



The Thyroid and Cardiovascular System: A clinical synergy

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Abstract:

The thyroid hormone exerts many direct and indirect effects on the heart and the cardiovascular system. The myocardial and vascular endothelial cells of the cardiovascular system contain the necessary receptors for the molecules of the Thyroid Hormone to bind to and are affected by the changes in the levels of the circulating hormones in the blood plasma. The significance of the hormonal action in maintaining the homeostatic balance of the cardiovascular system is based upon decades of clinical trials and experimental analysis. Even minor fluctuations in the concentrations of these hormones, such as in the case of sub-clinical hypothyroidism, can cause serious harm to the heart and vascular system. This review article will establish the precise course of action of the thyroid hormones on the heart and the cardiovascular system and discuss its potential therapeutic applications for improving patients' health conditions and resultant cardiovascular disorders.

Keywords: Thyroid Hormone; Cardiovascular disease; Hyperthyroidism; Hypothyroidism; Atrial Fibrillation

Frequently used abbreviations

Abbreviation	Expanded Form
T3	Triiodothyronine
T4	Tetraiodothyronine; Thyroxine
TH	Thyroid Hormone
TR	Thyroid Hormone Receptor
SVR	Systemic Vascular Resistance
AF	Atrial Fibrillation
LV	Left Ventricle

1. Introduction

The Thyroid Gland is a butterfly-shaped, highly vascular endocrine organ. It is located at the base of the neck, lying over the trachea. The Thyroid is the largest of the endocrine glands in the body and weighs about 15 to 25 g. in an average adult human. The hormones secreted by this gland are vital for tissue growth, metabolism, regulation of internal temperature and homeostasis, proper development of reproductive functions, and normal functioning of the body organs^{1,11}. The thyroid gland is also essential for the growth of bones the maturation of the central nervous system (C.N.S). Due to an increase in the basal metabolic rate, there is an increase in the synthesis of sodium (Na⁺)-potassium (K⁺)-ATPase, leading to an increase in oxygen consumption and increased heat production. Thus, the increased metabolic rate triggers an increase in glucose absorption, glycogenolysis, gluconeogenesis, lipolysis, protein synthesis, which are required for normal functioning and day-to-day activities². The Thyroid Stimulating Hormone (TSH) is a glycoproteinaceous hormone secreted by specialized cells of the anterior pituitary gland called the thyrotrophs. TSH acts on the follicular cells of the thyroid by binding to its conjugate receptors (TSHR) and stimulating the thyroid gland to produce its hormones. In addition to the production of hormones, TSH also stimulates cell differentiation for the normal growth of the Thyroid gland³. The release of TSH is stimulated by the TRH (thyrotropin-releasing hormone), which is secreted from centers in the Hypothalamus, and the production is under the regulation of the “negative feedback” mechanism by circulating thyroid hormones in the blood plasma^{10,19}. The thyroid gland principally secretes two iodinated hormones, T3 (3,5,3' - triiodothyronine) and majorly T4 (Thyroxine; 3,5,3',5' - tetraiodothyronine)^{12, 13}. T4 is converted to T3, the physiologically active form of the Thyroid Hormone, through the process of deiodination. While ≈20% of T3 originates from the thyroid gland, ≈80% of T3 is produced by peripheral conversion of T4 by 5'-deiodinase enzyme, especially type 2 5'-deiodinase (DIO2)^{3,12}. More than 99% of thyroid hormone is protein bound to thyroid binding globulin (T.B.G.), pre-albumin, and albumin proteins^{3,15}. To exert its action, T3 binds to its receptor in the nucleus; this

initiates the transcription of DNA, which promotes the translation of mRNA, which in turn activates the synthesis of new proteins involved in the functioning of the gland³. Iodine is the trace element in the body directly functioning of the Thyroid gland as it is an integral part of the hormones produced by the thyroid; the daily recommended daily intake is 150-200 μg¹⁴. The primary physiological role that Iodine is known for is in the synthesis of thyroid hormones^{14, 16}. The hormones influence the cardiovascular system and hemodynamics by increasing cardiac output, stroke volume, heart rate, and contractility of the heart by increasing the number of beta-1 (β1) receptors on the myocardium of the heart enabling the myocardium to be more sensitive to being stimulated by the sympathetic nervous system, thereby increasing contractility^{2,4}.

2. Molecular and Cellular Mechanisms of action of the Thyroid Hormone

To understand the effect of the Thyroid hormone on the functioning of the cardiovascular system and hemodynamics, we need to understand the molecular and cellular mechanisms by which the Thyroid hormone exerts its actions on the myocytes.

2.1 Physiology of the TH and TRs.

T4 and T3 are capable of generating biological activity in responsive tissues by binding to the thyroid hormone receptors. The affinity of the thyroid hormone receptors (TRs) is approximately ten folds higher for T3 than for T4^{12,13,17}. Therefore, the deiodination process is essential for T3 to exert potent TR-mediated effects. Although T4 is a prohormone (precursor hormone) for T3, T4 can show direct effects through thyroid hormone receptors in various tissues, such as blood vessels. For instance, L-thyroxine (T4) can interact with the receptor on the plasma membrane integrin α_vβ₃, which has been linked with hormonal modulation of angiogenesis (proangiogenic)^{12,18}. As stated previously, >99% of thyroid hormone is protein bound to thyroid binding globulin (T.B.G.), pre-albumin, and albumin proteins^{3,15}. The remaining minor part of unbound thyroid hormones circulates in the blood plasma by the action of three

intracellular seleno-cysteine enzymatic proteins called deiodinases. These circulating hormones enter target cells after the deiodination pathways^{10,12,15,19}. Type 1 deiodinases are found in the peripheral tissues like the hepatic and renal tissues, which help convert circulating T4 to T3. Type 2 deiodinases have a very high affinity for Thyroxine and are primarily found in the brain's tissues, pituitary, and brown adipose tissue; they are responsible for both- peripheral and intracellular conversion T4 to T3. Type 3 deiodinase is mainly found in the placenta, brain, and skin and, together with Type 1 deiodinase, converts T4 to reverse T3 (rT3), which is an inactive metabolite of TH which is subsequently degraded and excreted^{10,12,13,15,19}. TH transporters are located in the plasma membrane and can regulate TH uptake into cells^{13,20}.

T3 action is mediated by nuclear TRs that bind T3 with high affinity^{10,11}. TRs belong to the nuclear receptor (NR) superfamily that also includes the receptors for retinoids, peroxisomal proliferators, Vitamin D (steroid), fatty acids, and prostaglandins, as well as 'orphan receptors' with no identified endogenous ligands^{19,21-23}. A Thyroid Receptor is encoded by two genes, designated as TRa and TRb, located in chromosomes 17 and 3, respectively, in humans¹⁰. Alternative splicing from each TR gene leads to the generation of multiple isoforms of the TRs, including TR α 1, TR α 2, and TR α 3 from the TRa gene and TR β 1 and TR β 2 from the TRb gene^{10,11}. Similar to other members of NRs, TRs have modular structures with six regions (A–F) and three functional domains (Figure 1)^{10,11,13}.

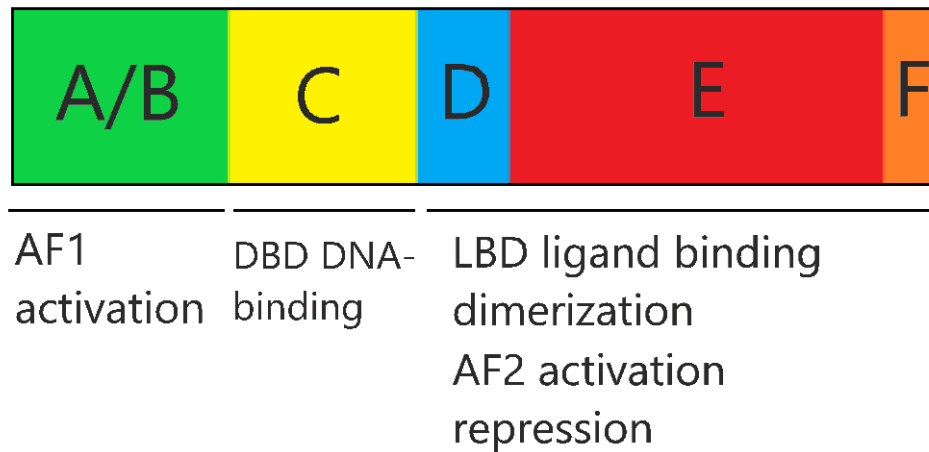


Figure 1: Modular structure of thyroid hormone receptor. Nuclear receptors, including TR, can be divided into six regions (A–F) with three functional domains: AF1, activation function 1 (A and B regions); DBD, DNA-binding domain (C region); LBD, ligand-binding domain (D, E, and F regions)¹⁰.

TRs act as ligand regulatory transcription factors because they can bind both TH and TH-response elements (TREs) that are typically located in the promoter regions of the target genes¹³. The principal function of a TR as a transcription factor is to regulate target gene expression directly through response elements of nuclear DNA. The T3 response element (TRE) is composed of repeated DNA sequences with varying configurations²⁴⁻²⁶. TRs can bind with TREs as monomers or by homodimerization¹⁰. The primary form of binding of the TR is TRE with any of the three isoforms of Retinoid X Receptor (RXR α , RXR β , or RXR γ) by heterodimerization^{27-30,49}. Contrary to steroids

important property of TRs is their ability to bind TREs constitutively independent of ligand occupancy TRs and are transcriptionally active^{10,21,31}. TRs are composed of a central DNA binding domain (DBD), which contains two projections of zinc that interconnect with the major and minor grooves of TRE nucleotide sequences, and a carboxy-terminal ligand-binding domain (LBD). The hinge region between these two domains contains a stretch of multiple lysine amino acids that are required for nuclear translocation of the receptor^{10,11,19}. X-ray crystallography shows that liganded TRa-1 LBD has been demonstrated that TH binds to a hydrophobic 'pocket' lined by

discontinuous stretches of amino acids, which implies that additional hydrophobic interfaces might be involved in Retinoid X receptor (RXR) heterodimerization³². TR and the Retinoid X Receptor (RXR), Vitamin D receptor (VDR), and peroxisome proliferator-activated receptors (PPARs) are mainly responsible for the binding of DNA response elements as heterodimers with RXRs²⁷⁻³⁰. The heterodimerization is proved to amplify DNA-binding affinity and provide target gene specificity of action^{21,22}.

Now that we have studied the physiology of the Thyroid Hormone and its interaction with the TRs, now let us explore the effect of the TH on the myocytes of the Heart.

2.2 Action of TH on myocytes of the Heart.

Owing to their lipophilicity, the circulating Thyroid Hormones can directly pass through the membrane of cells, including cardiomyocytes⁶⁷. Thyroid hormone protein receptors investigated are primarily of myocytic origin (heart cells) and cells of the smooth vascular muscles.⁵⁻⁷ The first step in the chain of events leading to the action of the thyroid hormone in cardiac cells is the transport of thyroid hormone across the plasma membrane, or sarcolemma of cardiac myocytes followed by transport across the nuclear membranes into the cell nucleus occurs⁶. The cell membranes of the cardiac myocytes have specific transport proteins for triiodothyronine⁵. The actions of triiodothyronine begin with binding the biologically active T3 hormone to these nuclear receptors, which results in the transcription of the genes responsive to triiodothyronine^{6,8}. Thyroid hormones exert myriad effects on the cardiovascular system, particularly on the heart. THs influence cardiac activity by three pathways: by direct genomic actions on cardiomyocytes by binding to nuclear receptors, which leads to the regulation, transcription, and expression of target cardiac genes. Secondly, extranuclear, nongenomic actions on the ion-regulated channels in the cardiomyocyte cell membranes. Lastly, the effects of T3 and T4 on the peripheral circulation, which determine cardiovascular hemodynamics, cardiac filling, and systolic contractility^{5,12,34}. The two main thyroid receptors in the cardiomyocytes are THR α 1, which is predominantly expressed in cardiomyocytes, and THR β ^{12,35}. As mentioned previously, TRs are unique in that they can bind to TREs even in the absence of thyroid hormones,

leading to the repression of transcription of target cardiac genes^{35,36}. Therefore, the regulation of essential genes in the cardiomyocyte is dependent on the availability of thyroid hormones^{36,37}. The two myosin heavy chains (α and β) are myofibrillar proteins that constitute the thick contractile filaments of cardiac myocytes^{5,41}. In humans, the β -myosin heavy chain predominates, and cardiac contractile function is markedly altered in patients with thyroid disease^{5,41,42}. Thyroid hormones activate the expression of genes which encode the Na(+)/K(+)-transporting ATPases, Myosin heavy chain- α (myosin 6; encoded by gene MYH6), and sarcoplasmic reticulum calcium ATPase 2 (SERCA2; encoded by gene ATP2A2), and negatively regulate the transcription of myosin heavy chain- β (myosin 7; encoded by gene MYH7) and phospholamban (PLN)³⁸⁻⁴⁰. Production of the sarcoplasmic reticulum proteins, calcium-activated ATPase (Ca²⁺-ATPase) and phospholamban, is regulated by the action of T3 through changes in the gene transcription^{6,44}. The release of Ca²⁺ and its reuptake into the sarcoplasmic reticulum are critical determinants of systolic contractile function and diastolic relaxation^{5,6,44}. SERCA2 and its inhibitor PLN are responsible for regulating, re-uptake, and releasing Ca²⁺ from the sarcoplasmic reticulum, thereby regulating the amount of calcium available for systolic contraction, which can determine diastolic relaxation of the heart. THs by inducing increased levels of SERCA2 and decreased levels of PLN in the sarcoplasmic reticulum promote the reuptake of calcium during diastole, leading to improved ventricular relaxation^{7,44,45}. The levels of activity of PLN are modified by the level of phosphorylation⁴⁴. Hence, changes in the relative amounts of these proteins and the state of phosphorylation of PLN may account for altered diastolic function in cases of congestive heart failure and a diseased thyroid^{44,46}. Thyroid hormones also exhibit a direct inotropic effect on the heart by positively regulating the gene expression of the β 1-adrenergic receptor⁴⁷. To study the effect of the TH on these receptors, administration of TH in rats demonstrated an increase of β 1-adrenergic receptors by almost 100% as assessed by (-)-[³H]-dihydroalprenolol binding. This increase in the number of β 1-adrenergic receptors is caused by a TH-induced augmentation of receptor synthesis. This increase in the number of β 1-adrenergic receptors led to an increased cardiac physiological

response such as increased heart rate, widened pulse pressure, and increased cardiac output^{48,50}. Clinical studies of the various components of the β -adrenergic-receptor complex in the sarcolemmae have shown that β -adrenergic receptors, guanine nucleotide regulatory proteins, and adenylyl cyclase (V and VI) are all altered by changes in the status of the TH levels^{51,52}. The ion-transporters in the plasma membrane, such as Na(+)/K(+) – ATPases, Na(+)/Ca²⁺ exchanger, and voltage-gated K⁺ channels, including Kv1.5, Kv4.2, and Kv4.3, are also regulated by THs and thus coordinating the electrochemical and mechanical responses of the myocardium^{53,54}. Additionally, the TH has extranuclear actions in cardiac myocytes. T3 has

the capability of making changes in the performance characteristics of various sodium, potassium, and calcium channels in the heart, and changes in intracellular levels of calcium and potassium can increase inotropy and chronotropy by its action^{55,56}. Therefore, it is the cumulative effect of the transcriptional and non-transcriptional pathways of the TH that modulates the functioning of the myocardium.

Now that the action of the Thyroid Hormone on the cardiomyocytes is explained, we can now witness how the TH affects the cardiovascular system by its action on the heart and on the dynamics of blood flow

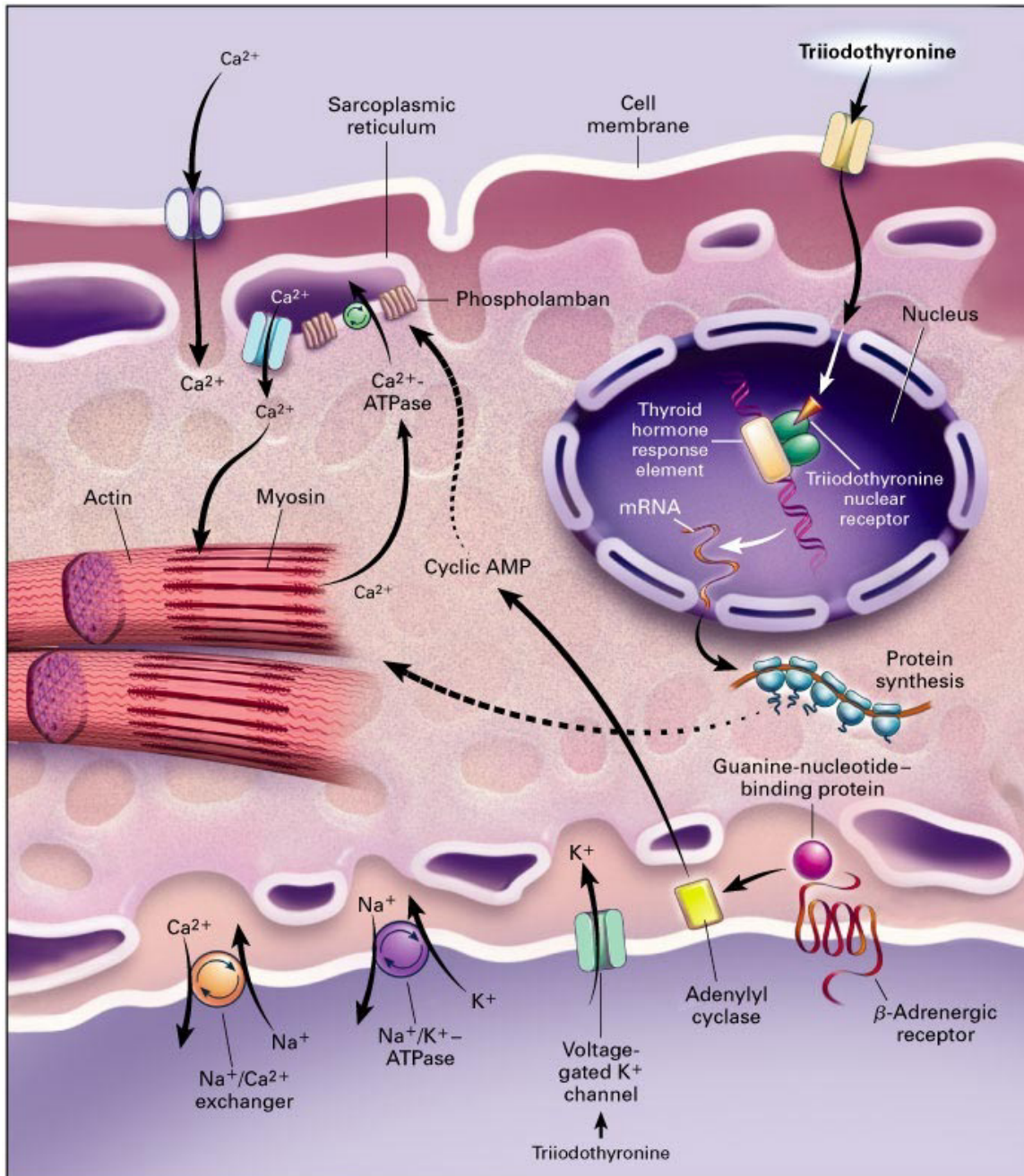


Figure 2: Sites of action of Triiodothyronine on Cardiac Myocytes³³.

3. Effects of Thyroid Hormone on Hemodynamics

In addition to the increase in peripheral oxygen consumption and substrate utilization by the action of thyroid hormone, it also causes a secondary effect- an increase in cardiac contractility⁵. T3 is also able to increase cardiac contractility directly^{6,57}. T3 decreases systemic vascular resistance (SVR) by dilating the resistance of the arterioles of the peripheral circulation⁵⁸. Vasodilation is due to a direct effect of T3 on vascular smooth muscle cells

that promotes relaxation⁷. The clinical correlation of this finding is that a high dose of T3 decreases SVR and increases cardiac output within hours after coronary artery bypass surgery⁵⁹. TH also leads to an increase in blood volume. The hepatic production of angiotensinogen, the substrate for the action of renin in blood plasma, is increased by thyroid TH as it increases for aldosterone⁶⁶. This happens due to the decrease in SVR, the effective arterial filling volume falls. The JGA apparatus of the kidneys is sensitive to changes in volume and pressure and in response to decreased effective

arterial filling volume, it causes an increase in the release of renin. This cascade of mechanisms leads to the activation of the angiotensin-aldosterone axis, which, in turn, stimulates renal sodium reabsorption, resulting in an increase in plasma volume^{60,61,63}. TH also stimulates the secretion of erythropoietin which increases RBC mass. Therefore, the combined effect of these two actions is an increase in blood volume and preload (hemodynamic force exerted on the ventricular wall during filling corresponding to ventricular end-diastolic wall stress), which further increases cardiac output^{34,60}. The action of TH on the vascular smooth muscle cells and endothelial cell function must also be taken into consideration while studying the effect of TH on hemodynamics. The non-genomic pathways target the membrane ion-regulated channels and endothelial nitric oxide synthase (eNOS), which decrease the SVR⁶². A

linear connection has been clinically established between the action of TH and systolic as well as diastolic pressure^{34,65}. TH is responsible for increasing the basal metabolic rate in almost every tissue and organ in the body. The increased metabolic demands lead to an increase in cardiac output, decrease in SVR, and increase in blood pressure^{2,4,66}. These associated changes are similar to the physiological response of the cardiovascular system to strenuous activity. Adrenomedullin, a polypeptide composed of 52 amino acids, is a potent vasodilator and is transcriptionally regulated by TH. It is expressed in the cardiac cells, and its serum levels are increased in thyrotoxicosis^{64,66}.

Now that we have understood the effect of TH on hemodynamics, we shall see how Thyroid dysfunction exerts adverse effects on the cardiovascular system

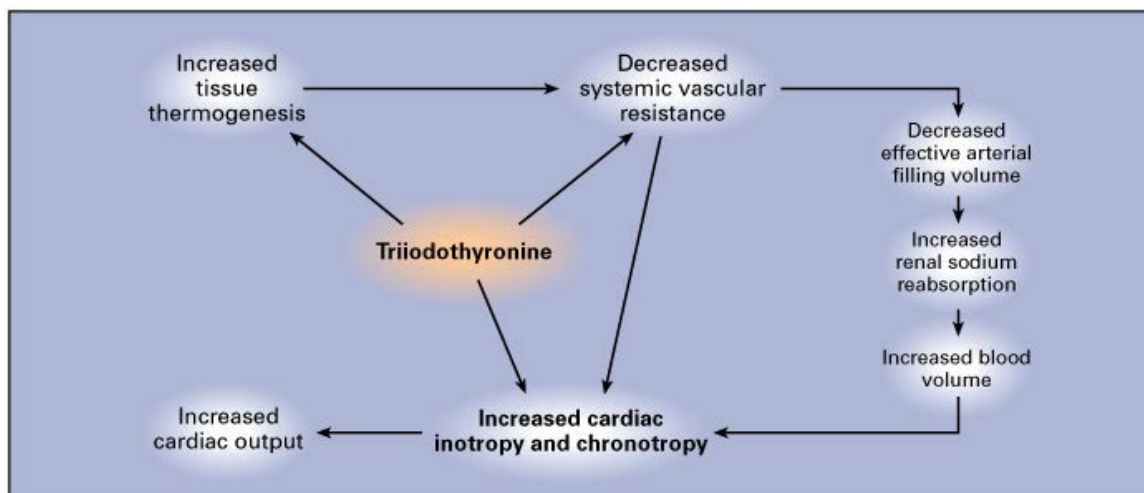


Figure 3: Effect of Thyroid Hormone on Cardiovascular Hemodynamics³³.

4. Ailments of the Thyroid and their clinical manifestations on the Cardiovascular System

4.1 Hypertthyroidism

Hypertthyroidism is an abnormal condition when the Thyroid gland secretes excess quantities of the Thyroid Hormones beyond the standard limit. The excess production of TH has a plethora of effects on the heart and the cardiovascular system⁷⁰. The diagnostic symptoms include intolerance to heat, weight loss, sweating, perspiration, tremors, diarrhea, and palpitations⁷⁰. The cardiovascular signs of hypertthyroid patients are a widened pulse pressure, atrial premature contractions, systolic

hypertension and shallow diastolic pressure, atrial fluttering, paroxysmal atrial tachycardia, and dyspnoea on exertion⁷⁰⁻⁷². Tachycardia is an abnormal condition of cardiac rhythm where the heart beats more than 90 bpm in a resting or sleeping condition, and there is an intolerance to exercise due to an exaggerated increase in heart rate^{5,72,73}. Atrial Fibrillation (AF) is the most common arrhythmia associated with a hypertthyroid condition⁷³, and the AF may lead to further complications such as thromboembolism and

congestive heart failure (CHF) ^{68,74}. Hyperthyroid patients have such clinical symptoms analogous to patients in a hyperadrenergic state ^{68,69}. These symptoms are direct consequences of dramatically increased cardiac output from 50% to up to 300% due to a substantial decrease in SVR and increase in preload, contractility, and heart rate ⁷⁵. In more advanced stages of hyperthyroidism, there may be the presence of peripheral and pulmonary edema as a consequence of elevated atrial filling pressure ^{70,76}. The syndromes for the prolapse of the bicuspid valve are more common in women suffering from Grave's disease. ⁷⁷. Hyperthyroid patients can manifest symptoms of angina even in the absence of CAD (coronary artery disease) ⁷⁸. An increased presence of hypertension is observed in thyrotoxic patients over 65 years ⁷⁹. Hypertension results from the blood vessels' inability to accommodate the increased cardiac output and high stroke volume; this also explains the intermittent presence of diastolic hypertension ^{68,78-80}. Patients suffering from hyperthyroidism have increased LV systolic and diastolic contractile function, a clinical finding which is consistent with changes in the expression of contractile and calcium-regulatory proteins, as described in section 2.2 ^{44,46}. Hyperthyroidism causes an increase in the rate of increase in intraventricular pressure during systole, the left ventricular ejection fraction, and the rate of blood flow across the aortic valve ^{5,81}. As a result, the rates of chamber relaxation and LV filling, measured as the flow across the mitral valve during diastole, are all increased ⁸². A study in which β -adrenergic-receptor antagonists to patients with hyperthyroidism slows the heart rate but does not alter systolic or diastolic contractile performance ^{82,83} this clinical study confirms that TH acts directly on the muscles of the heart ^{6,39,46}. When left untreated, hyperthyroidism may lead to heart failure owing to cardiac hypertrophy, arrhythmias, increased preload, and the inability of the heart to keep up with the abnormal increase in work ⁸⁴. Additionally, in a population-based study of individuals suffering from hyperthyroidism, those who did not receive a definite course of therapy had a higher long-term cardiovascular mortality ⁸⁵.

4.2 Hypothyroidism

Hypothyroidism is an abnormal condition when the Thyroid gland secretes lower quantities than the normally required quantities of the Thyroid Hormones. The underproduction of TH has cardiac

effects opposite to that of those in Hyperthyroidism ⁸⁶. Hypothyroidism is associated with several alterations in cardiac function manifesting as the reduction in cardiac output and cardiac contractility, reduced chronotropy and inotropy, a decrease in heart rate, and an increase in systemic and peripheral vascular resistance, resulting in an increase in afterload and a consequent overall reduction in stroke volume and cardiac output ^{34,73,91}. There are marked changes in modifiable risk factors for atherosclerosis that accompany hypothyroidism, including hyperlipidaemia and hypercholesterolemia (due to improper lipid metabolism), arterial stiffening, diastolic hypertension, and reduced production of eNOS ^{87,94}. These clinical diagnoses are reversible with the administration of thyroid hormone replacement therapy ⁸⁷. Patients can present symptoms such as dyspnoea on exertion, fatigue, and edema that may be the result of either pericardial effusion or CHF ⁶⁸. The effusion of the pericardial fluid may be misdiagnosed as CHF ⁸⁸. In most cases, patients with an underperforming thyroid are bradycardic ^{68,88}. Patients also have an increased incidence of hypercholesterolemia ⁸⁷ and hypertriglyceridemia ^{89,90}. Patients have an increased low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL), high-density lipoprotein (HDL) ⁸⁹ and apolipoprotein B-71 (Apo B⁷¹), and lipoprotein (a) (Lp[a] ⁹²) and these cholesterol levels can be lowered in these patients by administration of TH therapy ⁹³. Patients suffering from subclinical hyperthyroidism have also shown diastolic and systolic dysfunction during exercise, resulting in impaired exercise tolerance in these them ^{95,96}. According to a comprehensive analysis of databases by Rodondi N. et. al., subclinical hypothyroidism is associated with an increased risk of coronary heart disease and CHD-associated mortality in those with higher TSH levels, particularly those with a TSH concentration of 10 mIU/L or greater ⁹⁷. A clinical study by Kisse B. et al. in which hypertensive rats were treated with propylthiouracil (PTU) inducing hypothyroidism. They found that LV diameters in systole and diastole were increased, while wall thickness, ejection fraction, heart rate, and systolic blood pressure were decreased in these rats. Furthermore, TH dysfunction hypothyroidism in previously hypertensive rats led to systolic dysfunction and left ventricular (LV) dilation ⁹⁸.

This is in accordance with the clinical symptoms of patients suffering from hypothyroidism.

5. Therapeutic applications of THs in Cardiovascular diseases.

Cardiovascular protection by the application of THs is a novel route of therapeutic targeting for pharmacological intervention in both the acute and chronic phases of acute myocardial infarction, Heart failure, and abnormalities of the cardiovascular system. The main objective of cardioprotective therapies is to reduce or limit myocardial damage to avoid impairment of LV function, and several experimental and clinical studies have indeed proved its benefits^{12,86,99}. Cardiovascular protection is a complex phenomenon involving the stimulation of cell proliferation, neoangiogenesis, and metabolic adaptation, and in which the maintenance of mitochondrial integrity (as TH are critical regulators of tumour suppressor protein p53 which causes apoptosis of myocytes after accumulation)¹⁰¹ is a newly emerging field of research and its application in pharmacological therapies¹⁰⁰. In the trials conducted on animals, treatment of cardiomyopathy and subclinical hypothyroidism with thyroid hormones prevented progression of fibrosis and necrosis, loss of cardiac cells, and dilation and dysfunction of the LV^{104,105}. The up-and-coming role of thyroid hormones as a controller of the different molecular, tissue, and cellular elements requires further scientific analysis and exploration, particularly with accumulating data on the regenerative properties of thyroid hormones^{102,103}. The aims of cardioprotective therapies with thyroid hormones are to limit the extent of infarctions by reducing myocyte apoptosis through the activation of the cellular pathways that promote survival, PI3K/AKT, protein kinase C¹⁰⁶⁻¹⁰⁸, and by inhibiting p38 MAPK¹⁰⁹, as shown experimentally in rodent models of acute myocardial infarction treated with T3 and to limit LV post-ischaemic reconstruction through the antifibrotic and proangiogenic effects of thyroid hormones¹⁰⁰. Furthermore, T3 therapy induces the expression of hypoxia-inducible factor 1 α (HIF1A), which protects against reperfusion injury^{110,111}. Khalife WI. et. al. found that treating subclinically hypothyroid cardiomyopathic rats with THs

restored normal coronary blood flow, preventing LV dysfunction and loss of myocytes¹¹². Pingitore A. et al. showed that T3 supplementation in patients with ventricular dysfunction and low T3 syndrome reduced activation of the neuroendocrine system and improved left ventricle stroke volume¹¹³. Hamilton MA. et al. reported safe acute intravenous administration of T3 in patients with advanced heart failure¹¹⁴. We await further clinical studies and experimentation, which are crucial to evaluate the levels of safety and efficacy of THs for pharmacological administration; the currently available evidence suggests that thyroid hormone application is a promising therapeutic approach to heart failure and other cardiovascular ailments⁸⁶.

6. Conclusion

Thyroid functioning and the cardiovascular system are deeply connected. Thyroid hormones are vital for the normal functioning of the heart and the regulation of vascular physiological processes. This has been proved by the clinical studies, experimentation, and analysis which has spanned over decades. Knowing that thyroid hormones are essential for cardiovascular function, thyroid hormone supplementation therapy has been evaluated for the treatment of heart failure. Data analysis from epidemiological studies supports the fact of a higher risk of heart failure and a worse prognosis in heart failure in patients with low levels of thyroid hormones. Thyroid hormone therapy may provide promising results in the treatment of cardiovascular disease. TH therapy in patients with cardiovascular diseases having both a euthyroid sick state and hemodynamic abnormalities may prove to be helpful as the current data suggests it. Further clinical investigations are needed before routine replacement therapy can be recommended to treat patients with congestive heart failure, myocardial infarction, or those needing cardiac surgery.

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8. References

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