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Cardiovascular Complications of Hyperthyroidism

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ABSTRACT

Thyrotoxicosis is a clinical syndrome caused by an excess of thyroid hormones circulating in the body. Myocardium and blood arteries have thyroid hormone receptors; hence, an increase or decrease in thyroid hormone levels can alter cardiovascular function. Cardiovascular complications are obvious in-patient with hyperthyroidism. Palpitations, tachycardia, exercise intolerance, dyspnea with exertion, expanded pulse pressure, and on occasion atrial fibrillation are associated with hyperthyroidism, excessive endogenous thyroid hormone production, and thyrotoxicosis, the condition caused by excess thyroid hormone. In the early stages of hyperthyroidism, a high cardiac output and hypertrophy of the left ventricle are observed, followed by biventricular dilatation and congestive heart failure. Atrial fibrillation and pulmonary arterial hypertension can contribute to the higher morbidity associated with untreated hyperthyroidism. Therefore, early and effective treatment of hyperthyroidism is required to prevent thyrotoxic cardiomyopathy.

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Introduction

Hyperthyroidism is a medical condition characterized by excessive synthesis and secretion of the thyroid hormone by the thyroid gland [1, 2]. Thyrotoxicosis is the clinical state that develops when there is an excess of thyroid hormones circulating in the body [1]. Over 10% of the adult population suffers from thyroid gland and thyroid hormone problems [1, 2]. Thyroid hormones work as transcription factors, and both the heart and blood arteries have thyroid hormone receptors [3, 4]. Changes in the gene expression of cardiovascular system components can have profound effects on the contractile apparatus and sarcoplasmic reticulum of the myocardium [1, 5]. In addition, an increase or decrease in the concentration of these hormones affects the cardiovascular system's function [1, 6]. Resulting in alterations in the frequency, rhythm, and cardiac output of the heart [1, 7].

By directly influencing the pace at which cardiac muscle fibers contract, hyperthyroidism contributes to an increase in cardiac output. This, in conjunction with an increase in blood volume and a decrease in systemic resistance, reduces afterload [8]. Hyperthyroidism can also cause hypertension, systolic and diastolic myocardial dysfunction, dyslipidemia, and endothelial dysfunction [1, 9]. On short-, medium-, and long-term timescales, the activation of all of these physiological processes can indicate a grave and elevated risk of cardiovascular disease [9]. Therefore, it is essential to analyze and evaluate the significance and impact of changes in the levels of thyroid effector hormones in the body [10]. As cardiovascular complications caused by thyroid hormones continue to be the most common manifestations of thyroid hormone dysfunction [11].

In the United States, 1.2% of the population has hyperthyroidism, of which 0.5% have overt hyperthyroidism and 0.7% have subclinical hyperthyroidism [12]. Without treatment measures, both overt and subclinical cardiovascular risk factors can contribute to

cardiovascular disease, the leading cause of death worldwide. Recent studies have demonstrated that even moderate increases in thyroid hormones are associated with a 20 to 80% increased risk of cardiovascular mortality [13]. Yet, current therapeutic practices are primarily geared toward young and elderly patients with subclinical hyperthyroidism [14].

The purpose of this review is to examine the pathophysiological alterations occurring in the cardiovascular system because of hyperthyroidism, as well as the association between hyperthyroidism and the development of cardiovascular problems.

Molecular Mechanisms of Thyroid Hormone Action

Two pathways exert the intracellular cardiac actions of thyroid hormone: genomic and nongenomic. T3 binds to nuclear receptors, which then bind to thyroid-responsive elements (TREs) in the promoters of target genes to exert a number of the principal effects [15]. The binding of thyroid hormone to these TREs can either stimulate or inhibit gene expression, hence controlling the expression of specific messenger RNA and translated proteins and eliciting diverse tissue-specific responses. Importantly, genes controlled by thyroid hormone are also implicated in structural and regulatory proteins, and long-term exposure to high T3 levels can increase the synthesis of cardiac proteins, leading to ventricular hypertrophy and malfunction [16]. Extra nuclear nongenomic activities induce fast alterations in the plasma membrane and cytoplasmic organelles of cardiac myocytes. Changes in sodium, potassium, and calcium ion channels, actin cytoskeleton polymerization, and intracellular signaling pathways in the heart and smooth muscle cells are among them. To modulate heart function and circulatory hemodynamics, genetic and nongenomic processes collaborate. In addition, they boost the expression of the faster contractile isoforms of the myosin heavy chain (isoforms), which contributes to improved systolic function. T3 raises both the depolarization and repolarization rates of the sinoatrial node, hence raising heart rate. Therefore, thyroid hormones have positive inotropic and chronotropic effects on the heart, which, together with enhanced adrenergic sensitivity, explain for the elevated heart rate and contractility in hyperthyroidism [17].

Thyroid Hormone Action on Heart

The heart is a main organ of action for thyroid hormone. Nuclear and non-nuclear systems mediate the direct effect of T3 activity on the heart. Triiodothyronine shortens diastolic relaxation, i.e., the hyperthyroid heart relaxes faster (lusitropic activity) because of triiodothyronine [18]. This has a direct relationship with the rate at which free calcium concentration is lowered in the cytosol, which causes troponin C of thin filaments of myofibrils, which causes rapid diastolic relaxation because the gene coding for the calcium pump of the sarcoplasmic reticulum is markedly T3-responsive Ca2+ATPase (SERCa2) [13]. Interestingly, alpha-1 adrenergic stimulation decreases the induced expression of the SERCa gene in the rat heart [19]. According to research, T3 induces changes in Myosin Heavy Chains (MHC) in rats and rabbits [16]. In addition, T3 treatments inhibit the expression of MHC alpha and MHC beta by stimulating MHC alpha and MHC beta [20]. In addition, TH causes a significant rise in cardiac actin, a component of thin filament. TH increases the expression of the gene encoding the cardiac troponin I isoform in postnatal and young adult rats [21]. T3 significantly activates enzymes involved in calcium and iron transport. Additionally, it increases protein synthesis. T3 contributes to the breakdown of ATP within cells as well as an increase in oxygen consumption. Furthermore, TSH modifies the secretory activity of the heart [22]. Important structural and regulatory genes are modulated by thyroid hormones, which has a direct effect on heart function. The myosin heavy chain genes encode the two contractile protein isoforms of the thick filament in cardiac myocytes. The intracellular calcium cycle is controlled by the sarcoplasmic reticulum Ca2+-ATPase and its inhibitor, phospholamban. They are primarily responsible for enhancing the heart's capacity to contract and relaxing it during diastole [23].

Hyperthyroidism and Cardiovascular Hemodynamics

Thyroid hormone has a number of impacts on the heart and peripheral vasculature, including decreased SVR and elevated resting heart rate, increased left ventricular contractility, and increased blood volume. By directly altering VSM and reducing mean arterial pressure, thyroid hormone reduces peripheral arteriole resistance. In turn, this stimulates the renin-angiotensin-aldosterone pathway and increases renal salt absorption. Because of T3's increased erythropoietin synthesis, red cell mass increases. The combined impact of these alterations increase blood volume and preload. These combined actions increase cardiac output by 50 to 300 percent in hyperthyroidism compared to normal people [24]. The association between hyperthyroidism and increased vascularity suggests that T3 may stimulate angiogenesis in order to improve capillary density [25]. Moreover, the renin-angiotensin-aldosterone system is largely responsible for blood pressure regulation [26].

Hyperthyroidism and Atrial Fibrillation

10% to 25% of hyperthyroid persons have atrial fibrillation (AF), compared to 0.4% of the general population. Age increases the likelihood of AF in both populations. Having elevated thyroid hormone levels or subclinical hyperthyroidism raises the risk of AF [27]. Less than one percent of people with hyperthyroidism develop dilated cardiomyopathy with left ventricular systolic dysfunction [18]. Other cardiac symptoms of hyperthyroidism include symptomatic heart failure (occurs in around 6% of patients) [28]. Moreover, pulmonary arterial hypertension [29].

In thyrotoxic individuals, male gender, advanced age, ischemic heart disease, valvular heart disease, and congestive heart failure were risk factors for atrial fibrillation (AF). Other factors, including obesity, chronic kidney disease, proteinuria, female gender, serum-free T4 concentrations, and transaminase concentrations, have also been associated with the frequency of atrial fibrillation (AF) in hyperthyroidism. Despite the fact that there is an increased risk of atrial fibrillation when free T4 levels are at the upper end of the normal range, especially in younger individuals, TSH levels have not been associated to AF [30].

Hyperthyroidism and Heart Failure

In hyperthyroid hearts, a greater proportion is allocated to heat production, whereas in euthyroid animals, a greater proportion is allocated to usable contractile energy [31]. This poor use of chemical energy may account for the well-established fact that hyperthyroidism of long duration and severe severity ultimately results in heart failure. Significant modifications in cardiovascular functioning are linked to variations in plasmatic/tissue levels of thyroid hormone.

Patients with hyperthyroidism may have signs and symptoms of heart failure. Given that, the bulk of studies demonstrate higher cardiac output and contractility, this finding seems contradictory. This has been described in the literature as a high-output failure example. This description is incorrect. Nonetheless, in a subset of patients with severe and persistent hyperthyroidism, excessive sinus tachycardia or atrial fibrillation can lead to left ventricular dysfunction and heart failure. This explains why many patients with

the triad of hyperthyroidism, low cardiac output, and diminished left ventricular function are diagnosed with atrial fibrillation [32]. Due to the inability to reduce PVR, hemodynamic impairment caused by hyperthyroidism has a deleterious effect on myocardial contraction and impedes further increases in cardiac output and ejection fraction, particularly during exercise. As a result, the hyperthyroid heart performs at maximum capacity. A forced increase in preload and total blood volume increases the effort of the heart and promotes hypertrophy in response to this hemodynamic stress. Due to a doubling or triple of cardiac output and above-normal contractility, "high output" cardiac failure frequently manifests in young people with severe, long-term hyperthyroidism. In turn, this causes a rise in ventricular filling pressure, which controls pulmonary and peripheral congestion [33, 34, 35]. If a patient with hyperthyroidism already has ischemic or hypertensive heart disease, the development of heart failure may be more likely. Graves and Hashimoto's illnesses are both associated with a higher prevalence of mitral valve prolapse. In turn, this may increase the likelihood of atrial fibrillation and left atrial hypertrophy [8].

Specifically, thyrotoxic cardiomyopathy is defined as cardiac damage brought on by the toxic effects of excess thyroid hormone, resulting in altered myocyte energy production, intracellular metabolism, and myofibril contractile function [31].

Hyperthyroidism and Pulmonary Hypertension

Although the mechanism of PAH in hyperthyroidism is unknown, its reversal when euthyroidism is restored provides evidence of a causal connection [31]. Recent research reveals a link between TSH receptor antibodies and PAH, lending credence to the possibility of an autoimmune-mediated pulmonary vascular remodeling in this illness [36]. All PAH patients should be checked for hyperthyroidism, and all hyperthyroidism and dyspnea patients should be screened for PAH [37].

Role of Catecholamine's

Hyperthyroidism is characterized by an increase in resting heart rate, blood volume, stroke volume, myocardial contractility, and ejection fraction, as well as an improvement in diastolic relaxation, similar to a state of elevated adrenergic activity. Plasma catecholamines are unaltered or low in thyrotoxicosis, and the density of -adrenergic receptors is altered in a time- and tissue-dependent manner, resulting in an increase in tissue sensitivity to catecholamine's [1, 4].

Cardiovascular Complications of Hyperthyroidism

Some studies have reported cardiovascular complications in hyperthyroidism patients. Palpitations, tachycardia, exercise intolerance, dyspnea with exertion, widened pulse pressure, and occasionally atrial fibrillation are associated with hyperthyroidism, excessive endogenous thyroid hormone production, and thyrotoxicosis, a condition caused by excess thyroid hormone, whether endogenous (hyperthyroidism) or exogenous (thyroid hormone treatment) [32]. The most prevalent hyperthyroidism indications and symptoms are palpitations and tachycardia.

The failure to respond to exercise-induced increases in heart rate, ejection fraction, or SVR may be the cause of exercise intolerance in hyperthyroid individuals. Respiratory and skeletal muscle weakness may be the primary contributor to exercise intolerance in patients with severe or chronic illnesses and the elderly [17, 20].

Conclusion

Hyperthyroidism is a frequent thyroid disorder that affects virtually all organ systems, including bone metabolism, dermatological impacts, the gastrointestinal system, and the cardiovascular system. Cardiovascular effects are the most prevalent and hazardous symptoms, and they are typically the primary complaints that prompt hospitalization. Thyroid hormones exert their cardiovascular effects through a variety of physiological pathways, including complex and multisystemic interactions. Knowing the specifics of these systems may give us with helpful information for the treatment of patients [1].

In its early stages, hyperthyroidism generates a high cardiac output and left ventricular hypertrophy, and in its late stages, biventricular dilatation and congestive heart failure. Atrial fibrillation and pulmonary arterial hypertension can contribute to the higher morbidity associated with untreated hyperthyroidism. Preventing thyrotoxic cardiomyopathy requires prompt and efficient treatment of hyperthyroidism [9].

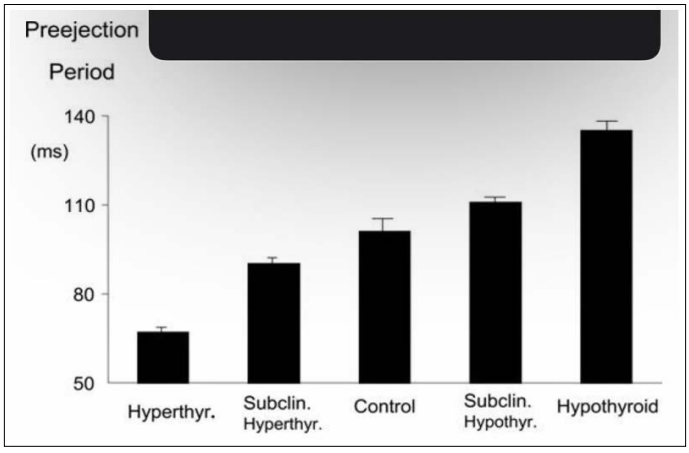
Hyperthyroidism and Its Effect on Heart

Thyroid Hormone Action on Heart

Heart is a major target organ for thyroid hormone action. Direct effect of T3 action in the heart is mediated by nuclear and extranuclear mechanisms. Triiodothyronine shortens diastolic relaxation i.e., hyperthyroid heart relaxes with higher speed (lusitropic activity) [38].

This has direct relation to speed with which free calcium concentration is lowered in the cytosol causes troponin C of thin filament of myofibrils which causes rapid diastolic relaxation as gene coding for calcium pump of sarcoplasmic reticulum is markedly T3 responsive Ca2+ATPase (SERCa2) [39]. Of interest, expression of alpha-1 adrenergic stimulation inhibits induced expression of rat heart SERCa gene [40]. Typical examples of T3 induce alterations in Myosin Heavy Chains (MHC)in rats and rabbits [41, 42]. T3 administrations stimulate MHC alpha and MHC beta to the detriment of its expression [43].

Table 1: The graph reflects the effects of cardiac contractility in milliseconds. Data are shown as mean value-SEM, Kruskall-Wallis test with P<0.0001



TH also leads to marked increase in cardiac actin which is a part of thin filament. TH especially influences the level of cardiac troponin I isoform in post-natal and young adult rats by increasing expression of gene coding for this protein [44]. Overall, T3 markedly stimulates enzymes involved in calcium and iron flux. It also results in increased protein synthesis. T3 contributes to ATP breakdown in cells and increased oxygen consumption. Finally, TSH modifies secretory activity of the heart [45, 46].

The modulation of the expression of important structural and regulatory genes by thyroid hormones has a direct impact on heart function. In the cardiac myocyte, the two contractile protein isoforms of the thick filament are encoded by the myosin heavy chain genes. Intracellular calcium cycling is governed by the sarcoplasmic reticulum Ca2+-ATPase and phospholamban, which is its inhibitor. They are mostly in charge of improving the heart's ability to contract and relaxing it during diastole (Table 2) [38, 47, 48].

Table 2: Effect of Thyroid Hormone on Cardiac Gene Expression

Positively Regulated	Negatively Regulated
α-Myosin heavy chain	β-Myosin heavy chain
Sarcoplasmic reticulum Ca^{2+}-ATPase	Phospholamban
Na^{+}/K^{+}-ATPase	Adenylyl cyclase catalytic subunits
β1-Adrenergic receptor	Thyroid hormone receptor α1
Atrial natriuretic hormone	Na^{+}/Ca^{2+} exchanger
Voltage-gated potassium channels (Kv1.5, Kv4.2, Kv4.3)	

Thyroid Hormone Effects on Cardiovascular Hemodynamics

Reduced SVR and elevated resting heart rate, increased left ventricular contractility, and increased blood volume are some of the effects of thyroid hormone on the heart and peripheral vasculature. By directly affecting VSM and lowering mean arterial pressure, thyroid hormone lowers resistance in peripheral arterioles. This, in turn, stimulates the renin-angiotensin-aldosterone system and promotes renal sodium absorption. Red cell mass increases because of T3's increased erythropoietin production. The effects of these modifications work together to raise blood volume and preload. These combined effects raise cardiac output in hyperthyroidism by 50% to 300% compared to normal people [49].

SVR declines with hyperthyroidism, whereas peripheral tissue blood volume and perfusion rise. The finding that hyperthyroidism is linked to enhanced vascularity suggests that T3 may boost angiogenesis to increase capillary density [50].

The control of blood pressure is mostly dependent on the renin-angiotensin-aldosterone system [51].

CVS Complications of Hyperthyroidism

Complications related to CVS are evident in patients with hyperthyroidism. Palpitations, tachycardia, exercise intolerance, dyspnea with exertion, widened pulse pressure, and occasionally atrial fibrillation are linked to hyperthyroidism, excessive endogenous thyroid hormone production, and thyrotoxicosis, the condition that results from excess thyroid hormone, whether endogenous (hyperthyroidism) or exogenous (thyroid hormone treatment) [52]. (Table 3)

Table 3: Cardiovascular complications of Hyperthyroidism

Symptoms and signs	Incidence (%)
Palpitations	85
Reduced exercise tolerance	65
Dyspnoea on effort	50
Easy tiring	50
Angina on effort	5
Tachycardia	90
Systolic murmur	50
Systolic hypertension	30
Atrial fibrillation	15

The most prevalent signs and symptoms of hyperthyroidism are palpitations and tachycardia. Exercise intolerance in hyperthyroid patients may be caused by an inability to exercise-induced increases in heart rate, ejection fraction, or SVR. Respiratory and skeletal muscle weakness may be the main contributing factor to exercise intolerance in people with severe or chronic diseases, as well as in the elderly [52, 53, 54].

Atrial Fibrillation

Atrial fibrillation (AF) affects 10% to 25% of hyperthyroid individuals, compared to 0.4% of the overall population [55]. In both populations, the likelihood of having AF rises with age. Having high thyroid hormone levels or subclinical hyperthyroidism increases the likelihood of having AF [56]. Less than 1% of hyperthyroidism patients experience dilated cardiomyopathy with left ventricular systolic dysfunction [57]. Other cardiac manifestations of hyperthyroidism include symptomatic heart failure (occurs in about 6% of patients) [57]. and pulmonary arterial hypertension [58].

Male sex, advancing age, ischemic heart disease, valvular heart disease, and congestive heart failure were risk factors for AF in thyrotoxic patients. Other variables, such as obesity, chronic kidney disease, proteinuria, female gender, serum-free T4 concentrations, and transaminase concentrations, have also been linked to the prevalence of AF in hyperthyroidism. TSH levels have not been linked to AF, even though there is an increased risk of AF when free T4 levels are at the upper end of the normal range, especially in younger individuals [59].

Of the 381 patients with uncontrolled hyperthyroidism, 70 had atrial fibrillation or flutter; 39 of these patients experienced a return to a stable sinus rhythm after receiving antithyroid and antiarrhythmic medication. In the first week of treatment, while they were still hyperthyroid, one-third of the patients who reverted did so. Reversion was more prevalent in younger patients and in those with recent-onset arrhythmia who had no other signs of heart illness, as expected. Eight individuals with arrhythmia had large arterial embolic events that were either proved (five) or probable (three). Of the eight patients, four passed away. When uncontrolled hyperthyroidism is present in patients with both atrial fibrillation and heart failure, embolism frequently develops early on. These findings imply that prophylactic anticoagulation may be suitable in this high-risk group, but larger trials are required before it can be said that prophylactic anticoagulation effectively prevents embolism [60].

Heart Failure

In hyperthyroid hearts, a larger fraction goes to heat production whereas in euthyroid animals more is spent on useful contractile energy [61, 62, 63]. This inefficient use of chemical energy may explain the well-established findings that hyperthyroidism of long duration and great severity leads-in the end- to heart failure. Changes in plasmatic /tissue thyroid hormone levels are associated with significant alterations in cardiovascular functions.

Patients with hyperthyroidism may have heart failure-related signs and symptoms. This finding is paradoxical given that most studies show increased cardiac output and contractility. This has been described as a high-output failure example in earlier literature. This description is not accurate. However, excessive sinus tachycardia or atrial fibrillation can result in rate-related left ventricular dysfunction and heart failure in a fraction of patients with both severe and chronic hyperthyroidism. This explains the finding that many patients with the trifecta of hyperthyroidism, poor cardiac output, and reduced left ventricular function are diagnosed with atrial fibrillation [52].

Hemodynamic compromise due to hyperthyroidism causes detrimental effect on myocardial contraction and disturbs further increase in cardiac output and ejection fraction especially during exercise due to the inefficacy to reduce PVR. Consequently, hyperthyroid heart functions to its utmost efficacy. To compensate for this hemodynamic burden, a forced increment in preload and total blood volume raises the work of the heart and promotes hypertrophy.

"High output" cardiac failure usually appears in young adults who had severe long-term hyperthyroidism due to doubling or tripling of cardiac output and above normal contractility. This in turn leads to rise in ventricular filling pressure and thus modulates the degree of pulmonary and peripheral congestion [61, 62, 64].

Heart failure may also be more likely to develop in the hyperthyroid patient if they already have ischemic or hypertensive heart disease. A higher incidence of mitral valve prolapse has been linked to both Graves' and Hashimoto's diseases. The latter, in turn, may increase the risk of atrial fibrillation and left atrial enlargement. A low TSH level is linked to an increased risk of atrial fibrillation in adults over 60, which could result in congestive heart failure [52].

It is also shown that systemic dysfunction is reversed when thyroid function is restored. The effect of hyperthyroid cardiomyopathy is unknown, but the possible explanation could be the detrimental effect of tachycardia.

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