Thyroid Hormones and the Metabolic Syndrome

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Abstract
Background: Clustering of various metabolic parameters including abdominal obesity, hyperglycaemia, low high-density lipoprotein cholesterol, elevated triglycerides and hypertension have been used worldwide as metabolic syndrome to predict cardiometabolic risk. Thyroid dysfunction impacts on various levels of these components. Objectives: The purpose of the present review is to summarize available data on thyroid hormone-dependent action on components of the metabolic syndrome. Methods: A PubMed search for any combination of hyperthyroidism, thyrotoxicosis or hypothyroidism and metabolic syndrome, blood pressure, hypertension, hyperlipidaemia, cholesterol, high-density lipoprotein cholesterol, glucose, diabetes mellitus, body weight or visceral fat was performed. We included papers and reviews published between 2000 and today but accepted also frequently cited papers before 2000. Results: There is convincing evidence for a major impact of thyroid function on all components of the metabolic syndrome, reflecting profound alterations of energy homeostasis at many levels.

Introduction

Thyroid dysfunctions and the metabolic syndrome are the two most common endocrine disorders with a substantial overlap [1]. Both are associated with significant morbidity and mortality and thus impact substantially on health care, worldwide [2, 3]. The concomitant presence of thyroid dysfunction and diabetes mellitus may be due to an overlap between autoimmune syndromes exemplified in polyglandular autoimmune syndrome type 2, where type 1 diabetes mellitus and Hashimoto’s disease are among the most frequently observed complications [4]. These syndromes are beyond the scope of this review and have been addressed elsewhere [5, 6]. The focus of the present review is to summarize the impact of hypothyroidism and hyperthyroidism on the individual components of the metabolic syndrome. We searched PubMed for any combination of hyperthyroidism, thyrotoxicosis or hypothyroidism and metabolic syndrome, blood pres-
Thyroid hormones (TH) are essential for cellular energy homeostasis and regulation. These actions are mediated both through the central nervous system and through the direct interaction of TH with peripheral target organs. Most informative are studies on different thyroid hormone receptor (THR) knockout mice together with isoform-selective agonists which suggest that thyroid hormone receptor (THR) knockout mice together get organs. The role of both isoforms of THR is further complicated by the fact that the unliganded THR may act as a repressor of TH signalling, which is reversed upon TH binding [16]. As this has major effects on the regulation of all components of the metabolic syndrome, we will review several recent landmark findings. They will comprise central effects of TH mediated via the hypothalamus which integrates effects on appetite regulation and peripheral effects on key targets such as brown (BAT) and white adipose tissue (WAT), liver, muscle and pancreatic β-cells. This crosstalk defines TH-dependent changes in lipogenesis, lipolysis, gluconeogenesis, glucose handling, insulin resistance which by interacting with appetite control define body weight and impact on blood pressure control.

Definitions

The metabolic syndrome, with insulin resistance as an essential causative factor, has been defined as the presence of visceral obesity with at least two of the following disorders: (1) raised triglyceride level or specific treatment, (2) reduced HDL cholesterol or specific treatment, (3) raised blood pressure or treatment of previously diagnosed hypertension, and (4) raised fasting plasma glucose or previously diagnosed type 2 diabetes. Threshold criteria for all measurements, still very similar, vary between definitions suggested by different organisations such as the International Diabetes Federation, the National Cholesterol Education Programme Adult Treatment Panel III or the World Health Organization [7]. For the present review, we followed the definition by the National Cholesterol Education Programme Adult Treatment Panel III if not indicated otherwise.

The criteria for thyroid disorders followed recent guidelines by the American Thyroid Association and European Thyroid Association on hypothyroidism and hyperthyroidism [8–10]. The definitions of subclinical forms of thyroid dysfunction varied considerably but were used according to the definitions given in the respective citations.

Thyroid and Energy Regulation: Pathophysiological Considerations from Animal Models

Changes within the Hypothalamus and Sympathetic Nervous System

Recent data from animal models helped to characterize the underlying targets of TH and their interactions with known hypothalamic centres of appetite and weight regulation. In 2007, Coppola et al. [17] identified type 2 deiodinase (DII) expressing glial cells in the arcuate nucleus in direct apposition to neurons co-expressing the orexigenic peptides neuropeptide Y and agouti-related protein. Fasting resulted in a local increase of DII activity, which stimulates the conversion of thyroxine (T4) to the intracellular ligand of THR triiodothyronine (T3). Locally generated T3 is transported to neuropeptide Y and agouti-related protein neurons and stimulates mitochondrial biogenesis, an event critical for increased excitability of these orexigenic neurons and involved in rebound feeding after starvation. Interestingly, this effect of T3 has previously been shown in other cellular models where T3 action is potentiated by an interaction with other stimulators of mitochondrial biogenesis [18]. More recently, Lopez et al. [19] elucidated the signalling cascade involved in these T3 effects. They showed that both, systemic or local (hypothalamic), T3 administration decreased adenosine monophosphate-activated protein kinase in hypothalamic nuclei. This subsequently increased malonyl-CoA, decreased carnitine-palmitoyl-transferase and as a net response the sympathetic nervous system (SNS) outflow. In contrast to fasting where DII is stimulated by nonthyroidal stimuli such as corticosteroids this pathway appears to be predominantly active under TH stimulation.

Direct evidence for this central control of sympathetic outflow by TH has been recently provided by the group of Fliers [20]. Following local application of T3 to TH-sensitive neurons in the paraventricular nucleus which caused no measurable systemic changes of TH, an increased sympathetic outflow to the liver was identified.
which significantly stimulated hepatic gluconeogenesis [20]. Currently, comparable human data on a hypothalamic mediated effect are missing. Indirect findings in hypothalamic versus strictly pituitary-lesioned subjects suggest however that a central wiring of SNS activity is operative in humans as well [21]. Additional evidence is provided from genetic studies blocking subtypes of THR. When THRA is blocked as in THRA−/− mice where all products of THRA are malfunctioning or in a specific heterozygous mutation, A384C, of THRA which has a 10-fold lower affinity for TH and acts unliganded as a dominant negative regulator, central SNS drive is increased [22, 23]. In both models distinct peripheral effects including a significant increase of gluconeogenesis are reported. The impact on other key peripheral target organs for the metabolic syndrome such as WAT, BAT, muscle and pancreatic β-cell mass and function will be discussed below.

The first descriptions of a THRA mutation in humans and detailed studies in animal models link TH directly to blood pressure control via hypothalamic mechanisms. In the recently published first patient with a THRA mutation blood pressure was very low [24]. Evidence for TH-dependent control via the anterior hypothalamus is provided by detailed studies of Mittag et al. [25] in the model of THRA A384C mutated mice. They identified a small group of parvalbuminergic THRA1-positive neurons in the anterior hypothalamus whose ablation induced hypertension and temperature-dependent tachycardia. The findings support well-known mechanisms on the autonomic regulation of blood pressure by the anterior hypothalamus but now integrate an acute and developmental control by TH which expands our understanding of the interaction of TH with blood pressure control.

**Peripheral Changes Related to Components of the Metabolic Syndrome**

The above-discussed central changes in autonomic regulation are intimately integrated with peripheral changes directly affecting body weight control, the altered lipid and glucose metabolism as well as blood pressure control observed in metabolic syndrome. In the following section, we will shortly review the effects obtained in animal models on peripheral regulation of gluconeogenesis and glucose handling (insulin resistance and direct effects on pancreatic β-cells) on lipid metabolism (direct modulation of WAT and BAT activity), whereas the global effects of TH on body weight control will be discussed below with the available human data.

When THRA is blocked as in THRA−/− mice, central SNS drive is increased resulting in a 25% increase of hepatic gluconeogenesis [23]. In contrast to expectations, clamp studies in these animals revealed increased insulin sensitivity with more efficient hepatic and peripheral insulin signalling, both under basal conditions and under high-fat diet. Previous studies of Sjögren et al. [22] in mice heterozygous for a THRA (A384C) mutation supported these findings. These mice are resistant to obesity following a high-fat diet and their muscular glucose uptake is improved. This was accompanied by histomorphological changes in WAT and BAT with small fat vacuoles as observed under fasting whereas muscle tissue was unaffected. Lipid utilization was increased with lower circulating levels of free fatty acids (FFA), triglycerides and cholesterol. This fits to the lower hepatic content of lipid intermediates such as diacylglycerol and subsequently improved insulin signalling observed THRA−/− mice. All these changes may reflect an increased peripheral energy demand due to an increased SNS activity in dominant negative THRA signalling. To test such a direct link to ligand-dependent activation of the THRA exogenous T3 was applied to overcome the lower sensitivity of the A384C mutation. As an alternative model the mice were crossed with mice bearing a THRB mutation which results in much increased circulating TH levels. In both models the high circulating TH concentrations switch the dominant negative action of the unliganded THRA into a positive regulation. Interestingly, these mice increased body weight and lost resistance to diet induced obesity. Gene expression profiling of WAT, BAT, liver and soleus muscle tissues revealed prominent but tissue-specific changes in lipogenesis, lipolysis and glucose handling. In WAT, both lipogenesis and β-oxidation was increased and similar but less dramatic changes were observed in BAT and liver. Glucose transport was differentially regulated with a significant upregulation of GLUT4 in WAT but not in other tissues. It supports well-known data on T3-related effects on FFA increase, an induction of hepatic, WAT, BAT and muscle-related gluconeogenesis and glycolysis [26–33]. This is further exemplified by data on the local availability of T3. Adipose tissues and liver rely on different sources of T3. Whereas WAT depends on circulating T3, hepatic T3 is dominantly derived from local type 1 deiodinase (DI) activity which is dramatically modulated in fasting [34]. Recent data on the mechanism of hepatic T3 effects suggests that T3 stimulates fatty acid β-oxidation and induces via THRA activation autophagy to deliver FFA to mitochondria [35]. Similarly, BAT depends on deiodinase activity but on subtype
DII which in fasted conditions is dramatically upregulated. This regulation is critically dependent on the current thyroid status [22, 36]. Studies in deiodinase knock-out (DII KO) animals support such notion. T3 generation from T4 is severely impaired in DII KO animals with intact THR activity which results in cellular hypothyroidism. When these animals are fed a high-fat diet, significant weight gain was induced as compared to wild-type controls and an increased deposition of triglycerides in the liver along with a reduced glycogen content and insulin resistance [37]. Comparable to the situation in the development of overt from subclinical forms of thyroid dysfunction these effects may be explained by a cross-talk of different tissue specific mechanisms. The work of Klieverik et al. [38] indicates that WAT uptake of energy rich FFA increases in the transition from hypothyroidism to a euthyroid state but is unchanged when comparing euthyroidism and hyperthyroidism. This pattern is altered in BAT where no change was observed when comparing euthyroid animals with experimental hypothyroidism but when animals are changed from euthyroidism to hyperthyroidism, a significant decrease in FFA was noted. Importantly, in the same study essential other TH target organs like heart, muscle but also liver show a continuous increase in fatty acid uptake between hypothyroidism and hyperthyroidism.

All these regulatory aspects may be further complicated by TH actions on the pancreatic β-cells. There is convincing evidence from independent research that T3 directly increases islet β-cell mass via THRA-dependent pathways [39, 40]. In contrast, insulin secretion from β-cells is potentially controlled by the truncated mitochondrial T3 receptor p43 [41]. Interestingly, these changes were associated with a decrease in specific glucose transporters, namely GLUT2 and Kir6.2, and may thus be more broadly mediated by the control of intracellular glucose availability which may have implications for other actions of TH (see below).

The role of TH in body temperature regulation may help to explain these complex alterations in energy regulation. It is well known that SNS drive critically depends on the ambient temperature. It is thus not surprising that not only the SNS outflow to BAT driven thermogenesis is critically regulated by the ambient temperature the study is performed in but all other aspects affecting components of the metabolic syndrome discussed above as well. We know from the rodent model that cold exposure acutely increases TH concentrations via central THR-TSH (thyroid-stimulating hormone) activation. BAT-dependent thermogenesis in mice kept at 4°C is approximately 80-fold increased and is related to an increased supply of glucose and FFA for thermogenesis [22]. Cold-induced SNS activation results in the transport of triglyceride rich particles to BAT and clearance from the blood [42]. Within brown adipocytes the local bioavailability of T3 is regulated by DII. Interestingly, isolated brown adipocytes lacking DII do not respond normally to adrenergic stimulation, indicated by impaired cAMP response with subsequently reduced oxygen consumption rates and lipolysis, these effects are reversed by pretreatment with T3 [43]. Cold exposure of DII−/− mice is associated with impaired adaptive thermogenesis and hypothermia, resulting in a compensatory hyperadrenergic reaction with 2.5-fold increased BAT sympathetic stimulation, as compared to controls [43, 44]. This hyperadrenergic reaction does not only impair the otherwise normal raised lipogenesis in BAT but also indicates an essential role of local TH signalling on SNS response. This is linked with mitochondrial regulation in target organs. Recent data on mice with a knock-out of the mitochondria-specific THRβ, p43, are mildly hypothermic and have a small decrease in resting energy expenditure (REE). The increased TH levels fit to a fine tuning of the system. Interestingly, these animals had significantly higher circulating glucose levels with marked insulin resistance and increased FFA but seem to compensate via muscular hypertrophy [45].

Furthermore, recently bile acids (BA) have been a recognized mechanism to regulate energy expenditure both in mice and humans [46, 47] by modulating deiodinase activity and thus local availability of TH. BA-binding raisins have been used in animals to improve insulin resistance and the metabolic syndrome [48]. This could not only pave the way for the development of new treatment strategies but also further exemplifies the complexity of TH regulation even by long-known substances previously not implicated in TH regulation.

In summary, these experimental studies in animals support a profound even though complex impact of TH status on all key components of the metabolic syndrome. Fitting to the nature of tissue-specific activation of TH a complex control mechanism integrating nutritional status, ambient temperature mainly via central mechanisms on SNS outflow with the local availability of T3 to the tissue-specific THR regulated by circulating TH levels and the local activation through deiodinases.

This pattern is further complicated by an important interaction between TH and other essential regulators of energy homeostasis. This is exemplified by leptin signalling. A decrease in WAT depots as well as starvation will result in lower leptin levels [49]. This will decrease TSH
and TH levels via action on THR synthesis and release from the periventricular nucleus. It will further counteract the increased SNS drive via central mechanisms thereby contributing to adaptations of energy homeostasis as response to altered availability of nutrients [50, 51]. A detailed description of the complex relationship between TH and WAT (including leptin) is beyond the scope of this article, but it has just recently been reviewed [52]. Figure 1 summarizes the pathophysiological considerations.

**Human Data**

An increasing number of studies has been published on thyroid dysfunction and components of the metabolic syndrome. These data even though obtained from large cohorts are hampered by the still insufficient statistical power. Given that the different components of the metabolic syndrome are analysed and mild or severe forms of hypothyroidism and hyperthyroidism are investigated, all data published so far are only sufficient to provide trends. A study by Lee and coworkers [53] attempted to circumvent these problems by analysing in 7,270 euthyroid subjects features of the metabolic syndrome in relation to circulating TSH levels. They described a significant increase in the number of components of the metabolic syndrome with increasing TSH concentrations [53] fitting to other data in almost 6,000 subjects which included subclinical forms of thyroid dysfunction [54]. The American Health Aging and Body Composition study (Health ABC study) in 3,075 subjects and 684 with metabolic syndrome evaluated the impact of increasing thyroid dysfunction on body circumference, blood pressure, HDL cholesterol, triglyceride concentrations and fasting glucose levels. They showed a significant impact on all components but waist circumference [1]. In the following, we will discuss human data on the relationship of thyroid dysfunction and individual components of the metabolic syndrome.

**Thyroid and Body Weight**

Thyroid dysfunction has a clear influence on body weight, overt hypothyroidism is associated with an increase in body weight, predominantly caused by oedema, whereas hyperthyroidism results in a reduction of weight, mainly due to catabolic effects on e.g. adipose and muscle tissue. Apart from overt dysfunction, changes in body weight also correlate with serum TSH concentrations even within the normal range [55], this cross-sectional, population-based study (included patients older than 40...

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**Fig. 1.** Schematic hypothalamic control of peripheral target organs of the metabolic syndrome through TH (red = inhibition, green = stimulation). The major THR subtypes active in target tissues are indicated.
years of age) describes a positive association of subclinical hypothyroidism with obesity. A study by Ittermann et al. [66] found a positive correlation of TH status and BMI in adolescence, which was stronger in individuals exposed to smoke (either actively or passively).

BMI may not reflect individual adipose mass or adipose tissue distribution, yet visceral obesity with subsequent adipocyte dysfunction is key to the development of the metabolic syndrome. In a recent smaller study, visceral adipose mass was the best predictor for TSH levels [57]. An influence of visceral obesity, indicated by waist circumference, on TH and TSH concentrations has also been observed in larger studies. In euthyroid adults, participating in the National Health and Nutrition Examination Survey 2007–2008, BMI and waist circumference positively correlate with TSH and fT3 levels, but not fT4 concentrations [58]. When female obese, normal weight and anorectic adolescents were evaluated before and after weight loss (in obese participants) and weight gain (in anorectic patients), TSH and fT3 seemed to be reversibly related to body weight. In this study leptin was suggested as pathophysiological link to explain alterations in TH status [59, 60]. Other studies revealed a reduction in T4 and T3, but not TSH, upon weight loss in obese children [61]. In obese adults with subclinical hypothyroidism, resting energy expenditure was affected when TSH levels are markedly elevated, whereas body composition and lipid profiles were unexpectedly unaffected [62]. The potential role of T3 versus T4 in targeting different components of metabolic syndrome has recently been evaluated in small experimental studies using different TH replacement regimes studied to evaluate T3 and T4 effects. In good agreement to the close relation seen between TH hormone status and resting energy expenditure between overt hypothyroidism, subclinical hypothyroidism, euthyroidism, subclinical hyperthyroidism, and overt hyperthyroidism alteration of REE is associated with relatively small changes in TH replacement doses [63]. Interestingly, T4 replacement in patients with hypothyroidism (e.g. after thyroidectomy) does not only result in REE differences but also in increased weight gain as compared to controls indicating a less than optimal replacement with the standard replacement regime used [64]. In another study, REE and TH were determined during a block and replace therapy (BRT, i.e. a combination of thyroidstatic drug and T4 replacement) for Grave’s disease and 12 weeks after cessation of the BRT [65]. Increases in free T3 to free T4 ratio were found to be a positive determinant of alterations in REE, further indicating that the balance of T3 and T4 is important for the regulation of energy homeostasis. In line with this notion, a combination of T4 and T3 for substitution in hypothyroid patients revealed a weight reduction after 15 weeks of 1.7 kg compared to minimal weight gain of 0.1 kg in patients taking T4 alone [66]. Another pilot study tested the effect of T3 substitution alone in 14 patients. It revealed again a significant weight loss and reduced levels of total cholesterol, low-density lipoprotein-cholesterol, and apolipoprotein B under T3 substitution when compared to conventional T4 replacement with identical TSH serum levels [67]. Both studies indicate that circulating T3 levels and the replacement of T3 in athyroid subjects may be more important than previously recognized.

Thyroid and Arterial Hypertension
The effects of hypothyroidism or hyperthyroidism on blood pressure have been evaluated in large population based studies. There is a small but convincing association between both systolic and diastolic blood pressure readings and TH status. This is particularly convincing in a study in children and adolescents, where the positive correlation between serum TSH levels and blood pressure (in the upper normal range) is less likely to be corrupted by other factors impacting on blood pressure control [68]. A recent meta-analysis revealed a rather weak relationship of subclinical hypothyroidism with increased systolic and diastolic blood pressure, whereas no association was found in subclinical hyperthyroidism [69]. However, when the effects of TH replacement was tested in a large meta-analytic approach no consistent alteration of systolic or diastolic blood pressure was found indicating that under conventional clinical conditions the effects of TH on blood pressure regulation are less marked.

Thyroid and Dyslipoproteinaemia
The intimate relation between TH status and lipid parameters have been well described within the past 80 years [70]. They have recently been reviewed in a number of excellent reviews [71, 72]. We thus focus here on the direct impact of TH on the lipid components which are part of the definition of metabolic syndrome, triglycerides and HDL cholesterol levels.

In hypothyroidism HDL cholesterol, particularly HDL2 levels are not uniformly increased but they are reduced in hyperthyroidism. This pattern was confirmed in large epidemiological studies but the effect is not uniformly visible. In the Health ABC study Waring et al. [1] determined the odds ratio of elevated triglyceride and low HDL cholesterol relative to thyroid function status. Triglycerides levels were positively related to overt and sub-
clinical hypothyroidism, whereas low HDL cholesterol concentrations were found in approximately 1/3 of all patients with overt hypothyroidism, mainly as part of dyslipidaemia type IIb but also of type IV. These relations are less clear in subclinical hypothyroidism where definitions of the disease, confounding factors and a generally smaller impact may contribute to controversial findings (summarized in [71]). The Norwegian HUNT study, a large epidemiological survey, suggests a significant increase in triglycerides in the transition from subclinical hyperthyroidism to subclinical hypothyroidism [73]. Treatment with TH on lipid parameters have been evaluated in generally small studies reviewed in a meta-analysis of only 247 subjects by Danese et al. [74]. There is a heterogeneous effect on HDL but a more consistent albeit small decrease on triglycerides. This was confirmed by further studies reviewed by Duntas and Brenta [71]. It may be due to an upregulation of apolipoprotein AV in hepatocytes which is able to decrease triglyceride levels [75].

Thyroid and Insulin Resistance/Diabetes Mellitus

The Health ABC study revealed a positive correlation of (subclinical and overt) hypothyroidism with elevated fasting glucose levels at baseline [1]. Smaller studies supported this and showed an increased glucose but also insulin response to an oral glucose tolerance test in patients with subclinical and overt hypothyroidism [76, 77]. When an oral glucose tolerance test is repeated in patients with subclinical or overt hypothyroidism interestingly again glucose and particularly insulin levels are raised supporting insulin resistance under hyperthyroid and hypothyroid conditions.

Blood glucose levels are determined by a balance of glucose ingestion and gluconeogenesis, as well as glucose disposal and metabolism in target tissues [78]. Overt and subclinical hypothyroidism is associated with decreased glucose transport in myocytes [79]. This is mediated by glucose transporters (GLUT) on the cell surface which regulate the intracellular glucose uptake. Basal expressions of GLUT are stimulated by TH. In hyperthyroidism GLUT1, GLUT3, and GLUT4 are increased [80], whereas GLUT5 has been shown to be the dominant GLUT (increased 15-fold) in skeletal muscle when hypothyroid patients are treated to euthyroidism [81]. Gluconeogenesis is increased and glycogen synthesis decreased in subclinical and overt hyperthyroidism, as compared to euthyroidism [77]. Hypothyroidism is associated with muscle and adipose tissue insulin resistance [82]. As discussed above for animal models there is as well an important impact of TH on insulin secretion and clearance. Several studies confirm higher insulin levels in hypothyroidism and a lower insulin clearance [83]. Together with the alterations in glucose handling this relates to an increased insulin resistance with higher TSH levels [84]. The importance of both pathways for glucose metabolism was strikingly shown in a patient with type A insulin resistance under very high doses of insulin treatment who developed a papillary thyroid carcinoma. When converted from normal thyroid function to subclinical hyperthyroidism in the post-operative management of the tumour, BAT was dramatically activated, REE increased 2-fold and insulin resistance disappeared [85]. Even though the very nature of the disease does not allow us to generalize these data, they provide strong evidence for the power of TH in their interaction with insulin resistance and diabetes mellitus.

Conclusions

There is an intimate interaction of TH with all components of the metabolic syndrome in animal models and man. Whereas mechanisms remain obscure in many aspects of the human data it is increasingly clear that hyperthyroidism as well as hypothyroidism induces insulin resistance, the pathophysiological hallmark of the metabolic syndrome. Recent data in animal models allow to further elucidate the complex nature of interactions between (1) TH and (2) glucose production, peripheral glucose uptake, lipolysis, and lipogenesis. These findings reflect profound alterations of energy homeostasis at many levels. Due to the nature of TH activation these effects are not linearly altered in the development of overt hypothyroidism and hyperthyroidism from subclinical thyroid disorders but may switch depending on the local concentrations of TH.

Disclosure Statement

The authors state no conflict of interest.
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