

Atherosclerotic and metabolic effects of hypothyroidism due to chronic thyroiditis

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Abstract

Hypothyroidism is the condition of decreased hormone production to provide the needs of peripheral tissues. Clinical symptoms may vary depending on patient's age, disease duration and thyroid hormone levels. Thyroid hormones are important determinants of basal metabolic rate and thyroid hormone status have a strong effect on different metabolic pathways (protein, carbohydrate, lipid) and atherosclerotic pathogenetic mechanisms.

This review focuses on metabolic and atherosclerotic effects of hypothyroidism due to chronic (hashimoto) thyroiditis.

Key Words: Hypothyroidism, basal metabolism, body composition, atherosclerosis

Introduction

Hypothyroidism refers to reduced hormone production in the thyroid gland and the inability to produce thyroid hormones that provides the needs for peripheral tissues. Primary hypothyroidism accounts for more than 95% of all hypothyroid cases. Primary hypothyroidism is characterized by elevated serum TSH levels and low levels of free serum thyroxine (fT4), and this phenomenon is also called overt hypothyroidism (1).

According to population studies, the prevalence of overt hypothyroidism varies from 0.1 to 2% (2). Chronic autoimmune (Hashimoto) thyroiditis is the most common cause of primary hypothyroidism in regions of the world with sufficient iodine. It is characterized by cellular and antibody-associated damage in the thyroid tissue. Cytotoxic T-cells may cause direct damage in thyrocytes. Furthermore, antibodies may develop in the serum against thyroglobulin (Anti-Tg), against thyroid peroxidase (thyroid microsomal antigen) (Anti-TPO) or against thyroid sodium/iodine transporter in 90% of patients with chronic autoimmune thyroiditis (3).

Clinical symptoms may vary depending on patient's age, disease duration and thyroid hormone levels. The standard treatment of hypothyroidism is hormone replacement therapy with synthetic thyroxine hormone (LT4). LT4 need varies depending on severity of disease as well as lean body mass and total body weight of patients.

Thyroid hormone statuses of a patient have a strong effect on different metabolic pathways and atherosclerotic pathogenetic mechanisms.

A PubMed search was performed using the terms "hypothyroidism" AND "basal metabolism, body composition, protein metabolism, carbohydrate metabolism, lipid metabolism and atherosclerosis". The titles were scanned manually and articles of interest regarding the metabolic and atherosclerotic effects of hypothyroidism were reviewed.

The effect of hypothyroidism on basal metabolism

Thyroid gland produces the thyroxine hormone with essentially low biological activity (3, 3', 5, 5'-tetraiodothyronine or T4). At intracellular level, the iodine in the outer ring is removed by type 1 deiodinase (D1) or type 2 deiodinase (D2), forming the 3, 3', 5 triiodothyronine (T3) which binds to thyroid hormone receptor with a 100-fold increased affinity compared to T4 (1).

Classically, thyroid hormones are known to exert their effect on energy homeostasis through peripheral tissues. This effect occurs through the metabolically active tissues such as liver, white and brown adipose tissue, heart and skeletal muscle. Brown adipose tissue shows paravertebral and perirenal distribution in adults and accounts for 20% of energy consumption. Thyroid hormones induce the lipolysis stimulating effect of norepinephrine in brown adipose tissue and also increase UCP (uncoupling protein) expression,

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thereby increasing the mitochondrial heat generation (thermogenesis) (4).

The norepinephrine from sympathetic nervous system binds to β_3 adenoreceptors in brown adipose tissue and increases cAMP levels, thereby activating protein kinase A and hormone-sensitive lipase, allowing lipolysis and leading to release of free fatty acids from triglycerides. Free fatty acids (FFA) are activated to acyl-CoA by acyl-CoA synthetase and transported to mitochondria via carnitine palmitoyltransferase 1a (CPT1a). β -oxidation of the acyl-CoAs from FFA occurs in mitochondria. This results in increased UCP1 synthesis, which provides mitochondrial heat generation. Uncoupling proteins stop ATP (adenosine triphosphate) production, causing the energy in nutrients to be released as heat only. UCP1 is an uncoupling protein found only in brown adipose tissue, and thyroid hormones are known to increase UCP1 gene expression. UCP2 and UCP3 are the other uncoupling proteins associated with metabolic and thermogenic effect of thyroid hormones found in muscle, fat and other tissues. Thyroid hormones increase the effect of norepinephrine (NE) in this pathway and also induce UCP1 gene expression, leading to increased uncoupling proteins and thereby increasing mitochondrial heat generation (4). Uncoupling protein-2 is another uncoupling protein which regulates the oxidation pathway. Decreased UCP2 mRNA expression has been shown in periumbilical subcutaneous adipose tissue biopsy in patients with hypothyroidism (5).

Another pathway related to the peripheral effect of thyroid hormones on thermogenesis (heat generation through physiological process) is the pathway associated with bile acids. The discovery that bile acids induce local thyroid hormones by activating type 2 deiodinase has led to demonstrating that thyroid hormones are effective in the thermogenesis increased through bile acids during the post-prandial period (6).

Recently, it has been understood that the effect of thyroid hormones on energy homeostasis does not occur only through peripheral tissues but also centrally through the nuclei in hypothalamus (arcuate, paraventricular and ventromedial). In hypothyroidism, basal metabolic rate (BMR) is thought to decrease owing to the effect on hypothalamic nuclei via the central route and the reduced thermogenic effect on peripheral tissues. Reduced thermogenesis clinically presents as cold intolerance in patients and contributes to storing energy (4).

The effect of hypothyroidism on body weight, body mass index and body composition

Thyroid hormones are important determinants of BMR. Hypothyroidism is associated with decelerated metabolic functions. Patients with hypothyroidism are known to have increased body weight. However, there

are contradictory publications regarding the primary factor responsible for this increase. Serum TSH levels are reported to exhibit a positive correlation with body weight and body mass index (BMI) (7-10). While some publications report a positive correlation between serum TSH levels and increased adiposity, some others claim no such association (9). In normal range, only elevated TSH levels have been reported to be associated with increased visceral adipose tissue measured by ultrasonography (11). Publications report different results regarding the changes in body weight and composition following treatment for hypothyroidism. A study reported weight reduction at 6 months after treatment in hypothyroid patients receiving replacement therapy, although the patients returned to their pre-treatment body weight at 24 months (12). Another study reported that correcting hypothyroidism did not lead to any changes in body composition evaluated by DEXA (13). A prospective study where patients with hypothyroidism receiving replacement therapy were followed for 12 months showed statistically significant weight reduction after treatment; however, the weight reduction was shown to be from lean body mass and not from adipose tissue (14). A study which evaluated body composition by DEXA before and after LT4 therapy in patients with hypothyroidism demonstrated significantly decreased BMI and significantly increased adipose tissue while soft tissue mass declined when euthyroidism was achieved with LT4 (5). Another study with DEXA showed weight gain in hypothyroidism and weight reduction after treatment, although the primary factor responsible for the reduction was lean body mass (15).

The effect of hypothyroidism on protein metabolism

Hypothyroidism has complex effects on protein metabolism. Overall, protein synthesis and degradation declines; however, patients with hypothyroidism remain at a positive nitrogen balance. Increased total modifiable albumin pool is seen in myxedema (16). Albumin is distributed to a broad volume, leading to increased capillary wall permeability. Increased glycosaminoglycan synthesis is observed (17). Extracellular protein mobilization occurs after treatment in patients with hypothyroidism, causing a temporarily negative nitrogen balance (18). Urinary excretion of potassium, phosphorus and nitrogen increases in late stage. This suggests that cellular proteins are also metabolized (19).

The effect of hypothyroidism on carbohydrate metabolism

Intestinal glucose absorption is slower than normal in hypothyroidism. Studies comparing fasting plasma glucose and fasting insulin levels versus controls have often reported normal results (20, 21). However, some

studies report the possibility of mildly low glucose levels and mildly high insulin levels (22-24).

The HOMA-IR (Homeostasis Model Assessment of Insulin Resistance) index used to measure insulin resistance reflects the insulin resistance at fasting state (particularly at hepatic level). Matsuda index is calculated using the insulin and plasma glucose levels measured during the oral glucose tolerance test and provides insight on insulin sensitivity in peripheral tissues (25). Comparison on HOMA-IR index in patients with hypothyroidism versus euthyroid controls revealed normal results in some studies (20, 21, 26) while other reported increased index in these patients (24, 27). Matsuda index has been reported to decline in hypothyroidism and show positive correlation with serum fT4 levels (21, 24). These studies suggest that while some patients with hypothyroidism may have insulin resistance at fasting state, decreased post-prandial insulin sensitivity is more common among hypothyroid cases. Decreased insulin-mediated glucose transfer has been shown in patients with hypothyroidism due to the disrupted GLUT-4 (glucose transporter-4) translocations in monocyte plasma membranes (24). Post-prandial glucose intake in muscle and adipose tissue has been reported to decrease in patients with hypothyroidism compared to euthyroids (21). Studies with euglycemic hyperinsulinemic clamp test have reported corrected insulin sensitivity in patients with hypothyroidism upon achieving euthyroidism (28).

The effect of hypothyroidism on lipid metabolism

Lipolysis and biosynthesis of fatty acids are decreased in hypothyroidism. Total cholesterol is increased and LDL-C (low density lipoprotein cholesterol) is the main factor responsible for this increase. Decreased T3-dependent gene expression of hepatic LDL-C receptors necessary for LDL-C clearance in the liver is reported to cause elevated LDL-C levels (29). Furthermore, LDL-C oxidability is also increased in hypothyroidism (30).

Increased HDL2 despite stable HDL3 levels in hypothyroidism is associated with the decreased activity of hepatic lipase which normally allows the transformation of CETP (cholesteryl ester transfer protein) and HDL2 to HDL3 (31).

While apolipoprotein B and AI are increased, no change is seen in apolipoprotein AII. In some patients, decreased lipoprotein activity in adipose tissue and therefore reduced triglyceride clearance is responsible for the increased triglyceride levels (31). Greater post-prandial lipemia (defined as more than 80% increase in triglycerides) was observed in patients with hypothyroidism compared to the control group in an oral lipid tolerance test study (37). Free fatty acid concentration is reported to be normal in hypothyroidism; however, some reports indicate

increased and some others report decreased concentrations as well (33). While some studies report increased lipoprotein (a) levels in hypothyroidism which declines with treatment, some others have reported no change in lipoprotein (a) levels (34-36).

A study in patients with short-term overt hypothyroidism showed increased total cholesterol and LDL-C levels with no change in small LDL particles, which are more atherogenic; and triglyceride levels were observed to be borderline high while no change in was seen in large VLDL particles, which are also more atherogenic. This study found a shift to large LDL, small VLDL and large HDL particles, which are less atherogenic, despite the increased levels of total cholesterol and LDL in hypothyroidism (37).

The effect of hypothyroidism on renal functions, water and electrolytes

Renal blood flow is decreased in hypothyroidism due to reduced cardiac output and blood volume. Glomerular filtration rate and effective renal plasma flow are also decreased. Serum creatinine and serum cystatin-C levels increase by 10-20% and return to normal following LT4 therapy (38). Total body sodium is essentially increased in hypothyroidism. The excess sodium is thought to bind to extracellular mucopolysaccharides. Reduced free water clearance is seen in hypothyroidism. Some studies have shown elevated levels of serum vasopressin (AVP). Inappropriate release of AVP in some hypothyroid patients may result in a predisposition to low sodium levels by dilution (39).

Increased serum uric acid levels have been shown in men and postmenopausal women with hypothyroidism due to the reduced renal blood flow (40). Some patients may experience mild hypocalcemia. Total magnesium levels may be increased; however, the bound fraction and urinary excretion are decreased with no change in serum potassium levels (41).

In conclusion, renal blood flow and glomerular filtration rate are decreased in hypothyroidism, renal urine dilution capacity is reduced, and hyponatremia may occur in cases with deep hypothyroidism and elevated serum creatinine levels (42).

The effect of hypothyroidism on cardiovascular system

Thermogenesis at tissue level is decreased by 5-8% in hypothyroidism. Peripheral arteriolar resistance is increased by the direct effect of T3 in vascular smooth muscle cells. The final cardiac load and diastolic blood pressure are also increased. Decreased myocardial contractility, cardiac chronotropy and inotropy are observed, resulting in a cardiac output drop to under 4.5 L/min (43). Achieving euthyroidism

normalizes peripheral vascular resistance and diastolic blood pressure (44).

Blood supply is reduced in both myocardial and peripheral tissues due to decreased cardiac output. The reason underlying the lack of ischemic symptoms despite reduced blood supply to myocardium is the simultaneous reduction in myocardial oxygen consumption. Cardiac contractility tends to decrease in hypothyroidism due to the myxedematous changes in myocardial fibers. The compensatory elongation of myocardial muscle fibers in order to perform the existing functions results in cardiomegaly in both right and left heart chambers. Post-treatment improvement appears to be slow and progressive within 3 weeks to 10 months. Decreased interstitial fluid also contributes to the improvement (43, 44).

Pericardial effusion is another factor responsible for the cardiomegaly seen in hypothyroidism; however, it is often mild and does not vastly affect cardiac hemodynamic. In addition to pericardial effusion, pleural and peritoneal effusions may also occur in hypothyroidism (45).

The effect of hypothyroidism on atherosclerosis

Atherosclerosis is reported to increase in hypothyroidism through several pathogenetic pathways (46). Total cholesterol and particularly LDL-C are increased with hypothyroidism. Increased plasma homocysteine levels which return to normal values after treatment have been shown in hypothyroid patients (47). Reduced non-HDL cholesterol levels have been observed following hormone replacement therapy both in subclinical and pronounced hypothyroidism (48). A population study conducted in the Netherlands has shown that subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction (49). Increased epicardial adipose tissue (EAT) has also been associated with atherosclerosis and increased EAT has been shown both in subclinical and overt hypothyroidism cases compared to healthy euthyroid controls (50). The increased EAT in hypothyroid patients has been demonstrated to regress after treatment and this is suggested to be a contributing factor to the atherosclerotic process seen in hypothyroidism (15).

Conclusion

In hypothyroidism, BMR is thought to decrease owing to the effect on hypothalamic nuclei via the central route and the reduced thermogenic effect on peripheral tissues. Body weight is increased in hypothyroidism and then decreased after treatment; however, the current literature is conflicting on whether hypothyroidism actually leads to obesity (increased adipose tissue). Atherosclerosis increases in hypothyroidism and in light of the currently available

literature, the factors responsible for this increase may include elevated LDL-C, increased homocysteine levels, diastolic hypertension, predisposition to hypercoagulability as well as the increased insulin resistance and EAT as reported in some studies. However, there may be other pathogenetic pathways which would clarify the effect of hypothyroidism on atherosclerosis and further studies are therefore required in this field.

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Ethical issues: All Authors declare that Originality of research/article etc... and ethical approval of research, and responsibilities of research against local ethics commission are under the Authors responsibility. The study was completed due to defined rules by the Local Ethics Commission guidelines and audits.

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