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An Overview of Influence of Thyroid Hormones on Cardiovascular Function

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Abstract

It has been very clearly established that thyroid hormones have a specific influence on cardio-vascular system. Hyper- or hypothyroidism induces cardiovascular disorders, atrial and ventricular arrhythmias, atherosclerotic vascular diseases, dyslipidemia and heart failure. Heart failure results from the impairment of ability of the ventricle to fill with or eject blood. Thyroid hormones contribute to cardiovascular events by directly acting on the cardiomyocyte via genomic and nongenomic pathways. Thyroid hormones play a critical role in maintaining cardiac homeostasis. Fluctuations in thyroid hormones due to hyper- or hypothyroidism has an adverse effect on the heart. Thyroid hormones have a direct influence on myocardial contractility, systolic and diastolic blood pressure, heart rate, heart mass, ejection fraction and heart output. Hyperthyroidism stimulates high cardiac output with low systemic vascular resistance and is associated with faster heart rate and increased left ventricular systolic and diastolic function and supraventricular atrial fibrillation. Hypothyroidism has an opposite effect on the heart rate and myocardial contractility. Hypothyroidism reduces cardiac repolarizing of K^+ currents such as transient outward potassium current and increase in L-type calcium current. Alterations in Thyroid Stimulating Hormone level bring about cardiac electrical disturbances. Subclinical hypothyroidism is associated with increased heart rate, atrial arrhythmias, LV mass and impaired ventricular relaxation, and increased risk of mortality due to cardio-vascular impairment. In this overview, with the available information and publications, the physiological and patho-physiological relationships between thyroid hormones and the cardiovascular system are discussed.

Keywords: Cardiovascular System, Hyperthyroidism, Hypothyroidism, Smooth Muscle Cells of the Vascular System, Subclinical Hypothyroidism, Thyroid Hormones, Thyroid Hormone Receptors, Thyroid Stimulating Hormone, Ventricular Contractions

1. Introduction and General Perspectives

Thyroid hormones are synthesized and secreted by the thyroid gland which is stimulated by Thyroid Stimulating Hormone (TSH) secreted by the pituitary gland. TSH, in turn, is regulated by the Thyrotropin Releasing Hormone (TRH) secreted by the hypothalamus. About 90% of the thyroid hormone secreted is Thyroxine (T4) and the rest is Tri-iodothyronine (T3). T3 is 20 times more potent than T4 and is the biologically active hormone. Most of the T3 is generated peripherally by the conversion of T4 by deiodinases, the enzymes further responsible for converting T3 into the inactive isomers, reverse T3 (rT3) and 3, 3'-di-iodothyronine (T2)[1,2].

There are three deiodinases with different roles. Type-1 deiodinase (D1) is localized in the plasma membrane and is expressed in the liver, thyroid and kidney. It is mainly responsible for the peripheral conversion of T4 into T3. Type 2 deiodinase (D2) is more efficient than D1. It is expressed in the brain, pituitary gland and skeletal muscle, and regulates the intracellular concentration of

T3 by converting T4 into T3. Type 3 deiodinase (D3) irreversibly inactivates T3 by converting it into T2 or rT3. D3 is considered is an important regulator of thyroid axis[3].

Thyroid hormones are active when not bound with Thyroid hormone Binding Proteins (TBP) and variations in binding proteins can change the peripheral availability of thyroid hormones[4-8]. Thyroid hormones must bind to their receptors to exert their action. These receptors are intra-cellular DNA binding proteins which bind as hormone-receptor complexes to Thyroid hormone Receptor Elements (TREs) in the regulatory region of target genes[5].

Thyroid hormones modulate important functions in the growth, development and metabolism of a variety of tissues and there are different sub-types of receptors as TR alpha 1, TR alpha 2, TR beta 1 and TR beta 2. In the myocardium TR alpha 1 is most expressed and regulates important genes involved in cell growth, contractile function and electrical activity[5,6].

TR-beta-1 is expressed at a lower level in the myocardium and TR-alpha-2 does not bind T3 but is able to bind TRE and exerts negative effect on gene expression[6].

Thyroid hormones play a pivotal role in maintaining cardiac homeostasis. Even subtle changes in the circulating thyroid hormones exert a significant influence on cardiovascular system. Myocardial and vascular endothelial cells have receptors for thyroid hormones. Such influences are manifested in blood volume, heart rate, cardiac output, systemic vascular resistance, and left ventricular ejection fraction[7]. The cardiovascular risks caused by thyroid dysfunction and acute and chronic cardiovascular diseases are known to alter thyroid hormone metabolism which further contributes to cardiovascular impairment.

Thyroid hormones have molecular and cellular mechanisms Thyroid hormones affect cardiovascular system through genomic as well as non-genomic mechanisms on cardiac myocytes. The genomic effects are mediated by transcriptional activation or repression of specific target genes which encode structural and functional proteins[9]. The biologically active thyroid hormone, T3, enters into the cardiomyocytes through specific transport proteins located in the cell membrane. There is no evidence of conversion of T4 to T3 in cardiomyocytes[10].

In the cardiomyocyte T3 arrives at the nucleus and interacts with the specific transcriptional activators, the nuclear receptor alpha-1 or nuclear receptor alpha-2. When T3 engages with these receptors there is recruitment of cofactors and this hormone-receptor complex binds or releases specific sequences of DNA which are thyroid responsive elements and they act on *cis* or *trans* regulators and modify the rate of transcription of specific target genes[11].

There are various proteins whose expression is modulated at transcriptional level. The myosin heavy chains and the sarcoplasmic reticulum proteins are involved in the regulation of intracellular calcium handling calcium activated ATPase and its inhibitory cofactor, phospholamban[12-15]. In humans, the beta isoform of the myosin heavy chain is more prevalent than alpha isoform[16].

In subjects with thyroid dysfunction, the calcium activated ATPase and phospholamban involve primarily in the regulation of systo-diastolic calcium concentrations in cardiomyocytes[9,12].

The rate of calcium uptake into the lumen of the sarcoplasmic reticulum is due to the calcium activated ATPase during diastole and is a major determinant of the velocity of the myocardial relaxation after contraction[1,9]. The calcium-activated ATPase activity of the sarcoplasmic reticulum is influenced by the level of expression of phospholamban as it is shown that higher phospholamban expression lowers calcium activated ATPase of sarcoplasmic reticulum[12]. Thyroid hormone up-regulates the expression of calcium activated ATPase of sarcoplasmic reticulum and down-regulates the expression of phospholamban, enhancing myocardial relaxation[9,12,16,17]. Increase in calcium uptake during diastole may favor myocardial contraction. At the end of diastole, greater reduction in cytoplasmic calcium increases the magnitude of the systolic calcium. This influx of calcium is helpful in the activation of tropomyosin units.

The expression of ion channels, Na^+/K^+ activated ATPase, Na^+/Ca^{++} exchanger and some voltage-gated[18] K^+ channel-Kul-5, KV-4.2 and KV.4.3 are found to be modified by thyroid hormones, which coordinate the chemical and mechanical responses of the myocardium[19,20,110-112].

The contractile apparatus of the cardiac myocytes has two sub-types of myosin heavy chains (MHCs, alpha MHC and beta MHC, the fast and slow myosins, respectively, and T3 up-regulates alpha MHC and down-regulates beta MHC.[21]. Therefore, it is presumed that hypothyroidism induces myocardial fetal gene

reprogramming which stimulates the expression of beta MHC and also inhibition of the expression of alpha MHC and also inhibition of calcium- activated ATPases in the sarcoplasmic reticulum[22]. This has a substantial implication on myocardial function and subsequent progression to heart failure[23].

Thyroid hormones exerts changes in cardiac ionotropism and chronotropism quite rapidly than regulation of gene expression which normally takes minutes to have to be phenotypically and functionally discernable[24,25]. This suggests an involuntary non-genomic mechanism.

Thyroid hormones promote the acute phosphorylation of phospholamban, and this action attenuates the inhibitory effects of phospholamban on calcium activated ATPase of sarcoplasmic reticulum[16,26]. This process is mediated at least in part by the activation of intracellular kinase pathways involved in the signal transduction of adrenergic stimulus[26]. Even though most of the cardiovascular manifestations associated with hyper- and hypothyroidism mimic a condition of increased adrenergic activity, the sensitivity of the cardiovascular system to adrenergic stimulation does not seem to be substantially altered in these conditions[27,28]. Thyroid hormones reduce peripheral vascular resistance by promoting relaxation of vascular smooth muscle cells[29-31].

2. Hypothyroidism

The blood levels of TSH are elevated with a decrease T3 and T4 in the hypothyroid state. One of the symptoms elicited is bradycardia, with systemic hypertension with narrow pulse pressure and mild increase in mean arterial pressure[32,33].

In most of the hypothyroid subjects, abnormal standard ECG, which includes lengthening and flattening of QT interval and inversion of T wave, manifesting prolonged cardiac action potential and prone in ventricular arrhythmias due to increased electrical dispersion in the myocardium[33,34]. Systemic hypertension is associated with higher blood pressure which is due to increase in peripheral vascular resistance and arterial stiffness[33-35]. Impairment in LV diastolic function is the most recognized abnormality in hypothyroid patients which is characterized by slowed myocardial relaxation and impairment with early ventricular filling. On the other hand, LV systolic function is only marginally affected with reduced values of ejection fraction and stroke volume. In hypothyroid state, the reduced cardiac preload with bradycardia and depressed myocardial contractility results in sub-normal cardiac output[36,37].

There is lower myocardial oxygen demand with worse myocardial mechanical work efficiency in hypothyroidism. The increased cardiac after load is one of the major factors of myocardial oxygen consumption. This may, to some extent, worsen angina in some of the subjects with ischemic heart disease[38,39]. Diastolic heart failure is known to be more associated in women with hypothyroidism[40].

3. Sub-clinical Hypothyroidism

The serum TSH levels are elevated with normal values of T3 and T4, which is common in the elderly people and in women over 60 years and in a majority of the patients serum TSH is between 5 to 10 uIU/ml and if thyroid antibodies are expressed, some of them may progress towards hypothyroid state. Subclinical hypothyroidism is classified as grade I where TSH is more than 4.00 to 4.50 mIU/ml but lesser than 10 mIU/ml. In grade 2 hypothyroidism, TSH is more than 10 mIU/ml[41]. It is observed that resting heart rate and blood pressure are normal in these patients but significant hypo-functional abnormalities in the parasympathetic nervous system and prevalence of systemic hypertension have been reported[2,43]. Sub-clinical hypothyroid state is associated with a higher risk of heart failure, morbidity and mortality[42,43].

A relationship between subclinical hypothyroidism and atherosclerotic cardiovascular disease independent of hypercholesterolemia and hypertension in post-menopausal women, reported in the Rotterdam study[44-46] have evidenced that there is increase in total and low density cholesterol, homocystine and elevated levels of oxidized low density lipoproteins[42,43]. Reduced endothelium-dependent and flow-mediated vasodilatation has been reported in subclinical hypothyroidism which is considered as an early hallmark of atherosclerosis[47]. Sub=clinical hypothyroid state may affect the haemostatic profile, and promote hyper-coagulable state[48].

Sub-clinical hypothyroidism is reported to increase peripheral insulin resistance and activate prothrobalic pathways and hypercoagulability[49].

Non-Thyroidal Illness Syndrome (NTIS), euthyroid sick syndrome or low T3 syndrome, there occurs a rapid decline in free thyroid hormone levels with marked elevation of reverse T3 (rT3) with normal range of TSH. In the underlying mechanism of this syndrome there is a reduced activity of deiodinase which coverts T4 to T3 with an increase in deiodinase (D3) which coverts T4 to rT3[50]. It is known that deiodinase 1 is the main pathway for rT3 clearance and due to the decrease in deiodinase 1 activity, an increase in rT3 is encountered[51].

In patients who are critically ill, the deiodinase 1 activity is down-regulated in the liver, and deiodinase 3 activity in the liver and skeletal muscle which contributes for the NTIS syndrome[52] In NTIS the decrease in T3-dependant gene expression is independent of circulating T3 level, which may suggest that after an ischemic heart event there is a potent and stable induction of deiodinase 3 in cardiac myocytes, resulting in local cardiac hypothyroidism[41].

In inflammatory responses one of the main events in NTIS is deiodinase 3 over-expression[53]. In subjects with acute myocardial infarction, there is an increase in Inerleukin-6 (IL-6) which is linked to decrease in T3[54]. IL-6 inhibits 5 deiodinase activity which reduces the conversion of T4 to T3[55]. Hypoxia also contributes to decrease of T3 as it stimulates hypoxia-induced factor-1 (HIF-alpha) which activates deiodinase 3 in myocardium[56].

NTIS is often associated with depressed myocardial function and is a strong predictor of mortality in heart diseases both in acute and chronic conditions[57]. Low T3 levels are also associated with dilated cardiomyopathy and 20-30% of the patients with this pathology have NTIS[58].

4. Hyperthyroidism

In hyperthyroidism TSH is subnormal and T3 and T4 levels in circulation are increased. Palpitations are commonly encountered in hyperthyroid subjects. The ECG monitoring for 24 hours indicate increase of heart rate[59,60]. Sympathetic vagal unbalancing with a relative increase in sympathetic tone is found in these subjects. Thyroid hormones can directly affect sinus node firing[61]. Hemodynamic changes with increase in cardiac output and reduction in peripheral vascular resistance have been reported.[62-64] Enlarged blood volume and increase in renin-angiotensin-aldosterone system are seen in hyperthyroid subjects[65,66]. Erythropoietin secretion is enhanced which in turn, with increase in blood cell mass, results in increased total blood volume in the hyperthyroid state[68].

Independent of the heart rate, an increase in early LV filling and a faster LV relaxation occurs in hyperthyroid state[69-71]. Through the advantageous modulation of hemodynamic loads, heart of hyperthyroid cases increases its performance[72]. This mechanism of utilizing myocardial contractility requires higher metabolic demand[73]. Reduced exercise tolerance is common in hyperthyroid state which may be due to reduced cardiovascular reserve[71]. The occurrence of atrial fibrillation in hypothyroid state may lead to Congestive Heart Failure (CHF). It is reported that the loss of atrial contribution to ventricular filling and reduced diastolic time may severely compromise diastolic dynamics to promote systemic congestion[74].

5. Subclinical Hyperthyroidism

In subclinical hyperthyroidism, normally subnormal or suppressed TSH in serum with normal thyroid hormones is seen[72]. The endogenous subclinical hyperthyroidism is suspected to be due to an intrinsic pathology of thyroid gland. The exogenous subclinical hyperthyroidism is due to suppressive replacement of L-Thyroxine (LT4) therapy.

Increased heart rate, supra-ventricular arrhythmias and enhanced LV mass are the mostly evident symptoms in subclinical hyperthyroid subjects. This is mostly associated with slightly enhanced systolic function with impaired diastolic function due to slowed myocardial relaxation[75-82]. The increase in LV mass is due to the increased wall thickness without changes of cavity dimension and it is said that this rarely corresponds to an actual LV hypertrophy and is related to the duration of subclinical hyperthyroidism rather than circulating thyroid hormone levels. It is assumed that the increase in LV mass is a response to a chronic hemodynamic overload due to the mild hyperkinetic cardiovascular state[79,83].

The abnormalities of LV morphology and function are returned to normal after attaining euthyroid state as with beta blocker drugs. Therefore, the cardiac involvement in subclinical hyperthyroidism is reversible and is mostly a functional mechanism[72,74,75]. The subclinical cardiac involvement is reversible as it is mostly due to functional mechanisms.

Subclinical hypothyroidism is accompanied by increased cardiovascular mortality[80]. In elderly subjects

with hypothyroidism there is increased risk of atrial fibrillation[81,82] and this may result in increased incidence of thromboembolic events[14,83]. The increase of LV mass even in the absence of clear LV hypertrophy and of the heart rate is associated with increased risk of sudden death[84,85]. Diastolic dysfunction may precede the development of more severe LV dysfunction. In elderly subjects, it may precipitate cardiac decompensation and CHF[70].

6. Elevated TSH in Subclinical Hypothyroidism

Functional TSH Receptors (TSH-R) are demonstrated in human heart and cultured cardiomyocytes[86,87]. In a patient with Grave's disease with cardio-myopathy and heart failure[88] TSH-R mRNA was identified in the heart using RT-PCR and DNA sequencing[87,88]. Therefore, it is derived that TSH and TSH-R antibodies act not only in thyroid tissue but also in other tissues including orbital tissue[89]. TSH–R mRNA was detected in the heart. Autoimmunity against TSH-R contributes to cardiomyopathy and ophthalmopathy[87-91].

TSH receptors are present in follicular cells of thyroid since. They are the major targets for TSH action. TSH receptors are detected in adiposcytes, hepatocytes, lymphocytes and fibroblasts as well[92-95]. TSH Receptors are active in ventricular myocytes[90,96-98]. TSH directly modulates cardiac electrical activity. In hypo- and subclinical hypothyroidism it is seen that there is reduction in cardiac repolarizing K^+ currents such as transient outward potassium current [I(to)] and increase in the L-type calcium current [I(Ca-L89)][99-102]. A correlation has been found between elevated serum TSH and repolarization abnormalities in hypo- and subclinical hypothyroidism[91,92,110-112]. Earlier, it was presumed that low T3 in hypothyroidism induces electrical abnormalities in the heart but now it has been shown that TSH is also involved in the cardiac electrical disturbances also[90,110-112].

7. Autoimmune Thyroid Disease and the Heart

It is seen that there is elevated glycosaminoglycan production in the orbital space, preorbital space and cardiac valves in patients with thyroid autoimmunity[105]. The glycosaminoglycans are long unbranched polysaccharide chains and composed of repeated disaccharide units. After their synthesis in the fibroblasts, most of them are released into the extracellular matrix and, since they are hydrophilic, they attract large amount of water and thus form hydrated gels even at low concentrations[106,107]. They accumulate in the cardiac valves leading to thickening of the leaflets. There is also additional synthesis of collagen which causes prolapse of redundant and thickened mitral valves into the left atrium, which is prevalent in patients with immunothyroiditis (36%) and in Grave's disease (33%). Mitral regurgitations are found in 28% of patients with thyroiditis, 22% of patients with myxomatous aortic valves and 6% of patients with myxomatous tricuspid valves[108,109].

8. Conclusion

Thyroid hormones influence cardiovascular system. Excess or low thyroid hormones induce cardiovascular disorders such as atrial and ventricular arrhythmias, atherosclerotic vascular diseases, dyslipidemia and heart failure. Heart disease is one of the major causes of death. Heart failure results from the impairment of ability of the ventricle to fill with or eject blood. Thyroid hormones contribute to cardiovascular physiology and they directly act on the cardiomyocyte through genomic and non-genomic pathways. Thyroid hormones play a major role in maintaining cardiac homeostasis. In addition the direct action of TSH in the heart, implications of autoimmune thyroid diseases on the heart valves are explained. From the available literature, the various impacts of hypo- or hyperthyroidism on the cardiovascular patho-physiology are presented.

9. References

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