and WC in women (not necessarily only euthyroid subjects)
Ambrosi *et al.*[24] (Italy)	Obese/overweight, EU	581	TSH was higher and FT4 lower in MetS **A** = TSH increased with severity of obesity; TSH was positively correlated with BMI and WC **G** = TSH positively correlated with insulin and HOMA-IR and negatively with QUICKI **L** = dyslipidemia had higher TSH levels **BP** = NA

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Table 2. (Continued)

Author (region)	Study population	Sample size	Results
Ruhla et al.[25] (Germany)	Euthyroid volunteers	1333	MetS was positively associated with TSH; OR: 1.7 (1.1–2.6) **A** = higher BMI and more obesity in the upper range of TSH **G** = TSH positively correlated with HOMA-IR **L** = TSH positively correlated with TG **BP** = NE
Garduno-Garcia et al.[26] (Mexico)	Population survey (comparing EU and SCH) and correlation with serum hormone levels in the entire group and EU subjects	3148	**A** = NA, when comparing EU and SCH, however WC positively correlated with TSH and negatively with FT4 **G** = HOMA-IR and insulin were positively correlated with TSH and negatively with FT4 **L** = TG was positively correlated with TSH and negatively with FT4; HDL was positively correlated with FT4 and negatively with TSH **BP** = DBP negatively correlated with FT4
Maratou et al.[27] (Greece)	Overt and SCH hyperthyroidism in comparison with euthyroid subjects	38	**G** = hyper and SC hyperthyroidism had higher postprandial glucose levels Hyperthyroidism had higher postprandial insulin levels HOMA-IR was increased in overt and SC hyperthyroidism
Marzullo et al.[28] (Italy)	EU, obese subjects	952	**A** = BMI was positively correlated with TSH and negatively with FT4 **G** = NA **L** = HDL positively correlated with FT4 **BP** = NE
Lai et al.[29] (China)	SHC and controls from a survey and study of correlations between serum hormone levels and endpoints in EU subgroup	1534	TSH higher in MetS **A** = TSH higher in obese/overweight; BMI positively associated with TSH; WC correlated with TSH **G** = neither FPG nor HOMA-IR were associated with thyroid status **L** = TSH higher in subjects with abnormal TG; no association between TG and TSH **BP** = TSH higher in HBP; no correlation with TSH
Lee et al.[30] (Korea)	EU subjects	7270	MetS diagnosis was associated with upper reference range of serum TSH **A** = BMI positively associated with TSH **L** = TSH correlated with TG in multivariate analysis
Liu et al.[31] (China)	Population survey (EU × SCH)	6339	The number of MetS components did not differ between groups **A** = WC was associated with SCH **G** = NA **TG** = higher in SCH **BP** = higher in SCH
Diez and Iglesias[32] (Spain)	Euthyroid obese, overweight and controls	778	**A** = TSH higher in obesity and positively correlated with BMI (not confirmed after excluding TPO-Ab+)

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Table 2. (Continued)

Author (region)	Study population	Sample size	Results
Taneich *et al.*[33] (Japan)	Euthyroid diabetic patients	301	**A** = FT4 positively correlated with BMI and VFA; FT3 positively correlated with BMI and VFA **G** = T3 negatively correlated with HbA1c; TSH negatively correlated with FPG and HbA1c **L** = T3 negatively correlated with TG **BP** = FT4 positively correlated with DBP; T3 negatively correlated with DBP and SBP
Park *et al.*[34] (Korea)	EU subjects	5998	**A** = WC was positively associated with FT4 and negatively with BMI **G** = NA **L** = TG positively associated with TSH and negatively with FT4; inverse associations for HDL **BP** = FT4 positively associated to DBP and SBP (for DBP, remained significant in multivariate analysis)
Kitahara *et al.*[35] (USA)	Euthyroid subjects from NHANES	3114	**A** = BMI and WC were positively associated with TSH and FT3 but not with FT4
Zhang *et al.*[36] (China)	Euthyroid subjects from population survey	1322	**A** = higher WC, % body fat and BMI in women, with all three parameters correlated with TSH **G** = NA **L** = NA **BP** = NA
Tamez-Pérez *et al.*[37] (Spain)	Diabetic and control subjects	5161	**G** = OR for hypothyroidism in diabetic patients was 3.45 (95% CI 2.51–4.79; $p < 0.0001$) when comparing the rate of hypothyroidism in diabetic group and non-diabetic group
Tarcin *et al.*[38] (Turkey)	Obese patients without overt thyroid dysfunction	211	MetS had higher T3 and T4 levels; however, lower FT3/FT4; no correlation with TSH **A** = positive correlation between WC and T3 **G** = T3 positively correlated with FPG and HOMA-IR; however, lower FT3/FT4 **L** = lower HDL-c in TSH >2.5 **BP** = positive correlation between FT4 and DBP and SBP
Aljohani *et al.*[39] (Saudi Arabia)	SCH × controls from an endocrinology unit	94	**A** = BMI higher in SCH **G** = NE **L** = TG higher in SCH **BP** = NE
Kwarkernaak *et al.*[40] (Europe)	Obese subjects and controls	74	**A** = BMI positively associated with TSH in obese **G** = NA **L** = NA **BP** = NE
Solanki *et al.*[41] (India)	Volunteers with TSH between 0.4 and 10.0	417	**A** = TSH increases with BMI
Oh *et al.*[42] (Korea)	Euthyroid young females (18–39 years)	2760	MetS was more frequent in TSH >2.5 **A** = WC positively associated with TSH **G** = NA in multivariate analysis **L** = TG positively associated with TSH **BP** = SBP and DBP positively associated with TSH

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Table 2. (Continued)

Author (region)	Study population	Sample size	Results
Kouidhi *et al.*[43] (Tunisia)	Overweight, obese and controls with TSH in the normal range	108	**A** = TSH higher in overweight and obese and FT4 lower; BMI WC positively correlated with TSH; WC negatively with FT4 **G** = insulin and HOMA-IR positively correlated with TSH
Karthlich *et al.*[44] (India)	Women with SCH and euthyroid controls	60	**A** = NA **G** = NA **L** = HDL lower and TG higher in SCH **BP** = SBP lower in SCH
Muscogiuri *et al.*[45] (Italy)	EU without DM	60	**A** = overweight and obesity were associated with higher TSH; TSH was correlated with VAT **G** = positive correlation between TSH and glucose uptake: not confirmed in multivariate analysis **L** = NA **BP** = NE
Vyakaranam *et al.*[46] (India)	Euthyroid subjects and SCH	2037	**A** = NA **G** = TSH positively and FT3 negatively correlated with insulin; FPG higher in SCH **L** = NE **BP** = NE
Roef *et al.*[47] (Italy)	Diabetic patients	490	**A** = BMI and WC were positively associated with FT3, TT3, FT3/FT4 and negatively with FT4 **G** = FPG positively associated with FT3, TT3 and FT3/FT4 **L** = TG positively associated with TSH, FT3, TT3, FT3/FT4 and negatively with FT4; HDL-c negatively with FT3 and TT3 **BP** = positively associated with TSH, FT3, TT3 and FT3/FT4
Bakiner *et al.*[48] (Turkey)	Obese, overweight and controls with serum TSH between 0.4 and 10.0	1097	No association with MetS **A** = NA **G** = NA **L** = NA **BP** = NA
Mamtani *et al.*[49] (Mexico and USA)	Population study from Mexico and NHANES	2540	**A** = thyroid function index was positively associated with BMI, WC, and central obesity **G** = diabetes diagnosis positively associated with thyroid function index (not confirmed in multivariate analysis) **L** = TG and HDL were not significantly associated **BP** = NA
Ren *et al.*[50] (China)	Population survey (euthyroidism)	1180	**A** = BMI, fat mass and WC positively associated with FT3 **G** = FPG and HOMA positively associated with FT3 **L** = HDL negatively associated with FT3 **BP** = NE

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Table 2. (Continued)

Author (region)	Study population	Sample size	Results
Giandalia *et al.*[51] (Italy)	DM2 with euthyroidism	490	**A** = BMI, high WC and visceral adiposity was more prevalent in the highest quartiles of TSH **G** = NA **L** = high TG more prevalent in the highest quartiles of TSH **BP** = HBP more prevalent in the highest quartiles of TSH
Sakurai *et al.*[52] (Japan)	Euthyroid employers	2037	**A** = positive association between TSH and BMI
Shin *et al.*[53] (Korea)	EU, non-diabetics	6241	IR was associated with highest quartiles of FT4 **A** = BMI and WC was negatively correlated with FT4 (not in multivariate) **G** = HOMA-IR was negatively correlated with FT4 that was also slightly correlated with FPG (not in multivariate analysis) **L** = TSH was slightly and positively correlated with HDL-c and negatively with FT4 (in multivariate analysis, a slightly positive association was found between FT4 and TSH in men) **BP** = NA
Udenze *et al.*[54] (Nigeria)	Staff from college of medicine	150	Sick euthyroid syndrome was more common in patients with MetS
Shinkov *et al.*[55] (Bulgaria)	Population survey (euthyroid)	2401	More MetS in the highest quartile **A** = NA **G** = NA **L** = low HDL-c and high TG more frequent in the highest quartile **BP** = NA
Gierach and Junik[56] (Poland)	Patients with MetS (comparing hypothyroid × EU)	441	**A** = WC did not differ between hypothyroid and euthyroid **G** = FPG did not differ **L** = HDL higher in Hypothyroid and TG higher (only in women's subgroups) **BP** = NA
Aras *et al.*[57] (Turkey)	Obese and controls	70	**A** = FT3/FT4 positively associated with WC; TSH higher in higher BMI **G** = FT3/FT4 positively correlated with FPG **L** = FT3/FT4 positively correlated with TG and tendency for negative association with HDL **BP** = FT3/FT4 tended to be positively correlated with SBP
Sieminska *et al.*[58] (Poland)	Post-menopausal women (EU × SCH)	372	**A** = higher WC in SCH **G** = NA **L** = higher TG **BP** = higher SBP and DBP in SCH
Ozdemir *et al.*[59] (Turkey)	Hypo-, hyperthyroid and control subjects	63	**A** = low BMI in Hyperthyroidism **G** = HOMA β higher in hypothyroidism; FPG higher in hyperthyroidism **L** = higher TG in hypothyroidism **BP** = NE

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Table 2. (Continued)

Author (region)	Study population	Sample size	Results
Lambrinoudak et al.[60] (Greece)	Healthy women, post-menopausal	194	**A** = FT4 was lower in high-fat mass, FT3 was higher; Fat mass increased in the highest quartiles of FT3; TSH was positively correlated with BMI
Betry et al.[61] (France)	Hospitalized obese patients for check-up	800	**A** = TSH positively associated with BMI
Petrosyan[62] (Armenia)	All with MetS	120	**A** = BMI higher in TSH >2.5 **G** = HbA1c higher in TSH >2.5 **L** = TG higher in TSH >2.5 **BP** = DBP higher in TSH >2.5
Meng et al.[63] (China)	Community-based health-check investigation (without known thyroid disease)	13,855	**A** = BMI and WC negatively correlated with FT4 (women) and TSH (men), also positively with FT3 (men) **G** = FPG positively correlated with FT4 and negatively with FT3 (women) **L** = HDL-c negative correlation with FT3 and positive with FT4 **BP** = positive correlation with TSH and FT4 and negative with FT3 (women)
Aksoy et al.[64] (Turkey)	SCH in LT4 use	104	**A** = BMI was not associated with TSH **G** = HOMA-IR was not associated with TSH **L** = NA **BP** = NA
Maskey et al.[65] (India)	Diabetic patients	271	**A** = BMI higher in diabetic patients with hypo **G** = insulin use and inadequate diabetic control was more frequent among hypothyroid patients **L** = HDL-c and TG higher in hypothyroidism **BP** = did not differ
Bensenor et al.[66] (Brazil)	Civil servants recruited in a survey (TSH evaluated in quintiles in the whole group and only in euthyroid subjects)	10,935	High TSH quintile was associated with IR/MetS **A** = higher WC and BMI **G** = FPG higher in low quintile with opposite effect on HOMA-IR **L** = higher TG in high quintile **BP** = NA
Nozarian et alk.[67] (Tehran)	Euthyroid patients with MetS and controls (ATPIII)	82	TSH, FT3 and FT4 did not differ between groups with or without MetS TSH in the upper range was associated with higher risk of MetS in multivariate analysis. **A** = TSH not related to TSH **L** = HDL not related to TSH in regression however associated with TSH >2.5–5.0 mIU/l
Lee et al.[68] (USA)	Framingham cohort: euthyroid subjects	3483	**A** = TSH positively associated with BMI and SCF; FT4 was negatively associated with obesity and VAT **G** = NE **L** = TSH positively and FT4 negatively associated with TG **BP** = not associated in multivariate analysis

(Continued)

Table 2. (Continued)

Author (region)	Study population	Sample size	Results
Peixoto de Miranda *et al.*[69] (Brazil)	Civil servants recruited in a survey (TSH evaluated in quintiles considering the whole group)	12,284	MetS did not differed **A** = BMI higher in the 5th quintile of TSH (including OH diagnosis) **G** = IR more frequent in 5th quintile of TSH **L** = high TG more frequent among subjects in the upper quintile **BP** = NA
Kim *et al.*[70] [South Korea]	Euthyroid middle-aged subjects	13,496	Higher risk for MetS in highest quartile of T3; no association with T4 or TSH **A** = TSH was lower; T4 and T3 was higher in obesity and overweight **G** = TSH was negatively associated with FPG and HbA1c; T3 was positively associated with glycemia **L** = HDL was negatively associated with TSH **BP** = T3 and T4 positively associated with SBP
Wang *et al.*[71] (Taiwan)	Non-obese, euthyroid, young women	229	TSH higher in the presence of IR
Temizkan ert al.[72] (Turkey)	Obese euthyroid patients	5300	**A** = NA **G** = FPI and HOMA-IR higher in the highest quartile TSH **L** = NA **BP** = NE
Kathiwada *et al.*[73] (Nepal)	Patients with MetS (SCH × EU)	169	**A** = WC was lower in EU (comparing to SC and overt hyperthyroidism); weak positive correlation between TSH and BMI and negative between BMI and FT3 and FT4 **G** = NA **L** = TSH negatively correlated with HDL **BP** = NA
Tiller *et al.*[74] (Europe)	Population surveys	16,902	**A** = TSH positively associated with BMI, WC and WC/height
Xu *et al.*[75] (China)	Population survey, EU	2356	**A** = higher BMI in the upper-half serum TSH **G** = FPG higher in the upper-half serum TSH **L** = NA **BP** = NA
Mehran *et al.*[76] (Iran)	Community-based study	5422	Highest prevalence of MetS in hypothyroidism **A** = higher BMI in overt hypothyroidism **G** = SC hyper had higher FSG and frequency of hyperglycemia. FT4 negatively associated with FSI **L** = HDL-c lower in SC hyper, and TG higher in OH **BP** = NA
Jayanthi *et al.*[77] (India)	Tertiary care hospital: obese, OW and diabetic patients	92	**A** = NE **G** = HOMA-IR negatively correlated with TSH and positively with FT4; HbA1c negatively with FT4 and positive with TSH **L** = T3 was positively associated with HDL-c in obese diabetic patients **BP** = NE

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Table 2. (Continued)

Author (region)	Study population	Sample size	Results
Wolffenbuttel et al.[14] (Netherlands)	Population survey (EU subjects)	26,719	**A** = WC positively associated with FT3 and FT3/FT4 and negatively with FT4 in multivariate analysis **G** = FPG positively associated with FT3 and FT3/FT4 and negatively with FT4 in multivariate analysis **L** = HDL-c positively associated with FT4 and negatively with FT3 and FT3/FT4 in multivariate analysis; TG positively associated with TSH and negatively with FT4 and positively with FT3/FT4 **BP** = DBP and SBP positively associated with FT3 and FT3/FT4
Al-Musa[78] (Saudi Arabia)	Primary healthcare	278	**A** = TSH higher in obese (FT3 and FT4 did not differ)
Lozanov et al.[79] (Bulgaria)	Hospitalized	118	TSH in upper reference had more MetS diagnosis **A** = BMI was associated with higher TSH **G** = hypothyroid patients had higher insulin levels at 120 min of OGTT
Kar and Sinha[80] (India)	Hypothyroid patients and controls	80	HOMA-IR higher in hypothyroidism
Gutsh et al.[81] 2017 (India)	Hospital-based cross-sectional study	200	TSH was higher and FT4 lower in MetS
Ferrannini et al.[82] (Italy)	Multicenter cohort with clinically healthy participants (sub-analysis of euthyroid participants)	1018	Insulin resistance was independently associated with higher FT3 **A** = BMI and WHR higher in the highest FT3 quartiles **G** = NA; higher insulin levels in highest quartiles **L** = TG higher and HDL-c lower in the highest FT3 quartiles **BP** = increase in higher quartiles
Witte et al.[83] (Germany)	Patients attending specialist consultations (87.9% euthyroid)	1719	**A** = NA between VAT and TSH
Racaitaianu et al.[84] (Romania)	Obese non-diabetic participants	82	**G** = TSH was higher when HOMA-IR >2.5; FT4 did not differ
Rahbar et al.[85] (Iran)	Euthyroid	140	**A** = higher BMI in highest TSH levels **G** = NE **L** = NA
Valdes et al.[86] (Spain)	Population survey	3928	Higher TSH levels in morbidly obese patients
Sami et al.[87] (Pakistan)	Obese	127	**A** = high frequency of SCH in obesity
Jang et al.[88] (Korea)	Population survey without known thyroid disease (sub-analysis of euthyroid participants)	1423	**A** = WC tended to be negatively associated with FT4 **G** = FPG positively associated with FT4 **L** = TG positively with TSH and negatively with FT4 **BP** = not associated
Liu et al.[89] (China)	Non-obese EU patients from endocrinology department of a university hospital	5608	**A** = BMI positively correlated with FT3 and negatively with FT4 **G** = FPG and HOMA-IR positively correlated with FT3 and FT4 **L** = HDL negatively with FT3 and FT4 **BP** = NE

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Table 2. (Continued)

Author (region)	Study population	Sample size	Results
Liu *et al.*[90] (China)	Community-based health-check program	13,505	**A** = NA
Zhou *et al.*[91] (Taiwan)	Patients from annual examination of a health examination center at hospital	12463	In multivariate analysis TSH was positively associated with MetS diagnosis **G** = diabetes or pre-diabetes Dx was not associated **BP** = HBP Dx was associated with higher TSH
Liu *et al.*[92] (Taiwan)	Patients from annual examination of a health examination center at hospital (EU *versus* SCH)	15,943	SCH positively associated with MetS and number of its components **A** = WC higher in SCH (men) **G** = NA **L** = TG higher in SCH (women) **BP** = SBP higher in SCH and DBP also higher (women)
Bermúdez *et al.*[93] (Venezuela)	Participants without thyroid diseases from a sectional study for MetS screening	391	Elements of MetS was more frequent in SCH **A** = WC did not differ between SCH and EU **G** = diabetes Dx as hyperglycemia was more common in SCH **L** = NA **BP** = NA
Mousa *et al.*[94] (Turkey)	Euthyroid under LT4	301	**A** = TSH correlated positively with BMI and FT3 with VAT **G** = TSH, FT4 and FT3 positively correlated with FPG and HOMA **L** = NA **BP** = NE
Amouzegar *et al.*[95] (Iran)	Population survey with euthyroid participants	1938	**FT4** negatively associated with metabolic obese subjects
Wang *et al.*[96] (USA)	Population survey (NHANES)	1560	IR was positively associated with low FT4 and negatively with low FT3 and TT3
Hamlaoui *et al.*[97] (Algeria)	Patients attending specialist consultations (hypo, hyper and EU)	<100	**A** = hypothyroidism had higher BMI and WC; more abdominal obesity **G** = NA **L** = lower HDL in hyperthyroidism **BP** = more hypertension in Hyper and higher SBP
Delitala *et al.*[98] (Italy)	Population survey (sub-analysis of euthyroid subjects)	6148	Positive association between components of MetS with TSH in euthyroid males and women without known thyroid disease **A** = FT4 negatively associated with WC **G** = FPG positively associated with FT4 **L** = TSH positively associated with TG; FT4 positively associated with HDL-c **BP** = DBP positively associated with FT4
De Vries *et al.*[99] (Netherlands)	Euthyroid subjects with high risk for CV disease	5542	**G** = NA between TSH and DM diagnosis

(Continued)

Table 2. (Continued)

Author (region)	Study population	Sample size	Results
Chang et al.[100] (China)	From a self-paying health examination program	24,765	Metabolic syndrome positively associated with TSH **A** = BMI, BF and WC associated with higher TSH **G** = TSH positively correlated with HbA1c, fasting insulin, HOMA-IR and HOMA-β; high HbA1c, hyperinsulinemia, high HOMA-β, increased HOMA-IR occurred more when TSH >2.9 **L** = high TG and low HDL-c associated with higher TSH **BP** = positively associated with TSH
Xu et al.[101] (China)	Euthyroid subjects from check-up evaluations	16,975	**A** = overweight and obese had high serum FT3, high FT3/FT4 and low FT4. **G** = FBG negatively associated with FT4 and positively with TSH **L** = HDL positively associated with TSH and negatively with FT3; TG positively associated with FT3 and negatively with FT4 **BP** = SBP and DBP positively associated with FT3
Kim et al.[102] (Korea)	Community survey (TSH = 0.6–6.68)	13,873	Non-obese subjects without MetS had lower TSH and higher FT4
Zhang et al.[103] (China)	Community survey (euthyroidism)	3590	**A** = BMI increased with higher TSH
Lertrit et al.[104] (Thai)	Population survey	2242	**A** = BMI positively associated with TSH and negatively with FT4 in multivariate analysis **G** = FPG positively associated with FT4 in multivariate analysis
Raposo et al.[105] (Portugal)	Population survey	486	MetS diagnosis was positively associated with FT3 **A** = NA **G** = FPG not associated; however, HOMA = IR and serum insulin were positively associated with FT3 **L** = TG positively associated with FT3 **BP** = NA

A, adiposity; ATPIII, Adult Treatment Panel III; BMI, body mass index; BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; DM, diabetes mellitus; Dx, diagnosis; EU, euthyroid; FPG, fasting plasmatic glycaemia; FPI, fasting plasmatic insulin; FSG, fasting serum glucose; FSI, fasting serum insulin; FT3, free triiodothyronine; FT4, free thyroxine; G, glucose metabolism; HbA1c, glycosylated hemoglobin; HBP, high blood pressure; HDL-c, high-density-lipoprotein cholesterol; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance index; IR, insulin resistance; L, lipid profile; MetS, metabolic syndrome; NA, no association; NE, not evaluated; NHANES, National Health and Nutrition Examination Survey; OGTT, overload glucose tolerance test; OH, overt hypothyroidism; OR, odds ratio; PPF, preperitoneal fat; SBP, systolic blood pressure; SCF, subcutaneous fat; SCH, sub-clinical hypothyroidism; SC hyper, sub-clinical hyperthyroidism; T3, triiodothyronine; TG, triglycerides; TH, thyroid hormone; TSH, thyrotropin; TT3, total triiodothyronine; VAT, visceral adipose tissue; WC, waist circumference; WHR, waist-to-hip ratio; QUICKI, quantitative insulin sensitivity check index; TPO-Ab+, positive antibodies against thyroperoxidasis on serum; VFA, visceral fat area; HSC, is the same as SCH (subclinical hypothyroidism); T4L, is the same as FT4 (Free Thyroxine); LT4, levothyroxine; OW: overweight.

lead to MetS development, and not solely focus on the diagnosis of its complete presentation but also the way in which TH may influence each one of the four main features (or components) of this important syndrome. The consequences of augmenting adiposity, which is a highly prevalent marker of MetS, may also interfere with thyroid function will also be described. Finally, a list of recent studies enrolling humans and intending to evaluate possible associations between thyroid function and MetS will be present. For this purpose, we will focus on research excluding specific populations, like pediatric or elderly subjects, and also patients with other diagnoses, such as polycystic ovary syndrome. Additionally, we do not intend to review data on patients that underwent bariatric surgery.

Table 3. Longitudinal studies evaluating the associations between MetS and thyroid function (from 2009 to July 2019).

Author (region)	Follow-up	n	Population	Main results
Marzullo *et al.*[28] (Italy)	4 months	100	Obese submitted to diet	**A** = weight loss was associated with reduction in TSH and FT3; also, with increase in FT4 levels
Ferrannini *et al.*[82] (Italy)	3 years	940	Euthyroid subjects	**G** = baseline FT3 and FT4 were positively associated with increases in FPG and decrease in insulin sensitivity measured by euglycemic clamp (CLAMP)
Nada[106] (Saudi Arabia)	Post-normalization	42	Women with OH	**G** = after LT4 replacement, there was no significant change in FBG or HOMA-IR as compared with before starting treatment, while fasting insulin significantly increased
Amouzegar *et al.*[95] (Iran)	9 years	1938	Population-based cohort study	**A** = increment in FT4 levels was accompanied by decreased risk of metabolically healthy obesity and metabolically healthy, normal-weight phenotypic development TSH increment was positively associated with metabolically unhealthy, normal-weight phenotypic development
Mehran *et al.*[76] (Iran)	3 years	2393	Frameworks of a community-based study	**BP** = FT4 was associated with higher odds of high BP after adjusting for age, sex, smoking, BMI, and HOMA-IR; no significant associations between TSH and BP
Langén *et al.*[107] (Finland)	11 years	2486	Population-based cohort	**L** = no association with TSH
Langén *et al.*[108] (Finland)	11 years	3453	Population-based cohort	**BP** = TSH did not predict incident hypertension and was inversely associated with change in SBP and DBP in men
Volzke *et al.*[18] (Germany)	5 × years	2910	Population-based cohort	**A** = NE **G** = NE **L** = NE **BP** = SC hyper was not associated with changes in BP or incident hypertension in multivariate analysis
De Vries *et al.*[99] (Europe)	7.6–5.9 years	5542	Metanalysis of population surveys	**G** = no more risk for incident DM
Itterman *et al.*[109] (Europe)	5 years	10,048	Population survey	**BP** = High TSH was not associated with incident HBP
Liu *et al.*[110] (USA)	2 years	811	Obese and overweight submitted to diet protocols	**A** = Baseline FT3 and FT4 predicted weight loss; FT3 and TT3 were positively associated with changes in body weight, BP, G, insulin, and TG; without associations with FT4 or TSH
Eray *et al.*[111] (Turkey)	6 months	129	Obese before and after pharmacological treatment	No effects on TSH, FT3 and FT4
Teixeira *et al.*[17] (Brazil)	1 year	103	Ambulatory from a tertiary hospital (EU, SCH, OH)	**A** = no significant changes in BMI and BF% **G** = no significant changes in HOMA-IR **L** = reduction in TG with OH treatment **BP** = NE

(Continued)

Table 3. (Continued)

Author (region)	Follow-up	n	Population	Main results
Park *et al*.[34] (Korea)	3 years	5998	EU, SCH, SC hyper	Changes in TSH was positively associated with MetS development **A** = WC was not associated with changes in TSH or FT4 **G** = glucose and HOMA-IR were positively associated with changes in TSH **L** = TG was positively associated with changes in TSH and negative with FT4 **BP** = positively associated with changes on FT4 and TSH
Chen *et al*.[112] (Taiwan)	11 years	38,200	Hypo-, hyperthyroid participants and controls	**G** = there was significantly higher occurrence of T2D in the hypothyroidism and also hyperthyroidism groups than in the control group
Lee *et al*.[68] (USA)	6.1	2912	EU participants	**A** = NA with TSH or FT4 **G** = NA with TSH or FT4 **L** = NA with TSH or FT4 **BP** = NA with TSH or FT4
Tiller *et al*.[74] (Europe)	5 years	2912 (713 for body composition)	Population-based cohort studies	**A** = serum TSH at baseline was inversely associated with anthropometric changes (WC, BMI); however, with a positive association with TSH changes **G** = NE **L** = NE **BP** = NE
Chang *et al*.[113] (Taiwan)	4.2 years	66,822	EU at baseline	Higher risk for SCH development in MetS (HR = 1.12) **A** = NA **G** = NA **L** = higher risk for SCH development when high TG **BP** = an increased risk of SCH was associated with high BP
Caixàs *et al*.[114] (Spain)	Post-normalization	51	Hyper- and hypothyroid patients (pre- and post-treatment)	**G** = Patients with hyperthyroidism showed higher glucose, insulin concentrations and HOMA-IR than their controls; after normalization of thyroid function, glucose and HOMA-IR decreased to the normal range
Chaker *et al*.[115] (Netherlands)	7.9 years	8452	Population survey	**G** = risk for developing diabetes 1.09 times higher for every doubling of TSH levels; higher FT4 levels within the normal range were associated with a decreased risk of diabetes; In participants with pre-diabetes, the associated risk of developing diabetes was 1.13 times higher for every doubling of TSH levels The risk of progression from pre-diabetes to diabetes was higher with low–normal thyroid function (HR 1.32; 95% CI, 1.06–1.64 for TSH and HR 0.91; 95% CI, 0.86–0.97 for FT4) Absolute risk of developing T2D in participants with pre-diabetes decreased from 35% to almost 15% with higher FT4 levels within the normal range

(Continued)

Table 3. (Continued)

Author (region)	Follow-up	n	Population	Main results
Bjergved *et al.*[116] (Denmark)	11 years	1577	Population survey	**A** = positive association between BMI changes and TSH changes
Soriguer *et al.*[117] (Spain)	6 years	479	784	**A** = obesity development was related to higher concentrations of FT3 and FT4; weight gain with FT3

A, adiposity; BMI, body mass index; BP, blood pressure; BF, body fat; CI, confidence interval; DBP, diastolic blood pressure; DM, diabetes mellitus; EU, euthyroid; FPG, fasting plasmatic glycaemia; FT3, free triiodothyronine; FT4, free thyroxine; G, glucose metabolism; HBP, high blood pressure; HDL-c, high-density-lipoprotein cholesterol; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance index; HR, hazard ratio; IR, insulin resistance; L, lipid profile; MetS, metabolic syndrome; NA, no association; NE, not evaluated; OH, overt hypothyroidism; SBP, systolic blood pressure; SCH, sub-clinical hypothyroidism; SC hyper, sub-clinical hyperthyroidism; T2D, type 2 diabetes; TG, triglycerides; TSH, thyrotropin; TT3, total triiodothyronine; WC, waist circumference; QUICKI, quantitative insulin sensitivity check index; TPO-Ab+, positive antibodies against thyroperoxidasis on serum; VFA, visceral fat area; HSC, is the same as SCH (subclinical hypothyroidism); T4L, is the same as FT4 (Free Thyroxine); LT4: levothyroxine.

Molecular mechanism of action of thyroid hormones: general overview

THs act on several target peripheral tissues *via* several mechanisms. Briefly, thyroxine (T4), which is the main product of the thyroid gland, is converted to the active hormone, T3, an enzymatic reaction catalyzed by type 1 (D1) or type 2 5′deiodinases (D2). T4 and T3 can be inactivated by type 3 5-deiodinase (D3). T4 and T3 enter cells through specific membrane transporters, and T3, originating from the circulation or from intracellular conversion of T4 to T3, binds to TH receptors, subtypes α1, β1 or β2, located at the nucleus to regulate the transcriptional activity of target genes.[118] This is the canonical pathway; however, recently, other non-classical pathways have been reported. TH actions may be mediated by cytoplasmic or mitochondrial TH receptors (TR), or through binding to unspecific membrane proteins that activate intracellular signaling cascades.[118–121] These non-canonical signaling pathways have been reported to be especially important to the cardiometabolic effects of thyroid hormones.[121] In that elegant study, the authors employed genetically manipulated mice to differentiate between T3 effects mediated by the canonical and non-canonical pathways. They showed that the acute hypoglycemic effect of T3 is dependent on TRβ but does not require deoxyribonucleic acid binding. Its action involves activation of the phosphatidylinositol 3-kinase (PI3K) signaling cascade. The same non-canonical signaling pathway is involved in a T3-lowering effect in serum and hepatic triglycerides. In addition, T3 actions in metabolic rate and energy expenditure, as well as in the exogenous control of heart rate have important contributions of the non-canonical signaling pathways.[121]

It is also important to mention that tissue responsiveness to TH may vary with age and sex, which may be related to tissue-specific alterations in T4 to T3 conversion.[122–124] The interplay between age and sex are particularly interesting in TH-induced changes in body weight and energy expenditure in mice, with sex modifying the response of TH differently in old males compared with old females.[122–124]

Mechanisms by which thyroid function may interact with components of metabolic syndrome

TH may be involved in each one of the four major components of MetS *via* several mechanisms. This involvement is not necessarily unidirectional, since target tissues of TH may also be involved with thyroid function. TH actions lead to specific effects that influence endpoints regarding body adiposity, glucose or lipid levels, and BP.[11,120,125–127] In this way, all four features of MetS may be influenced by TH levels as separately described in specific following sections.

In summary, adiposity may be the consequence of the role of THs (or its metabolites) on the regulation of metabolic rate, appetite control or even sympathetic activity.[9,11,13] This sympathetic stimulus by THs also influences glucose and lipid metabolism as it impacts cardiovascular system regulation.[9,11–13] Hyperglycemia may be the consequence of reduced glucose uptake in hypothyroidism or the consequence of increased glucose liver production in hyperthyroidism.[128] Glucose-stimulated insulin secretion and insulin degradation are also regulated by THs.[128] Dyslipidemia may be related to thyroid function, since THs

also act stimulating both lipid synthesis and degradation.[129] Finally, high BP (HBP) may be the consequence of TH action on the vasculature and in the heart by TR-mediated gene regulation at the nucleus or *via* other non-classical pathways at the cytoplasmatic and cellular membrane levels.[130]

However, it is notable that the augmentation in adiposity, especially central adiposity, which is one of the hallmarks of MetS, appears to generate an increase in several hormones, cytokines, and other compounds that influence thyroid function *via* different pathways.[131,132] The proposed mechanisms involved in these actions will be summarized in the next sections.

Thyroid hormones influencing adiposity

Adiposity gain or loss depends primarily on the balance between energy expenditure (EE) and energy intake (EI). Resting EE (REE) is solely used in the cellular process to maintain life.[133] EE can be stimulated by physical activity or acceleration of different metabolic processes, resulting in heat production (facultative thermogenesis).[134] The balance between EE and EI depends mainly on satiety control, sympathetic nervous system (SNS) activity, and the endocrine system. THs are strong regulators of the metabolic rate with consequent effects on different outcomes, including adiposity.[135] However, as previously described, the relationship between TH and adiposity is bidirectional, since TH and also thyroid-stimulating hormone (TSH) levels have effects on adiposity, which in turn may act on thyroid function and perhaps on the structure of this gland.[136,137] Adiposity leads to production of several hormones, cytokines, and other compounds that influence thyroid function, as described in the next sections.

THs, especially T3 produced by enzymatic reaction catalyzed by type 1 (D1) or type 2 5′deiodinases (D2), are enrolled in controlling metabolic rate by several mechanisms, as explained in the following sections of this manuscript. In summary, they exert direct effects on adenosine triphosphate (ATP) utilization, uncoupling synthesis of ATP, mitochondrial biogenesis and have inotropic and chronotropic effects on body. THs also act controlling core body temperature, appetite, and sympathetic activity. Additionally to T4 and T3, other TH metabolites exert similar effects.[138,139] It has been demonstrated that 3,5

diiodo-L-thyronine (T2) prevents high-fat-diet-induced adiposity by means of increasing EE and promoting anti-adipogenic and anti-lipogenic pathways in white adipose tissue (WAT).[138,139] Also, studies have demonstrated that decarboxylated TH molecules, termed thyronamines, when given to animals, lead to metabolic effects that generally oppose the direction of T3. Thyronamines are primarily produced in the thyroid, but there is evidence that they may be produced in other tissues.[139–141] The physiological and clinical relevance of TH metabolites is under intense investigation.[139–141]

The thermogenic effects of TH, especially T3, are well known, and hyperthyroid patients have an increase in heat production and are heat intolerant. Hyperthyroid patients are opposite to hypothyroid patients, who produce less heat and are cold intolerant.[142] After thyroid hormone administration there is an increase in oxygen consumption in most tissues.[142] THs cause a direct increase in adenosine triphosphate (ATP) utilization leading to acceleration of anabolic and catabolic pathways in the macronutrient metabolism, such as lipolysis/fatty-acid oxidation and increased protein turnover.[143] In addition, THs stimulate the sodium/potassium (Na^+/K^+) ATPase and the sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA) that mediate ion transport through membranes, processes that require ATP utilization, leading to increasing of it consumption and contributing to thermogenesis.[144] Therefore, thyroid hormone increased the utilization of energy reserves, such as lipids from the adipose tissue.

Another mechanism by which TH may increase the REE is related to the hormones' inotropic and chronotropic effects, exerted in conjunction with the SNS, since it is well known that part of REE is related to cardiac function.[145]

TH actions at the mitochondria are very important in thermogenesis. In addition to promoting mitochondrial biogenesis, THs act to uncouple the synthesis of ATP from heat production in the mitochondria.[142] This uncoupling is mediated by their action on mitochondrial uncoupling proteins (UCP) that lead to non-shivering thermogenesis *via* conversion of chemical energy to heat without an increase in ATP production. The presence of this mechanism, in which promoting uncoupling phosphorylation in brown adipose tissue (BAT) is promoted, is one of the markers of

evolutionary process of mammals; however, for many years it was thought that BAT was not present in adults. Nevertheless, in the past decade, the presence of active BAT in adult humans has been demonstrated and its amounts are inversely associated with body weight and serum glucose levels.[146,147–152] The action of TH in this tissue gains attention as additional mechanisms enrolled in MetS.

In BAT, type 1 UCP (UCP1) is the hallmark of thermogenesis. This UCP expression is stimulated by T3, which is locally generated from T4 by intracellular D2. This D2 is positively regulated by beta-adrenergic activity.[152] THs cause an upregulation of adrenergic receptor expression, leading to an amplified effect on UCP1 expression, which is also activated by the SNS.[152] Studies have shown that D2 is very important to TH-induced adaptive type of thermogenesis in BAT.[152] D2 also responds to other thermogenic inductors, as highlighted by a recent study showing that the adipokine, adipocyte fatty-acid-binding protein (A-FABP), requires BAT D2 activity to exert its thermogenic effects.[153]

Another postulated effect of THs in BAT is the stimulation of WAT 'browning,' which consists of the acquisition of brown-fat characteristics by a certain group of WAT cells, termed beige cells.[154] Although it would be an attractive tool in obesity treatment, evidence in humans is still scarce,[152] and a recent experimental study does not support that TH-induced browning is accompanied by an increase in thermogenesis.[155] TH also stimulates the expression of other UCPs, such as UCP2 and 3, and the latter is very important to thermogenesis and fatty oxidation in muscle.[156]

In addition to acting on peripheral tissues, THs also have relevant modulatory actions in the central nervous system with respect to core body temperature, satiety control, and activity of the SNS.[157] The action of T3 on the hypothalamus, more specifically on the ventromedial hypothalamus (VMH), stimulates the SNS that not only stimulates TH production but also acts in combination with THs in those same peripheral tissues that affect the MetS components.[125–127]

Central T3 administration results in increased body temperature, concomitant with reduction of levels of hypothalamic AMP-activated protein kinase (AMPK), increased tone in the sympathetic nerves innervating BAT.[158,159] Hypothalamic AMPK and fatty-acid metabolism mediate thyroid regulation of energy balance.[158–160] Those responses involve UCP1, since they were abrogated in UCP1 knockout mice.[161]

Hyperthyroid individuals frequently have hyperphagia even in the presence of weight lost,[157] which is related in great part to the direct effect of THs on appetite stimulation. In the hypothalamic nucleus arcuate, T3, produced locally by D2, increases the expression of the orexigenic peptides neuropeptide Y (NPY) and agouti-related peptide (AgRP), and decreases the anorexigenic peptide, pro-opiomelanocortin (POMC),[160] and the reverse events occur in hypothyroid rats.[162] Acting at the VMH, T3, in low doses, was shown to induce an increase in food intake and potently stimulate the sympathetic activity and BAT thermogenesis.[126,163,164] In contrast, Hameed and colleagues demonstrated that ablation of the β isoform of the TR only at the VMH of adult rats led to increase in AgRP/NPY and reduction in POMC pathways, with a concurrent augmentation in food intake and weight gain.[165] This effect was not observed when both isoforms of TR had downregulated functions in the VMH.[160] Therefore, not only the availability of T3, but also the specific TR isoform, determines the final effect of THs in control of hypothalamic circuits controlling energy homeostasis.

The action of TH in the regulation of EE may be indirect *via* controlling the action with or without expression of other circulating or local factors. Recently, it has been reported that irisin, a hormone produced in striate muscle after exercise,[166] induces browning of WAT and shows a possible relation with thyroid function.[167] However, human studies present conflicting results regarding the association between thyroid function and irisin levels, with some studies demonstrating higher levels in hyperthyroidism[168,169] and low levels in hypothyroid patients.[170–172] However, these results were not confirmed in all studies.[173–175]

Altered thyroid function can modify circulating levels of fibroblast growth factor 21 (FGF21), fetuin A, and neuregulin 4 (NgL-4), among others, which modulate EE.[27,48] NgL-4 is an epidermal growth factor (EGF) family member that is secreted by BAT and promotes augmentation in EE, inhibition of hepatic lipogenesis, and reduction of fat-mass storage.[176] A study with 129

hyperthyroid patients demonstrated that they had higher levels of NgL-4 than controls, which showed a reduction in these levels after restoring euthyroidism with treatment.[177] Studies evaluating possible opposite effects, leading to reduction of NgL-4 in hypothyroidism, are still lacking.

In addition to TH, TSH has been shown to act directly in adipose tissue that expresses TSH receptors. In differentiated human adipocytes, TSH induces lipolysis and inhibits insulin signaling through protein kinase B (Akt) phosphorylation,[178] which might contribute to IR. However, Ma and coworkers showed that TSH appears to stimulate adipocyte differentiation and lipogenesis in the pre-adipocyte cell lineage 3T3-L1 through a mechanism involving peroxisome-proliferated-activator–receptor (PPAR) gamma.[179] In agreement with a role of TSH as an adipogenic factor, mice that did not express the TSH receptor and were under TH supplementation, exhibited resistance to high-fat-diet-induced obesity.[179]

Adiposity influencing thyroid function

Leptin is a hormone produced by adipose tissue in direct proportion to the quantity of adipose tissue mass. Leptin acts mainly at hypothalamic neurons to induce satiety and increase EE. Patients with genetic mutations in the leptin gene or leptin receptor are obese, and chronic reposition of leptin caused normalization of their body weight. However, most obese patients have hyperleptinemia but are resistant to the anorexigenic central action of leptin.[180,181]

In addition, leptin was shown to regulate the production of neurohormones in the medio-basal hypothalamus, among them, thyrotropin-releasing hormone (TRH) neurons of the periventricular nucleus.[181,182] In another study, leptin activated TRH neurons both directly and indirectly, acting through the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway.[182,183] The increase in TRH release was shown to lead to higher pituitary secretion of TSH,[182–184] which in turn, stimulates thyroid function and proliferation.

Besides acting as a stimulatory agent for TRH secretion, the overall response of the thyroid axis to leptin is controversial among species and depends on nutritional status.[185] Both rodents and humans subject to fasting show suppression of TH function, with concomitant decreases in serum levels of leptin, and replacement of leptin partially restored normal concentrations of thyroid hormones.[186–189] Therefore, during caloric deprivation, the reduction in leptin seems to contribute to an integrated response to fasting, including thyroid-function suppression. However, in conditions with hyperleptinemia or at physiological levels, the role of leptin in thyroid function is less clear and may also reflect other leptin actions in the pituitary, thyroid, and peripheral tissues. Leptin receptors have been found in the anterior pituitary and thyroid gland, and direct inhibitory actions on TSH secretion and on the expressions of the Na$^+$/I$^-$ symporter (NIS) and thyroglobulin messenger ribonucleic acid (mRNA) in thyroid cell lines have been reported.[184,190] Additionally, there is experimental evidence from rodent studies that thyroid hormone metabolism may be modulated by leptin. Exogenous leptin administration caused an increase in D1 activity in the liver and pituitary, while causing a reduction in D2 activity at the hypothalamus and in BAT. Therefore, leptin may modulate thyroid hormone actions in target tissues, but collectively, these studies indicate that nutritional status and thyroid state clearly modify the responses to leptin.[191–194]

Another postulated mechanism of the way in which obesity is related to thyroid disfunction concerns chronic low-grade inflammation in adipose tissue that secretes cytokines and may affect thyroid function. It has been demonstrated that tumor necrosis factor alpha (TNF-α) and interleukins 1 and 6 (IL-1 and -6) inhibit the mRNA expression of the NIS.[195] Additionally, pro-inflammatory cytokines have been associated with inhibition of D1 in HepG2 hepatocarcinoma cells[196] and induction of D3,[197] resulting in a decrease in serum T3, one feature of the low T3 syndrome associated with chronic diseases.[198]

Finally, IR, in conjunction with leptin levels, appears to be related to obesity and leads to augmentation of serum TSH levels.[199,200] Recent studies give support to this hypothesis, showing that metformin, a drug used to improve insulin sensitivity, may cause a reduction in serum TSH levels.[201,202] Different mechanisms have been proposed and the activation of the AMP-activated protein kinase (AMPK) pathway may be enrolled.[158,159,203,204]

Thyroid function acting on glucose metabolism

Hypothyroidism is associated with peripheral IR due to a reduction in glucose uptake, and on the other hand, hyperthyroidism increases glycemia due to an increase in liver production.[205–207] T3 acts directly on the liver through TRβ, regulating genes involved in hepatic gluconeogenesis, glycogen metabolism, and insulin signaling.[205,206] In addition, TH also acts centrally on the hypothalamus to increase sympathetic flow to the liver.[126] As a consequence, in the liver, there is a decrease in glycogen synthesis and increase in gluconeogenesis and glucogenolysis,[126,207] leading to an increase in glucose output.[208] T3 increases the translocation of the glucose transport 4 (GLUT 4) to the plasma membrane in skeletal muscle and adipose tissue, which is associated with better glucose tolerance.[208–215] T2 administration has also been associated with better glucose tolerance in animal models. It induces inhibition of hepatic gluconeogenesis gene expression[216–218] by means of modulation of microRNA,[217] and regulation of the activity of the protein kinase mammalian target of rapamycin complexes 1 (mTORC1) and 2 (mTORC2).[218]

Although THs play a role in islet trophic state maintenance,[219] hyperthyroidism impairs glucose-stimulated insulin secretion and accelerates insulin degradation.[220] In the insulin-producing cell line, INS-1 cells, at high concentrations, T3 induced B-cell apoptosis and death.[221] Also, T2, at high concentrations, is able to decrease the glucose-induced insulin secretion, even though both T2 and T3 have a stimulatory effect at low concentrations.[222] The importance of maintaining low levels of T3 in pancreatic β cells was shown in mice with specific β-cell pancreatic deletion of D3 that showed a decrease in pancreatic islet area, insulin-gene expression, and glucose-stimulated insulin secretion, even though the mice were euthyroid.[223]

Thyroid function acting on lipid metabolism related to metabolic syndrome

The lipid abnormalities related to MetS are hypertriglyceridemia and low serum HDL-c levels. These abnormalities will be the focus of the present revision despite a high number of studies evaluating several other alterations in lipid profile associated with thyroid function.[224,225]

THs have effects throughout the whole body, stimulating both lipid synthesis and degradation, but in the hyperthyroid condition, there is a predominant increase in lipolysis from fat stores.[142] In the liver, THs stimulate the re-esterification of free fatty acids into triacylglycerol and also induce *de novo* lipogenesis from glucose metabolism.[226] However, THs also concurrently stimulate fatty-acid oxidation, and, under physiological conditions, the result is a balance that does not increase hepatic triacylglycerol levels.[226] The mechanisms of TH action involve direct regulation of the transcription rate of specific lipogenic/oxidative genes, in addition to alterations in the concentrations of metabolites, energy state of the cells, and post-translational modifications of proteins involved in the liver lipid metabolism.[117,226]

TH increases cholesterol clearance because even though they stimulate endogenous cholesterol synthesis, they potently increase hepatic cholesterol uptake and excretion as bile acids.[227] Low-density lipoprotein (LDL)-c accumulates in the serum of hypothyroid patients since the LDL-receptor and the sterol regulatory element-binding protein 2 (SREBP2) are under-expressed in hypothyroidism. LDL-receptors mediate liver uptake of cholesterol that comes from peripheral tissues. SREBP2 is a key transcription factor that induces the expression of lipogenic-related genes, including *Ldlr*.[227] Levels of very-low-density lipoprotein (VLDL) in the liver and in serum are influenced by lipoprotein lipases that are up-regulated by thyroid hormones, a mechanism that may contribute to the high serum triglycerides in hypothyroidism.[228] In addition, ApoB100 levels are reduced by THs contributing to the increase in VLDL and LDL production observed in the liver during hypothyroidism.[229]

An increase in serum HDL-c has been reported in hypothyroid patients; this finding appears to be related to a decrease in activity of the cholesterol ester transfer protein (CEPT).[228] CEPT, which is positively regulated by THs, mediates the exchange of cholesteryl-ester between HDL-c and VLDL and also has a pro-atherogenic role. Higher expression of CEPT would lead to higher cardiovascular risk, related to augmentation of serum levels of VLDL and reduction of HDL-c. However, as serum levels of HLD-c are also influenced by several other mechanisms, and are

reduced in states of IR and obesity, there are disagreements with respect to the results of human studies regarding thyroid function and serum HDL-c, as shown in Table 2. HDL-c levels in hypothyroid patients might also be reduced when obesity diagnosis is present with marked reduction of insulin sensitivity or MetS.

Additionally, administration of T2 in rodents has hypolipemic action, affecting the hepatic lipid metabolism.[129] It has been demonstrated that T2 is able to increase hepatic lipid oxidation and contrary to T3, does not stimulate the lipogenic pathway in animals fed a high-fat diet,[230] which potentially contributes to the important effect reported in avoiding lipid accumulation in the liver of those animals. Despite the evidence in rodents, the physiological role of T2 in human metabolism, and potential therapeutic use, need further clarification.[231,232] Serum levels of 3,5-T2 have been associated with several clinical conditions, like impaired renal function, sepsis, and oral LT4 (levothyroxine) supplementation;[232] however, further studies are necessary to evaluate causative effects between the found associations. These studies may benefit from a recently developed method to measure 3,5-T2 in human serum by mass spectrometry, which, interestingly, showed correlation with T2 isomer 3,3'-T2, but not with serum T3 or T4.[233] Likewise, other methods to measure 3,5-T2 by mass spectrometry have been tested.[234–236]

Thyroid hormone acting on blood pressure

THs act on the vasculature and in the heart by TR-mediated gene regulation in the nucleus and also *via* other non-classical pathways at the cytoplasmatic and cellular membrane levels.[130,237]

In myocytes, and also in vasculature, THs, especially T3 with greater affinity, bind to TH nuclear receptors in its two isoforms, TRα and TRβ. Thereafter, the complex formed by TH response elements at the promoter regions of specific responsive genes lead to positive or negative regulation of several genes enrolled in cardiac function and vascular resistance. The sarcoplasmic reticulum calcium ATPase (SERCA2), the myosine-have chains-α (αMHC), the Na^+/K^+ ATPase, the voltage-gated K^+ channels, the adenine nucleotide translocase (ANT1) and the β-adrenergic receptor are positively regulated by THs. In opposite, the myosine-have chains-β (βMHC), the phospholamban, the Na^+/Ca^{2+}

exchanger (NCX1), the TRα1, adenylyl cyclase (types V, VI) and TH transporters 8 and 10 are negatively regulated by THs.[130,237]

Additionally to genomic effects of TH on cardiac myocytes, and also on vasculature, there are important and faster non-genomic actions, like those related to direct modulation of membrane ion channels.[130]

THs have important inotropic and chronotropic effects on the heart and concomitantly, they cause vasodilatation in the systemic circulation, leading to a decrease in systemic vascular resistance. Hyperthyroid patients exhibit tachycardia, increased heart contractility, and decreased cardiac after-load, resulting in increased cardiac output, which leads to systolic hypertension. Hypothyroid patients may exhibit diastolic hypertension, associated with impaired endothelial-dependent vasodilatation.[238] Alterations in the microcirculation of hypothyroid patients have also been reported, such as a decrease in blood-flow velocity and impaired vasodilation after a short period of ischemia.[239] The mechanism involves TH stimulation of nitric oxide production and regulation of other local regulatory factors, resulting in a decrease in vascular smooth muscular tone.[239–242]

In addition, TH actions in the central nervous system have an influence on autonomic regulation of BP. Recently, a group of parvalbuminergic neurons at the anterior hypothalamus, which act to decrease BP, was described, and their development appears to be dependent on TRα signaling.[243] This finding may explain the hypotension present in patients with TRα mutations.[244] Different from peripheral systemic vasculature, the pulmonary vasculature does not respond to the vasodilator effect of TH and may explain reversible pulmonary hypertension related to hyperthyroidism.[245]

Studies evaluating the association between metabolic syndrome, or its components, and thyroid function in humans

Table 2 summarizes the results of different cross-sectional studies of the association between MetS and thyroid function that have been published in the last decade through July 2019. We excluded studies focusing on pediatric patients, elderly patients, and patients with a secondary diagnosis,

such as polycystic ovary syndrome. Different criteria for defining MetS were adopted for these studies. However, the NCEPT/ATPIII was the most commonly applied criteria for diagnosis.[14,16,19,25,26,38,48,54,68,69,73,77,92,94,97,98,102] Other authors used the IDF criteria,[42,47,55,56,75,81,93] the World Health Organization or American Heart Association criteria,[45,62,79] or even local/regional or pre-established criteria defined by a joint interim statement.[29,45,52,76,96] Finally, some studies defined MetS by the presence of IR according to an abnormal Homeostatic Model Assessment of Insulin Resistance index (HOMA-IR) or euglycemic clamp result.[24,49,57,71,82,84,96,100] As previously reported, not all studies evaluated the MetS diagnosis. However, the number of MetS components, or the presence of one or more of its features, were considered in many of the studies.

Almost all studies evaluated thyroid function through the assessment of serum TSH. Some studies combined assessments of serum TSH levels with the measurement of FT4. Serum FT3 or total T3 were also evaluated in some studies.[15,16, 22,27,33,35–38,45–47,49,54,57,60,73,74,77–79,81,82,85,86, 89,93,96,101,105–110]

When there was an observed association between serum TSH and the diagnosis of MetS, this association was commonly related to higher TSH levels.[19,25,29,30,42,55,67,71,76,79,91,92,98,100,102,105] In some instances, it was detected among euthyroid subjects even in the presence of normal TSH levels.[19,29,30,42,55,71,79,102] The association between serum FT4 and MetS diagnosis was not always found. However, when this association occurred, it was reported as positive (with higher serum FT4 levels) in some studies,[38,53,102] while negative in others.[24,54,95] Higher levels of serum FT3 related to MetS were also detected in some studies.[38,82,96,105]

As previously reported, obesity is commonly associated with high serum TSH level and with increment of deiodinases' activities, converting T4 to T3. Thus, this hormonal profile (high TSH and FT3 levels and low serum FT4, even in its respective reference ranges) might be associated with MetS *via* mechanisms previously described that mediate the interaction between thyroid function and clinical components of metabolic syndrome.

As demonstrated in Table 2, glycemia or glycosylated hemoglobin might be positively[37,46,62,75,93, 94,100,153] or negatively[33,66,76] associated with serum

TSH levels. A positive association between TSH levels (or reduced thyroid function) and abnormal glucose metabolism may be related to the importance of the action of TH in different pathways related to glucose transport, especially those related to the expression of GLUT 4, as previously described. This hypothesis is supported by longitudinal studies that found a higher risk for diabetes mellitus (DM) development in patients with low thyroid function or higher levels of serum TSH.[34,115]

In fact, a positive association between fasting plasmatic insulin or HOMA-IR index and TSH levels has been described in some cross-sectional studies,[16,24,25,59,66,70,82,84,94,100] which was confirmed in a cohort analysis of 5998 subjects.[34] However, the increase in serum TSH levels may be an effect of weight gain based on several previously described mechanisms. Consequently, it may be solely a biomarker for MetS and not necessarily a causative effect of the studied endpoints related to MetS. Since patients diagnosed with MetS concomitant with IR may demonstrate lower levels of serum FT4 due to conversion of FT4 to T3, the absence of a correlation between glycemia or HOMA-IR and FT4 has been observed in a large number of studies, especially those examining euthyroid subjects (Table 2).

The adverse effects of glucose metabolism are not only associated with the reduction of thyroid function or higher serum TSH levels in humans, but the adverse effects are also associated with higher serum TH levels. Longitudinal studies found a higher risk for DM development correlated with higher levels of serum FT4.[82,110,114] In fact, overt and subclinical (SC) hyperthyroidism were associated with fasting glycemia or abnormal glucose metabolism in different studies.[27,59,76,114] However, the association between serum FT4 levels in the upper reference range and serum glucose was not consistently observed in all human studies (Table 2). Finally, a cohort analysis involving 38,200 individuals revealed a higher risk for DM development in patients with either hypothyroidism or hyperthyroidism. It seems reasonable to attribute a U-shaped pattern of risk to THs and glucose metabolism abnormalities.

Despite the lack of a consistent association between THs and HDL-c levels, a reduction in thyroid function and consequently, elevation of

serum TSH levels, were shown to be associated with higher levels of serum TG in almost all human studies (Table 2). It is important to remember that a possible elevation of serum TSH levels as a consequence of obesity may be caused by both hormonal and metabolic abnormalities related to weight gain. Attributing this increase in serum TSH levels merely to reduced primary thyroid function may underestimate the effects of weight gain on thyroid function and overestimate hypothyroidism diagnostics, leading to possible overtreatment of conditions that should be first addressed by dietary modifications.

Not all human studies have demonstrated a correlation between TH levels and BP. However, a positive association between FT4 levels (even those levels in the reference range) and BP has been reported.[20,22,34,38,63,76,98] However, the opposite results have also been found.[26] Furthermore, associations between SC hypothyroidism[58,89,90,100] or SC hyperthyroidism[97] and higher BP have also been reported in some studies (Table 2).

Some longitudinal studies (Table 3) have shown that weight reduction is associated with lowering levels of serum TSH and FT3.[28] Similarly, MetS development[34,95,113] and weight gain[74,116] have been found to be positively associated with TSH-level changes. However, these results have not been validated in other studies.[17,67,69,110] Some researches only found this positive association for MetS development and not for changes in body mass index.[34,113]

Final considerations

The interaction between thyroid hormone levels and all components of MetS is complex. The potential role of T2 and novel factors, like irisin, FGF21, fetuin A and NgL-4, have been identified in recent studies that contribute to this multifaceted interaction. Researchers of human studies evaluating this association need to consider all confounding variables. Of note, longitudinal studies controlling each of those potential variables are still needed in order to assess this intriguing association, with special attention to age-, sex- and tissue-specific effects of THs.

Author's note

PFS Teixeira and CC Pazos-Moura contributed to the conception and the design of the work; drafting the work and revising the manuscript.

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