Heart Follows Thyroid

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Introduction

Thyroid gland disorders are among the 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 disorders 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 reported 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 thyocytes, 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 (T3) 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.
affecting the heart and the vascular system [8-11]. In some cases, hyperthyroidism can have the form of a tyrocardiac state concealing hyperthyroidism and can be the only symptom of elevated level of T₃ [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]. T₃, 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. T₃ 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 T₃-binding receptor isoforms (α₁, β₁, β₂, and β₃) [15]. After T₃ and TRs connection, homo- or heterodimers have been made and they attach to the thyroid hormone response elements (TRE) in DNA promoter region. T₃ 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 lowering exercise activity 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, T₃ promotes α-MHC expression and causes increase of speed contraction and cardiac growth. In hypothyroidism was observed lower α-MHC concentration with compensatory bigger increase of speed contraction and cardiac growth. In hypothyroidism (α₁, β₁, β₂, and β₃) [15]. After T₃ and TRs connection, homo- or heterodimers have been made and they attach to the thyroid hormone response elements (TRE) in DNA promoter region. T₃ regulates positive or negative expression of some genes encoding structural sarcomere’s elements and regulating proteins for cardiomyocytes [16].

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 T₃ 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 T₃ is an ATP. Ca²⁺ activated pomp localized in sarcoplasmic reticulum (SR), called SERCA2. It plays a key role in relaxation time during diastolic phase by Ca²⁺ active transport from the cytosol to the SR. A period of time, when Ca²⁺ leaves cytosol and doesn’t bound to troponin C determines the length of cardiomyocyte contractibility and relaxation. T₃ 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 Ca²⁺ 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 SERCA2 blockage and Ca²⁺ is transported into the SR [16]. There is a T₃, negative relationship to PLB gene expression. T₃ leads to a decreased PLB quantity and makes SERCA2/PLB ratio higher [28]. Mouses PLB depleted revealed better contractility parameters [29]. Beside this, T₃ 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⁺/Ca²⁺ exchanger (NCX) [29,31]. Working together, they are responsible for electrochemical responses of the myocardium. First Na⁺/K⁺ ATPase is under positive T3 regulation [13]. An increase in Na⁺/ K⁺ ATPase expression occurs independently of increased cardiac work [31]. NCX exchanger expression is opposite to T₃ 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 T₃ 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, was investigated that expression of Kv1.5 channels is selectively present on the ventricular cardiomyocytes [35].

It isn’t without importance, that T₃ 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 T₃ 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

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

In vascular endothelial cells, through α1 isoform of thyroid receptor (TRα1), T₃ 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 T₃ 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 T₃ and thyroxine (T₄) on microcirculation has also been evaluated. The application of T₃ and T₄ 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 T₄ to T₃ 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 T₃, 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 T₃ blood is associated with positive and time-limited cardiac events [54]. When this state prolongs, it can cause established cardiac disturbances (mp). T₃ positive inotropic effect occurs as increased left ventricular ejection fraction (LV EF) 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 worse.

![Figure 2: T3 regulates expression of some genes.](image)

![Figure 3: T3 coordinates blood pressure and cardiac output.](image)
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’\(\text{H}^+\) 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]. Pathophysiologically 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 TSH 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 T3, T4, 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. Besides 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 inverted 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 distantly consequences of that silent process are obvious (mp).

Hypothyroidism

In contrast to hyperthyroidism, deficiency of thyroid hormones in bloodstream is associated with opposite cardiac events. Due to a slowdown 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, that it exacerbates lipid profile, endothelium damage and hypertension. Due to the decreased heart rate, low cardiac output, suppressed thyroxine 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) function 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 hypotension [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].

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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
thyroid metabolism (reduction in biologically active T3) have been reported in Wassen et al. study, which has evaluated disorder than unloaded heart (mp). Connected with HF are more expressed with already exiting cardiac patients having similar LVEF but normal total T3 [110]. Disturbances of overloaded heart [113]. This mechanism can be interpreted as a cardiac compensatory process.

Preserved Ejection Fraction). Patients were divided into two groups age of 67±14 years and female predominance) with HFpEF (HF with Reduced both LVEF and total T3, showing higher mortality of hypothyroidism [10, 106-109]. There was an interrelation between 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 T3, showing higher mortality than in patients having similar LVEF but normal total T3 [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 T3) 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 T3 [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 T3, 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 T3 level. The study consisted of 89 consecutive patients (mean age of 67±14 years and female predominance) with HFP EF (HF with Preserved Ejection Fraction). Patients were divided into two groups based upon median T3 level (108 ng/dl). T3 reference range was 87-178 ng/dl with the clinical cut-point for reduced T3 was 87 ng/dl. Results indicated, that 22% of HFP EF patients had T3 under range rate. Moreover, they had higher NYHA functional class and BNP levels. The study showed that T3 is inversely associated with markers of HFP EF 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 quieter 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,
Cardiac Remodelling

Chronic hypothyroidism leads to induction of maladaptive changes in the shape of myocytes and their disorganization [106]. It leads to cardiac phenotypical 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 additionally tests.

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 T3. 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].

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 T3 level. The study is conducted by Dr Iervasi [137].

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].

References


