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Heart Follows Thyroid

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Abstract

In humans both hyper- and hypothyroidism can have different clinical manifestations. Among these symptoms, there is a numerous group dealing with the cardiovascular system. Thyroid hormones affect the hemodynamic state of organism and regulate expression of some cardiomyocyte structural genes. Thyroid disorders may also contribute to accelerate the underlying heart problems. Unfortunately, since thyroid dysfunction remains undiagnosed, cardiological treatment is not effective enough. In this paper, the authors show and explain the main cardiac consequences of an overactive and underactive thyroid gland. Additionally, some new data about thyroxine application in cardiac remodeling and fetal phenotype creation as a result, are included in this review.

Keywords: Thyroid hormones; Hyperthyroidism; Hypothyroidism; Cardiovascular system

Introduction

Thyroid gland disorders are most frequently endocrinological disturbances. Their prevalence varies according to the studied population. In Poland hyperthyroidism is present at 1-2% and hypothyroidism at 1-6 % until the age of 60 years [1]. According to the PolSenior Study, thyroid disturbances are present in over 10% of people from the age of 55 (hyperthyroidism – 2,95% and hypothyroidism – 7,95%) [2]. Among the US population it was shown, that 4.6% of them suffer from hypothyroidism (0.3% clinical and 4.3% subclinical) and 1.3% had hyperthyroidism (0.5% clinical and 0.7% subclinical) [3]. The main cause of hyperthyroidism is Graves' disease (60-80% of all hyperthyroidism) with a peak onset at 20-50 years [1]. Hypothyroidism, in areas of iodine sufficiency is in most cases caused by Hashimoto's thyroiditis [4]. Thyroid disturbances are more common among women. From 6 (in hypothyroidism) to 10 (in hyperthyroidism) more times it is more likely to occur in woman [1]. Thyroid hormones are one of many most important hormones strongly affecting cardio-vascular system [5,6]. The hemodynamic effects of hyperthyroidism are opposite to those connected with hypothyroidism, but the later may be less obvious in clinical symptoms, at least at the beginning of disease. Moreover, for those with existing cardio-vascular disease (CVD), disorders of the thyroid gland can worsen old cardiac symptoms or cause new ones [7]. This review integrates some mechanisms of thyroid hormone action in cardiomyocyte and show how hormone insufficiency and excess can impact on cardio-vascular system. Some new data have also been reporter regarding the possibility of heart remodeling process with the help of thyroid hormones delivery.

Physiology of Thyroid Gland

Thyroid gland (lat. glandula thyroidea) is an unpaired endocrine organ regulating all the metabolic processes in the human body. It's located in the lower front part of the neck and consists of two lobes. Their upper border reaches the half of thyroid cartilage of larynx. Thyroid hormone synthesis is a multistep process localized in thyrocytes, which requires iodine environmental sufficiency. Figure 1 shortly illustrates this process.

Hypothalamic–pituitary–thyroid axis (HPT axis) regulates thyroid hormone blood concentration according to the negative feedback loop. Triiodothyronine (T_3) regulates the metabolism of the whole body, adjusts to its currently needs and stimulates human's growth during their whole life.

Mechanism of T3 Action in Cardiovascular System

It has been extensively demonstrated that disturbances in functioning of the thyroid gland can modify cardiac performance

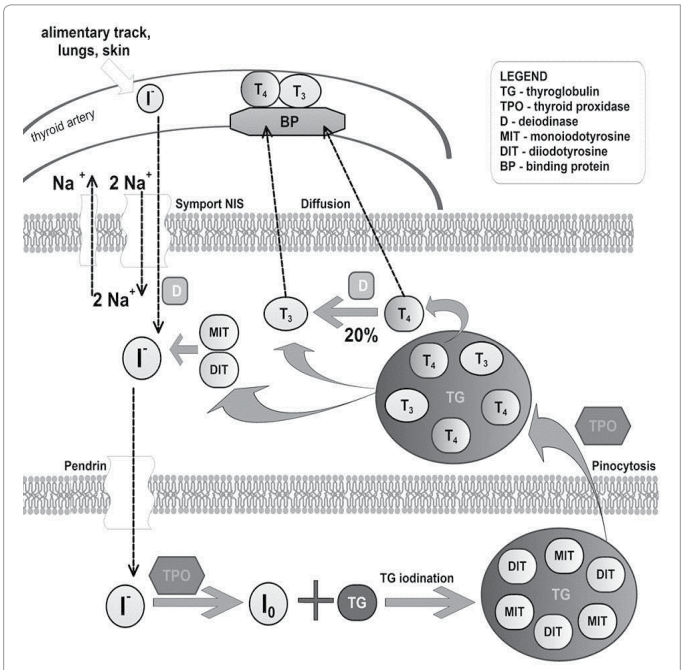

Figure 1: Synthesis of thyroid hormones.

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affecting the heart and the vascular system [8-11]. In some cases, hyperthyroidism can have the form of a tyreocardiac state concealing hyperthyroidism and can be the only symptom of elevated level of T_3 [12].

There are two groups of thyroid hormone action in the cardiovascular system. These are genomic processes, when triiodothyronine interacts with cardiomyocyte nucleus receptor and non-genomic ones, affecting sympathetic nervous system, peripheral circulation and heart rate [8,13]. T_3, being an active form of thyroid hormones plays a greater role in binding to the nucleus receptor in cardiomyocytes [14]. That is why, authors will use this term talking about its thyroid effect. T_3 commonly binds to specific nuclear thyroid hormone receptors (TRs), which belong to the steroid receptor group (mainly retinoid X receptor, RXR). It regulates the transcriptional and posttranscriptional processes. Two TRs genes, α and β, encode four T_3-binding receptor isoforms (α1, β1, β2, and β3) [15]. After T_3 and TRs connection, homo- or heterodimers have been made and they attach to the thyroid hormone response elements (TRE) in DNA promoter region. T_3 regulates positive or negative expression of some genes encoding structural sarcomere's elements and regulating proteins for cardiomyocytes [16].

One of the most important among them is myosin heavy chain (MHC), being the main structural part of sarcomere. There are 2 cardiac MHC isoforms, α- and β-MHC with genes encoding them (MYH6 and MYH7 respectively) located on 14 chromosome. Human heart has 20-30% of α-MHC mRNA of the total MHC mRNA and the rest constitutes as isoform β but this isoform is related to having lower activity than α-MHC [16,17]. Quantitative changes between its two isoforms impact on contractile velocity. Human hemodynamic status, heart diseases and thyroid status can alter expression of the MHC genes. Namely, T_3 promotes α-MHC expression and causes increase of speed contraction and cardiac growth. In hypothyroidism was observed lower α-MHC concentration with compensatory bigger cell size and stimulation of anabolic processes in cardiomyocyte. Contractile velocity was poorer [18]. Similar α-MHC changes have been observed in failing heart and fetal phenotype [19]. After the T_3 delivery, there was a increase of α-MHC and decrease of β-MHC [18]. Moreover, some DNA and proteins caring DNA are of importance in this regulation. Haddad et al. have investigated, that altered thyroid state induces histone modifications in the chromatin associated with the cardiac MHC genes [20].

A novel regulating mechanism of cardiac myosin heavy chain gene by naturally occurring anti - sense transcription was elucidated via pre-mRNA analysis. Haddad et al. reported the expression of an antisense myosin heavy chain RNA in the normal rodent myocardium [21]. It was also found, that hypothyroidism and diabetes were correlated with an increased expression of the sense β-MHC pre-mRNA and a dramatically decreased expression of both the antisense β-MHC RNA and sense of α-MHC pre-mRNAs [22]. The study of Danzi et al. [23] confirmed the above mentioned results. In hypothyroid rat ventricle, it's been proved that β-MHC antisense RNA expression is minimal, while in the euthyroid rat ventricle, there is a maximal β-MHC antisense RNA. In hypothyroid humans, there was a study suggesting, that after T_3 therapy there was also an α-MHC increase but with no change in β-MHC activity. It was positively correlated with better clinical stage of the patient [24].

Proportion in MHC isoforms depends on the heart's condition. In the course of heart failure there was effectively no detectable α MHC protein in the left ventricles [25]. Physiological consequence of this state can be perturbed contractibility and increased cardiac work and as a result cardiac hypertrophy [23].

Next important gene, which expression depends on T_3 is an ATP- Ca^{2+} activated pomp localized in sarcoplasmic reticulum (SR), called SERCA2. It plays a key role in relaxation time during diastolic phase by Ca^{2+} active transport from the cytosol to the SR. A period of time, when Ca^{2+} leaves cytosol and doesn't bound to troponin C determines the length of cardiomyocyte contractibility and relaxation. T_3 stimulates SERCA2 gene expression and accelerates relaxation time in diastolic phase. It shows a positive lusitropic activity [26]. It was also reported, that both in hyperthyroidism and short-term cold exposure was observed an increase in oxygen consumption and heat production during Ca^{2+} transport via SERCA2 in cardiomyocyte [27]. SERCA2 action is conjugated with phospholambam (PLB) activity. It is an integrative protein in the SR, which blocks SERCA2 activity. It is activated, when being in dephosphorylated form. Its activity is necessary to keep a properly length of systolic phase. Its phosphorylation by protein kinase A (PKA) stops SERCA blockage and Ca^{2+} is transported into the SR [16]. There is a T_3 negative relationship to PLB gene expression. T_3 leads to a decreased PLB quantity and makes SERCA2/PLB ratio higher [28]. Mouses PLB depleted revealed better contractility parameters [29]. Beside this, T_3 increases cAMP production in cardiomyocytes and as the consequence increases the activity of PKA and phosphorylates PLB. That is why, it can be said that PLB regulates the inotropic heart effects [16].

Thyroid hormones regulate also the expression of some ion channels located in cell membrane. Among them are Na^+/K^+ ATP-ase pomp [13,15], voltage-gated K^+ channels, (Kv1.5, Kv2,1, Kv4,2, Kv1,2, Kv1,4) [30] and Na^+/Ca^{2+} exchanger (NCX) [29,31]. Working together, they are responsible for electrochemical responses of the myocardium. First Na^+/K^+ ATP-ase is under positive T_3 regulation [13]. An increase in Na^+/K^+ ATPase expression occurs independently of increased cardiac work [31]. NCX exchanger expression is opposite to T_3 regulation [32,33]. Depending on the form of voltage-gated K^+ channels, their expression differs. There was investigated that Kv1,5; Kv2,1 and Kv4,2 are in direct proportion to T_3 presence. Whereas expression of Kv4,3 is not altered due to thyroid state [30]. These observations are similar with other study conducted by Shimoni et al. beside the Kv4,3 expression, which was hound to increase due to hyperthyroidism [34]. Moreover, is was investigated that expression of Kv1.5 channels is selectively present on the ventricular cardiomyocytes [35].

It isn't without importance, that T_3 contributes to down regulating the expression of angiotensin receptors in vascular smooth muscle cells. Angiotensin II type 1 receptor (AT1R) mRNA and its protein were down regulated in the aorta of T3-treated rats. It becomes an essential point for T3-induced vascular relaxation [36]. The opposite effect is for sympathetic nervous system by increasing β1 adrenergic receptor gene expression in ventricles. It works by double effect, that is, increase of β1 receptor function and density [37]. These genes and others being under T_3 regulation one are presented in Figure 2. To sum up, these genomic effects lead to an increased cell proliferation and as a result of higher anabolic cardiomyocyte rate can be one of the causes of pathological heart hypertrophy.

Thyroid hormone non-genomic action acts independently to nuclear thyroid receptor. Thus, these effects start quickly and include changes in various membrane ion channels, effects on cytoskeleton like actin polymerization and a variety of intracellular signaling pathways in heart and vascular smooth muscle cells. Thyroid hormones cross-couple to the phosphatidylinositol 3-kinase (PI3-kinase) localized under the cell membrane and the signaling process incorporates to

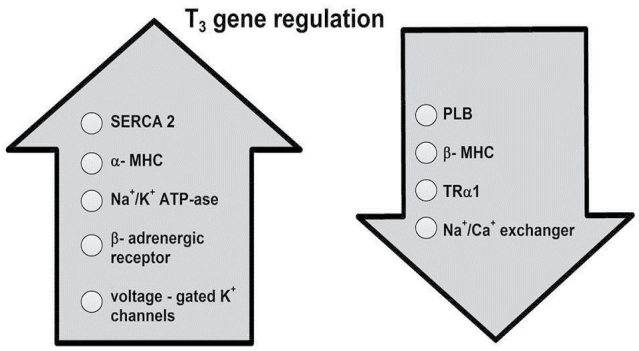

Figure 2: T3 regulates expression of some genes.

protein kinase B (AKT) pathway involved in cell proliferation and survival processes.

In vascular endothelial cells, through α1 isoform of thyroid receptor (TRα1), T_3 leads to activation of endothelial nitric oxide (eNOS) [38]. Acting together, in association with decreasing density of angiotensin receptors, vasodilatation effect becomes larger (mp).

This vascular dilatation effect contributes to maintain the homeostasis of systemic blood pressure. Smooth muscle cells isolated from a rat's aorta relax rapidly during T_3 exposure. It leads to decreased arterial resistance and as a result decreased blood pressure and increased cardiac output [39]. Studies on hypothyroid human model confirm this suggestion. Organism depleted of thyroid hormones revealed increased blood pressure, particularly diastolic one, connected to the peripheral vascular resistance. There was observed higher blood level of catecholamine's and decreased arterial compliance [40,19]. Thus, the cardiac preload increases and accordingly to Frank-Starling's mechanism, cardiac output elevates until a certain value (mp). Figure 3 is an illustration of cooperating processes leading to increase a cardiac output.

The role of T_3 and thyroxine (T_4) on microcirculation has also been evaluated. The application of T_3 and T_4 induced dose-dependent dilation of arterioles within 2.0 ± 0.5 and 16 ± 2 min from administration, respectively. It also seems that local conversion of T_4 to T_3 represents a crucial step for the dilation of the microcirculatory system, which can be now considered a target for a TH action [41].

Looking at the blood volume value and its regulation due to T_3, it is necessary to remember about the interplay between thyroid, kidneys and higher erythropoietin release [42,43]. Furthermore, it was found, that thyroid hormones increases accumulation of hypoxia induced-factor 1 protein (HIF-1) by increasing HIF-1 protein synthesis rather than leading to its proteasomal degradation. Increased synthesis of HIF-1 may also contribute to the adaptive response of increased oxygen demand under hyperthyroid conditions [44].

Thyroid hormones have also proangiogenic effect and can stimulate vascular growth both in normal heart and after myocardial infarction [45]. In this process an adhesive molecule integrin avb3 is included, acting as the key element. There is a place in structure of this integrin, where thyroid hormones join and lead to activation of mitogen-activated protein kinase and induction of angiogenesis [46]. Beside this, it's known that vascular endothelial growth factor (VEGF) is also involved in thyroid hormone-induced angiogenesis process [47-49]. This is mainly in the course of Grave's disease, when VEGF serum concentrations are higher than in euthyroid people [49]. That is why, greater vascularity is observed within the thyroid. VEGF and additionally fibroblast growth factor (FGF) increased expression can also affect the hypertrophy of cardiomyocytes [50,51].

Hyperthyroidism

Cardiological symptoms of hyperthyroidism may display as a result of both hyperthyroidism per se and its impact on already existed heart disease [52]. Thyroid affects cardio-vascular system on different ways. It has direct effect by chronotropic and inotropic positive effect. Additionally by the intervention in peripheral resistance and blood volume cardio-vascular effect is amplified or more evident. An increase of β-adrenergic receptors within heart is also significant thyroid hormone action as well. All cardiac and vascular events correlated to hyperthyroidism are called a hyperdynamic circulation state. This typically occurs as spontaneous increase of cardiac output and increase in systolic pressure due to reduction of peripheral vascular resistance and decrease in diastolic blood pressure [53]. Short-lived concentration of the overt T_3 blood is associated with positive and time-limited cardiac events [54]. When this state prolongs, it can cause established cardiac disturbances (mp). T_3 positive inotropic effect occurs as increased left ventricular ejection fraction (LVEF) at rest but paradoxically its significant fall during exercise is to be observed. Characteristic for hyperthyroid state is a decrease of cardiac output with clinical left ventricular failure symptoms during exercise [54].

In hyperthyroidism, at rest, myocardial contractility has been already increased due to molecular changes as altered synthesis of MHC, increase of SERCA2 expression. Physical exercises can't raise it more and lead to opposite effect (mp). Due to peripheral decrease of vascular resistance and increased blood flow, afterload reduces. Cardiac output rises as well. Heart metabolism accelerates and glucose uptake is also higher. Thus, an increase of heat production is observed. When there is additional burden of exercise it induces increase in afterload and heart cannot increase its capacity, because heart, even at rest, still works near its value being [55]. This paradoxical response disappeared within a few weeks of the patients becoming euthyroid [56]. A patient with undestroyed heart can feel, like mentioned above, a fall of physical tolerance, but a person with an organic heart disease can feel much

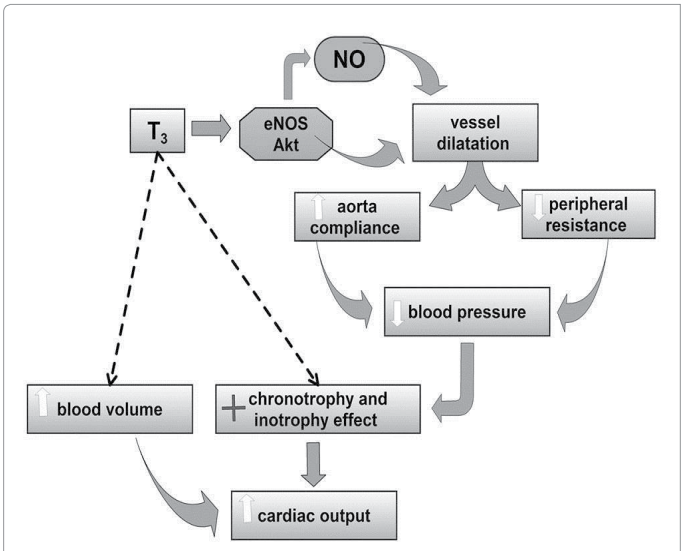

Figure 3: T3 coordinates blood pressure and cardiac output.

worse all the time. Dyspnea can be a main clinical symptom of it. Additionally, in the course of hyperthyroidism respiratory muscles work poorer and heart contraction is less efficient, which can intensify shortness of breath [57]. Myocardial ischemia is presumably caused by the increased demands of the thyrotoxic myocardium. However, a coronary spasm may be an additional factor and myocardial infarction can occur in the absence of significant atheroma [58].

Due to the fall of vascular resistance, kidneys' vessels relax and as a consequence, serum concentrations of angiotensin converting enzyme and erythropoietin increase. It causes absorption of renal Na^+ (increase of Na^+\$H^+$ATP-ase activity) and polycythemia [59]. It leads to expanded blood volume and increase of end diastolic pressure (mp). As positive chronotropic cardiac event, sinus tachycardia is the most popular. The combination of rapid diastolic depolarization and shortage of the action potential of the sinoatrial cells causes this effect [54].

It can be clinically silent in young people, because human body can adaptate to persistent tachycardia. As a consequence this state can be revealed during a period appointment. Sometimes, mainly among children, tachycardia can be masked in special behavior. They could be nervous, unable to concentrate for a longer time or irritated. This state can be wrongly correlated to the psychological base of this behavior, like hyperactivity syndrome (mp).

Among a variety of atrial and ventricular tachycardia described in hyperthyroidism, atrial fibrillation (AF) is the most common one [55]. Pathophysiological view on AF is the shortage of refractory time in atrial cardiomyocytes' and increased sinoatrial activity [60], which causes difficulties to keep sinus rhythm, particularly in older people with some accompanying cardiac disorders like e.g. angina, arteriosclerosis or valvulopathies (mp). AF occurrence in population rises with age, from 0.1% among adults younger than 55 years to 9.0% in person in the age of 80 years or older. It makes AF the main tachyarrhythmia in society [61].

A Danish study, conducted by Frost et al. [62] included more than 40,000 patients with hyperthyroidism and it was shown that nearly 8.3% of them were diagnosed with AF or atrial flutter in the time of 30 days of the hyperthyroidism lasted. Because of its high percentage, it's necessary always to check thyroid function, when AF has been pronounced [63]. It's also important to exclude also subclinical hyperthyroidism (SH). AF can be the first symptom of that disorder [64].

It has been investigated, that prolonged atrial electromechanical coupling time and impaired mechanical atrial functions can be in the relationship with the increased prevalence of arrhythmias. Positive correlation has been found between intra- and interatrial delay and THS blood level in subthyroid patients, whereas negative correlation between TSH and interatrial delay in subclinical hyperthyroid patients have been observed [65].

Clinically patient may feel 'palpitations', which he/she explains as rapid, irregular heart rate. During patient's auscultation, doctor can recognize arrhythmia absoluta and a peripheral pulse deficit (mp) 60% of patients with hyperthyroid AF revert spontaneously to sinus rhythm within a few weeks after restoring normal tests of thyroid function. But it is often necessary to add a β-adrenoceptor antagonist to achieve adequate rate control [63,64].

Additionally, in hyperthyroidism there is a well-proved action of β-blockers in inhibiting T_4 T_3 conversion (non-selective ones). Newest data shows, that during paroxysmal AF in euthyroid patient who had suffered from hyperthyroidism in the past and need amiodarone treatment to prevent sudden cardiac death, preventive radioiodine therapy (RAI) can be considered. Retrospective analysis showed, that this procedure, applied to 17 patients aged from 65 to 87 years old, was safe. Amiodarone-induced hyperthyroidism has performed in 5 patients and additional RAI was investigated. After 6 and 12 months, 14 patients revealed sinus rhythm during control examination [66].

When thinking about AF, there is a point of anticoagulation to prevent stroke due to embolization. However, some statistical data about the risk or benefits associated with this therapy in hyperthyroidism remain difficult to quantify [67,68].

That is why, the decision about anticoagulant therapy delivery should be analyzed in the context of patient age and coexistence of cardiovascular disorders, which lead to greater risk of stroke [69].

Despite the fact, that among younger patients with structurally normal hearts benefit from anticoagulation is not known at all, there are some case reports of arterial thromboembolism associated with AF in the course of hyperthyroidism [70].

It would be recommended to check, if during transoesophageal echocardiography (TEE) there is no atrial thrombus assertion. Beside this, patients with hyperthyroidism are associated to present an increased sensitivity to warfarin and its enhanced effects [69]. Doses of warfin should be reduced to avoid severe coagulopathy [71].

Many of clinical symptoms of hyperthyroidism seem to be close to these performed in the course of pheochromocytoma. However, serum and urinary catecholamine concentrations remain in correct range or they are even low in hyperthyroidism. It may be an argument for independently cellular action of hormones and catecholamines but with other signaling pathways within cardiomyocyte [55].

An isolated right ventricular failure is a possible, yet not very common disorder, due to hyperthyroidism. In literature, there are some clinical cases correlated with this state [72,73].

Lozano et al. conducted a case report with a young woman suffering from rapid progressive right-sided heart failure together with pulmonary hypertension and with no secondary causes of these disorders. Her only concurrent illness identified was Grave's disease. This state totally reversed after thyreoistatics therapy [74].

Giovambattista has also described similar kind of right failure case. It was a 51 year old woman with overt hyperthyroidism. She has stopped tiamazole therapy at the same month, when she presented obligatory semi-orthopnoic decubitus, severe edema, ascites and bilateral pleural effusion and echocardiographic findings of right ventricle volume overload was also observed [75]. Potential cardiac abberations performed in hyperthyroidism are seen in Figure 4. Long-term exposure to thyroid hormone excess, affect pathologically effects on cardiac morphology and function because of cardiomyocyte hypertrophy [76]. Morphological chances lead to an increase of left ventricular mass and its index (increase of left ventricular posterior wall together with the increase of intraventricular septum) [77-79].

LV hypertrophy is correlated with cardiac remodelling, that is overgrown cardiomyocytes, fibrosis of parenchyma and increase of apoptosis is observed. Missing cells are replaced with fibroblasts, which leads to less effective cardiac work [80].

Adrenergic activity is also increased. As a result, diastolic dysfunction exists and symptoms of heart failure can occur [54, 81]. β-blockers were proved to inhibit cardiomyocyte hypertrophy and

fibrosis effect caused by many disorders [80, 82].

Additionally, suppressive thyroxine treatment as obligatory treatment procedure after thyroid cancer also leads to cardiac hypertrophy even in the first year of therapy. Left ventricular mass and left ventricular index are increased. When β-blocker (e.g. bisoprolol) is added to suppressive therapy, after 6 months combination treatment hypertrophic changes inhibits and come back to range before suppressive therapy [83].

Whereas, big Framingham Heart Study evaluated that TSH was not related to LV mass, LV wall thickness or left atrial size and LV systolic function in either sex. Only an inversed correlation to LV contractility was observed [84].

NT-pro brain natriuretic peptide (NT-pro-BNP) as a cardiac dysfunction marker was measured to change its blood concentration level due to thyroid state. In hyperthyroidism, both overt and subclinical one, there was an increased NT-pro-BNP level than in control group (overt hyperthyroidism: 1,129.7 ± 1,119.8 pg/ml vs. 138.9 ± 173.3 pg/ml; subclinical hyperthyroidism: 598.1 ± 639.2 pg/ml vs. 138.9 ± 173.3 pg/ml), whereas in hypothyroid patients this effect wasn't observed. Moreover, L-thyroxine treatment increased plasma levels of this parameter [85].

In 2012 an interesting study was conducted with the aim to estimate thyroid function and morphology state before and after a cardiac invasive treatment - Percutaneous Coronary intervention (PCI) and percutaneous transluminal coronary angioplasty (PTCA) with single burden iodine contrast. The study showed that thyroid function alterations seen in laboratory blood tests are transmitted but both measurement of fT_3 and TSH blood level before cardiac invasive treatment and monitoring after this procedure should be necessary [86].

Hypothyroidism

In contrast to hyperthyroidism, deficiency of thyroid hormones in bloodstream is associated with opposite cardiac events. Due to a slow-down of the metabolism rate and nearly whole body functions, cardiac work diminishes as well. However cardiac symptoms aren't so evident as during excess of TH and are usually only prominent in patients with profound longstanding thyroid failure. A decreased cardiac output, heart rate, stroke volume, and myocardial contractility are observed, whereas systemic vascular resistance increases [55].

The authors want to present a development of coronary heart disease (CHD) as the first disorder connected to the hypothyroidism. Overt hypothyroidism contributes to its evolution on two ways. First theory is, that it exacerbates lipid profile, endothelium damage and hypertension. The second point of view is because of chrono- and inotropic activity reduces and oxygen deficit improves, which may provoke underlying coronary ischemia [87,88]. There is prevalent increased risk of CHD events and mortality correlated with different hypothyroidism state [89]. The hazard ratio (HR) for CHD was 1.89 for a TSH level of 10 to 19.9 mIU/L [90]. Increased prevalence of ischemic heart disease has also been reported in patients under 65 of age, affected patients affected by subclinical hypothyroidism (SH) [91].

Mayer et al. [92] tried to assess association with hypothyroidism as conventional cardiovascular risk factor in Czech Republic. Among 1240 participants taking part in the study, the overall prevalence of hypothyroidism was 6.8% in males and 13.8% in females. The relative risk of hypothyroidism was increased in males with manifest vascular disease, in females above 55 years old. Hypertension also contributed to that state. Moreover, the risk ratio increases in males and females with a positive TPOAb among euthyroid subjects.

What is characteristic for hypothyroidism is a change in lipids levels. In many cases its incorrect result, that is elevated LDL concentration and hypertriglyceridemia are the main point of appointment [87]. Moreover, sometimes patient can have revealed distorted lipid profile and hypothyroidism during periodical medical checkup. Organism can be adapted to this state, that is why no clinical symptoms are visible, but distantly consequences of that silent process are obvious (mp). Disturbed lipid profile probably results from reduced catabolism of lipoproteins, and simultaneously there is a decreased expression of lipoprotein receptors in the liver [93].

Tromsø's study has investigated, that TSH blood level remains in direct proportion with LDL and total cholesterol serum increases [94].

Inflammatory markers and homocysteine level are also elevated and contribute to creating an inflammation and oxidative stress in atherosclerosis [89,95].

These lipid disturbances together with slow energy metabolism, increased blood pressure can become the components of metabolic syndrome (MS). Roos et al. evaluated that in low, but still within range, fT_4 blood levels are related to abdominal obesity, triglycerides, high-density lipoprotein cholesterol, and blood pressure. What is more, low normal thyroxine level was found to increase insulin resistance [96]. Similar findings were obtained in a bigger study called Health ABC [97]. Due to the investigation of the thyroxine treatment was total cholesterol level reduced by 0.4 mmol/l and slight effect on HDL fraction of cholesterol were observed [98].

Among elderly patients with a cardiological burden, start of thyroid hormones supplementation therapy can even intensify myocardial ischemia or acute coronary events [55,87]. That is why, doses of thyroxine are increased gradually and more extended in time, moving towards euthyroid state. Hypertension, mainly diastolic one, occurs in about 30% of patients. Pathophysiological base of hypertension is due to impaired vascular smooth muscle cells relaxation. Reduced NO production and endothelial dysfunction lead to increased vascular resistance. However, this disorder can reverse rapidly after thyroxine therapy [99].

Cardiac-echo parameters and changes in left ventricle's (LV) work are not so noticeable and clinically evident as the opposite ones performed in hyperthyroidism. Its severity depends on hypothyroid progression (mp). Due to the decreased heart rate, low cardiac output is observed. Moreover, the afterload increases because of hypertension [10,100].

Due to overt hypothyroidism systolic and diastolic functions are reduced. It was observed both at rest and during exercise, and may display as dyspnea and fall of physical tolerance [54].

In a study, which evaluated subclinical hypothyroidism correlated with LV impairment (30 cases of SH and 15 of healthy control), a significant diastolic dysfunction in SH compared to healthy control (mean Ei/Ai = 1.35 ± 0.53 vs. mean Ei/Ai = 2.11 ± 0.26) has been shown with no significant impairment of systolic function [101].

Similar study has described the effect of T_4 therapy. It was demonstrated, that after 1 year of thyroxine therapy, only balance in hormones blood level was obtained and there were no signs of better cardiac-echo parameters. However, after a yearly follow-up, diastolic

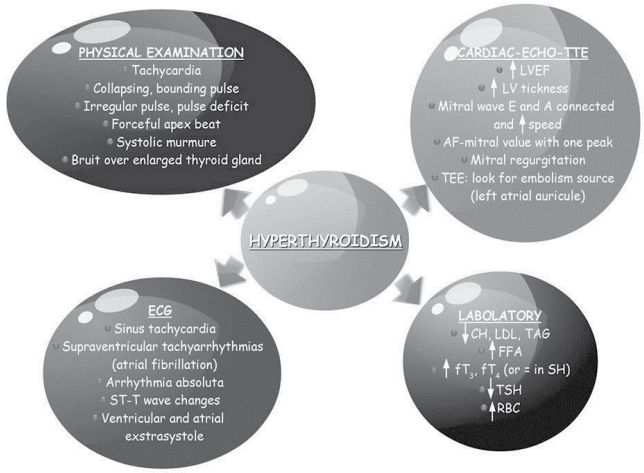

Figure 4: Deviations in physical examination in hyperthyroid patients and additional tests.

dysfunction and echocardiographic features improved in these patients [102].

Cardiac preload decreases as well, due to the impaired diastolic function and the decreased blood volume [54, 103]. Moreover, hypothyroidism leads to chamber dilatation and impaired myocardial blood flow [104-106]. In connection with all the above mentioned hemodynamic changes, a loss of coronary arterioles, reduced cardiac oxygen consumption, higher progression of arteriosclerosis and impaired blood flow, a heart failure (HF) can develop in the course of hypothyroidism [10, 106- 109]. There was an interrelation between reduced both LVEF and total T_3, showing higher mortality than in patients having similar LVEF but normal total T_3 [110]. Disturbances connected with HF are more expressed with already exiting cardiac disorder than unloaded heart (mp).

Changes in thyroid heart metabolism (reduction in biologically active T_3) have been reported in Wassen et al. study, which has evaluated local hypothyreosis in cardiomyocytes within overloaded and failured heart. It is because of increase in activity of deiodinase D3, inactivating T_3 [111]. The same effect was seen after myocardial infarction [112]. This mechanism can be interpreted as a cardiac compensatory process of overloaded heart [113].

Molecularly, in the absence of T_3, concentration of β-MHC isoforms increases, containing low ATP-ase activity. Thus, cardiac contractibility decreases [114].

Cardiac remodeling in hypothyroidism is presented in chronic HF. Cardiomyocytes change its shape and disorganize. The pathophysiological changes in HF and hypothyroid have similar components, that is why, authors want to underline this theme [115-117].

More recently, cases of hypothyroidism and reversible dilated cardiomyopathy have been reported [24,118]. Selvaraj's et al. [119] study tried to estimate the correlation between Brain Natriuretic Peptide (BNP) value and diastolic LV dysfunction and determine, whether BNP and diastolic dysfunction were independently associated with T_3 level. The study consisted of 89 consecutive patients (mean age of 67±14 years and female predominance) with HFpEF (HF with Preserved Ejection Fraction). Patients were divided into two groups based upon median T_3 level (108 ng/dl). T_3 reference range was 87-178 ng/dl with the clinical cut-point for reduced T_3 was 87 ng/dl. Results indicated, that 22% of HFpEF patients had T_3 under range rate. Moreover, they had higher NYHA functional class and BNP levels. The study showed that T_3 is inversely associated with markers of HFpEF severity (BNP and diastolic heart dysfunction) . Heart failure progression performed in hypothyroidism is illustrated in the Figure 5.

Going to physical examination, delayed relaxation after ankle jerk reflex examination is special and its escalation correlates positively with TH deficit [4]. Although cardiological physical symptoms are not so obvious and characteristic in hypothyroidism (mp). That is why differential cardiac diagnosis should be always undertaken. As the first sign, doctor usually auscultates bradycardia and discovers bradycardia. Heart sounds seem to be quitter due to pericardial effusion but it's not an evident symptom, because an overweight or obese patient can demonstrate the same. X-ray examination can show an accumulation of fluid in pulmonary space. When there is concurrent HF, cardiac X-ray shadow can be enlarged as well. ECG reveals low QRS voltage as the one of more popular signs of hypothyroidism. Because of impaired ventricular blood-supply in the course of CHD, ventricular conduction can be disturbed and QRS complex can last more than 150 ms. Among arrhythmias performed in hypothyroidism the most common sinus bradycardia, is mentioned above (mp). Sometimes, when bradycardia becomes more intense, A-V block can occur [120]. The prolongation of the QT interval can also perform and it has similar morphology to the one, seen in euthyroid patients receiving class 3 antiarrhythmic agents [121]. More cardiac and laboratory symptoms can be seen in Figure 6. To better illustrate the interrelation between hemodynamic changes performing in hypo- and hyperthyroidism authors have created Figure 7.

Kidneys function is very important from a cardiological point of view. Their good work helps to maintain circulatory system competent and doesn't overload the heart (mp). In hypothyroidism kidneys reveal decreased perfusion with a consequent reduction in glomerular filtration, impaired free water clearance and hyponatremia [10].

On the other side, the prevalence of hypothyroidism associates with chronic kidney disease. An increasing hypothyroidism prevalence (overt and SH) directly proportional to lower levels of GFR was shown,

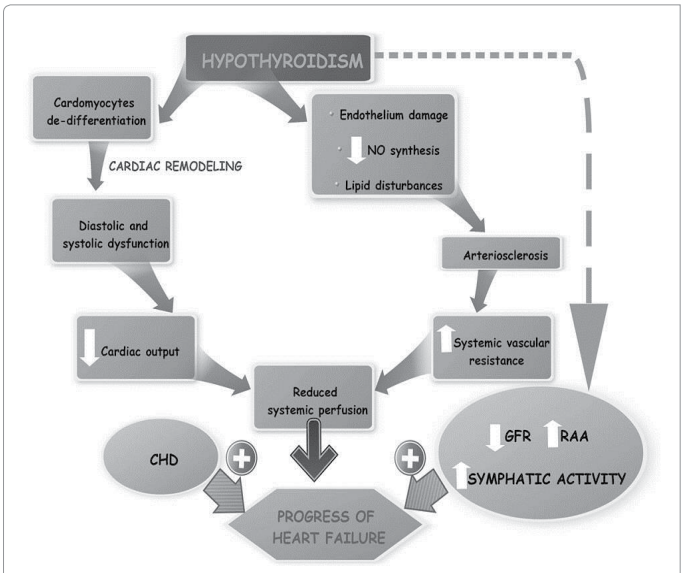

Figure 5: Heart failure progression due to hypothyroidism.

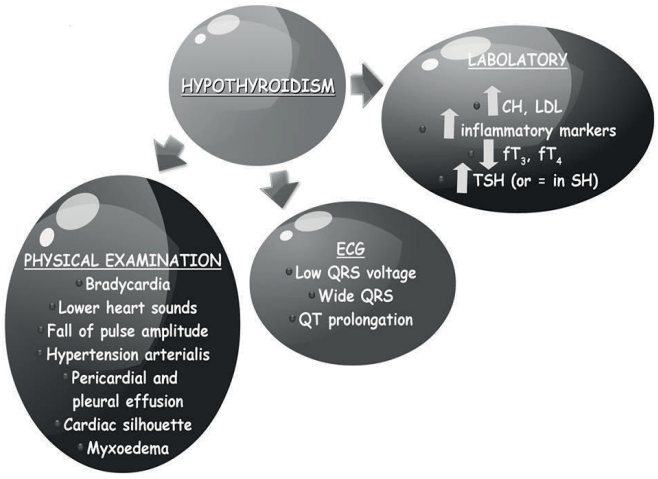

Figure 6: Deviations in physical examination of hypothyroid patient and additionally tests.

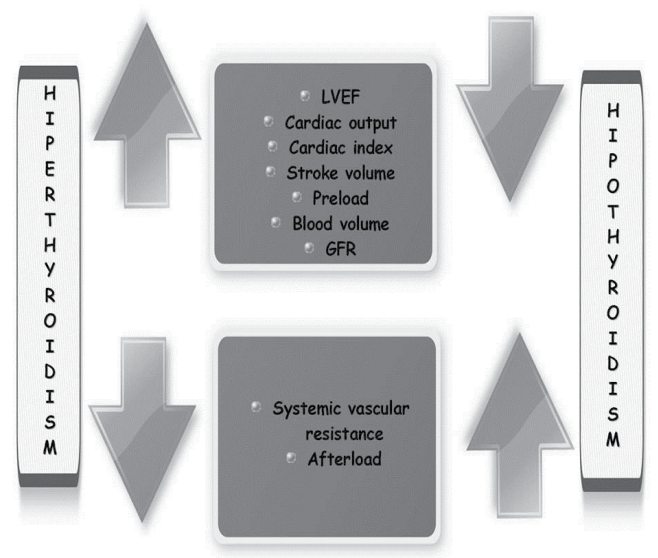

Figure 7: Interrelation in hemodynamic effects in hyper- and hypothyreosis.

occurring from 5.4% of subjects with GFR >/=90 mL/min/1.73 m^2, to 23.1% with GFR <30 mL/min/1.73 m^2 [122].

Cardiac Remodelling

Chronic hypothyroidism leads to induction of maladaptive changes in the shape of myocytes and their disorganization [106]. It leads to cardiac phonotypical remodelling as a stress response and contributes to pathological events such as ischemia, mechanical loading, and metabolic changes. In the short term, this response seems to be time-limited [123]. When it prolongs, it was investigated, that cardiac phenotype reminds the fetal one. Cells are described as de-differentiated [123]. Thus, features of fetal heart metabolism occur and glucose metabolism over fatty acids is presented as energy substrates. Transcription of some genes alters and among them are sarcomeric proteins such as these, already performed in hypothyroidism, increase in β-MHC expression [124]. Fetal replacement acts like "low-energy state", adapting and protecting already damaged myocardium [125]. The hypothesis about the opportunity to regenerate overloaded heart, was gained by the fact, that the return to fetal phenotype and cell dedifferentiation become an introductory allowable state for regeneration after stress. De-differentiated cells seem to have the ability to proliferate and/or grow and then to re-differentiate to specialized cells, affecting the regenerated structure or organ [126]. This regenerative potential is regained in adult life after return to fetal phenotype. However, cells' ability to re-differentiate may be diminished upon intense and sustained stressful stimuli [127]. Our point in this chapter is to show, that thyroid hormones delivery can enhance re-differentiation and restore damage. It was investigated that thyroid hormones' pathways signalling via TRα1 receptor may promote endogenous regeneration of damaged myocardium [128]. Several data of experimental evidence support this notion [129-132]. Moreover, thyroid hormones are shown to involve redox regulated signaling pathways [133], leading to altering cardiac cell shape, their differentiation process and up-regulating some molecules like heat shock proteins, which can increase tolerance of the cell against ischemia [134- 136].

Furthermore, TRα1 receptor appears also to mediate TH-induced cardioprotection [123]. Here, a paradox of TH action has been shown, being rather protective than detrimental for the ischemic heart, although it increases oxygen consumption (by accelerating heart rhythm and increasing cardiac contractility) and depletes the heart from glycogen [136].

In 2009 the phase II has been started, randomized, double blind, placebo-controlled Thyroid Replacement Therapy and Heart Failure Study (THiRST) by the use of substitutive doses of synthetic L-triiodothyronine in patients with STEMI (ST-Elevation Myocardial Infarction) infarction, having borderline or reduced circulating T_3 level. The study is conducted by Dr Iervasi [137].

Conclusions

Thyroid hormones have significant cellular actions, which determine homeostasis in cardio-vascular system and contribute to its god work. Both hyper- and hypothyroidism have its own characteristic way of cardiac symptoms connected to excess or insufficiency of T_3. An excess of thyroid hormones can cause an increase of cardiac output, heart action, ejection fraction, systolic and diastolic function, blood volume and systolic cardiac pressure. Simultaneously a decrease of peripheral resistance and diastolic blood pressure is observed [5]. Insufficiency of T_3 isn't so evident in clinical practice and its symptoms are opposite to hyperthyroidism. Authors hope that this paper give the reader broad point of view on thyroid cardiac clinical manifestations and explain cellular base of them.

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