Review Article

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# Association between Thyroid hormone abnormality and Cardiovascular disorder

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**Abstract:**
The heart is a very complicated and intrigued part of human anatomy. Minor factors can fluctuate its functionality. Knowing the root causes of the relationship is a breakthrough as this will help in better diagnosis and, hence, better treatment. The thyroid hormones can control cardiac functionality, so any deviation from the expected value gives rise to cardiovascular dysfunction. In this review article, various mechanisms are discussed, which will provide greater insight into the correlation between thyroid status and cardiovascular dysfunction. Hyperthyroidism, hypothyroidism, hyperlipidemia, electrical activity, and thrombosis seem to be general terms so, their contribution in studying the relation is of more excellent value. Further, the case study that the article includes supports the findings**.**

**Keywords:** T3(triiodothyronine), cardiovascular, genomically.

## 1. Introduction

### 1.1. Thyroid hormone regulation

The thyrotropin-releasing hormone secreted by the hypothalamus regulates thyroid-stimulating hormone secreted by the pituitary gland. The thyroid gland releases thyroid hormone located in our neck region. It is an endocrine gland. The gland secretes hormones like T3 and T4. The concentration of Thyroid-stimulating hormone by the pituitary decides the amount of T3(triiodothyronine) and T4(tetraiodothyronine) hormones secreted.

The average levels of Thyroid Stimulating hormone are 0.40-4.50 mIU/mL. The average value for T3 and T4 is 80-220 ng/dl and 5.4-11.5mcg/dl, respectively 1. Any deviation from these standard values indicates a disorder. If the values are higher than usual, it is hyperthyroidism, and if it is lower than normal, it is hypothyroidism.

"Subclinical thyroid dysfunction" is a condition in which the thyrotropin levels differ from expected values [1].

### 1.2. Cardiovascular function under thyroid regulation

The causes of thyroid abnormalities can be due to pituitary diseases, autoimmune disorders, effects of the drug, unknown mutations and structural modification in the thyroid gland [2, 3,4].

There is an increase in metabolic rate in hyperthyroidism, and hence the cardiac output also increases. An increase of thyroid hormone affects the myocardial genes, which leads to a rise in the amount of calcium to contract the cardiac muscles [5]. The smooth muscle forces peripheral to the cardiac muscles push the ventricles and atria due to an increase in thyroid hormone.

There are various ways in which a slight change in thyroid hormone levels affects cardiac function.

Which, if left untreated, may lead to myocardial infarction and many other cardiovascular disorders. The amount, duration, and type of thyroid hormone play a vital role in regulating cardiac function. Pulmonary hypertension is among the cause of death in hyperthyroidism [6]. This interrelation can boost or break the heart's activity. In difficult situations, life-threatening conditions can come into account. Hence studying the correlation between the two will help find the unknown cure to specific disorders. The study shall open the doors to various treatment opportunities and help us find answers to the underlying conditions.

## 2. Discussion

### 2.1. Cardiac activity regulation by thyroid hormone

The T4 hormone often releases in excess compared to T3, so T4 is converted to T3 in muscles by type I and type II deiodinases [7,8]. T3 mainly regulates cardiac functions genomically by binding to thyroid hormone nuclear receptors known as a nuclear mechanism or by extranuclear mechanism [9]. The binding of T3 to receptors increases the affinity to carry out the transcription of many genes. THRA and THRB are the genes encoding TRa1, TRb1 and TRb2 receptors [10]. Thyroid receptors interact with other receptors like the retinoic X receptor. The cardiac function can be briefly summarised as T3 entering the cell, crossing the nuclear membrane, binding to the thyroid hormone nuclear receptors, and finally, mRNA transcription to protein synthesis [11]. Various genes regulate $Na^+/K^+$ ATPase, $Ca^{2+}$ ATPase and voltage-dependent potassium channels [12].

Moreover, thyroid hormone can be regulated non -genomically also, especially in the cardiovascular system. $Na^+/K^+$ channels open when T3 increases. $Ca^{2+}$ ATPases can activate non-genomically in myocardial sarcolemma [12].

### 2.2. Hyperthyroidism

Hyperthyroidism is responsible for increased heart rate and muscular contractility. Due to this, systemic vascular resistance decreases significantly. In extreme situations, it may lead to heart failure. The mechanism of action of T3 influences systolic depolarization and diastolic repolarisation. This leads to an increase in the action potential duration. The blood volume increases in the short-term hyperthyroidism, leading to a rise in left ventricular end-diastolic volume. As there is an increase in blood volume, it decreases blood pressure. Hence stroke volume and heart rate increase, eventually increasing the cardiac output [5]. This increase in cardiac output leads to systolic and diastolic dysfunction; finally, the result is cardiovascular dysfunction [11].

Cardiovascular complications include chest pain cardiac ischemia, as seen in the ECG with increased palpitations [13]. This action induces extraordinary demands on the heart to work above the average rate, increasing the demand for oxygen in older patients with underlying conditions of coronary artery disease. Especially those with TSH values above 10mIU/litre have higher incidences of heart failure in the more ageing age population [14].

A ten-year study was conducted on individuals 60 or above years to support the above findings. The relationship between low thyrotropin levels and cardiovascular abnormalities was established [15]. Low thyrotropin levels, a pituitary hormone, are responsible for hyperthyroidism. Which can lead to complications like increased blood pressure atrial fibrillation and hence aiding mortality.

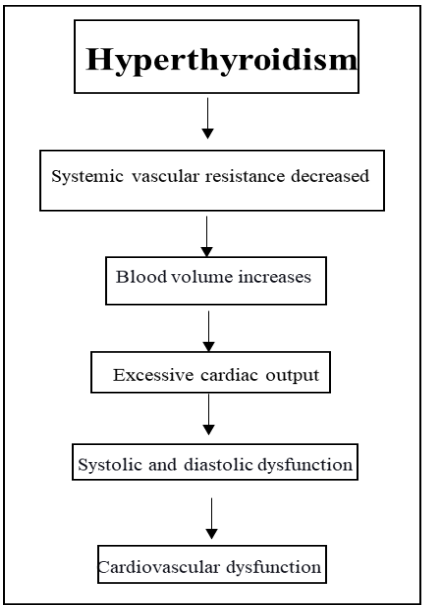


**Figure 1**. Flow chart representing a mechanism of action between hyperthyroidism and the heart.

### 2.3. Hypothyroidism

An abrupt decrease in thyroid hormone leads to hypothyroidism. Its working and effect on cardiac activity are opposite to hyperthyroidism [5]. It slows down cardiac function, increasing vascular

resistance and diastolic dysfunction [16]. Cardiac load reduces. Hence, cardiac output reduces; this is detrimental because systemic perfusion reduction occurs, decreasing blood channelling to all body parts, including cardiac muscles. Low blood transport to the heart can lead to heart cell's death and system failure [11].

Hypercholesterolemia, hypertension, increase in carotid thickness, and plug formation includes further complications related to hypothyroidism. Thyroid hormone replacement treats such conditions as, in this case, the prognosis is very harmful [5,17].
Nitric oxide synthetase catalyzes the production of nitric oxide from L-arginine and oxygen. Out of the three forms of NOS known as endothelial(eNOS), neuronal(nNOS), and isoform (iNOS), nNOS is responsible for NO regulation in the myocardium [18,19]. Vasoconstriction and blood pressure rises as NO inhibition is due to hypothyroidism 20**.** This vasoconstriction applies pressure on the heart to pump blood more efficiently, which can be fatal. Patients with hypertension have shown impaired vasodilatory effects [18,19].

Another way NO regulates cardiac activity is by acting as a feedback mechanism to angiotensin II. Angiotensin II is responsible for vasoconstriction, and hence it increases blood pressure. NO works against it by undergoing vasodilation, so endogenous modulation of both pathways is essential to regulate blood pressure and cardiac functions [21].

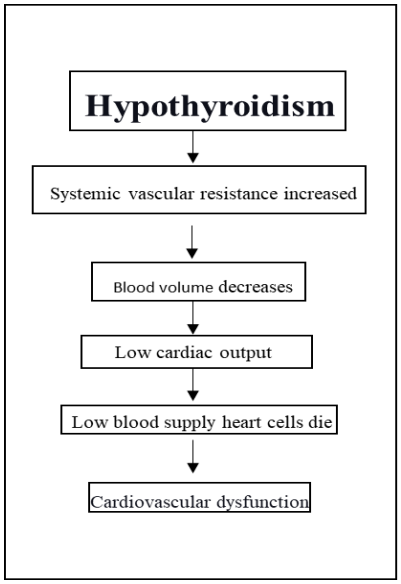


**Figure 2.** Flow chart representing a mechanism of action between hypothyroidism and the heart.

### 2.4. Hyperlipidemia

There is no doubt that even hypothyroidism is associated with hyperlipidemia, and eventually, hyperlipidemia is associated with cardiovascular dysfunction [22]. As the level of thyroid hormones decreases, that ability to metabolize biomolecules like lipids also decrease and hence is evident by the accumulation of high levels of low-density lipids [23].

There is an increase in the oxidation of LDL, which leads to atherogenesis [24]. High LDL levels relate to an accumulation of fats on the circumference of arteries; this proves a primary reason how indirectly thyroid levels control the heart's well-being. The fatty deposition prevents oxygen supply to the heart, blocking the significant arteries and as arteries being narrower than veins becoming the primary target. Another reason is the decrease in LDL receptors, which affects the clearance of fats from the liver. Thyroid Hormone activates 7α-hydroxylase, which is responsible for the degradation of cholesterol [25].

### 2.5. Contractile and electrical activity of the heart

Sodium and potassium ions work to carry out the electrical activity in all organs of our body. Similarly, the Thyroid hormone also influences the activity of these ions, eventually affecting the electrical activity of the heart. The thyroid hormone controls the potassium channels. Mainly T3 (triiodothyronine) receptor regulates the gene expression for sodium-potassium ATPase and voltage-activated potassium channel genes [26].

Hypothyroidism attributes to repolarisation abnormalities, i.e., prolonged QTc interval [27]. Though short-term exposure to TSH has no direct effect on cardiac activity but long-term exposure, a long action potential observes. This could be due to decreased repolarizing potassium currents [28].

Moreover, hyperthyroidism may increase the risk of new-onset or recurrent supraventricular arrhythmias, such as atrial fibrillation and atrial flutter [29].

### 2.6. Direct effects

The non-genomic regulation of thyroid hormone is mainly controlled by $Ca^{2+}$ uptake in the sarcoplasmic reticulum in cardiac muscles. The $Ca^{2+}$ ATPase under the control of SERCA2 acts as a $Ca^{2+}$ pump moving $Ca^{2+}$ from cytosol to sarcoplasmic reticulum to which T3 hormone increases SERCA2 transcription [30,31]. Any changes to the level of proteins affect the relaxation and contraction of the cardiac muscle cells [32]. Various

proteins like the α- and β -myosin heavy chains positively and negatively regulate T3 respectively [33]. It has been researched that a variety of proteins in the cardiac myocyte, phospholamban (PLB) and sarcoplasmic reticulum (SR) calcium-activated adenosine triphosphatase (SERCA2), regulates the thyroid hormone. *Phospholamban* is a phosphoprotein that regulates SERCA2 activity. The SERCA2/PLB protein ratio helps determine calcium movement in myocytes. This further can be correlated to T3 increasing the SERCA2/PLB ratio, which increases calcium cycling and, finally, high cardiac activity. Also, phospholamban pathway through which phospholamban phosphorylation is mediated. Phosphorylation/dephosphorylation cascades may underlie the cellular actions of thyroid hormones on the heart [34].

The myocardial fibroblast is under the control of thyroid hormone; hence deposition of collagen is a cause of concern as it obstructs coronary circulation [35].

Due to the mechanism of action of β-adrenergic receptors, cAMP, a secondary messenger, accelerates the diastolic depolarization, finally increasing the heart rate [32]. Catecholamines are responsible for cardiac control in hyperthyroidism. In thyrotoxicosis, catecholamines production is low, and the β-adrenergic receptor density alters, resulting in increased tissue sensitivity to catecholamines. The thyroid hormone maintains a response to β-1 adrenergic agonists in the normal range [36,37]. Total arterial stiffness increases due to hyperthyroidism in response to β-1-adrenergic receptors [38].

### 2.7. Thrombogenesis and Thyroid hormone

Hyperthyroidism has been accused of causing an increase in thrombus formation in the artery [25]. Non-genomically concentrations of L-thyroxine (T4) activate human platelets. a structural protein integrin αvβ3 contains a receptor for thyroid hormone [39]. The endothelial growth factor controls other platelet forming factors that stimulate this interaction with receptors. The above mechanism leads to cascade impact creating plug or platelet aggregation on the artery walls. Plug formation restricts blood flow, altering the circulatory system's hemodynamics. The plug, in turn, creates a barrier for blood flow to the heart and cell death, or alteration in blood Pressure affecting the heart's ability to pump efficiently. Increased T4 also risks the formation of venous thrombosis [40].

**Table 1**. Research papers support the above studies and their correlation.

| Refe-rence No. | Author and journal name | Corresponding study |
|---|---|---|
| **41** | Walsh, J. P.; Bremner, A. P.; Bulsara, M. K.; O'Leary, P.; Leedman, P. J.; Feddema, P.; Michelangeli | Subclinical hypothyroidism and cardiac dysfunction |
| **42** | Squizzato, A.; Romualdi, E.; Büller, H. R.; Gerdes, V. E. A. | Hyperthyroidism on thrombosis |
| **43** | Osman, F.; Franklyn, J. A.; Holder, R. L.; Sheppard, M. C.; Gammage, M. D. | Hyperthyroidism association |
| **44** | Boekholdt, S.M.; Titan, S. M.; Wiersinga, W. M.; Chatterjee, K.; Basart, D. C. G.; Luben, R.; Wareham, N. J.; Khaw, K.-T. *Clin. Endocrinol. (Oxf).***2010**, *72* (3), 404–410. | Cardiovascular risk to older women with already suffering from thyroid abnormalities observed. |
| **45** | Cappola, A. R.; Fried, L. P.; Arnold, A. M.; Danese, M. D.; Kuller, L. H.; Burke, G. L.; Tracy, R. P.; Ladenson, P. W. *JAMA* **2006**, *295* (9), 1033. | Subclinical hyperthyroidism and atrial fibrillation. |

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