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Artigo Revisão

Subclinical Thyroid Dysfunction and Cardiovascular Disease

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A B S T R A C T

Thyroid hormones are intricately related to the cardiovascular system. Therefore, it is expected that thyroid dysfunction, including subclinical thyroid disorders, significantly impacts the cardiovascular system, contributing to both cardiovascular and all-cause mortality.
Subclinical hyperthyroidism, defined by low or undetectable levels of serum thyroid-stimulating hormone with free triiodothyronine and thyroxine concentrations within the reference range, has been linked to an increased risk of hypertension, atrial fibrillation, coronary artery disease, endothelial dysfunction, and thromboembolic events.
Subclinical hypothyroidism, defined as increased serum thyroid-stimulating hormone in the presence of normal circulating free triiodothyronine and thyroxine levels, is associated with increased prevalence of cardiovascular-associated risk factors, such as hypertension and obesity, as well as low levels of high-density lipoprotein. It also increases the risk for atherosclerosis and myocardial infarction.
The prognosis of heart failure is known to be adversely impacted by both subclinical thyroid dysfunctions. Subclinical hyperthyroidism appears to increase the risk of acute heart failure, possibly by incrementing the risk of arrhythmias, such as atrial fibrillation. In turn, subclinical hypothyroidism has been associated with the development of heart failure in patients with and without underlying heart disease.
Although treatment of these subclinical thyroid dysfunctions could be beneficial and alter the course of several cardiovascular diseases, its benefit on cardiovascular risk and mortality remains unclear. There is still no clear evidence to support an undeniable benefit of treatment of subclinical hypothyroidism or hyperthyroidism.

Disfunção Tiroideia Subclínica e Doença Cardiovascular

R E S U M O

As hormonas tiroideias encontram-se intrinsecamente relacionadas com o sistema cardiovascular, pelo que é expectável que as disfunções da função tiroideia, incluindo as disfunções subclínicas da tiroide, tenham um impacto significativo no sistema cardiovascular, contribuindo para a mortalidade de causa cardíaca e por todas as causas.
O hipertiroidismo subclínico, definido por concentrações séricas diminuídas ou indetetáveis de hormona estimuladora da tiroide e valores séricos normais das hormonas tiroideias, parece associar-se a um risco acrescido de hipertensão arterial, fibrilhação auricular, doença arterial coronária, disfunção endotelial e eventos tromboembólicos.

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O hipotiroidismo subclínico, definido por concentrações séricas aumentadas de hormona estimuladora da tiroide e valores séricos normais das hormonas tiroideias, está associado a um aumento da prevalência dos fatores de risco cardiovasculares, tais como hipertensão e obesidade, bem como níveis diminuídos de lipoproteína de alta densidade. O hipotiroidismo subclínico também se associa ao aumento do risco de aterosclerose e de enfarte agudo do miocárdio.
Além disso, o prognóstico de insuficiência cardíaca poderá ser prejudicado por ambas as disfunções subclínicas da tiroide. O hipertiroidismo subclínico parece aumentar o risco de insuficiência cardíaca aguda, possivelmente pelo aumento do risco de arritmias, tais como a fibrilhação auricular. Por sua vez, o hipotiroidismo subclínico tem sido associado ao desenvolvimento de insuficiência cardíaca em doentes com e sem doença cardíaca subjacente.
Embora o tratamento destas disfunções subclínicas da tiroide possa ser benéfico e alterar o curso de várias doenças cardiovasculares, o seu benefício sobre o risco cardiovascular e a mortalidade permanece pouco claro. Ainda não há evidência clara que sustente um benefício inegável do tratamento em doentes com hipotiroidismo ou hipertiroidismo subclínico.

Introduction

It is widely recognized that the thyroid function is intricately related with the cardiovascular system.[1,2] Likewise, thyroid dysfunction, including subclinical thyroid disorders, and cardiovascular diseases (CVDs) are highly correlated.[3–5]

Subclinical thyroid dysfunction comprises both subclinical hypothyroidism (SHypo) and subclinical hyperthyroidism (SHyper) and presents as altered serum levels of thyroid stimulating hormone (TSH), elevated or decreased, respectively, but levels of thyroxine (T4) and triiodothyronine (T3) within their respective reference ranges.[6]

Given the high prevalence and clinical relevance of both subclinical thyroid dysfunction and CVDs, we aim to highlight the pathophysiological and clinical links between both entities.[4]

SHypo is defined as increased serum TSH in the presence of normal circulating free T4 and T3 levels and comprises two categories regarding TSH levels: mild SHypo which presents with mildly increased TSH (above upper reference limit to 10.0 mIU/L) and severe SHypo with severely increased TSH (>10 mIU/L).[7] Usually, it is an asymptomatic condition. If present, symptoms are similar though less evident than those observed in overt hypothyroidism. It is a common disorder, with a prevalence ranging from 4% to 15% in the general population and up to 20% among women aged over 60 years, especially those with a positive thyroid autoimmunity and/or rich diet iodine intake.[8–11] Raposo *et al* estimated a prevalence of 2.7% of mild SHypo and 0.6% of severe SHypo in the Portuguese population, both being more common among women.[7]

Elevated TSH levels are believed to have the same aetiology as overt hypothyroidism, Hashimoto's thyroiditis being the most common cause. Another cause could be a slight decrease in thyroid function in the elderly which leads to slightly higher TSH levels that tend to increase with age, even in the absence of thyroid disease.[11,12]

SHyper can be defined as persistently low levels of serum TSH with free T3 and T4 concentrations within the reference range. SHyper comprises two categories according to its severity: grade 1 when low levels of serum TSH are detected (0.1 mIU/L to below the lower reference limit), and grade 2, when serum TSH is very low or undetectable (<0.1 mIU/L).[7] This condition is common in the general population and its frequency is variable, depending on sex, age, and iodine intake. It is particularly common in elderly patients, affecting 10%-15% in patients over 65 years of age.[8,13–15] Raposo *et al* estimated a prevalence of 0.8% of SHyper grade 1 and 0.6% grade 2 among Portuguese people.[7]

SHyper may be caused by endogenous or exogenous factors, such as multinodular goiter, thyroid adenomas or treatment with levothyroxine (LT4) in doses used to suppress TSH in differentiated thyroid cancer.[16,17] SHyper is often asymptomatic and, therefore, this diagnosis is usually made incidentally through the detection of alterations in screening exams.[8]

Methods

The search strategy used for this review article was to search PubMed with the terms "Thyroid Hormones", "Thyroid Diseases", "Subclinical Thyroid Disorders", "Cardiovascular Diseases", "Cardiovascular Risk Factors", "Heart Failure", "Cardiometabolic Risk Factors" and combinations of these terms. We selected original and review articles published in English.

Thyroid Hormones Physiology

The main thyroid hormones (THs) consist of T4 and T3 and are produced by the thyroid gland, which takes part in a self-regulatory circuit called the hypothalamic-pituitary-thyroid axis.[13,18–20] The thyroid gland releases THs mostly as T4, which is de-iodinated peripherally to T3 via deiodinases type I and II or transformed irreversibly into inactive isomers such as reverse T3 and 3,3-diiodothyronine (T2) by deiodinase type III.[18,19,21]

THs regulate major basal metabolic pathways and almost every tissue in the body has thyroid hormone receptors (TRs). THs main effects at the genomic level are mediated by nuclear TRs, that are closely associated with chromatin and bind to THs with high affinity and specificity. The receptors consist of intracellular DNA binding proteins that bind to T3 with a higher affinity than T4, making T3 twenty times more potent than T4. These hormones are lipophilic and circulate in the body mostly bound to transporter proteins. After binding to the receptor, they form hormone-receptor complexes and bind to thyroid hormone response elements (TREs) in the regulatory regions of target genes, modulating essential functions in growth, development, and metabolism of several tissues. TREs are considered ligand-regulatable transcription factors as they bind to THs and DNA to regulate transcription.[18,19,21–23]

Thyroid Hormones and the Cardiovascular System

THs act on the heart through genomic and nongenomic effects mostly mediated by T3.[24,25] The effects of T3 in the heart appear through the action of TRs, specifically the alfa isoform (TRα), which is the main TR isoform present in this organ. THs lead to physiologic hypertrophy and have positive ionotropic, chronotropic and lusitropic effects.[14,24–27] At a vascular level, most effects of THs are mediated through non-genomic pathways.[28]

Genomic effects

Evidence suggests that T3 regulates the calcium concentration in cardiomyocytes through the upregulation of sarcoplasmic reticulum calcium-activated ATPase 2 (SERCA2a), which lowers the intracellular concentrations of Ca^{2+} by pumping this ion into the sarcoplasmic reticulum during diastole.[26,27] In turn, T3 promotes the downregulation of phospholamban, enhancing the velocity of myocardial relaxation.[24,29] Additionally, T3 affects multiple ion channels including Na^+/K^+ ATPase, Na^+/Ca^{2+} exchanger, and voltage-gated K^+ channels (Kv1.5, Kv4.2, Kv4.3).[29] It has been described that T3 promotes signalling pathways which alter gene expression leading to cardiac hypertrophy through the increase of adenosine triphosphatase (ATP), SERCA2a, upregulation of myosin heavy chain α gene (*MHC*α) and downregulation of *MHC* β gene expression.[27] The increase of atrial natriuretic peptide (ANP) and decrease of protein kinase C (PKC) both lead to physiologic cardiac hypertrophy as well. Additionally, β1 adrenergic receptor is positively regulated by T3 leading to its inotropic and chronotropic cardiac effects.[27,29]

Non-genomic effects

Thyroid hormones also act through nongenomic mechanisms, producing faster effects on cardiac inotropism and chronotropism. This is achieved through the promotion of acute phosphorylation of phospholamban, mediated by intracellular kinase pathways, leading to the attenuation of its inhibition of SERCA2a.[27]

Additionally, THs have important effects on the vascular system. T3 reduces peripheral vascular resistance through activation of phosphatidylinositol 3 kinase (PI3K)/ serine/threonine-protein kinase (AKT) signaling pathways inducing endothelium-derived nitric oxide (NO) synthase phosphorylation, therefore increasing NO production.[24,30,31]

T3 downregulates angiotensin II type 1 receptor mRNA expression at both transcriptional and posttranscriptional levels, further promoting vascular relaxation.[32] Evidence suggests that T3 contributes to angiogenesis and augments the density of small arterioles, including coronary arterioles.[24]

The cardiovascular system is sensitive to small and persistent alterations of THs concentrations, such as those present in subclinical thyroid dysfunction. It is therefore expected that these conditions would lead to significant changes in cardiovascular homeostasis.[14]

The Impact of Thyroid Hormones on Cardiovascular Risk Factors

Regulation of body weight

THs are important regulators of food intake, adiposity as well as lipid and glucose metabolism, and therefore have an impact in energy expenditure and body weight. There is a bidirectional relationship between THs and weight changes as both influence one another.[33]

Hypothyroidism and SHypo are associated with higher body mass index and obesity. SHypo is also associated with metabolic syndrome (MetS).[9,33] Moreover, SHypo seems to be an independent predictor of NASH and NASH-related advanced fibrosis among patients with non-alcoholic fatty liver disease (NAFLD).[34] On the other hand, in hyperthyroid patients, enhanced energy expenditure and weight loss is usually seen.[33]

Obesity impacts the hypothalamic-pituitary-thyroid axis and is associated with impaired thermogenesis and insulin tolerance.[33] The latter leads to hyperleptinemia which enhances TSH secretion. TSH promotes the differentiation of adipocytes and contributes to the maintenance of obesity. Obese patients have increased levels of inflammatory cytokines which lead to a reduction in iodide uptake and could lead to morphological alterations in the thyroid gland.[35]

Lipid metabolism

THs largely influence lipid metabolism by the regulation of cholesterol synthesis and degradation, through the activity of essential enzymes. THs act on the liver, mainly on TRβ-1, enhancing the expression of the sterol response element-binding protein 2 (Srebp-2) which in turn, increases the expression of LDL receptors (LDLRs) leading to increased hepatic cholesterol uptake.[8,18,36,37] Evidence suggests that THs decrease proprotein convertase subtilisin/kexin type 9 (PCSK9), which consists of a downregulator of the expression of LDLRs.[38,39] THs promote the activity of both lipoprotein lipase in adipose tissue and hepatic lipase activity in the liver.[40] It is therefore widely accepted that thyroid dysfunction can lead to impaired lipid metabolism.

Hypothyroidism characteristically presents with increased total and LDL cholesterol levels, and slightly decreased or within the normal range HDL levels. This is also evident in patients with SHypo, suggesting that this condition might be linked to dyslipidaemia/hypercholesterolemia. There is evidence suggesting SHypo may be linked to hypertriglyceridemia.[40] These changes increase the risk of developing atherosclerosis and coronary artery disease (CAD).[9,10,14] In contrast, hyperthyroidism leads to a catabolic state presenting with reduced plasma levels of cholesterol (Fig. 1).[37]

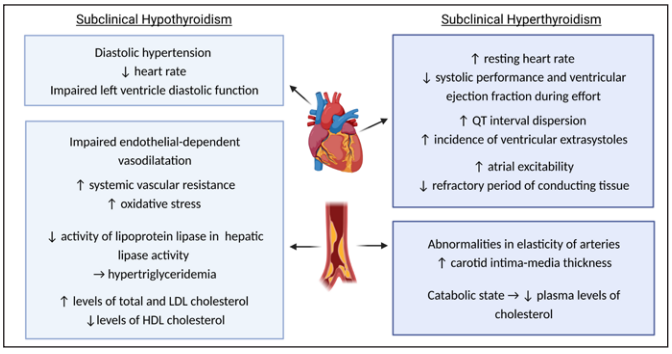

Figure 1. Effects in the heart and vessels of subclinical hypothyroidism and subclinical hyperthyroidism.

Regulation of glucose metabolism

THs are involved in the regulation of glucose metabolism by acting peripherally on a myriad of different organs modulating insulin secretion and glucose uptake. THs promote pancreatic β-cell growth and enhance insulin and glucagon secretion by pancreatic β-cells and α-cells, respectively.[43,44]

THs act on the pancreas, specifically T3, by stimulating β-cell development and acting as an anti-apoptotic factor for these cells, thus improving glucose metabolism on diabetic mice (Fig. 2).[41,43]

THs act peripherally in the gastrointestinal tract; T3 promotes

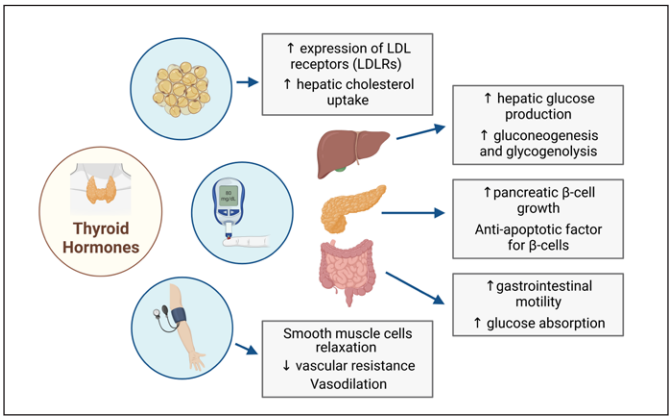

Figure 2. Effects of thyroid hormones on cardiovascular risk factors.

gastrointestinal motility, which increases glucose absorption leading to oxyhyperglycemia, by rapidly increasing blood glucose after oral glucose intake (Fig. 2).[42] In the liver, T3 enhances the expression of glucose transporter 2 (GLUT2) which favours the uptake of glucose by the hepatocytes, and potentiates both gluconeogenesis and glycogenolysis (Fig. 2).[41,44]

Although through different mechanisms, both hyperthyroidism and hypothyroidism are associated with increased risk of insulin resistance. In hypothyroidism, there is decreased glucose utilization by peripheral tissues. In hyperthyroidism there is predominantly enhancement of glucose production, absorption, and utilization.[45]

Hypothyroidism and SHypo are associated with insulin resistance and glucose intolerance. Diminished levels of THs potentiate gluconeogenesis, negatively impact glucose absorption and delay glucose uptake peripherally.[41,46] Treatment of hypothyroidism leading to a euthyroid state reportedly ameliorates insulin homeostasis. SHypo confers around 13% increased risk of developing type 2 diabetes mellitus (T2DM).[33]

Patients with T2DM seem to have a significantly increased risk of developing SHypo when compared with patients without diabetes.[47] Patients with T2DM and SHypo appear to have an increased risk of developing diabetic complications, such as, diabetic nephropathy, retinopathy, peripheral neuropathy and peripheral arterial disease.[42,47]

Although hyperthyroidism enhances glucose transporter type 4 (*GLUT4*) gene expression and glucose uptake in skeletal muscles, its potentiation of glucose absorption on the gastrointestinal tract, along with the enhancement of gluconeogenesis and glycogenolysis poses a great risk for developing T2DM later in life.[8,41,48]

Regulation of systemic blood pressure

THs are regulators of systemic blood pressure. This regulation is mediated by inotropic, chronotropic and lusitropic cardiac effects, as well as vascular effects which lead to reduction of systemic vascular resistance (Fig. 2).[13,49]

SHyper may result in abnormalities in elasticity of arteries, with increased carotid intima-media thickness but the mechanisms behind these alterations remain unclear (Fig. 1). It has been largely associated with increased blood pressure, predominantly systolic blood pressure.[13,49,50]

In turn, SHypo can lead to impaired endothelial-dependent vasodilatation, due to a decrease of production of NO, resulting in endothelial dysfunction and diastolic hypertension (Fig. 1).[51] Evidence suggests that the level of elevation of TSH correlates with the magnitude of these effects.[37] These patients also seem to have an attenuated vasodilatory response to acetylcholine and present with increased carotid artery intima-media thickness, thus increasing arterial stiffness.[51]

Regulation of coagulation and inflammation

Coagulation parameters seem to be impaired by THs disorders resulting in increased cardiovascular risk. Hypothyroidism leads to a state of hypocoagulability and hyperfibrinolysis culminating in an increased risk of bleeding. It is associated with an acquired von Willebrand syndrome type 1 and these patients frequently have lower levels of von Willebrand factor and coagulating factor VIII, as well as increased prothrombin time, activated partial thromboplastin time (aPTT), and clotting time when compared to control individuals.[52,53]

In contrast, SHypo and SHyper are associated with prothrombotic states.[53,54] SHypo seems to be associated with a prothrombotic effect, due to the increased levels of coagulation factor VII, plasminogen activator inhibitor-1 (PAI-1) and diminished global fibrinolytic activity seen in this thyroid dysfunction.[53] Likewise, SHyper favours hypercoagulability and diminishes fibrinolysis.[53,54]

Overt hypothyroidism reduces the effect of vitamin K antagonists (VKAs) while hyperthyroidism increases its effects due to modulation of VKAs' sensitivity.[55] Although SHyper does not seem to impact therapy with VKAs, SHypo may be a cause of international normalised ratio lability.[55,56]

Inflammation results in a decreased peripheral conversion of T4 to T3. Elevated C-reactive protein and serum homocysteine levels are considered risk factors for the development of atherosclerosis and have been reported in patients with overt hypothyroidism but not SHypo.[57]

Both hyperthyroidism and hypothyroidism lead to oxidative stress. In hyperthyroidism there is enhanced reactive oxygen species production whereas hypothyroidism is associated with diminished levels of antioxidants.[58]

Effects of Subclinical Hypothyroidism on Cardiovascular Function and Disease

Subclinical thyroid dysfunctions have been associated with an increased risk of all-cause mortality in both men and women.[75]

These conditions have been linked to cardiovascular risk factors, such as alterations in blood pressure, and enhanced risk for atherosclerosis.[59–61]

SHypo seems increase the risk of CVDs in those with higher plasma TSH levels, particularly above 10 mU/L and in adults younger than 65 years old.[8,11,14]

Potential mechanisms for the linkage of SHypo with CVDs include arterial stiffness, increased systemic vascular resistance, increased oxidative stress, an inflammatory state driven by TSH apoptosis-derived microparticles, cardiac dysfunction and diastolic hypertension.[16,30,62] SHypo also leads to lower heart rate (Fig. 1) and impairment of myocardial relaxation, diminishing cardiac preload.[14]

It is well established that SHypo increases the risk for atherosclerosis and myocardial infarction.[63,64] Due to the fact that these patients are more prone to develop hypertension, dyslipidaemia, endothelial dysfunction, and myocardial fibrosis, their risk of CAD events and subsequent death is augmented, especially in people under 65 years old.[14,65–67]

The evidence regarding the link between SHypo and stroke is inconsistent. While some studies found no association others

found a higher risk of stroke in SHypo patients younger than 65 years old and with higher TSH concentrations.[60]

Effects of Subclinical Hyperthyroidism on Cardiovascular Function and Disease

SHyper is frequently associated with an increased resting heart rate and left ventricular mass, often accompanied by impaired left ventricular relaxation and diastolic filling. It has been reported that it reduces systolic performance and ventricular ejection fraction during effort and consequently decreases exercise tolerance.[17,68] The cardiovascular risk in patients with SHyper may be significantly affected by their age and the presence of comorbidities.[15]

SHyper may be associated with a slight increase in QT interval dispersion, incidence of ventricular extrasystoles, elevated nocturnal arterial blood pressure, and heart rate variability (Fig. 1). It may also be related with a sympathovagal imbalance state, characterized by diminished cardiovascular vagal modulation with relative higher sympathetic activity and increased renin angiotensin-aldosterone axis activation. The assessment of heart rate variability and QT dispersion in patients with SHyper could represent a useful tool in the monitorization of cardiovascular risk and support the decision of whether to treat patients with this condition.[69,70] Enhancement of atrial excitability and shortening of the refractory period of the conducting tissue are likely contributors to the adverse arrhythmogenic effects.[17]

Persistent SHyper leads to altered cardiac morphology and function causing arrhythmias, namely atrial fibrillation (AF). Both SHypo and SHyper appear to increase the risk of AF as there seem to be a "U shaped" relationship between the risk of this arrythmia and TSH levels.[71]

The risk of AF seems to be two or three times higher in patients with SHyper than in subjects with normal levels of serum TSH, especially after the sixth decade of life. This risk augments with the lowering of TSH levels, especially for those below 0.10 mIU/L.[12,15,49,72] Moreover, in a study by Li *et al*, in patients who underwent radiofrequency catheter ablation for AF, those with SHyper were associated with a markedly higher prevalence of recurrence of AF, than those with SHypo. The latter had a similar recurrence rate of AF to those without TH dysfunction.[73] Reduced levels of TSH also seem to potentiate the risk of AF, leading to more than five-fold higher incidence of this disease.[74]

The relationship between SHyper and the incidence of stroke is yet to be enlightened although it is possible that this condition increases the risk of stroke due to its association with AF.[8]

Evidence suggests that SHyper causes increased risk of hypertension, CAD events and deaths and increased thrombogenicity.[75,76] SHyper is also associated with a augmented risk of major adverse cardiovascular events (MACE), especially in women, although when follow-up is longer than ten years, SHypo contributes to a higher risk of MACE than SHyper, according to Fang *et al*.[77]

Differentiated thyroid cancer (DTC) is relatively prevalent at a young age. Long-term TSH suppression therapy has been associated with increased CVDs and all-cause mortality and increased risk of AF, independently from known risk factors.[78,79] Therefore, the initial standard treatment of DTC does not include TSH suppression therapy for all patients anymore and only patients with biochemically or structurally incomplete disease are presently recommended to undergo moderate to total suppression, whilst the other stages are treated with mild to no suppression.[80]

Subclinical Thyroid Hormone Dysfunction and Heart Failure

Heart failure (HF) is a major public health issue and an important cause of morbimortality worldwide.[67] HF is a chronic and progressive disease characterized by structural or functional impairment of ventricular filling or blood ejection.[67,81] It is one of the most common causes of hospitalization in geriatric patients above 65 years old.[82]

As mentioned, THs can influence the expression of genes involved in calcium handling and contractile properties of cardiomyocytes.[67] They have influence on inotropic, chronotropic and lusitropic properties of the myocardium, cardiac growth, myocardial activity and vascular function.[67] Due to the myocardium's sensitiveness to THs, persistent subclinical thyroid dysfunction can lead to the development of HF, secondary to systolic and/or diastolic myocardial dysfunction.[9,83]

Both SHyper and SHypo are associated with adverse prognosis of HF and with more severe symptoms.[84]

Patients with SHypo, particularly those with TSH levels above 10 mIU/L, have a higher risk of developing HF, regardless of the presence of underlying heart disease.[67] Additionally, SHypo is thought to worsen the prognosis of those with previously diagnosed HF, increasing the risk of hospitalization and death. This risk is especially elevated in the geriatric population, which have a higher risk for CVDs.[62,82,84] Therefore, subclinical thyroid dysfunction may potentially be a useful and promising predictor of the long-term prognosis in these patients.[85]

SHyper may increase the risk of acute HF, possibly by increasing heart rhythm, but also due to its association with an increased risk of atrial arrhythmias, such as AF, which can cause acute decompensated HF.[81]

Previous studies have shown that administration of T3 has increased cardiac output and decreased peripheral vascular resistance in patients with SHypo.[9] Levothyroxine supplementation on SHypo may be beneficial, particularly in regard to the heart´s functioning; however, its beneficial role in cardiovascular risk or mortality remains to be clarified.[82]

Table 1. Clinical cardiovascular effects of subclinical hypothyroidism and hyperthyroidism.

Subclinical Hypothyroidism	Subclinical Hyperthyroidism
↑ LDL cholesterol	↑ risk of atrial fibrillation
↑ risk of atherosclerosis	Increased thrombogenicity
↑ risk of cardiovascular disease, namely myocardial infarction	Possible ↑ risk of stroke
↑ risk of myocardial fibrosis	↑ risk of hypertension
↑ risk of hypertension	↑ risk of major adverse cardiovascular events
↑ development of chronic HF	↑ risk of cardiovascular death
↑ risk for progression of chronic HF	↑ risk of acute and decompensated HF

Treatment of Subclinical Thyroid Disorders on Cardiovascular Disease

Subclinical hypothyroidism

There is still no clear evidence to support an undeniable benefit of replacement treatment with levothyroxine for reducing the

risk of CVDs in individuals with SHypo, especially in those with milder forms of this thyroid dysfunction (TSH levels below 10 mU/L) or older subjects (above 75 years of age).[9,10,40,59]

The retrospective observational analysis of the Whickham survey cohort was the first study that suggested the potential advantages of using levothyroxine as a treatment for SHypo, showing a significant reduction in all-cause mortality among subjects treated with levothyroxine.[86] Similar results were described by Anderson *et al*, although only among patients under 65 years old.[87] A broader cohort study found significantly lower events of ischemic heart disease and all-cause mortality in treated participants between 40 and 70 years old.[88]

In the opposite direction, several studies did not find significant benefits in the use of levothyroxine in subjects with SHypo. A cohort study with patients older than 18 years old found no differences in all-cause mortality, MACE or hospital events.[89] The randomized clinical trial TRUST included participants older than 65 years old but was underpowered to evaluate differences in cardiovascular events.[90]

Patients with SHypo may benefit from levothyroxine replacement treatment as it seems to improve the lipid profile, with a decrease in total and LDL cholesterol levels that, although modest, could be significant in terms of reduction of the incidence of CAD. Left ventricular function and markers of subclinical atherosclerosis and endothelial dysfunction also seem to improve, and early treatment of SHypo could prevent the progression to overt hypothyroidism.[10,91]

American Thyroid Association recommends the treatment with levothyroxine whenever TSH levels surpass 10 mIU/L and that it should be considered in patients with TSH levels above 4.5 mIU/L with elevated CVD risk.[92] Initial dose of levothyroxine should be lower for treating patients with SHypo and should be titrated slowly as need, maintaining close monitoring of the onset of cardiac symptoms.[93]

European Thyroid Association recommends levothyroxine treatment for patients younger than 65 years old with TSH levels above 10 mIU/L or with SHypo and have symptoms consistent with hypothyroidism.[94] Since it is possible to identify TSH levels transiently increased, it is suggested to repeat TSH, T4 and thyroid peroxidase antibodies ideally in a 1 to 3 month period after initial documentation of increased serum TSH and T4 within reference range.[94]

The Portuguese Society of Endocrinology, Diabetes and Metabolism and the Thyroid Study Group, recommend an individualized decision to treat SHypo for young adults with symptoms suggestive of hypothyroidism, goiter, thyroid peroxidase antibodies, marked elevation of TSH levels, dyslipidemia or CVD (except tachyarrhythmias).[95]

Due to the lack of evidence to support the guidelines for treatment of SHypo with HT, Bekkering *et al* suggested that asymptomatic patients with SHypo or with non-specific symptoms should not be treated.[96]

Therefore, the decision to treat SHypo should be based on clinical judgment, clinical practice, and expert opinion. It should consider specific and individualized evaluation, based on patient's age, degree of TSH elevation, symptoms, pre-existent cardiovascular risk, and other co-morbidities.[11,97] Treatment institution must be gradual, and closely monitored. Special attention must be taken when initiating levothyroxine treatment for SHypo in the elderly.[59]

Subclinical hyperthyroidism

International guidelines support treatment in patients aged above 65 years old presenting with TSH levels under 0.10 mU/L, in order to decrease the risk of cardiovascular events and progression to overt hyperthyroidism.[98] To this day, clinical trials regarding the treatment of SHyper are lacking. Therefore, the decision to treat SHyper should be based on patient age, symptoms related with hyperthyroidism, level of TSH suppression, and overall cardiovascular risk.[8,13]

Treatment of SHyper is the same as for hyperthyroidism and comprises thionamides, radioactive therapy and thyroid surgery. Cardioselective beta blockers, such as propranolol, atenolol or metoprolol, can be used to treat adrenergic symptoms. Due to the possible side effect of hypotension, blood pressure should be monitored in patients using beta blockers.[99]

The treatment of SHyper with reestablishment of normal serum TSH values, can reduce heart rate and left ventricular thickness. Moreover, treatment of SHyper may prevent the possible progression to complex arrythmias and to more advanced heart disease.[100]

Conclusion

Subclinical thyroid dysfunctions have a significant impact on the cardiovascular system contributing to cardiac and all-cause mortality.

Subclinical hypothyroidism has been linked to an increased prevalence of several cardiovascular-associated risk factors, such as hypertension and obesity, as well as low levels of high-density lipoprotein. There is evidence that elevated TSH concentrations related to this disorder are associated with increased risk for ischemic heart disease and HF.

Subclinical hyperthyroidism is associated with an increased risk of endothelial dysfunction, hypertension, atrial fibrillation, CAD events, thromboembolic events and acute HF.

Treatment of these dysfunctions could be beneficial, but its benefit in cardiovascular risk and mortality is still not clear. Therefore, more studies, ideally randomized clinical trials, should be performed to clarify the utility of treatment of subclinical thyroid dysfunction in CVDs.

Contributorship Statement / Declaração de Contribuição:

IML and JCC: Conceptualization, writing the initial draft and review. ARL, MBC, MHV, CV, ALM, JSN: Conceptualization and review. All authors approved the final version to be published.

Responsabilidades Éticas

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