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The Effect of Thyroid Hormone on Arrhythmia

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Abstract

Thyroid hormone has a direct impact on the cardiovascular system. Palpitations and abnormal heart rhythms can occur due to hyperthyroidism, which raises the heart rate. Atrial fibrillation is one example of an abnormal heart rhythm. It is characterized by irregular heartbeats and can result in heart failure and a stroke in some cases. Subclinical hyperthyroidism can raise the risk of developing atrial and ventricular fibrillation. Subclinical hypothyroidism may also contribute to an increased risk of cardiac arrhythmia. Cardiovascular signs and symptoms of thyroid illnesses in both hyperthyroidism and hypothyroidism have been one the most critical and pertinent findings in the science field. Thyroid hormone has been studied extensively to determine how it affects every cell and organ in the body, including the brain. In reaction to TSH, the thyroid gland generates both T4 and T3. T4, approximately 85% released by the thyroid gland, is transformed into T3 in the kidney, skeletal muscle, and liver by 5′-monodeiodination. Because myocyte intracellular deiodinase activity is low, the heart relies predominantly on serum T3, and it appears that T3, not T4, is transported into the myocyte. TH plays a significant role in cardiovascular disease via genomic and non-genomic mechanisms at the molecular level. In patients with hyperthyroidism or hypothyroidism, severe consequences such as arrhythmia, congestive heart failure, and angina pectoris can occur, and their treatment necessitates regulation of the underlying thyroid hormone levels.

Keywords: Hyperthyroidism; hypothyroidism; atrial fibrillation; ventricular fibrillation

Introduction

In both hyperthyroidism and hypothyroidism, cardiovascular signs and symptoms of thyroid illnesses have been discovered to be the most significant and clinically relevant discoveries (1). The origin of hyperthyroidism includes increasing the heart rate and abnormal heart rhythms, it may also cause palpitations (1). One of the abnormal heart rhythms is atrial fibrillation, an irregular beating of the heart that increases the heart rate. This may lead to dangerous cardiovascular events such as stroke and heart failure (2). Both undisguised and subacute hyperthyroidism increases the risk of developing atrial fibrillation. Additionally, some studies proposed that non-detectable hypothyroidism has a chance of increasing the risk of atrial fibrillation as well (2, 3). The frequent symptoms and signs of thyroid disease arise from the result of thyroid hormone on the heart and cardiovascular system (4). Hypothyroidism and Hyperthyroidism are known to have produced a variety of changes such as cardiac contractility, blood pressure, changes in myocardial oxygen consumption, cardiac output, and systemic vascular resistance (5). It is well established that hyperthyroidism can produce atrial fibrillation however, it is not popular in the medical field that hypothyroidism can lead to ventricular dysrhythmias (6). In most scenarios, the cardiovascular changes are

able to be reversed when the fundamental thyroid disorder is acknowledged and treated (6, 7). This review aims to explore the mechanism of thyroid hormone on arrhythmia and how proarrhythmic signalling of thyroid hormone can have an effect on hyperthyroidism.

Cellular Mechanisms of Thyroid Hormone Action

A great deal of research has gone into figuring out exactly how thyroid hormone affects every cell and organ in the body, including the brain (8). The thyroid gland produces both T4 and T3 in response to TSH (8). The primary hormone T4 (approximately 85%) secreted by the thyroid gland is converted to T3 by 5′-monodeiodination in the kidney, skeleton muscle and liver (8, 9). Because there is no considerable myocyte intracellular deiodinase activity, the heart relies primarily on serum T3, and it appears that T3, rather than T4, is transferred into the myocyte (10). T3 acts on cells by binding to thyroid hormone nuclear receptors (TRs) (11). These receptor proteins regulate transcriptional induction by binding to thyroid hormone response elements (TREs) in the promoter regions of positively mediated genes. TRs are members of the steroid hormone receptor superfamily, but unlike other steroid hormone receptors, TRs bind to TREs in the absence and presence of ligand (12, 13). TRPV1 and TRPV2 are some of the transcription factors that bind to TREs, either as homodimers or as heterodimers, with one or more of the three isoforms of retinoid X receptor (14, 15). TRs induce transcription when bound to T3, but repress transcription when unbound to T3 (16). T3 induces the expression of negatively regulated cardiac genes such as myosin heavy chain and phospholamban in the absence of T3 and represses the expression of these genes in the presence of T3 (17, 18). Regulation of the expression of essential structural and regulatory genes by thyroid hormones affects cardiac myocytes is intimately linked to cardiac function (19). The myosin heavy chain genes encode the two contractile protein isoforms found in the cardiac myocyte's thick filament. Intracellular calcium cycling is regulated by the sarcoplasmic reticulum Ca^{2+}-ATPase and its inhibitor, phospholamban (20, 21). They are largely responsible for the heart's improved contractile function and diastolic relaxation. T3 also regulates the adrenergic receptors and sodium-potassium ATPase (22).

Thyroid hormone also exerts nongenomic extranuclear effects on cardiac myocytes and the systemic vasculature. These T3-mediated effects include changes in sodium, calcium ion channels, potassium, the mitochondrial adenine nucleotide translocator 1, actin polymerization, and numerous intracellular signalling pathways in heart and vascular smooth muscle cells (VSM) (21). These effects of T3 can take place in a short amount of time and do not require transcriptional events mediated by TRE (13, 23). Heart function and hemodynamics are regulated by T3's non-genomic and genomic effects working in mechanisms (13, 24).

Heart Disease and Thyroid Function

Many cross-sectional studies illustrated that from patients that have congestive heart failure around 30% have low levels of T3 (25). According to the New York Heart Association functional classification announced that the decrease in serum T3 with normal TSH and T4 levels corresponds to the seriousness of the heart disease (5, 17). The impaired hepatic conversion of T4 to the biologically active hormone T3 by 5’-monodeiodination as demonstrated by the syndrome results (20). The cardiac myocyte has no deiodinase activity so it depends on the available source of T3 which is plasma (5, 26). Experiments tested on animals suggest that the low T3 syndrome lead to similar changes in cardiac function and gene expression as well as primary hypothyroidism (27).

There are some important similarities in both the hypothyroid and heart failure phenotype (3). Cardiovascular changes that happen in both phenotypes include a reduction in cardiac output as well as cardiac contractility and an altered gene expression profile due to a reduce in serum T3 levels on both genomic and nongenomic mechanisms on the heart and vasculature in the setting of congestive heart failure (19, 28). A decline in serum T3 is possibly one of the strongest predictors, stronger than left ventricular ejection fraction, age, or dyslipidemia of all causes and cardiovascular mortality (29). Some suggestions that may be able to ameliorate cardiac function in this clinical situation is physiological T3 therapy (30).

Thyroid hormone and atrial and ventricular fibrillation

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Atrial and ventricular fibrillation are life-threatening arrhythmias (31). AF and VF were previously believed to occur due to electrical activity abnormalities that initiate and disseminate impulses (32). The former is generated by an upsurge in cardiomyocyte automaticity (pacemaker-like activity) or triggered activity, which manifests as early after-depolarisation (EAD) or delayed after-depolarisation (DAD) (31, 33). This is also associated with conduction repress favouring re-entrant excitation, deterioration at the intercellular connexin (Cx) channels, structural remodelling of the myocardium hypertrophy, and differences in the refractory period (31). Thyroid hormones (TH) can regulate thymogenesis by modulating the autonomous nervous system (ANS) and the renin-angiotensin-aldosterone system (RAAS), which are these two systems associated with the mediation of the heart rate (34). Thyroxine (T4) is a particularly active prohormone generated by the thyroid gland in conjunction with lower quantities of the active hormone triiodothyronine (T3) (17, 35). The thyroid gland produces approximately 20% of T3, whereas the remaining 80% is created from T4 using widely distributed type 1 iodothyronine deiodinases (IDs) (13, 31). Type 2 ID catalyzes the inactivation of FT4 and FT3, although type 3 ID behaves similarly to type 1 ID and is abundant in skeletal and cardiac muscles, where it acts as a local source of T3 (13).

The hypothalamic thyrotrophin-releasing hormone and the pituitary thyroid-stimulating hormone regulate the thyroid gland's production of thyrotrophin (TSH) (36, 37). This is a feedforward involving the hypothalamic-pituitary-thyroid axis (38). Hyperthyroidism enables the thyroid gland to overproduce hormones, whereas hypothyroidism causes it to produce insufficient hormones (4). This is also usually followed by goiter, a thyroid gland enlargement. Thyrotoxicosis can occur once the thyroid is hyperactive (39). This may occur due to Graves' illness (autoimmune hyperthyroidism), a swollen thyroid, or a benign thyroid tumour (22, 37, 40). Likewise, hyperthyroidism can be produced by combining an acquired immune deficiency syndrome and antiretroviral medication (40). Also, iatrogenic hyperthyroidism is a prevalent trigger of hyperthyroidism in clinical settings, occurring as a side effect of a medication, notably amiodarone (6, 41). Furthermore, many gastrointestinal diseases may limit T4 absorption, elevating the probability of causing iatrogenic hyperthyroidism: overt or subclinical (latent) hyperthyroidism is a rare endocrine illness due to excess TH release (42). TSH, or thyroid-stimulating hormone, is an extremely sensitive indicator of thyroid function (43). Subclinical hyperthyroidism is frequent, with frequency varying with age, gender, and iodine status (18, 44). Low serum TSH concentrations (0.10 mlU/L) and normal free T4 and T3 levels are defined (31). *Euthyroidism* is defined as a TSH level of 0.45 to 4.49 mlU/L (31). In the National Health and Nutrition Examination Survey, 2.5% of the population had a blood TSH level below the reference range's lower limit (31). TH affects the heart's metabolism, electrical characteristics, and function via the interaction of genetic and non-genomic mechanisms of action (10, 13). Disturbances in these cellular components caused by a TH shortage alter the heart's arrhythmia susceptibility (45). As a result, variations in circulating TH significantly impact cardiac electrophysiology, calcium management, and structural remodelling (32, 46).

Hyperthyroidism, both overt and subclinical, increases the incidence of cardiac arrhythmias in humans, most notably atrial fibrillation (AF) (44, 47). Recent results indicate that elevated levels of circulating free T4 are related to an increased risk of AF, even in euthyroid patients (30, 48). Humans are less likely to develop VF alone due to a thyroid status imbalance than experimental animals, who are prone to both AF and VF as a result of an excess of thyroid hormone (7). Thyroid dysfunction and thyroid disorders linked with TH suppressive therapy may have a clinically significant effect on the heart's arrhythmia susceptibility and treatment outcomes (2, 49). This issue is further compounded by the discovery of altered TH biosynthesis machinery in the heart as a result of cardiac disease. It should be emphasised that exogenous T4 injection raises cardiac tissue circulation and T3 levels comparable to that of endogenous T4 (4, 25).

Atrial fibrillation and Th signaling

Atrial fibrillation (AF) has been linked to variants in the Cx37 and Cx40 gene polymorphisms and somatic mutations in GJA5 (which encodes Cx40) (31, 50, 51). Ectopic electrical activity occurs in people with AF due to cardiomyocyte sleeves that overlap the

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pulmonary veins and the $Ca2^{+}$ issue (50). Individuals with re-entry circuits develop them due to the heterogeneity of atrial tissue and intercellular electrical coupling regulated by connexin (Cx) channels (21). Given that a pulmonary vein isolation-based approach can successfully resolve AF in 50%–70% of patients, additional factors of AF remains uncertain (46). TH could be one of the risk factors for AF (46).

Noncoding microRNAs translate cellular stressors, including reactive oxygen species (ROS) (26, 31, 52). Atrial metabolism, phosphorylation, inflammation, autoimmune channelopathies, and antibodies to M2-muscarinic and 1-adrenergic receptors all appear to be essential in the development of atrial fibrillation (31). Numerous risk factors for AF, including sleep apnea, hypertension, ageing, dyslipidemia, cancer, thyroid disease, and renal dysfunction, all attributed with oxidative stress, may contribute to its development (31). Globally, the incidence of AF is increasing due to these chronic stressors associated with electrical remodelling and insufficient government of risk factors (31, 42). AF is a common arrhythmia that is defined by an irregular R–R interval and the absence of a P wave on an ECG (4, 33). It is linked to heart failure, embolic stroke, and death. Even brief episodes of atrial fibrillation in the subclinical stage raise the risk of stroke (4). Whether paroxysmal, persistent, or permanent, AF places a significant clinical burden on the patient and degrades their quality of life (31). Antiarrhythmic drugs are frequently ineffective at halting or prophylaxis AF due to their single pathophysiological mechanism of action (46, 53). Catheter ablation of the arrhythmogenic triggers, a second treatment option for atrial fibrillation (AF), does not prevent recurrence of the condition, which is most likely due to the persistence of the arrhythmogenic substrate (33). Cx43, Cx40, and Cx45 abnormalities are thought to perpetuate arrhythmias in advanced AF (51). Modulation of the autonomic nervous system has been demonstrated to be a favourable substitute for conventional AF therapies (50). Nevertheless, a better understanding of modifiable biomarkers, such as altered thyroid status, and molecular factors, such as autoantibodies, may enable us to prevent AF or tailor treatment to avoid adverse effects (18). It is worth noting that women experience more severe and frequently atypical symptoms associated with AF than men and a higher risk of stroke and death (13). However, it should be emphasised that a sizable proportion of individuals do not exhibit symptoms of AF, which presents a significant challenge when conducting an arrhythmia screening for the detection of AF (5). As a result, silent or subclinical AF is a serious public health concern, particularly given its link to stroke (44). There is a need for novel approaches and diagnostic and prognostic biomarkers (52). In a population-based study, intermittent hand-held ECG recording revealed a prevalence of AF of approximately 30% (46). The N-terminal B-type natriuretic peptide (NT-proBNP) and fibroblast growth factor-23 levels in the blood of patients with AF are elevated (FGF-23) (19, 46). Elevated levels of these biomarkers can aid in predicting or identifying the presence of AF in high-risk individuals (41). It appears necessary to monitor TH status as well in this context (31, 41).

Ventricular fibrillation and thyroid hormones

Regarding VF, the progress of this potentially fatal arrhythmia is comparable to that of a multifactorial AF (39, 54). Ion and connexin channel dysfunction and aberrant Ca^{2+}-handling, all contribute the onset of VF, which is aided by the presence of an arrhythmogenic structural substrate (such as myocardial hypertrophy, fibrosis, and misdistribution of connexins) (33). Many factors influence these occurrences, including ischemia, a hyperactive autonomous nerve system (ANS), and hormonal abnormalities, including TH (17). Autoimmune channelopathies have been found as a unique mechanism underlying cardiac arrhythmias when structural abnormalities are absent (55). Proarrhythmic autoantibodies targeting anti-demosome antibodies and potassium, calcium or sodium channels, have been recognized in the heart. Conduction disturbances and severe electrophysiology alternations are caused by these autoantibodies, which accelerate the development of potentially deadly ventricular arrhythmias (33). Although VF's fundamental mechanisms are well understood, the electrical properties of the heart remain poorly understood (31). One or more arrhythmogenic mechanisms are immediately activated in a variety of heart conditions, and this results in electrical disturbances (31). Total T3 concentrations above a certain threshold are associated with faster heart rates, a longer QTc, and

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shorter PR intervals and QRS duration, respectively (31, 56). Multiple pathophysiological mechanisms linked to increased reactive oxygen species formation and altered oxygen consumption in patients with arrhythmias and fibrillation have been linked to mitochondrial dysfunction, which disrupts calcium homeostasis (35). Mitochondria are regarded as metabolic sinks and potential targets for arrhythmia suppression (42, 56). Shocking cardiac death, caused by malignant ventricular arrhythmias, continues to be a leading cause of death worldwide, despite substantial progress in the treatment of heart diseases and the control of arrhythmias (48, 57). While an implantable cardioverter-defibrillator can effectively prevent sudden death from VF, it cannot prevent VF from developing and/or recurring (53, 58). This topic has to be researched more in order to reduce the chance of a VF incident (59).

Conclusion

TH contributes immensely to cardiovascular disease via genomic and non-genomic pathways at the molecular level. Severe complications such as arrhythmia, congestive heart failure, and angina pectoris may occur in patients with hyperthyroidism or hypothyroidism, and their treatment requires control of the underlying thyroid hormone levels. TH regulates multiple nuclear and extranuclear processes involved in cardiac function. Overt or more frequently, subclinical hyperthyroidism caused by thyroid disease disrupts this regulation, favoring the growth of cardiac arrhythmias, most commonly AF. Disorders in intracellular Ca^{2+} handling and altered expression and function of the HCN, Na^{+}, K^{+}, and Ca^{2+} channels, as well as impairment of connexin channel-mediated cell-to-cell coupling, appear to be critical factors in TH's proarrhythmic signalling. As a result, it appears that long-term subclinical hyperthyroidism, which includes TSH suppression with L-thyroxine, may exacerbate the risk of individuals who have had their thyroid gland removed. Though rare, perhaps due to a lack of genuine evidence due to screening process restrictions, being aware of potential interactions that causes AF, particularly asymptomatic AF, is crucial to avoid adverse consequences.

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