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.

Keywords: thyroid hormone, metabolism, metabolic syndrome.

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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. 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. 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. 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). The four features present in both criteria are also usually reported in other defining criteria, irrespective of the adopted standard recommendations **(1)**.

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 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)**.

Table 1. Criteria of metabolic syndrome **(1)**.

	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

At the same time, the prevalence of hypothyroidism in different population surveys has been reported to be just around 8–15%. Additionally, this prevalence increases with age, reaching almost 20% of elderly subjects. 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. Sectional studies have shown that the overlap between both diagnoses is common, justifying a high association between them. 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, but the majority just evaluated the presence of one or more specific features related to MetS and not necessarily its diagnosis **(3)**.

Cohort studies also do not seem to be capable of showing that a unidirectional pathway justifies this association, and the hypotheses that both thyroid dysfunction leads to MetS and that this condition also influences thyroid function has gained credibility. THs, and also some of their metabolites, regulate metabolic rate, leading to variations in weight gain and adiposity. 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. Also, pro-inflammatory cytokines related to obesity and IR may impact thyroid function and perhaps its structure. 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 **(4)**.

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. In this way, all four features of MetS may be influenced by TH levels. **(5)**.

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. This sympathetic stimulus by THs also influences glucose and lipid metabolism as it impacts cardiovascular system regulation. Hyperglycemia may be the consequence of reduced glucose uptake in hypothyroidism or the consequence of increased glucose liver production in hyperthyroidism. Glucose-stimulated insulin secretion and insulin degradation are also regulated by THs. Dyslipidemia may be related to thyroid function, since THs also act stimulating both lipid synthesis and degradation. 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 **(6)**.

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 **(1)**.

1.1. 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. EE can be stimulated by physical activity or acceleration of different metabolic processes, resulting in heat production (facultative thermogenesis). 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. 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. Adiposity leads to production of several hormones, cytokines, and other compounds that influence thyroid function **(7)**.

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. After thyroid hormone administration there is an increase in oxygen consumption in most tissues. 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. 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 its consumption and contributing to thermogenesis. Therefore, thyroid hormone increased the utilization of energy reserves, such as lipids from the adipose tissue **(8)**.

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. 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. 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. The action of TH in this tissue gains attention as additional mechanisms enrolled in MetS **(9)**.

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. THs cause an upregulation of adrenergic receptor expression, leading to an amplified effect on UCP1 expression, which is also activated by the SNS. Studies have shown that D2 is very important to TH-induced adaptive type of thermogenesis in BAT. 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. 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. Although it would be an attractive tool in obesity treatment, evidence in humans is still scarce, and a recent experimental study does not support that TH-induced browning is accompanied by an increase in thermogenesis. 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 **(10)**.

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. 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. 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. Hypothalamic AMPK and fatty-acid metabolism mediate thyroid regulation of energy balance. Those responses involve UCP1, since they were abrogated in UCP1 knockout mice **(11)**.

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, induces browning of WAT and shows a possible relation with thyroid function. 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. 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. 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 Studies evaluating possible opposite effects, leading to reduction of NgL-4 in hypothyroidism, are still lacking **(12)**.

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, 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. 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 **(13)**.

1.2. 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. 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. 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. The increase in TRH release was shown to lead to higher pituitary secretion of TSH, which in turn, stimulates thyroid function and proliferation **(14)**.

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. 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. 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. 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 **(15)**.

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. Additionally, pro-inflammatory cytokines have been associated with inhibition of D1 in HepG2 hepatocarcinoma cells and induction of D3, resulting in a decrease in serum T3, one feature of the low T3 syndrome associated with chronic diseases. Finally, IR, in conjunction with leptin levels, appears to be related to obesity and leads to augmentation of serum TSH levels. 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. Different mechanisms have been proposed and the activation of the AMP-activated protein kinase (AMPK) pathway may be enrolled **(16)**.

1.3. 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. T3 acts directly on the liver through TRβ, regulating genes involved in hepatic gluconeogenesis, glycogen metabolism, and insulin signaling. In addition, TH also acts centrally on the hypothalamus to increase sympathetic flow to the liver. As a consequence, in the liver, there is a decrease in glycogen synthesis and increase in gluconeogenesis and glycogenolysis, leading to an increase in glucose output. 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. T2 administration has also been associated with better glucose tolerance in animal models. It induces inhibition of hepatic gluconeogenesis gene expression by means of modulation of microRNA, and regulation of the activity of the protein kinase mammalian target of rapamycin complexes 1 (mTORC1) and 2 (mTORC2) **(17).**

Although THs play a role in islet trophic state maintenance, hyperthyroidism impairs glucose-stimulated insulin secretion and accelerates insulin degradation. In the insulin-producing cell line, INS-1 cells, at high concentrations, T3 induced B-cell apoptosis and death. 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. 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 **(18).**

1.4. 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. 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. In the liver, THs stimulate the re-esterification of free fatty acids into triacylglycerol and also induce *de novo* lipogenesis from glucose metabolism. However, THs also concurrently stimulate fatty-acid

oxidation, and, under physiological conditions, the result is a balance that does not increase hepatic triacylglycerol levels. 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 **(19)**.

TH increases cholesterol clearance because even though they stimulate endogenous cholesterol synthesis, they potently increase hepatic cholesterol uptake and excretion as bile acids. 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*. 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. In addition, ApoB100 levels are reduced by THs contributing to the increase in VLDL and LDL production observed in the liver during hypothyroidism **(20)**.

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). 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. HDL-c levels in hypothyroid patients might also be reduced when obesity diagnosis is present with marked reduction of insulin sensitivity or MetS **(1)**.

1.5. 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. 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 **(21)**.

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. 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. 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. 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 **(22)**.

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. This finding may explain the hypotension present in patients with TRα mutations. 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 **(23)**.

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

However, the NCEPT/ATPIII was the most commonly applied criteria for diagnosis. Other authors used the IDF criteria, the World Health Organization or American Heart Association criteria, or even local/regional or pre-established criteria defined by a joint interim statement. 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. 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 **(1)**.

When there was an observed association between serum TSH and the diagnosis of MetS, this association was commonly related to higher TSH levels. In some instances, it was detected among euthyroid subjects even in the presence of normal TSH levels. 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, while negative in others. Higher levels of serum FT3 related to MetS were also detected in some studies. 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 **(24).**

Glycemia or glycosylated hemoglobin might be positively or negatively 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 **(25)**.

In fact, a positive association between fasting plasmatic insulin or HOMA-IR index and TSH levels has been described in some cross-sectional studies, which was confirmed in a cohort analysis of 5998 subjects. 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 **(26)**.

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. In fact, overt and subclinical (SC) hyperthyroidism were associated with fasting glycemia or abnormal glucose metabolism in different studies. However, the association between serum FT4 levels in the upper reference range and serum glucose was not consistently observed in all human studies. 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 **(27)**.

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. 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. However, the opposite results have also been found. Furthermore, associations between SC hypothyroidism or SC hyperthyroidism and higher BP have also been reported in some studies **(1)**.

Some longitudinal studies have shown that weight reduction is associated with lowering levels of serum TSH and FT3. Similarly, MetS development and weight gain have been found to be positively associated with TSH-level changes. However, these results have not been validated in other studies. Some researches only found this positive association for MetS development and not for changes in body mass index **(28)**.

2. Thyroid hormone and metabolic syndrome in elderly cases:

2.1. Thyroid functions in aged cases:

There has been long standing controversy about the thyroid function test results in the elderly. Serum TSH, free T4, and free T3 concentrations change with aging. The first Whickham survey, published in 1977, showed that TSH levels did not vary with age in males but increased markedly in females after the age of 45 years. The rise of TSH with age in females was virtually abolished when persons with thyroid antibodies were excluded from the sample. However, in this landmark study, the number of individuals aged 75 or more was quite small, thus limiting the ability to detect a significant increase in TSH in this age group. The 20-year follow-up Whickham survey showed that with increasing age, the incidence of positive antithyroid antibodies and hypothyroidism also increased **(29)**.

This follow-up study, though, was unable to assess longitudinal change in serum TSH and thyroid hormones as more sensitive assays had been utilized, thus making any meaningful comparisons difficult. The larger and more recent NHANESIII survey showed that serum TSH concentrations as well as serum thyroid peroxidase (TPOAb) and thyroglobulin (TgAb) antibodies rise with age in both men and women. In this study, the median TSH increased and T4 decreased after age 20 in all ethnic groups, even after excluding thyroid antibody status and other risk factors. In a subsequent further analysis, Surks and Hollowell examined the NHANESIII data which showed a progressive increase in mean, median, and 97.5 centile for TSH concentration with age in the disease-free and reference populations. This analysis suggested that the 97.5 centile is about 3.6 mIU/litre in people who are 20–39 yr of age and 5.9 and 7.5 mIU/litre in those who are 70–79 and 80 yr old and older, respectively. They also demonstrated that about 70% of older patients who would be classified as subclinical hypothyroidism with TSH greater than 4.5 mIU/litre were within their age-specific reference range. Consequently, the authors have suggested that age-based reference ranges for TSH should be considered **(30)**.

Moreover, a recent longitudinal study from Western Australia (Busselton survey), for the first time, showed that serum TSH increases (mean increase of 0.32 mU/L over 13 years) with no significant change in free T4 concentrations with aging. Similarly, another longitudinal thyroid function evaluation in a very elderly subgroup (mean age 85 years) of the Cardiovascular Health Study (All Stars Study) found that serum TSH increased by 13% over an average of 13 years of follow-up associated with a 1.7% increase in FT4 and a 13% reduction in total T3 levels **(31)**.

All the above studies (Whickham, NHANESIII, Busselton, and CVHS All Stars Surveys) have been conducted in iodine sufficient areas. Contrary to these findings, a cross-sectional study performed in an area of borderline sufficient iodine intake showed that serum TSH concentrations decreased gradually with age throughout life, whereas FT4 levels increased only in participants older than 60 years. The authors hypothesized that this finding could be a result of development of thyroid autonomy after longstanding iodine insufficiency although iodine status itself was not measured in this cohort. An earlier study performed in a previously iodine deficient area in Germany showed a lower reference range (0.25 to 2.12 mIU/litre) for serum TSH in people without thyroid disease **(32)**.

Moreover, there are studies which show that subclinical hypothyroidism and subclinical hyperthyroidism may correct spontaneously over time. A study by Parle et al. showed that over 1 year follow-up, TSH returned to normal spontaneously in 5% of people aged 60 years or more with subclinical hypothyroidism and in 76% of patients with low but detectable TSH. In another similar and larger study, albeit in adults across all age groups, over a 5-year period, TSH normalized without any intervention in more than 50% of patients with elevated or decreased serum TSH level **(33)**.

Setting an upper limit for the normal value of TSH for a population has implications for the diagnosis of subclinical hypothyroidism as well as related issues such as screening, association with comorbidities, especially cardiovascular risks, and treatment. Thus, the current data support the view that serum TSH rises slightly with aging, but the data on free T4 is conflicting. Prospective large studies are required to confirm whether age-specific reference ranges should be utilized when reporting thyroid parameters **(29)**.

2.2. Thyroid status and longevity:

There have been few studies exploring the effect of thyroid disease on mortality and longevity in the elderly population. It is important to point out that these results differ from studies in younger population, and they should not be extrapolated to them. As mentioned earlier, the Leiden 85+ study showed that higher TSH concentrations and lower free thyroxine levels were associated with a survival benefit. In this study, participants with low levels of TSH at baseline had highest mortality rate, and participants with high TSH levels and low FT4 levels had the lowest mortality rate. The authors speculated that lower thyroid function may lead to lower metabolic rate

which in turn could cause caloric restriction. Lower metabolic rate and caloric restriction have both been shown to be associated with improved survival in several animal studies **(34)**.

Atzmon et al. conducted their study in elderly Ashkenazi Jews with the median age of study population being 98 years. They demonstrated that centenarians have significantly higher median serum TSH concentrations compared with younger Ashkenazi controls (median age 72 years) and in a population of thyroid disease-free individuals (median age 68 yr) from the US National Health and Nutrition Examination Survey 1998–2002 **(35).** Similar results were noted that low serum free T4 was associated with a better 4-year survival in men aged 73 to 94 years. No difference in mortality in elderly population with subclinical thyroid disorders. Another recent study in men aged > 65 years concluded that there was no beneficial or detrimental effect of subclinical thyroid dysfunction in older men **(32)**.

On the other hand, various studies have shown subclinical hyperthyroidism to be associated with higher mortality or no association with mortality. The studies by van den Beld et al. have not shown any change in mortality in their subjects with subclinical hyperthyroidism **(36)**. Previously, Parle et al. showed that a single measurement of low serum thyrotropin in individuals aged 60 years or older is associated with increased mortality from all causes, and in particular mortality due to circulatory and cardiovascular diseases **(37)**. Similar results were found by Collet et al. that endogenous subclinical hyperthyroidism is associated with increased risks of total as well as IHD mortality, with highest risks of CHD mortality and AF when TSH level is lower than 0.10 mIU/litre **(38)**.

2.3. Metabolic syndrome in elderly cases:

During the past 2 decades, rapid economic growth, changes in lifestyle and longer life expectancy have led to an increasing worldwide geriatric population. Moreover, cardiovascular and cerebrovascular problems with a high morbidity and mortality are frequently seen in this population, including the clustering of several metabolic and cardiovascular risk factors termed the metabolic syndrome (MetS), of which abdominal obesity, high blood pressure, increased glucose concentration, and dyslipidaemia are the most important components. In 1988, Reaven introduced the concept of syndrome X for the clustering of cardiovascular risk factors. The syndrome has also been given several other names, including the insulin resistance syndrome, the plurimetabolic syndrome, and the deadly quartet. The name insulin resistance syndrome has been widely used and refers to the concept that the underlying pathophysiology is thought to be related to insulin resistance. Recent studies show that there are other components of MetS, which are disturbances of coagulation, fibronolysis, endothelial dysfunction, and elevated markers of low-grade inflammation **(39)**.

Despite years of study, the use of MetS as an entity remains controversial. Some researchers have stated that MetS is a strong risk factor for the development of cardiovascular disease, cerebrovascular problems, and an increased risk of mortality, which is relatively independent from

the risk conferred by the single risk factors that compose the syndrome, for both adult and middleaged populations. Others have focused on its limited clinical usefulness with respect to relevant outcome **(40)**.

Since the first description of the MetS, a number of studies have reported that this condition is highly prevalent in the adult population, with rates in the male adult population from 7% to 34%, and 5% to 22% for women. The prevalence depends to a great extent on which definition of MetS is used, as there is still not a consensus on which one should be universally applied. The World Health Organization (WHO) criteria and the National Cholesterol Education Program (NCEP) criteria are most frequently employed in epidemiological studies, although more recently, the International Diabetes Federation (IDF) has formulated a new worldwide definition. Although the geriatric population is increasing, there is a paucity of studies regarding the prevalence of MetS in older persons. This article seeks to examine the level of evidence in the literature concerning the prevalence of MetS and discerns the impact of MetS on life expectancy and comorbidity for the elderly population (65+). It also provides an overview of the current definitions for MetS **(41)**.

2.4. Effects of natural aging:

A cross-sectional Japanese observational study suggested age-specific changes in the prevalence of MetS, which agreed with previous studies conducted in other countries and with other ethnicities. A survey in Iran showed that prevalence increased with age, with the lowest prevalence at 20-29 years and the highest at 60-69 years in both genders **(42)**. A cross-sectional survey in China also demonstrated that the prevalence of MetS increased among men and women until age 65 years, and then the prevalence decreased slightly among men and remained constant among women. Another case in point from the NHANES III study, a USA cohort of 8,814 people, revealed that MetS was present in almost half of those aged 70 years and older, while in the younger age group it was much lower (almost 7%) **(43)**.

2.5. Metabolic Syndrome as a Predictor of Cardiovascular Disease and Mortality

Controversy exists regarding the cardiovascular risk associated with MetS. How well definitions predict the risk for adverse events in people with the MetS is only now being learned. One way to judge the utility of the definitions of the MetS is to examine what outcomes are linked to it and the strength of these links. In general, the NCEP definition yields independent prognostic information for stroke. In only 2 studies that employed the WHO and IDF definitions there was no significance with stroke. Almost all surveys claimed that regardless of using NCEP or WHO criteria there was significance in predicting CHD events. However, there was no increased risk for CHD in 1 study using WHO criteria or in women using NCEP criteria (22). If MetS increases the risk of mortality this is likely to become a more serious point of discussion **(44)**.

Using the NCEP criteria Maggi et al showed no significant risk with CV mortality, and all-cause mortality using either NCEP, ACE, IDF, or WHO criteria; however, the same study alculated an increased risk for CV mortality and CHD mortality. While it is clear that the MetS predicts

increased risk for CVD in several studies, it is not clear whether this adds additional information **(45)**.

In August 2005, the American Diabetes Association and the European Association for the Study of Diabetes issued a statement discouraging the use of the term 'metabolic syndrome'. According to this statement there is no evidence that the CVD risk associated with MetS is greater than that of the sum of its parts. The accompanying meta-analysis and relative risks for the adult population suggested that the fraction of the population to which MetS could be attributed is limited. One possible explanation for the low estimates of relative risk is that people who do not have MetS but are obese or have hypertension are included in the reference group, and this potentially raises the incidence rate in the reference group, thereby lowering estimates of relative risk **(46)**.

However, the author remarked that the population attributable fraction might be larger in certain population subgroups. For example, the prevalence of MetS increases with age, reaching a prevalence > 40% in people aged > 60 years. Following this meta-analysis of 2005, several population-based studies in adult and middle-aged population prospectively investigated the link between MetS and fatal or non-fatal cardiovascular end-points. Most of these studies concluded that MetS was a significant predictor of cardiovascular disease and mortality **(47)**.

2.6. Metabolic Syndrome and Disability

There is also evidence that MetS increases functional limitations and disability even after adjustment for aging effects, BMI, and the onset of new comorbidities. In older Mexican Americans, MetS was associated with progression of mobility/strength limitation over 3 years, although not with progression of ADL/IADL (instrumental activities of daily living) disability. This association is reasonable because mobility and strength limitations are considered to arise earlier in the disablement pathway that results in IADL and ADL disability. The relationship of MetS with mobility/strength impairment might occur because of the association with obesity, common in people with MetS **(39)**.

Another study conducted in Brazil that included 420 elderly individuals older than 60 years suggested that alterations of MetS itself (rather than its obesity component alone) promote pathological aging, physical dependence, depression, cognitive impairment, and low health-related quality of life (HRQol) in later life. MetS was significantly and independently associated with a 2.2 to 2.4 higher odds of physical dependence in ADLs and IADLs, a 2.3 higher odds for cognitive impairment, a 2.1 higher risk of coexisting depression, and a 1.9 higher change of low HRQoL. If MetS were removed from this population, dependence, depression, cognitive impairment, and low QoL would be reduced by 15% to 21.4%. These effects were also independent of clinical stroke and ischaemic heart disease. MetS itself might lead to decreased neuromotor and cognitive function via an accelerated biological neuroaging process **(48)**.

One possible mediation mechanism for dependence is hyperglycaemia, often seen in MetS, which has been associated with general weakness, muscle cramps, blurred vision, and dizziness. Decreased propioception due to peripheral neuropathy might also bring dependence. For example, a study of identical elderly male twins also showed that the most significant determinants of late-life white matter lesions were glucose levels, HDL cholesterol, and systolic blood pressure, all of which are MetS components **(39)**.

Moreover, insulin levels were significantly higher in patients with lacunar strokes and selective cognitive, affective, and neuromotor dysfunctions. Together, these neurofunctional abnormalities constitute what has been considered a new geriatric nosological entity, namely the frontal-subcortical (ischaemic) geriatric syndrome. Frontal-subcortical dysfunction might also be a key point in explaining the concomitant and interrelated decline in cognitive, affective, and neuromotor functions in older people. Periarterial disease is just minimally associated with increased risk for dependence, and although small vessel disease might be one of the pathological hallmarks for mean physical and cognitive functions to decline steeply after the 7th decade of life, it might also explain the heterogeneous character of this transition. Small-vessel disease and clinical stroke are involved in the aetiology of cognitive impairment in older people **(49)**.

Moreover, in the study of Roriz-Cruz et al, MetS was found more strongly associated with cognitive impairment in the stroke-free population compared to stroke in the original population. These findings suggest that MetS might be more associated with the features of small-vessel cerebrovascular disease than with clinical stroke **(50)**. In fact, MetS (but not its conventional risk factors) was recently shown to be independently associated with intracranial atherosclerosis and lacunar (often silent) stroke **(49)**.

MetS also might increase the risk of depression simply by promoting more functional dependence, although even after adjusting for functional status, MetS was still significantly associated with a higher chance of having depression. This result points to a straight forward effect of MetS on depression and suggests that its influence on the brain directly mediates this effect. In addition to promoting stroke and cerebral small-vessel disease, MetS also seems to accelerate age-associated loss of serotoninergic innervation and responsivity, a phenomenon associated with higher risk of depression **(39)**.

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