Thyroid Hormones, Subclinical Hypothyroidism and Its Importance in Cardiovascular Disease

María Luz Gunturiz A

Specialized Professional, Project Bank Team, Public Health Research Division, National Institute of Health, Colombia

*Corresponding author: María Luz Gunturiz A, Specialized Professional, Project Bank Team, Public Health Research Division, National Institute of Health, Avenue Street 26 No 51-20 CAN, Bogotá, D.C., Colombia. Tel: +57-12207700; Email: mgunturiz@ins.gov.co

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Abstract

Hypothyroidism is a common endocrine disease that is classically described as a low level of thyroxine (T4) and triiodothyronine (T3) and high plasma level of thyroid stimulating hormone and that affects between 5 to 8% of adult women and a lower percentage of men. Several cardiovascular manifestations are associated with chronic hypothyroidism including low cardiac index, decrease in intravascular volume, increase in systemic vascular resistance and hypertension.

Determining when hypothyroidism leads to cardiac infarction is difficult because it can generate cardiovascular changes that overlap with it, such as decreased minute volume and inotropism, an increase in the diameter of cavities/parietal thickness, among others. Several potential cellular mechanisms are those that can lead to infarction in hypothyroidism, such as alteration of plasma lipids, accelerated atherosclerosis, stimulation of myocardial fibrosis, vasoconstriction, induction of a genetic program that resembles hypertrophic pathology and ventricles with thin and dilated walls.

With this review it is intended to show the importance of the good functioning of the thyroid hormones and their association with the pathology of cardiovascular and metabolic diseases.

Keywords: Cardiovascular disease; Subclinical hypothyroidism; Thyroid hormones; Thyroxine; Thyroid function

Abbreviations

TSH: Thyroid Stimulating Hormone; TH: Thyroid Hormones; T4: Thyroxine; T3: Triiodothyronine; SH: Subclinical Hypothyroidism; SVR: Systemic Vascular Resistance; DM1: Diabetes Mellitus type 1; DM2: Diabetes Mellitus type 2; HTA: Arterial Hypertension; SERCA2: Calcium ATPase of the Sarcoplasmic Reticulum; MHC: Heavy Myosin Chains; PLB: Phospholamban; MetS: Metabolic Syndrome; TG: Triglycerides; LDL: Low-Density Lipoprotein; HDL-C: High-Density Lipoprotein Cholesterol; CVD: Cardiovascular Diseases; RT3: Nuclear Receptors of Thyroid Hormones; PKA: Protein Kinase A; ER: Endoplasmic Reticulum; MV: Minute Volume; HF: Heart Failure; DLP: Dyslipidaemia; LV: Left Ventricle; AMI: Acute Myocardial Infarction; MI: Myocardial Infarction

Introduction

Thyroid Hormones (TH) have important effects on the cardiovascular system, on the heart and circulation, including hemodynamic alterations and effects mediated on the cardiac myocyte through gene expression [1-3].

On the other hand, thyroid function may alter carbohydrate metabolism via influence of insulin, which may in terms of derangement of thyroid function and insulin function result in the development of type 2 Diabetes Mellitus (DM2) [4].

Hyperthyroidism, for example, is associated with an increased risk of arrhythmias, while hypothyroidism can cause atherosclerosis. Additionally, studies have been conducted to identify the changes associated with aging in thyroid function and its relevance for cardiovascular morbidity and mortality in the elderly. There is knowledge that both hyperthyroidism and hypothyroidism are potential causes of Heart Failure (HF)
and it has been reported that subclinical hypothyroidism (sub-hypo) is associated with atherosclerosis, development of HF and cardiovascular death.

Several of the symptoms of hypothyroidism and hyperthyroidism are due to an increased or reduced function of thyroid hormone in the cardiovascular system, and for example, heart rate, cardiac output and systemic vascular resistance are closely related to thyroid function. Specifically, Triiodothyronine (T3), an active form of thyroid hormone, decreases peripheral vascular resistance causing relaxation of smooth muscle, which in turn causes a decrease in filling pressures, stimulating renin release and activation of the renin-angiotensin axis aldosterone, which, finally, will stimulate the renal reabsorption of sodium, increasing plasma volume, preload and consequently cardiac output [5].

Subclinical Hypothyroidism (SH) is defined by values of Thyroid Stimulating Hormone (TSH) elevated with normal serum thyroid hormone levels. This clinical condition has a variable prevalence in the general population (3,4-10%), which increases around the 3rd-6th decades of life and may be related to certain cardiovascular risk factors or enhance them [5,6].

**Thyroid Hormone and the System Cardiovascular**

Hypothyroidism is classically described as a low level of T4 and T3 and high plasma TSH levels. It is a common endocrine disease, affecting between 5 to 8% of adult women and a lower percentage in males. A range of cardiovascular manifestations, as it will develop posteriorly, are associated with chronic hypothyroidism including low cardiac index, decreased intravascular volume, increased Systemic Vascular Resistance (SVR), and Arterial Hypertension (HTA) in a subgroup of patients [1].

The Minute Volume (MV) is decreased at rest, due to the reduction of both stroke volume and heart rate, reflecting HT actions in chronotropism and cardiac inotropy. Due to the increase in SVR, and the reduction of intravascular volume, a decrease in the pulse wave, prolonged circulation time and a lower perfusion in certain tissues is triggered. The decrease in skin perfusion is responsible for the pallor of the skin and cold intolerance [1,7]. In most tissues, the decrease in blood flow is proportional to the lower oxygen consumption; therefore, the arteriovenous oxygen difference remains within normal values.

In severe and primary hypothyroidism, the cardiothoracic index increased, and heart sounds decreased in intensity. These findings are mainly due to a pericardial frame of a fluid with protein content and glycosaminoglycans. In addition to the changes observed at the pericardial fluid level, the myocardium is also dilated. Rarely, the pericardial text is of enough magnitude to produce cardiac tamponade [6,8]. In contrast, in pituitary or secondary hypothyroidism, the cardiothoracic index does not change [1,9].

The echocardiographic findings of hypothyroidism consist of a high frequency of asymmetric septal hypertrophy and an obstruction in the left ventricular outflow tract suggesting a subaortic stenosis [10,11]. This response is reversed when the mixture is treated with hormone replacement therapy. The combination of cardiac enlargement, hemodynamic and electrocardiographic changes and changes in plasma enzymes (creatine kinase, aspartate aminotransferase and lactate dehydrogenase), which are found in this pathology, the “myxoedematous heart”. If there is no presence of underlying heart disease, hormone replacement therapy can correct hemodynamic, electrocardiographic and enzymatic marker alterations and return the cardiothoracic index to the previous values. The low cardiac index is caused by bradycardia, a decrease in ventricular filling and lower myocardial contractility [12,13]. The SVR can be increased by 50%, and on the other hand the diastolic relaxation and slowed down filling. However, HF is rare because the cardiac index is usually enough for low peripheral oxygen emissions [1,14].

The synthesis of T4 and T3 happens inside the thyroid gland. The T4 is the main product mostly inactive. The conversion of T4 to T3 does not occur in the myocyte; 85% of T3, the biologically component active, is derived from the peripheral conversion of T4 by the enzyme 5 monodeiodinasa, mainly occurs in the liver and kidney [1,2,15-18].

Both T4 and T3 circulate almost entirely (95%) united to the protein family and the remaining 5% does so freely. T3 is the biologically relevant TH in the cardiac myocyte, as well as in other cells, there is evidence that the membranes cells contain specific carrier proteins for T3 [1,2,18,19].

It is well described in the literature that T4 and T3 have an action on the cellular metabolic rate. The direct action of HT in the vasoconstriction of vascular smooth muscle could explain the characteristic changes in SVR that accompany thyroid diseases. T3 decreases SVR through dilation of peripheral arterioles [1,17,19] and by an increase in the metabolic rate and in oxygen consumption. Additionally, HT increases oxygen consumption and peripheral requirements, which secondarily causes an increase in cardiac contractility, in addition to its known direct effect [1,17,20].

Vasodilation is due to a direct action of T3 over smooth muscle cells that promotes its vasodilation and to through its indirect action by the release of vasodilators locally secondary to its metabolic and consumption activity of oxygen. Regarding its direct action, the T3 modifies the sodium and potassium channels producing a decrease in smooth muscle contractility and vascular tone. On the other hand, TH decreases the SVR, generating a fall in the effective arterial volume causing an increase in the
activation of the renin angiotensin system and a stimulation of the angiotensinogen-aldosterone axis generating a greater absorption of renal sodium, which leads to an increase in plasma volume. TH stimulates the secretion of erythropoietin. The combination of these two actions causes an increase in intravascular volume and preload by increasing the cardiac index. T3 produces a rapid activation of the cardiac sarcolemma and of Ca\(^{2+}\) ATPase of the Endoplasmic Reticulum (ER) and in the activity of the sodium, potassium and calcium channels. This suggests that changes in the flow of ions in the myocardium and vascular smooth muscle may explain the action of T3 as an inotropic and vasodilator agent. Because MV and SVR are independent, it is often difficult to distinguish direct cardiac effects from reflex changes mediated by alterations in vascular tone [1,21].

In addition to the direct action on the heart and blood vessels, T3 can modify the sensitivity to circulating catecholamine’s, participate in the regulation of specific myocardial genes and in the expression of thyroid hormone receptors, increased cardiac contractility and decrease in SVR. On the other hand, indirectly, it can generate an increase in adrenergic activity and cardiac work, cardiac hypertrophy and increased intravascular volume [1,21].

In hypothyroidism, a low cardiac index and a marked increase in SVR are observed. One of the first observed responses to the administration of T3 in hypothyroidism is a reduction in SVR [1,13,14].

Specifically, hypothyroidism shows a marked decrease in stroke volume and MV and is associated with prolonged relaxation time that is reversed with hormone replacement. Diastolic function, too, is affected by thyroid status. The influences on the expression and activity of the Ca\(^{2+}\) ATPase of the specific cardiac ER can in part explain the changes in diastolic function directly related to the level of plasma TH in different thyroid diseases.

Several cardiovascular manifestations are associated with chronic hypothyroidism including low cardiac index, decrease in intravascular volume, increase in SVR, and hypertension in a subgroup of patients. Some of the hemodynamic changes observed in hypothyroidism are SVR (dynes/sec/cm) 2100-2700; heart rate (beats/minute) 60-80; ejection fraction (%) <60%; minute volume (litres/min) <4.5; isovolumetric relaxation time (msec) >80 and intravascular volume (% of normal value) 84.5 [1,13,14].

The most common signs are bradycardia, high blood pressure mild, small pulse pressure, and a precordial activity attenuated by physical examination. Other nonspecific characteristics are the high concentration of plasma cholesterol and creatinine kinase. On the other hand, pericardial effusion and myxoedema can occur in patients with severe and long-dated hypothyroidism [1,9].

There is evidence to suggest that a screening for subclinical hypothyroidism and a substitute treatment with levothyroxine in subjects with increased cardiovascular risk (>20% by Framingham), metabolic syndrome or certain conditions (plasma cholesterol 200-239 mg/dL, blood pressure greater than or equal to 140/90 mmHg, hereditary dyslipidaemia, presence of 2 or more cardiovascular risk factors), that could act as an adjuvant to the measures of classic prevention established for cardiovascular disease, but more studies are needed to check the benefit and justification of the treatment with levothyroxine dependent on TSH values [5,22-25].

The increase in heart rate and cardiac output in patients with hyperthyroidism, despite normal concentrations of catecholamine’s, is due to the role of thyroid hormone in the regulation of many ions and adrenergic activity and cardiac work. The cardiac output is increased by 50 to 300% [26] and this condition is due to an increase in the heart rate, in the contractility of the left ventricle, in the ejection fraction and in the intravascular volume. They also have an increase in systolic blood pressure and a decrease in diastolic blood pressure and increased pulse pressure. 5 to 15% of patients with hyperthyroidism present atrial fibrillation and up to 13% of patients with atrial fibrillation of unclear cause have elevated levels of thyroid hormone. Patients with hyperthyroidism can be long-term with heart failure, especially in elderly patients with ischemic and/or hypertensive heart disease, due to the inability of the heart muscle to respond to the metabolic demands of hyperthyroidism. Atrial fibrillation can compromise coronary perfusion, due to a decrease in diastolic time and loss of atrial systole that contributes to ventricular filling. Cardiac failure due to cardiomyopathy secondary to hyperthyroidism has also been described. Subclinical hyperthyroidism (characterized by suppressed TSH and normal levels of circulating thyroid hormones) has been related to an increase in heart rate and a higher prevalence of supraventricular arrhythmias and left ventricular mass involvement. Additionally, compromise of systolic and diastolic function due to alteration in myocardial relaxation [27]. The increase in left ventricular mass is characterized by an increase in thickness, but not size. These patients also have an increased risk of developing atrial fibrillation [1,26].

**Metabolic Syndrome, Diabetes and Thyroid Hormone**

Metabolic Syndrome (MetS), it is defined as a pool of metabolic disorders including obesity, raised blood pressure, dyslipidaemia, and elevated fasting glucose, among others. MetS is
one of the most important complications of excess weight, with an increase in the prevalence of obesity and overweight in children and adolescents [28]. This syndrome is demarcated by elevated plasma Triglycerides (TG), blood pressure, fasting glucose and waist circumference, reduced High-Density Lipoprotein Cholesterol (HDL-C). Beyond traditional lipid markers and elevated blood glucose, patients with metabolic syndrome have a substantial residual risk of Cardiovascular Disease (CVD). On the other hand, chronic low-level inflammation, prevalent in MetS, is associated with a reduction in the antioxidant capacity of HDL. The ability of HDL to perform reverse cholesterol transport, another key atheroprotective function, may also be compromised by factors associated with MetS [28,29]. Additionally, it is suggested that preclinical MetS and dyslipidaemia in particular are associated with altered variation of myocardial signal intensity [28,30].

This syndrome may be of special interest because of the increased prevalence with age [28,31]. In addition to the predominant criteria to diagnose MetS, it is associated with other metabolic abnormalities related to cardiovascular diseases such as, plasma increases in plasminogen activating factor and fibrinogen, hyperuricemia, elevated levels of C-reactive protein, hyperhomocysteinemia, the increase in the expression of tumour necrosis factor alpha in adipose tissue and the decreased concentrations of adiponectin [28,31,32].

Clinical hypothyroidism increases the concentrations of Low Density Lipoproteins (LDL), C-reactive protein and homocysteine and induces diastolic blood hypertension, which favours the risk of coronary disease [33,34]. There is an association between low concentrations of free T4 and insulin resistance, in addition to an increase in the accumulation of fat in the pericardium; data that are consistent with the increase in cardiovascular risk [35-37].

In subclinical hypothyroidism, has observed a greater presence of the components of the metabolic syndrome in patients with thyrotropin in limits higher than normal, but with normal thyroid hormones. This has been considered an independent and additive risk factor for silent coronary disease [38,39].

However, the role of subclinical hypothyroidism as a cardiovascular risk factor is still controversial. In addition, most patients admitted to intensive care units with an acute cardiovascular event do not present alterations in the thyroid profile [35,40-42].

The correlation between SH and the MetS varies and is associated with demographic and geographic characteristics, attributable not only to genetic aspects and lifestyle. For example, in Asian population there is no increase in the prevalence of MetS, or its components, in patients with SH [43,44]. In studies with Korean postmenopausal women it was observed an increase in the prevalence of metabolic syndrome when the concentration of the thyroid-stimulating hormone (thyrotropin) was greater than 2.5 mIU/L [45]. On the other hand, for Mexican population, a prevalence of 14.6% of SH in women with MetS with age average of 44.5 years; but no significant correlation was found between the concentrations of free thyroxine and thyrotropin, nor with the different components of the metabolic syndrome [35,46,47].

About 7% of the population suffers from some type of thyroid disease and is more common in women than in men. Among people with (DM2), that proportion increases to almost 12%. People with type 1 diabetes (DM1) are more likely to develop a thyroid disorder, between 17 and 30% of people with DM1 have autoimmune disease of thyroid disease and about 1 in 4 children with DM1 diabetes have thyroid autoantibodies. The link with DM2 is less clear, but some experts believes it may be related to aging. Thyroid disease is more common among older adults and people who are overweight and obese. In Colombia, the DM reported an average mortality rate between 2009 and 2011 of 10.4 per 100,000 inhabitants, placing it within the first 10 causes of general mortality, being more than 50% preventable. DM was within the first twenty causes of healthy life years lost by 2010 in population ≥45 years [48].

In DM2, where hypertension is more frequent, a state of insulin resistance develops secondary, in many cases, to a state of alpha-adrenergic hyperactivity and peripheral vasoconstriction. This state of poor peripheral metabolism of glucose leads to secondary hyperinsulinism and a decrease in insulin clearance. Hyperinsulinemia can increase blood pressure by one or more of the following mechanisms. First, it produces renal sodium retention through an increase in its reabsorption at the tubular level (at least acutely) and increases the activity of the sympathetic nervous system. Another mechanism is hypertrophy of vascular smooth muscle secondary to the mitogenic action of insulin, which produces vascular remodelling. Insulin modifies the transport of ions through the cell membrane, thus increasing the cytosolic calcium levels of the vascular tissues, which causes a state of vascular hyper reactivity to the vasoconstrictive agents. Finally, it is known that the ability of insulin to induce vasodilation, an effect demonstrated in endothelial cell cultures through the increase in nitric oxide synthesis, is reduced in situations of insulin resistance and diabetes, probably by inactivation of nitric oxide or by a reduction in ability of the vascular endothelium to synthesize it [48].

**Cellular Mechanisms of Thyroid Hormone**

The TH once it reaches the myocyte, interacts with molecules strongly associated with chromatin known as “nuclear receptors of thyroid hormones (RT3)”. The RT3 belong to the “superfamilies of nuclear receptors”, which derive evolutionarily from a common ancestral gene. Every one of them is a dependent nuclear transcription factor of the ligand that regulates the rate of transcription of genes.
Subclinical Hypothyroidism and Its Association with Cardiac Diseases

Subclinical Hypothyroidism (SH) is a condition characterized by low levels of serum thyrotropin and normal concentrations of serum thyroid hormone and high values of TSH, levels with normal free thyroxine T4. This condition has been associated with coronary and carotid artery disease, although the association between SH and MetS is still controversial.

SH is a common disease defined by elevation of the TSH with circulating levels of TH within the values of the normal. The prevalence of it in the general population is 5.6% to 10.8% [55,56], reaching around 15% in women over 60 years old. Most of the cases of SH is due to a slow progression of thyroid dysfunction, caused by autoimmune thyroiditis. It is thought that the most of these patient’s progress to clinical hypothyroidism [1,55,56]. The symptoms and signs presented in the SH are not pathognomonic, therefore the diagnosis and monitoring of the treatment depend fundamentally on the measurement of plasma TH and TSH.

Since the nineties, it has been described that this state is associated with some anomalies in cardiac function. On the other hand, improved systolic function and impaired diastolic function due to slow myocardial relaxation may cause an increase in left ventricular mass as well as an increase in heart rate and arrhythmias, by mechanisms like those of overt hyperthyroidism. In people over 60 years of age subclinical hyperthyroidism is associated with tripled risk of atrial fibrillation during a 10-year follow-up period [57-61].

Patients with subclinical hyperthyroidism show higher QT dispersion and lower heart rate variability, which means impaired sympathovagal balance, increased sympathetic tone in the presence of decreased vagal tone and increased inhomogeneity of ventricular recovery times [57,62]. Besides antithyroid treatment strategies β-blocker therapy reduces heart rate and improves left ventricular recovery times [57,62]. Besides antithyroid treatment strategies β-blocker therapy reduces heart rate and improves left ventricular recovery times [57,62].

Although clinical relevance remains to be determined of SH, these patients present an increase in LDL levels, prevalence of coronary heart disease and peripheral arterial disease, and a negative haemostatic profile [65]. In addition, various cardiac abnormalities such as diastolic dysfunction of the left ventricle at rest and alteration of systolic function during exercise are observed. These abnormalities are probably responsible for the broad spectrum of symptoms of thyroid dysfunction observed in patients with SH [1,65,66].

Diastolic dysfunction is observed in patients with SH, in addition, there is evidence of the existence of systolic dysfunction in mild thyroid dysfunctions even at rest. In patients with autoimmune thyroiditis who still maintain TSH levels within normality, there are alterations in both diastolic and systolic function.

There is no doubt, that patients with SH have diastolic dysfunction, what remains in discussion is whether systolic function is generally affected in this group. Some authors conclude that systolic dysfunction is even in the resting stage [1,65].
It has been demonstrated by different non-invasive methods (textural analysis of myocardial ultrasonography, cardiographic impedance, radioisotopic and image methods of tissue Doppler), which in these patients is affected by systolic phase at rest. Specifically, the findings that they find in this group are: the alteration in the ejection of the left ventricle, the diastolic relaxation and the ventricular filling.

On the other hand, it has been described that SH is an independent predictor of coronary disease [1,66]. These results were in agreement with those observed in the previously published studies, in which an association was found between HS and coronary disease in selected groups: 55-year-old women or majors, the survivors of Japan’s atomic bomb [56,67], men under 50 and in the study of older residents in the New Mexico [68,69]. The only study that differed with these findings was the recently published in subjects of 85 years or higher, in which subclinical hypothyroidism was associated with greater survival; The latter is not well understood, but it may be implied that HS has a different behaviour in individuals older than 85 years compared to the general population. Cholesterol increases in parallel with the TSH increase from 5 μU/L [70].

It was shown that the rate of atherosclerosis and Acute Myocardial Infarction (AMI), in women with subclinical hypothyroidism, the odds ratio increases by 1.7 and 2.3 respectively. It should be noted that the presence of antithyroid antibodies would indicate an increased risk [56].

An interrelation between HS and cardiovascular disease is biologically plausible, because the HS is associated with hypercholesterolemia (although the evidence for this is only convincing in individuals with TSH > 10 μU/L), diastolic dysfunction of the Left Ventricle (LV), to the alteration of endothelium-dependent vasodilation, the latter as a marker of atherosclerosis. Therefore, the association between subclinical hypothyroidism and risk factors for atherosclerosis are not simply caused by Dyslipidaemia (DLP) [67,71].

A variety of studies indicate that changes in SVR may be the result of alteration in endothelium-dependent vasodilation, probably due to an alteration in ON and in the pathway of ON-L arginine.

In patients with subclinical hypothyroidism, an increase in C-reactive protein and homocysteine is observed, both associated with an increased cardiovascular risk [72]. Due to cardiac abnormalities, endothelial dysfunction and DLP, which predispose to atherosclerosis, it would appear to be recommended the use of hormone replacement therapy in patients with subclinical hypothyroidism [73].

There are several possible mechanisms that explain the adverse prognosis of hypothyroidism in patients with HF. First, in some studies it has been described that hypothyroidism has an influence on the structure and function of the heart and these alterations can be reversed with thyroid hormone replacement therapy [6,63,74,75]. Additionally, several studies have reported the relationship between hypothyroidism and pulmonary hypertension, which is associated with mortality in patients with HF. Thyroid hormone replacement therapy can lead to the modification of pulmonary hypertension [6,76-80]. Third, hypothyroidism can significantly reduce cardiac preload, while increased cardiac afterload produces a consistent reduction in stroke volume and cardiac output, so that thyroid hormone replacement therapy can normalize completely alterations in haemodynamic [6,81]. Finally, of the possible mechanisms mentioned above, hypothyroidism can also lead to an altered lipid metabolism, a high C-reactive protein (and a higher prevalence of aortic atherosclerosis, which may increase the prevalence of MI and mortality in patients with HF [6,56,62-85].

In summary, the evidence provided in this review shows that HT has a direct effect on the heart and that patients with hypothyroidism or hyperthyroidism have an increased risk of CVD and MetS.

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