

## REVIEW ARTICLE

# The Role of Thyroid Diseases and their Medications in Cardiovascular Disorders: A Review of the Literature

Negar Omid<sup>1</sup>, Mohammadrafie Khorgami<sup>2,\*</sup>, Farbod Z. Tajrishi<sup>3</sup>, Amirhosein Seyedhoseinpour<sup>4</sup> and Parichehr Pasbakhsh<sup>5</sup>

<sup>1</sup>Cardiac Primary Prevention Research Center, Tehran Heart Center and Department of Cardiology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran; <sup>2</sup>Rajaie Heart Center and Department of Pediatric Cardiology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran; <sup>3</sup>School of Medicine, Babol University of Medical Sciences, Babol, Iran; <sup>4</sup>School of Medicine, Tehran University of Medical Sciences, Tehran, Iran; <sup>5</sup>Department of Anatomical Sciences, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran

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**Abstract:** The association between thyroid disease and cardiovascular manifestations is significant and undeniable. Previous studies have explained several aspects of the effects of thyroid hormone on the heart and cardiovascular system. Accordingly, both hyper and hypothyroidism can cause important alterations in cardiac rhythm, output and contractility as well as vascular resistance and blood pressure. Since treating the thyroid abnormality, especially in its initial stages, could lead to a significant improvement in most of its resultant cardiovascular disturbances, early suspicion and recognition of thyroid dysfunction, is necessary in patients with cardiovascular manifestations. In this in-depth review, we discuss the physiological roles as well as the effects of abnormal levels of thyroid hormones on the cardiovascular system. We also review the effects of the medications used for the treatment of hyper and hypothyroidism on cardiac function. In the end, we discuss the association between thyroid function and amiodarone, an effective and frequently-used antiarrhythmic drug, because of its well-known effects on the thyroid.

**Keywords:** Hyperthyroidism, hypothyroidism, heart, amiodarone, myocardium, thyroid disease.

## 1. INTRODUCTION

Thyroid disorders, including hypothyroidism and hyperthyroidism, are a relatively prevalent condition frequently encountered in the clinical setting. According to the American Thyroid Association, more than 12% of Americans develop a form of thyroid disorder during their lifetime, with females being at least five times more susceptible than men in this regard [1]. These data point to the roughly equal importance of thyroid ailments in comparison to other endocrinological conditions such as diabetes mellitus, which has a prevalence rate of 8.5 to 9.4% [2, 3]. The overall prevalence rate of thyroid disorders previously has been assessed by large cohorts. For example, the Wickham Survey (performed in the UK), reported a prevalence of 1.9% in female and 0.16% in both female and male patients, respectively [4]. In another large cohort, the Colorado Study, the prevalence of hypo- and hyperthyroidism was 0.4% and 0.1%, respectively. The same study also reported a prevalence of 9% for subclinical hypothyroidism and 2.1% for subclinical hyperthyroidism [5]. Evidence also suggests these rates may vary

among different age/gender groups [6]. Considering the significant prevalence of thyroid disorders and the close connection between the thyroid gland and the cardiovascular system [7], we comprehensively reviewed the existing literature on the connection between thyroid disorders, the cardiovascular system and the commonly used thyroid and cardiovascular medications that affect both the systems at the same time.

## 2. HYPERTHYROIDISM AND THE EFFECT OF THYROID HORMONES ON THE CARDIOVASCULAR SYSTEM

### 2.1. Effects of Hyperthyroidism on Heart Conduction

#### 2.1.1. Mechanism of Thyroid Hormones on Conduction System

Thyroid hormones influence electrical impulse generation and cardiac conduction *via* several genomic and non-genomic molecular pathways. The thyroid implements its electrophysiological effects on the heart mainly through T3 and its ability to increase systolic depolarization and diastolic repolarization rate [7]. T3 also modulates cardiac conduction by decreasing refraction period and the duration of action potential of AV node and atrial myocytes [8]. Interest-

\*Address correspondence to this author at the Rajaie Heart Center and Department of Pediatric Cardiology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran; E-mail: rafikhorgami@gmail.com

ingly, while both arrhythmogenic and anti-arrhythmic potential have been suggested for thyroid hormones [7], arrhythmias are mostly associated with hyperthyroidism rather than hypothyroidism, which instead increases the risk of atherosclerosis and myocardial infarction [9]. Hyperthyroidism is associated with a variety of arrhythmias, the most common of which include sinus tachycardia, atrial fibrillation and atrial flutter. Reports have also demonstrated the association between excess thyroid hormones and the first degree AV block, QT interval shortening, nonspecific T wave abnormality, reentrant AV nodal tachycardia and other ventricular arrhythmias [7, 9]. Table 1 depicts these changes.

**Table 1. ECG change and arrhythmias associated to hyperthyroidism.**

↓ <sup>1</sup> QT interval
↓ PR interval
Tachycardia
First Degree AV-Block
Atrial Fibrillation/Flutter
Nonspecific T-wave abnormality
Reentrant AV nodal Tachycardia

1: Decreased.

### 2.1.2. Tachycardia

Sinus tachycardia is the most common arrhythmia seen in hyperthyroidism. It can occur both at rest and during sleep. Hyperthyroid patients may also experience exaggerated tachycardia during exercise. Thyroid hormones can induce tachycardia *via* multiple mechanisms. An electrophysiological study on rabbit sinoatrial node cells revealed that sinus tachy- and bradycardia associated with hyper and hypothyroidism directly result from the effects of thyroid hormone on diastolic depolarization rate of sinoatrial cells [10]. Other suggested mechanisms for the chronotropic effect of thyroid hormones include decreasing the duration of the repolarization phase of the membrane action-potential, modulating the number of sodium pumps on cell membrane and sodium and potassium ion permeability, as well as affecting L-type calcium 1D channel, which has an important role as pacemaker [11, 12]. Furthermore, similarities between clinical findings of hyperthyroidism and beta-adrenergic stimulation suggest possible interactions between thyroid hormones and adrenergic nervous system [13]. Thyroid hormone can increase beta-adrenergic receptor density, G-protein expression and reduce the production of adenylyl cyclase subunit, all of which lead to a sympathomimetic effect on the heart rate [14, 15]. However, it is important to note that T3 can also affect the heart independent of beta-adrenergic receptors. Olshausen and colleagues further demonstrated this independence in their study on cardiovascular effects of thyroidectomy and chemical sympathectomy in animals. Their findings revealed that thyroidectomized animals had a significantly lower heart rate than the ones undergoing sympathectomy. This is while both the groups responded similarly to T3 treatment after the pro-

cedure, indicating a direct effect of T3 on the heart rate even in the absence of sympathetic activity [12].

### 2.1.3. Atrial Arrhythmias

A large study on more than 40,000 hyperthyroid patients reported a combined prevalence of 8.3% for Atrial Fibrillation (AF) and flutter among them [16]. AF is the most important arrhythmia occurring in hyperthyroidism with reported incidence rates ranging from 2 to 20%. The association between these two conditions goes both ways and 5-15% of all AF patients are hyperthyroid [17-19]. Studies have confirmed hyperthyroidism as a risk factor for developing AF [20]. Thyroid hormones decrease atrial refractory period and activation of electrical triggers while increasing the prevalence of delayed afterdepolarization, hence making hyperthyroid patients susceptible to AF [21]. The abnormal triggers often originate from the cardiomyocytes residing in the pulmonary vein region [22]. Increased expression of L-type calcium channels in the atrium can also trigger AF in subclinical hyperthyroidism [23]. Furthermore, changes in myocardial architecture caused by hyperthyroidism can lead to cell to cell coupling abnormalities which can increase the risk of AF [24]. Male sex, older age, and the presence of underlying heart disease such as coronary heart disease, heart failure and valvular heart disease are factors associated with an increased risk of developing AF in hyperthyroid patients [13]. Increased prevalence of AF in older age is probably a result of a lower threshold for fibrillation, a higher prevalence of the underlying heart disease and delayed diagnosis [17]. A study demonstrated that the prevalence of AF in patients with hyperthyroidism was fivefold higher in those older than 60 years compared with the younger ones (25% vs. 5%) [25]. In another study performed on patients with toxic nodular goiter, the prevalence was 43% in the older group, in comparison to 10% in the younger group [26]. Subclinical hyperthyroidism is also associated with AF/atrial flutter. An investigation revealed no significant differences between subclinical and overt forms of hyperthyroidism in terms of the prevalence of atrial arrhythmias [20]. Evidence suggests that subclinical hyperthyroidism is associated with increased 10-year cardiovascular mortality and a coexisting AF may be one of the reasons for the excess mortality rate [27]. Generally, AF increases the risk of blood clot formation that leads to thromboembolism, stroke and serious cerebrovascular events. However, whether AF accompanied by hyperthyroidism increases the risk of thromboembolism more than AF of other causes is yet to be determined. In hyperthyroid patients with AF, treating hyperthyroidism can reverse AF to sinus rhythm. About two thirds of patients returned to sinus rhythm within 4 months of thyroid function normalization [28]. Older age and longer duration of AF can reduce the chance of rhythm improvement and may indicate the need for intervention to treat AF [29]. Management of AF and atrial flutter associated with hyperthyroidism mainly follows the routine protocols. The most important difference to keep in mind is that rhythm control should be performed only after normalizing thyroid function because an untreated hyperthyroid state could result in AF treatment failure. In the meantime (*i.e.* while normalizing thyroid function with anti-thyroids), beta-blockers are the first option for rate control strategy, unless contraindicated, in which case nondihydropyridine calcium channel blockers can be used. In case digi-

talis is selected for rate control in these patients, higher doses are usually indicated. Guidelines also suggest amiodarone as a safe choice for rate control in patients with both hyperthyroidism and AF/atrial flutter while evaluating serum TSH levels at least every six months. In addition to a combined strategy of antithyroids and heart rate control, oral anticoagulants are also necessary to lower the risk of cardio embolic events caused by AF [28].

**2.1.4. Ventricular Arrhythmias**

Unlike atrial arrhythmias, ventricular arrhythmias are not common in hyperthyroid patients without underlying heart disease and their prevalence is similar to that of normal population [12, 30]. However, this fact should not exclude the importance of these arrhythmias in hyperthyroidism because of the great risk they pose to patient survival. Also, one should note that ventricular arrhythmias can rarely occur during and after anti-thyroid therapy [12]. Several changes occur in a hyperthyroid heart, make it prone to the development of ventricular arrhythmias. These include shortened QT intervals, increased number of cardiac adrenergic receptors and their response to adrenergic stimuli, along with decreased myocardial electrical stability [9]. Furthermore, hypokalemia, post-ischemic reperfusion and burst of electrical stimulation are some other predisposing factors for the formation of ventricular arrhythmias in hyperthyroidism. Thyroid hormones can also increase the duration of action potential in Purkinje fibers while reducing the action potential of ventricular myocytes- alterations that can lead to ventricular arrhythmias such as ventricular fibrillation [31].

**2.2. Effects of Hyperthyroidism on the Myocardium**

**2.2.1. Influence of Thyroid Hormones on Cardiomyocytes**

The thyroid affects cardiomyocytes mainly through the actions of T3 on genomic and non-genomic pathways in these cells. The genomic pathway starts when T3 enters the cell and binds to the nucleus-based thyroid hormone receptors (TR), thereby affecting the transcription and expression of several genes [7, 19, 32]. Non-genomic mode of action, on the other hand, works through the effects of T3 on plasma membrane, mitochondria and sarcoplasmic reticulum [33]. Thyroid hormones affect multiple vital mediators of cardiac muscle function, including myosin heavy chains, calcium-dependent adenosine triphosphatase ion pump and its inhibitor phospholamban, β-adrenergic receptors, cardiac troponin I and atrial natriuretic peptide [19, 34, 35]. T3 induces the transcription of myosin heavy chain α (MHCα) gene while inhibiting the expression of MHCβ [7, 19]. This can lead to physiological hypertrophy and is in contrast to the pathological hypertrophy of other etiologies such as hypertension or infarction in which the expression of MHCβ is prominent. Moreover, thyroid hormone upregulates the expression of reticulum calcium-dependent adenosine triphosphatase ion pump, while downregulating the expression of phospholamban. This can lead to more Ca<sup>2+</sup> uptake into the sarcoplasmic reticulum, which in turn enhances myocardial contractile function and increases the rate of diastolic relaxation [19, 34, 36, 37]. Thyroid hormone can also affect other ion channels such as Na<sup>+</sup>/K<sup>+</sup> channel, Na<sup>+</sup>/Ca<sup>2+</sup> exchanger and some voltage-gated K<sup>+</sup> channels, all of which playing a role in ion homeostasis of cardiac muscle cells and their contractility

[38]. Another important role of TH on cardiac contractility is through its effects on the vascular bed. T3 decreases systemic vascular resistance by rapid relaxation of vascular smooth muscle cells which results in increased cardiac output [7, 19]. It also decreases coronary vascular tone and modulates coronary arteriolar angiogenesis, and therefore, facilitates the delivery of blood supply to cardiomyocytes. It is worth noticing that thyroid hormone can increase systolic blood pressure and is associated with pulmonary hypertension [7]. Moreover, it has some positive effects on endothelial integrity and is a regulator of the effects of renin-angiotensin-aldosterone system on vascular system [39]. The thyroid hormones effects on cardiovascular system are demonstrated in Tables 2 and 3.

**Table 2. Thyroid hormones mechanism effects on heart.**

<b>Conduction System</b>
↑ <sup>1</sup> Systolic Depolarization Rate
↑ Diastolic Repolarization Rate
↓ <sup>2</sup> Refractory Period
↓ AV Node A-P Duration
↓ Atrial A-P Duration
<b>Cardiomyocyte</b>
↑ MCHα Gene Transcription
↓ MCH β Gene Expression
↑ Reticulum Ca-dependent ATP Ion Pump Expression
↓ Phospholamban Expression
↑ Ca <sup>2+</sup> Uptake into SR
↓ Na/Ca Exchanger
↑Na/K ATPase
↑β <sub>1</sub> Adrenergic Receptors
Physiological Hypertrophy
<b>Enhanced Cardiac Remodeling after Acute MI</b>
<b>Vascular System</b>
↓ Coronary Vascular Tone
↑ Coronary Arteriolar Angiogenesis
<b>Anti-atherosclerotic Effect</b>
↑ Renin
↑ ACE Expression
↑ Angiotensin II
↑Coronary Spasm

**Abbreviations:** AV, Atrioventricular; A-P, Action-Potential; MCH, Myosin Heavy Chain; ATP, Adenosine Triphosphate; SR, Sarcoplasmic Reticulum; MI, Myocardial Infarction; ACE, Angiotensin Converting Enzyme. 1: Increased; 2: Decreased.

**Table 3. Hyperthyroid and hypothyroid cardiovascular features.**

Hyperthyroidism	Hypothyroidism
↓ SVR	↑ SVR
↓ Afterload	↑ Afterload
↑ Blood Volume Preload	↓ Blood Volume Preload
↑ CO	↓ CO
↑ Stroke Volume	↓ Stroke Volume
↑ Cardiac Contractility	↓ Cardiac Contractility
↑ Venous Resistance	↑ PVR
↓ Arterial Resistance	↑ Circulation Time
↓ DBP	↑ DBP
↑ SBP	↓ Exercise Tolerance
↑ Pulse Pressure	↓ Pulse Pressure
Tachycardia	Bradycardia
↑ Pulse Amplitude	↓ Pulse Amplitude
↓ Atherosclerosis	↑ Atherosclerosis
↑ First Heart Sound	Faint Heart Sound
Possible Third Heart Sound	↑ Insulin Resistance
Pulmonary Hypertension	Peripheral or Pleural Effusion

**Abbreviations:** SVR, Systemic Vascular Resistance; CO, Cardiac Output; PVR, Peripheral Vascular Resistance; DBP, Diastolic Blood Pressure; SBP, Systolic Blood Pressure.

### 2.2.2. Cardioprotective Effects of Thyroid Hormones

There are several possible signaling mechanisms suggesting cardioprotective roles of thyroid hormone. Recent studies have demonstrated that Protein Kinase C (PKC) has cardioprotective effects against ischemia-reperfusion injury and can increase myocardial tolerance against ischemic stress [40]. Studies have also indicated the over-expression of PKC in hyperthyroid patients, which can suggest an underlying mechanism for the aforementioned cardioprotective effects of thyroid hormones [40]. P38 Mitogen-activated Protein Kinase (MAPK) is another signaling molecule, whose transient activation during ischemic stress and at reperfusion can have protective effects on the heart. p38MAPK's activation is modulated by thyroid hormones [40, 41]. Thyroid hormones also upregulate ERK kinase and Akt pathways that are known as prosurvival pathways and modulators of reverse remodeling [41, 42]. Heat shock proteins and HSP27, in particular, are also suggested to have an important protective role. They protect myocardial cells by increasing the resistance of cardiomyocytes to stress-induced injury *via* strengthening the myocardial cytoskeleton [41]. HSP70 is another cardioprotective factor that prevents proteins from misfolding and aggregation during synthesis and stress conditions as well as inhibiting apoptosis [40]. Evidence suggests that thyroid hormones can increase both the expression

and phosphorylation of heat shock proteins, leading to myocardial protection [40].

### 2.2.3. Hyperthyroidism and Cardiomyopathy

There is no evidence suggesting a direct association between hyperthyroidism and cardiomyopathy; however, some precipitating factors for developing cardiomyopathy, such as atrial fibrillation, high cardiac output and tachycardia are present in hyperthyroidism. Furthermore, several case reports have stated possible associations between thyroid function abnormality and Takotsubo cardiomyopathy [43].

### 2.3. Hyperthyroidism, Heart Failure and Myocardial Infarction

The protective effects of thyroid hormones on the heart extend to conditions such as heart failure and myocardial infarction. There is overwhelming evidence indicating the role of low thyroid hormone in promoting heart failure and its contribution to systolic and diastolic dysfunction. Heart failure is associated with the down-regulation of nuclear TR and thyroid hormone signaling pathways [7, 44]. Studies on animal models have revealed the effects of these pathways on cardiac remodeling [40]. After acute myocardial infarction, a portion of contracting myocardium loses its function and the burden on the remaining viable myocardium is increased. The cardiac response to this chronic state is remodeling, through which the heart overcomes pressure overload and the extra burden. Several studies have demonstrated the beneficial effect of thyroid hormones on cardiac remodeling after acute MI [40]. Administration of thyroid hormone improves heart response to ischemia, enhances cardiac contractility and affects angiogenesis and tissue engineering [45, 46]. In one study, T3 administration in patients with heart failure and cardiomyopathy increased cardiac output while decreasing systemic vascular resistance without any major complications [47]. Another study demonstrated that thyroid hormone administration for on-pump cardiac surgery increased cardiac output and reduced tissue injury [48]. Because of these outcomes, thyroid hormones have been recognized to have therapeutic uses in heart failure.

While thyroid hormones and maintaining a euthyroid state can have all the aforementioned positive effects, a hyperthyroid state and thyroid hormone excess in both sub-clinical and overt hyperthyroidism can contribute to the development of heart failure or exacerbate its symptoms in several ways. For instance, thyroid hormone-induced tachycardia increases myocardial oxygen demand while reducing the duration of diastole, during which coronary perfusion is the highest. The resultant increased demand and decreased supply result in higher risk of myocardial ischemia. Also, lower peripheral vascular resistance caused by hyperthyroidism results in higher amounts of venous return, which in turn, put the heart in a congestive state. This hemodynamic overload, in addition to the activation of the renin-angiotensin system and increased cardiomyocyte contractile protein synthesis in hyperthyroidism, leads to left ventricular hypertrophy [27, 49]. Since diastolic filling is already impaired in a hypertrophic left ventricle, a coexisting AF, that is NOT a rare phenomenon in hyperthyroidism, can worsen this situation by further impairing ventricular diastolic filling. Furthermore, the elevated levels of angiotensin II caused

by hyperthyroidism increase the apoptotic rate of these hypertrophied cardiomyocytes. Studies with long-term follow-up periods have demonstrated increased cardiac and cerebrovascular mortality in hypertrophied patients [50]. In one study on patients with symptomatic heart failure and ejection fractions of less than 35%, risk of death was significantly higher in the ones with abnormal thyroid function, after controlling for known mortality predictors [51]. All this evidence emphasizes the importance of maintaining a euthyroid state especially in patients with dire cardiac conditions such as heart failure and myocardial infarction.

Low T3 syndrome is a state occurring during acute and chronic illnesses, including cardiovascular disorders, and is considered with low plasma concentrations of T3 and/or fT3 along with elevated reverse T3 (rT3) in the absence of intrinsic thyroid disease [52]. Several studies have suggested low T3 syndrome to be an independent predictor of early and late mortality [52-54]. Studies have also reported a prevalence rate ranging from 5% to 35% for low T3 syndrome in ACS and approximately 30% in CHF patients [14, 52, 53, 55, 56]. The syndrome tends to occur more frequently in STEMI rather than NSTEMI, although one cross-sectional study of 400 patients admitted at the coronary care unit revealed no significant difference [57]. The exact time course of TH alteration during acute MI is not clear, but it occurs within the first 5 days of developing ACS. The inflammatory response and pro-inflammatory cytokines seem to be responsible for these alterations [56, 58]. Studies have indicated a prognostic value for thyroid hormone alterations in ACS. In one study, the increased level of rT3 was associated with higher one-year mortality [56]. Other studies have as well-linked abnormal thyroid hormone levels with worse prognosis [54] and increased short and long term mortality [54]. A specific association between lower fT3 and all-cause mortality in patients with ACS has also been stated [59]. Evidence also suggests a link between lower fT3 levels and lower LVEF as well as higher levels of cardiac biomarkers of myocardial injury after MI [60-62]. Conversely, however, in a study where cardiac MRI was performed on patients with STEMI, higher T3 level was associated with a greater extent of transmural myocardial involvement of the myocardium 40 days after the incidence. This observation may be due to the cardioprotective effect of low T3 state that reduces energy demand and prevents further ischemic injury and transmural necrosis. Some studies have suggested thyroid hormone replacement before ischemic reperfusion and on post-ischemic recovery to be beneficial [19, 40]. Although a hyperthyroid state causes the depletion of myocardial glycogen storage which can in turn make the heart more susceptible to post-ischemic adverse effects, short-term pre-ischemic treatment with thyroid hormones has not been effective in restoring glycogen storage [40]. The hyper metabolic state caused by hyperthyroidism results in increased oxidative metabolism and production of free radicals, along with reduced heart tolerance to oxidative stress [40, 53]. These alterations can cause further tissue damage and poorer prognosis for ACS in hyperthyroid patients.

## 2.4. Cardiometabolic Risks of Hyperthyroidism

### 2.4.1. Atherosclerosis

There is overwhelming evidence suggesting an increased risk of atherosclerosis and its severity as well as a higher

prevalence of myocardial infarction in hypothyroid patients [63-67]. These observations suggest an anti-atherosclerotic role for thyroid hormones [68]. Studies have also suggested several mechanisms for these effects. There are 4 types of Thyroid Receptors (TR) in Vascular Smooth Muscle Cells (VSMC):  $\alpha_1$ ,  $\alpha_2$ ,  $\beta_1$  and  $\beta_2$ . Studies have revealed the role of TR $\alpha$  in vascular tone regulation and its protective effects against atherosclerosis. Also, T3, at physiological concentrations, increases Matrix Gla protein- an inhibitor of vascular calcification. Another point to consider is that T3 leads to downregulation of angiotensin II type 1 receptor in VSMCs while inhibiting the effect of Platelet-Derived Growth Factor (PDGF) on DNA synthesis in these cells and their growth [69]. Thus, T3 can play its anti-atherosclerotic role by inhibiting VSMC growth through its effect on Gla protein, angiotensin II and PDGF.

T3 also induces angiogenesis through certain mechanisms. Angiogenesis can have both positive and negative effects on the cardiovascular system: In a hypertrophied heart, the formation of collateral arteries can reduce ischemia and prevent further damage. Neovascularization in atherosclerotic plaques, on the other hand, is a negative effect of angiogenesis [70]. The effect of T3 on the upregulation of Fibroblast Growth Factor (FGF) and increased expression of Hypoxia-Inducible Factor (HIF) that leads to Vascular Endothelial Growth Factor (VEGF) production can modulate angiogenesis [45, 71]. Thyroid hormones also increase the production of Nitric Oxide (NO)- a crucial part of angiogenesis and its regulation [72]. By activating NO synthesis in endothelium and VSMCs, thyroid hormone induces vasodilation that leads to decreased systemic vascular resistance [45, 69, 73]. Increased production of adrenomedullin and adenosine as vasodilator agents is another proposed factor contributing to T3-induced reduction of vascular resistance [69].

### 2.4.2. Blood Pressure

Thyroid hormones also affect the Renin-Angiotensin System (RAS) which is involved in cardiovascular remodeling, atherosclerosis, heart failure and blood pressure regulation. T3 increases the production and secretion of renin, while also increasing angiotensin production from the liver at the same time, and therefore, inducing the expression of Angiotensin-Converting Enzyme (ACE). This generally results in higher levels of angiotensin II [69, 74]. However, reduced expressions of ACE in the heart and aorta are also noted [74].

In addition to the effect of thyroid hormone on RAS which can affect blood pressure, recent studies have suggested associations between subclinical hyperthyroidism and alterations in diastolic and systolic blood pressure levels at night [75]. The association between hyperthyroidism and coronary artery spasms has not been clearly defined, but there is some evidence indicating a higher prevalence of coronary spasms in a hyperthyroid state [76].

## 3. HYPOTHYROIDISM

Generally speaking, the effects of hypothyroidism on the cardiovascular system are opposed to the ones associated with hyperthyroidism. Hypothyroidism induces a state of low oxygen and substrate demand and uptake in all major

organ systems, including the myocardium. Moreover, hypothyroidism can directly affect heart muscle function by altering the expression of particular genes necessary for the activity of myocytes [14]. There is a strong body of evidence indicating that a hypothyroid state can cause decreased cardiac output and contractility while increasing systemic vascular resistance. The condition is also associated with accelerated atherosclerosis and coronary artery disease [13, 14]. Hypercholesterolemia and diastolic hypertension are also linked with hypothyroidism and may partially account for these cardiovascular changes [64]. The good news is hormone replacement therapy with levothyroxine can reverse most of the aforementioned alterations [77]. However, it is important to note that the cardiovascular dysfunction caused by hypothyroidism is usually silent. Some of the detectable signs and symptoms include bradycardia, pericardial effusion and edema that is most commonly non-pitting. Pericardial effusions may be large and massive. They are also relatively frequent, occurring in almost 25 percent of patients with hypothyroidism. Another possible sign of hypothyroidism is hypertension, which is mainly caused by increased peripheral vascular resistance and decreased levels of Endothelial-Derived Relaxing Factor (EDRF). Furthermore, dyspnea on exertion and exercise intolerance are common in patients with hypothyroidism and may be considered as a sign of cardiovascular dysfunction theoretically. However, these symptoms are mainly associated with fatigue and impaired skeletal muscle function [7, 13, 14].

### **3.1. Effects of Hypothyroidism on Heart Conduction**

#### **3.1.1. Atrial Arrhythmias**

Hypothyroidism can result in impaired SA node function. This dysfunction may present itself as sinus bradycardia or an acceleration failure of the SA node during cardiac stress caused by conditions such as systemic infection, fever or heart failure [78]. Hypothyroidism is also linked with both significant and insignificant cardiovascular changes, all of which theoretically are able to make one susceptible to Atrial Fibrillation (AF). However, the infamous Framingham Heart Study revealed that in contrast to hyperthyroidism, hypothyroidism is not associated with Atrial Fibrillation (AF) [79].

#### **3.1.2. Ventricular Arrhythmias**

Treatment with amiodarone can produce hypothyroidism and in turn further, predispose the ischemic heart to ventricular arrhythmias. Evidence suggests that hypothyroidism is associated with a lower incidence of Ventricular Fibrillation (VF) [80]. Additionally, animal studies have suggested the decreased heart rate and excitability caused by hypothyroidism to have protective effects against arrhythmias in a morbid heart [81, 82]. Conversely, reports indicate that prolonged QT interval is quite common in hypothyroid patients. Prolonged QT interval makes these patients susceptible to ventricular premature beats and, in rare cases, ventricular tachycardia with a long QT interval (torsade de pointes) [83]. This is particularly important in patients with an underlying heart condition, as it can increase morbidity and mortality in such patients. However, one can generally conclude that hypothyroidism is associated with a reduced incidence of arrhythmias.

#### **3.1.3. Heart Blocks**

Atrioventricular (AV) blocks of all forms and with various intensities as well as low QRS complexes, have been reported in hypothyroid patients [21].

### **3.2. Effects of Hypothyroidism on the Myocardium**

Hypothyroid hearts tolerate ischemia better than normal hearts. Studies have demonstrated that patients with chronic angina have lower thyroid hormone levels and are less likely to develop dangerous infarctions, which suggests a cardioprotective role for low thyroid hormone levels [53]. As mentioned earlier, during a hypothyroid state, oxygen and energy consumption decreases in heart muscles, especially during the mechanical activity of the myocardium. This is partially due to the prominent presence of V3 Myosin isoform in hypothyroid hearts. Moreover, in contrast to hyperthyroidism, thyroid hormone status in hypothyroidism results in increased glycogen storage in the myocardium, along with a decline in the expression of the sodium-proton exchanger protein. The condition also causes myocardial ATP levels to not collapse quickly during episodes of ischemia. Furthermore, the expression of Protein Kinase C, a regulator of cardiac contractility with a major role in ischemia-reperfusion pathway of myocardial cells, is increased in hypothyroidism. These mechanisms along with the suppression of the apoptotic c-Jun N-terminal Kinases (JNKs) account for the resistance of cardiac muscle to ischemia-reperfusion in hypothyroidism [40]. However, as mentioned earlier, low levels of thyroid hormones could also mean a reduction in their cardioprotective effects and are associated with higher all-cause and cardiovascular mortality in heart failure patients. Therefore, maintaining a balanced thyroid hormone level is a challenging, yet necessary issue especially in patients who have an underlying heart condition such as MI or heart failure. We have discussed the association between MI and low thyroid hormone levels elsewhere in this review (hyperthyroidism-heart failure and MI).

### **3.3. Hypothyroidism and Heart Failure**

Although hypothyroidism impairs almost every aspect of left ventricular function and results in a decreased cardiac output, the ventricular dysfunction caused by the condition is mainly diastolic, due to the resulting impaired cardiac muscle relaxation [84]. Though the cause of the depressed ventricular function is not entirely clear, some have proposed that alterations in the expression of the genes involved in the production and regulation of myocardial calcium channels could have a role [13, 14]. As already mentioned, thyroid hormone controls multiple modulators of calcium current in heart muscle cells, such as the calcium-dependent adenosine triphosphatase and its inhibitor, phospholamban. In contrast to hyperthyroidism, lower levels of thyroid hormone reduce the expression of the sarcoplasmic reticulum Ca<sup>2+</sup>/ATPase, while increasing the expression of phospholamban- alterations that are partially responsible for the decreased contractility and diastolic dysfunction in hypothyroidism [7]. Associated conditions such as diastolic hypertension and coexisting coronary artery disease could amplify the diastolic dysfunction caused by hypothyroidism. Severe heart failure and myocardial infarction could result in a decrease in the pro-

duction of T3- an important modulator of gene expression in myocardial cells, as mentioned earlier. Evidence suggests that reduced T3 levels are also associated with impaired heart muscle function and its remodeling as well as higher mortality rates in patients with heart disease [19, 85]. Echocardiographic studies have confirmed impaired muscle relaxation (diastolic dysfunction) in patients with subclinical hypothyroidism as well as those with the overt form of the disease. Prolonged isovolumic relaxation and reduced E/A ratio, both seen in subclinical hypothyroidism, indicate abnormality in early relaxation stages of heart muscle that leads to decreased cardiac output, stroke volume and heart rate [86]. It has also been suggested that hypothyroidism could increase vascular permeability as well as reducing lymphatic drainage of the pericardial space, and as a result, facilitates the development of exudative pleural and/or pericardial effusions [87]. In addition, the condition is associated with reduced expression of beta-agonist receptors, causing the hypothyroid heart to respond weakly to catecholamine induction of contractility. All these mechanisms could contribute to hypothyroidism-associated heart failure.

### 3.4. Cardiometabolic Risks of Hypothyroidism

#### 3.4.1. Atherosclerosis

Hypothyroidism, especially in its overt form, increases the risk of atherosclerosis by affecting several factors. Studies on patients with overt hypothyroidism and those with myxedema coma demonstrated an increased rate of atherosclerosis among these patients compared with controls [88, 89]. Thickening of carotid intimal media, hypercholesterolemia and diastolic hypertension are all factors associated with both hypothyroidism and atherosclerosis [7, 14, 73, 84]. Hypertension and hypercholesterolemia are discussed elsewhere in this review. Intima Media Thickness (IMT) of the carotid artery indicates early stages of atherosclerosis and an increased risk for future cardiovascular complications [90]. Studies on hypothyroid patients undergoing one year of replacement therapy with levothyroxine have revealed that carotid IMT can be reversed in these patients [91]. The mechanism of the association between carotid IMT and low thyroid hormone levels, however, remains mainly unknown. As suggested by some studies, microRNAs may play a role since they observed higher serum levels of microRNA21-5, a modulator of the proliferation and migration of vascular smooth muscle cells in hypothyroid patients with carotid IMT [92, 93]. Another important risk factor for atherosclerosis seen in these patients is the decreased production of Nitric Oxide (NO), a known vasodilator, from vascular endothelial cells [94]. This form of endothelial dysfunction improves after thyroid hormone replacement in patients with both overt and subclinical hypothyroidism [73, 95]. In addition to the aforementioned factors, higher serum levels of homocysteine, C-reactive Protein (CRP) and plasminogen activator inhibitor-1 are other atherogenic risk factors seen in hypothyroidism. High serum levels of homocysteine that is a frequent finding in hypothyroid subjects and responds to treatment [96], is a known risk factor for atherosclerosis [97]. A meta-analysis has also revealed a correlation between the extent of hypothyroidism and serum homocysteine levels [98]. Other studies have demonstrated that in contrast to the overt form of the disease, subclinical hypothyroidism is not

associated with serum homocysteine levels [99]. The proposed mechanism for the effect of homocysteine on atherosclerosis includes endothelial dysfunction, increased thrombosis formation and oxidative stress [100]. However, the mechanism by which thyroid hormone affects homocysteine levels is not fully understood. A high plasma CRP level is also common in patients with overt hypothyroidism but not those with the subclinical form of the disease [99, 101]. CRP is a known predictive factor for future cardiovascular complications [102]; however, its association with atherosclerosis should be further examined.

#### 3.4.2. Blood Pressure

Thyroid hormone has a significant effect on blood pressure homeostasis. A study on patients with thyroid cancer and normal blood pressure who underwent thyroidectomy and withdrawal of T4 for six weeks revealed the development of diastolic hypertension in these patients [103]. Moreover, 20 to 40 percent of patients with hypothyroidism have hypertension despite decreased cardiac output [13, 104]. Although hypothyroidism also increases systolic blood pressure, it mainly affects diastolic pressure. The suggested mechanisms for elevated blood pressure in hypothyroidism include an increase in peripheral vascular resistance [84] and the stiffness of arteries [105]. Peripheral vascular resistance increases because of the contraction of vascular endothelial cells caused by decreased amounts of EDRF in the course of hypothyroidism [73]. These alterations are mainly responsible for the increase in systolic blood pressure, while arterial stiffness accounts for the diastolic part of hypertension. Subclinical hypothyroidism also affects blood pressure. Patients with these conditions have shown increased diastolic blood pressures compared with normal controls [106].

#### 3.4.3. Diabetes

In a hypothyroid state, peripheral glucose accumulation and decreased glucose clearance frequently occur [107]. More importantly, hypothyroidism, even in its subclinical form, is associated with increased insulin resistance because of a decrease in the production of glucose transporter 2 (GLUT-2) and renal insulin clearance [108]. These changes, along with atherosclerosis and the alterations in lipid profiles that are mentioned below, may lead to metabolic syndrome in hypothyroid patients.

#### 3.4.4. Lipid Profile

Changes in lipid profiles are frequent in both overt and subclinical hypothyroidism. Common findings with this regard in the overt form of the disease include higher levels of serum total and Low-Density Lipoprotein (LDL), total cholesterol and apolipoprotein B. Low thyroid hormone levels reduce the expression and activity of LDL receptors in the liver, as well as lowering the activity of cholesterol- $\alpha$ -monooxygenase- an enzyme that breaks down cholesterol [87, 109]. The latter causes decreased hepato-biliary cholesterol clearance. High amounts of serum triglyceride and Very-Low-Density Lipoprotein (VLDL) are also seen in hypothyroid patients but to a lesser extent. In a 1993 study on 295 hypothyroid patients, only 8.5 percent had a normal lipid profile. The study reported a prevalence of 56% for isolated hypercholesterolemia and only 1.5% for isolated hypertriglyceridemia [110]. Interestingly, another study

demonstrated that 4.2% of patients with hyperlipidemia had co-existing hypothyroidism [111]. The incidence rate was almost half in the general population, indicating the need for more investigations on the necessity of thyroid profile evaluation in patients with hyperlipidemia and vice versa. Besides, a recent study has suggested that the effect of age and gender should be taken into account when evaluating the association between hypothyroidism and lipid profile [112]. Regarding the effects of subclinical hypothyroidism on lipid profile, individual studies and their results have been variable and to some extent controversial. However, a meta-analysis performed by Liu *et al.* demonstrated that patients with subclinical hypothyroidism had significantly higher amounts of serum LDL and triglyceride. Their study did not yield the same result about HDL cholesterol [113]. In support of these findings, another meta-analysis revealed that levothyroxine therapy in patients with subclinical hypothyroidism had a mild effect on reducing LDL but not HDL cholesterol [114]. Therefore, evidence suggests that the subclinical form of the disease can indeed affect lipid profile of the patients, but its influence is unsurprisingly less significant than the overt form of the disease.

### 3.5. Subclinical Hypothyroidism- General Considerations

Subclinical hypothyroidism is a clinically asymptomatic state of the disease with abnormal laboratory findings, *i.e.* a TSH level above the normal cutoff range with normal thyroid hormone levels. The condition has a considerable prevalence of 4.3% to 9.5% in the United States. Subclinical hypothyroidism can also progress to overt hypothyroidism with an annual risk of 1 to 5 percent. Nevertheless, many of the cardiovascular changes seen in overt hypothyroidism including vascular endothelial dysfunction, diastolic hypertension and dyslipidemia can also be present in the subclinical form of the disease [115]. There is no strong evidence on the extent of cardiac involvement caused by the condition and studies with this regard have produced controversial results. However, a meta-analysis of 11 prospective cohort studies has revealed an association between subclinical hypothyroidism and increased risk of cardiovascular complications such as coronary heart disease and mortality [116]. In addition, another meta-analysis by Singh *et al.* [117] demonstrated that subclinical hypothyroidism was significantly related to coronary artery disease and cardiovascular mortality. As a result, even subclinical hypothyroidism can be considered as a risk factor for cardiovascular disorders, although further evidence on this matter seems necessary.

## 4. MEDICATIONS

### 4.1. Hypothyroidism Medications

Treating overt hypothyroidism with levothyroxine improves a large portion of the cardiovascular dysfunction caused by the disease, including lipid profile, diastolic dysfunction, cardiomyopathy, hypertension, heart rate and its variability during exercise. Levothyroxine is also effective for interrupting the progression of atherosclerosis in these patients [14]. However, in patients with a pre-existing arrhythmia or myocardial ischemia, levothyroxine could potentially exacerbate the underlying heart condition. There-

fore, for patients who are older and those who have a history of angina or arrhythmias, replacement therapy with levothyroxine should be started with low doses. The dose can then be gradually increased with caution if necessary. However, increasing the dosage should be delayed to at least four to six weeks after initiating therapy as T4 takes time to reach optimal action and normalize thyroid hormone levels [13]. Although levothyroxine treatment is relatively associated with increased morbidity in terms of arrhythmias, mild to moderate ischemic and cerebrovascular diseases, all-cause mortality is not increased in these patients [118]. Besides, one should not forget that the positive effects of T4 replacement therapy in these patients usually outweigh the risks and treatment should not be stopped. A large study on hypothyroid subjects suggested that angina may improve or at least stop recurring in these patients after treatment with levothyroxine [119]. Moreover, evidence suggests that although long-term levothyroxine therapy increases daily heart rate by approximately 10 percent, it does not significantly affect the frequency of arrhythmias such as premature ventricular and atrial contractions (PVCs and PACs) [120]. Another point to notice is the interaction of hypothyroidism and warfarin therapy. A hypothyroid state interferes with the clearance of several medications, including warfarin. In patients undergoing anticoagulation therapy with warfarin who also have hypothyroidism, the required dose of warfarin increases. This effect is reversible with levothyroxine treatment [14]. With regard to subclinical hypothyroidism, the evidence is present but not enough to conclude treatment with thyroid hormones therefore, improvement in cardiovascular markers is required. In one study, patients with subclinical hypothyroidism and a coexisting coronary artery disease, showed diastolic dysfunction when received placebo. The case group on the other hand, underwent treatment with levothyroxine and showed no significant changes in echocardiography indices [121]. In another investigation, treatment with levothyroxine (L-T4) in middle-aged women with subclinical hypothyroidism has been effective in improving myocardial performance (Left ventricular Tei) index [122]. Still, further evidence is required on this matter.

### 4.2. Hyperthyroidism Medications

Methimazole and its prodrug, carbimazole, along with propylthiouracil (PTU) are the main anti-thyroid drugs available to treat hyperthyroidism [123]. There is not enough evidence suggesting a direct effect of these drugs on the heart. Studies have demonstrated that chronic hyperthyroidism is a cause of cardiovascular mortality regardless of the treatment modality [124]. It is noteworthy though, that some studies have linked the use of methimazole/carbimazole to congenital heart defects such as atrial septal and ventroseptal defects [125, 126]. However, further investigations with special focus on the first trimester are necessary to confirm such an association and identify the underlying mechanism. Because these two drugs are associated with a relatively high risk of congenital anomalies in general, current guidelines recommend the use of PTU instead of methimazole/carbimazole in pregnant women [127]. Radioiodine, as another treatment option for hyperthyroidism, does not seem to be associated with cardiovascular complications [128]. Not surprisingly,



overtreatment of hyperthyroidism with anti-thyroid drugs and the subsequent hypothyroid state can result in all the aforementioned cardiovascular disturbances caused by hypothyroidism.

### 4.3. Role of Amiodarone

Amiodarone is a widely accepted, effective class III antiarrhythmic drug with almost 40 percent of its weight consisting of organic iodine. The high iodine content can interfere with thyroid function and may lead to either hyperthyroidism or hypothyroidism [19, 129, 130]. Reports indicate that 15-20% of patients treated with amiodarone have abnormal thyroid function tests [129].

#### 4.3.1. Amiodarone-induced Hypothyroidism

Amiodarone inhibits the activity of 5'-deiodinase and therefore suppresses the conversion of T4 to T3 without affecting serum TSH levels in the short term. If prolonged, this will result in amiodarone-induced hypothyroidism, especially in the presence of preexisting thyroid disease [130-132]. Guidelines suggest regular follow-up TSH testing for patients receiving amiodarone and recommend treatment with levothyroxine while continuing amiodarone if the condition causes an overt and persistent increase in serum TSH levels [128, 131].

#### 4.3.2. Amiodarone-induced Hyperthyroidism

In comparison to the hypothyroid state caused by the drug, amiodarone-induced hyperthyroidism/thyrototoxicosis (AIT) accompanies a significantly higher risk for major adverse cardiovascular events [14]. The condition is categorized into 2 types [133]: Type I AIT is a result of the high iodine portion of amiodarone and occurs more frequently among populations with low iodine intake and preexisting thyroid disorders such as goiter. In type I AIT, hyperactivity of the thyroid gland may cause increased vascularity in color-doppler ultrasonography and elevated (>10%) radioactive iodine uptake (RAIU), therefore providing a guide to physicians to distinguish between the two types of AIT which is difficult in most cases. In contrast, type II AIT is due to inflammatory mechanisms, resulting in a destructive process in the thyroid gland that is marked by decreased vascularity in color-doppler ultrasonography and lower amounts (<3%) of RAIU [14, 129, 133]. It is important to distinguish between 2 types of AIT because the conditions require different treatments. Although color-Doppler ultrasonography may help, a definitive diagnosis is not always easy. RAIU should not be routinely used as it has proven diagnostically ineffective. Moreover, mixed AIT can also occur, further complicating the diagnosis. Despite some controversies, guidelines usually suggest treatment with antithyroid drugs for type I AIT and oral glucocorticosteroids for the inflammation-based type II form of the disease. For mixed AIT, a combination of steroids and antithyroid drugs has proven relatively useful [134, 135]. Beta-blockers, if not contraindicated, are also suitable choices to relieve cardiovascular symptoms in all types of AIT. AIT patients should undergo regular follow-up thyroid function testing [15]. Most protocols recommend discontinuing amiodarone and initiation of the high-dose antithyroid to patients after the development of AIT.

However, the evidence is not sufficient for a definite recommendation [33, 133]. Furthermore, it is not always safe to discontinue amiodarone or change it to another antiarrhythmic drug. The decision requires the judgment of both the cardiologist and endocrinologist which can only be achieved by a close coordination between the two specialists [129]. Evidence suggests thyroidectomy as an appropriate treatment option for resistant AIT [129]. It is worth mentioning that AIT also increases vitamin D metabolism and clearance, resulting in a decrease in the required therapeutic dose of warfarin. This is particularly important because many patients use amiodarone and warfarin at the same time for coexisting cardiovascular problems. As a result, regular monitoring of prothrombin time is necessary in these patients. Studies suggest consistent checking both during AIT and in the subsequent months after recovery [14].

### CONCLUSION

Thyroid hormone abnormalities significantly affect the cardiovascular system. Both hyper and hypothyroidism can directly influence several mechanisms in cardiac conduction, contractility and function as well as cardiometabolic and vascular homeostasis. Although thyroid hormones have cardioprotective effects and are necessary for cardiac function, their excessive levels as seen in hyperthyroidism can result in dysrhythmia, especially tachycardia and atrial fibrillation, as well as high cardiac output and pathological left ventricular hypertrophy that may lead to ventricular dilatation and congestive heart failure if left untreated. Hypothyroidism, on the other hand, can promote atherosclerosis by causing dyslipidemia, diastolic hypertension and impaired endothelial function, hence predisposing the patients to the acute coronary syndrome. Evidence suggests that the treatment of both hyper and hypothyroidism in their early stages can reverse most of these cardiovascular abnormalities. However, larger randomized clinical trials seem necessary for developing a more precise treatment guideline. In patients with serious cardiovascular conditions such as myocardial infarction and heart failure, maintaining a euthyroid state is the key to control cardiovascular adverse events and is particularly challenging. With all the evidence linking thyroid to cardiovascular conditions, we strongly suggest special attention to be given to the thyroid status of patients with heart ailments.

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### CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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