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Structure and Function of the Circulatory System in Hypothyroid Patients

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1. Introduction

Hypothyroidism, thyroid gland hormone deficiency, is quite a common disease, affecting more women than men. Patients with an elevated risk of hypothyroidism comprise postpartum women, patients affected with autoimmune diseases as well as patients with autoimmune family history, primary pulmonary hypertension, Down's and Turner's syndromes. The main causes of congenital hypothyroidism are endemic iodine deficiency, agenesis or dysgenesis of the thyroid gland and impaired synthesis of the thyroid hormones. The causes of the primary hypothyroidism are autoimmune thyroiditis, injury by surgery, irradiation or drug side effects. Secondary hypothyroidism is caused by pituitary adenomas, adenoma treatment by surgery or radiotherapy, tumors of the suprasellar region, sarcoidosis or hemochromatosis.

Hypothyroid patients complain of cold intolerance, weight gain, constipation, dry skin, bradycardia, hoarseness and dementia (Roberts & Ladenson, 2004). However, thyroid hypofunction, and a consequent lower level of thyroid hormones in the blood, has also been observed in heart disease patients. In patients with acute myocardial infarction, both total and free levels of triiodotyronine were seen to be lower. Moreover, a transient decrease of tyroxine has been observed while the level of TSH was unchanged (Franklyn et al., 1984). Similar data was obtained on children who had undergone open heart surgery. In this case, decreased levels of free and total triiodothyronine, total thyroxine and TSH were observed; all of which, except TSH, remained depressed until the 5th to 8th days after surgery. These results support the statement that the pituitary-thyroid axis is suppressed in patients with open heart surgery (Mainwaring et al., 1994). According to the above data, a vicious circle is postulated (Klein & Ojaama, 2001; a); heart disease induces suppression of the thyroid gland function, which in turn, may influence the structure and function of the heart.

The heart is composed of several cell types: cardiomyocytes, fibroblasts / myofibroblasts, endothelial cells and smooth muscle cells of the blood vessels. Cardiomiocytes comprise more than 50% of the volume of the organ and exhibit contractile properties. Cardiac fibroblasts comprise as much as 67% of the cells in the heart of rats. The fibroblasts are responsible for the synthesis and catabolism of the extracellular matrix (collagen type I and III, elastin and laminin), influence the electrophysiological properties of cardiomyocytes as

well as regulate myocyte growth and blood vessel formation in the heart (Krenning et al., 2010).

The cardiovascular system remains under the regulatory influence of thyroid hormones. Since dysfunction of the thyroid gland results in complex changes within the heart, the structure and function of the heart is disturbed in both hypothyroidism and hyperthyroidism. Hypothyroidism affects the electrophysiological, contractile and hemodynamic functions of the heart and is associated with disturbances of the heart's connective tissue stroma.

The effects of thyroid hormones on the circulatory system have both genomic and non-genomic bases. T_3, triiodothyronine (3, 5, 3'-triiodo-L-thyronine), the active thyroid hormone, is transported to the cardiomyocyte by a specific protein situated in the cell membrane (Everts et al. 1996) where it is then moved to the nucleus and bound by thyroid nuclear receptors: two α isoforms (TRα1, TRα2) and three β isoforms (TRβ1-TRβ3). Of these isoforms, TRα1 and TRβ1 bind 40% of the T_3 each, and the remaining 20% is bound by the TRβ2 receptor; TRα2 is unable to bind triiodothyronine. (Schwartz et.al., 1994; Kahaly & Dilmann, 2005). The receptor-hormone complex is bound to thyroid responsive elements (TRE) and, acting as gene regulator, may influence target gene expression (Brent et al., 1994). Several genes are upregulated by T_3: the α isoform of myosin heavy chains (Morkin et al., 1993), calcium activated ATPase (Dillman et al., 1990), β1 adrenergic receptor (Fazio et al.2004). The expression of other genes is inhibited by T_3: β isoform of myosin heavy chains or phospholamban (Fazio et al. 2004).

2. Electrophysiological function of heart

T_3 has been demonstrated to have a general regulatory effect on heart rate; bradycardia, a typical symptom of the patient with hypothyroidism, is related to a lowered level of triiodothyronine (T_3). In an isolated rat atrial neonatal myocyte model, T_3 was shown to increase the pacemaker rate mainly by elevation of the slope of spontaneous depolarization. Several ionic currents that may determine the pacemaker activity were considered as potential targets for the action of the thyroid hormones. The electrogenic Na^+-Ca^{2+} exchange current ($I_{Na/Ca}$) density was influenced by T_3 application. Thus, $I_{Na/Ca}$ alterations by thyroid hormone may change the slope of the spontaneous depolarization and modify the pacemaker rate (Sun et al., 2001).

The I_f current is defined as the current determining spontaneous diastolic depolarization and influence the activity of the heart pacemaker (Er et al, 2003). In vertebrates, proteins deriving from HCN genes form pores of the I_f current; three HCN isoforms have been found in the human heart : HCN1, HCN2 and HCN4. The experiments performed on neonatal rat ventricular cardiac myocytes showed that triiodothyronine (T_3) evoked a positive chronotropic effect on spontaneously beating myocytes. In myocytes with overexpression of the thyroid hormone receptor TRα1, increased beating activity linked with accelerated depolarization velocity and shortened action potential duration, as well as increased I_f current density and increased HCN2 and HCN4 transcripts and proteins were observed. The effect of thyroid hormones on CHN2 subunit expression is thought to be responsible for a positive chronotropic effect. The changes in both HCN2 and HCN4 gene expression seem not to be influenced by direct binding of thyroid hormone to the TREs in the promoter

region of the two genes. On the other hand, in cells with TRβ1 overexpression, lower beating activities, inhibition of phase 4 depolarization and prolongation of the action potential were found. Reduced transcription of HCN4 was also obseved (Gassanow et al., 2009). Thus, the thyroid hormones would apper to be involved in regulation of the heart rate, and their low level could be responsible for bradycardia development.

In patients affected by hypothyroidism, atrioventricular blocks are rarely described. A complete atrioventricular block has been observed in a patient with severe hypothyroidism, complaining of bradycardia (15 beats/min), fatigue, dizziness and syncope (Schoenmakers et al. 2008). In another patient, bradycardia (44 beats/min) was caused by a 2:1 atrioventricular block with subclinical hypothyroidism (Nakayama et al., 2006). The blocks in two described patients were resolved after thyroxin supplementation. The functional blocks have been diagnosed.

Apart from bradycardia, the typical electrocardiographical changes in hypothyroid patients comprise prolongation of the PQ interval, reduced QRS complex voltage, elongation of the QT interval and flattening or inversion of the T wave. An acquired elongation of QT with a tendency toward ventricular arrhythmias has also been shown in many patients affected with hypothyroidism. The QT interval (Fig. 1) is the marker of ventricle repolarization. Prolongation of the QT is usually caused by prolongation of the action potential due to a reduction of repolarizing currents or elevation of the inward current (Antzelvitch, 2004). In patients with overt primary hypothyroidism, Galetta and coworkers (2008) highlighted the prolongation and increased dispersion of the QT interval, partial reduction of which was seen after replacement therapy. In addition, the reduction of heart rate variability parameters seen in the study suggests a sympato-vagal imbalance in hypothyroid patients. An increase of QT interval dispersion was also found in women with subclinical hypothyroidism. The differences of QTc (- QT dispersion corrected for heart rate) were normalized when TSH level (>10mIU/l) was lowered (Bakiner et al., 2008). The cardiomyocytes isolated from hypothyroid rats are characterized by a very long action potential duration compared with euthyroid cardiomyocytes, however application of T_3 reduces their action potential duration by 24% (Sun et al., 2000). The mechanism of QT prolongation in the hypothyroid subjects is not very well explained. However, prolongation of ventricular repolarisation is thought to be due to fibrous tissue accumulation in the heart and swelling due to excessive deposition of the osmotic compounds in the heart wall (Galetta et al., 2008).

Sun et al. (2000) postulate that both the genomic and non-genomic effects of the thyroid hormone (T_3) could be involved in the prolongation of action potential in the ventricular myocytes of hypothyroid rats. The genomic effects are involved with modulation of T_3-specific cardiac gene expression. I_{to} transient outward current density (Fig. 1) was decreased in the ventricular cardiomyocytes of hypothyroid rats compared to euthyroid cardiomyocytes; this effect is connected with reduced expression of KCND2 genes, which encode proteins of the voltage-dependent K^+ channel Kv4.2 (Nishiyama et al., 1998). The Kv4.2 and Kv4.3 gene products are molecular components determining the I_{to} current. I_{to} current is responsible for early repolarisation (phase 1) of action potential and is composed of the rapid form $I_{to,f}$ and slower form reffered as $I_{to,s}$. Le Bouter and coworkers (2003) found reduced transcription of several genes (KCNA5, KCNB1, KCND2 KCNK2) in hypothyroid mice while the expression of other genes was upregulated (KCNQ1, KCNE1); these genes

encode the proteins of the voltage-gated K^+ channel proteins. The results were confirmed on the protein level and were linked with reductions of $I_{to,f}$ and delayed rectifying K^+ current (I_{kslow}) densities and elevation of slowly activating delayed rectifier (I_{ks}) density in cardiomyocytes isolated from hypothyroid mice. The thyroid hormone is thought to regulate the components of I_{to} on the transcriptional level (Shimoni & Severson, 1995). The reduction of I_{to} density could be partially responsible for prolongation of the action potential and QT interval elongation (Sun et al., 2000).

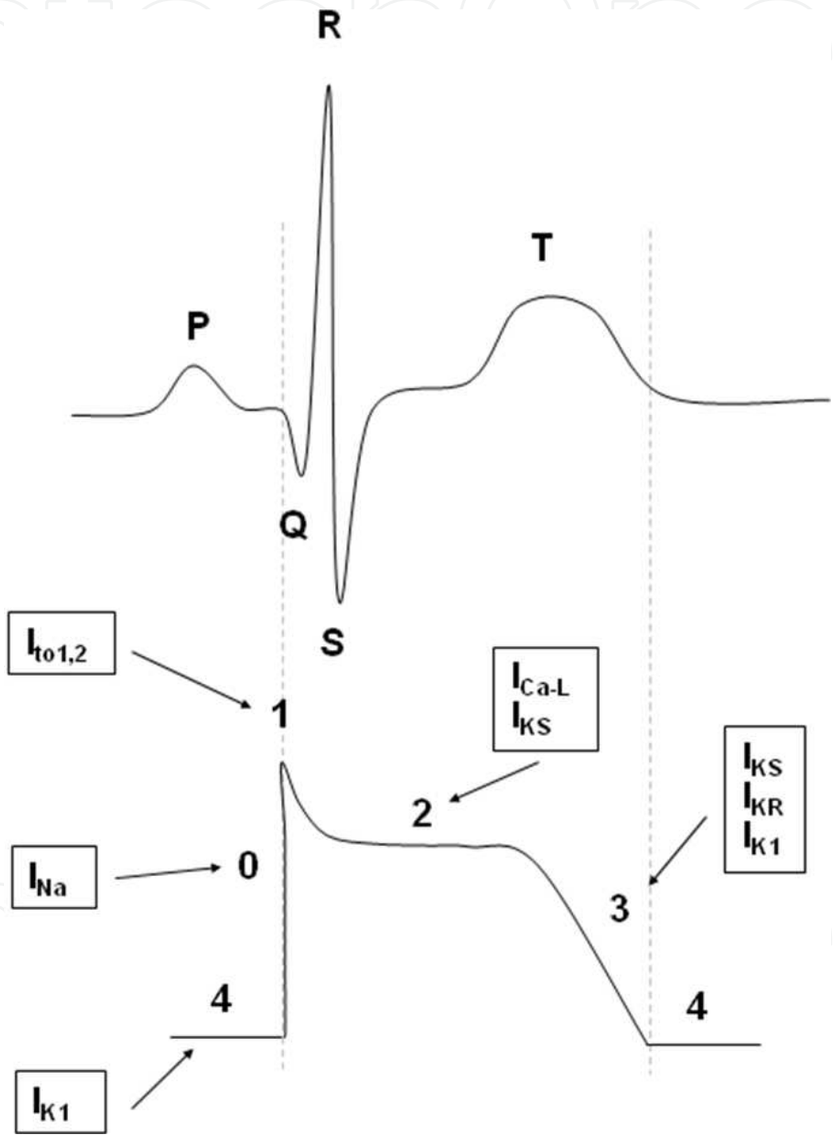

Fig. 1. The action potential of the cardiomyocyte (lower part) and surface electrocardiogram (upper part). The cardiomyocyte action potential is consisted of phases 0-4 and is generated by following currents: I_{Na} sodium current, I_{to} transient outward K^+ current, I_{Ca-L} voltage-gated calcium current, I_{Ks} slowly activating delayed rectifier current, I_{Kr} rapidly activating K^+current, I_{K1} inward rectifier K^+ current.

Ionic characteristics however are not rapidly influenced by addition of T_3 to cardiomyocytes isolated from the hypothyroid rats, implying that changes in I_{to} current density are regulated at the transcriptional level (Sun et al., 2000). On the other hand, the rapid effect of T_3 treatment on the I_k current, the effects being seen in only 5-15 min, suggests a non-genomic influence of the thyroid hormone; transcription and translation processes need more time (Sun et al., 2000). Thus, different types of regulation have been noted for I_{to} and I_K (delayed rectifier): transcriptional and non-genomic regulation respectively. Non-genomic regulation was demonstrated also for the sodium channel and the I_{K1} channel: The action potential duration was shortened by T_3 application, which was linked with an increase of whole cell inward rectifier potassium current (I_{K1}; Sakaguchi et al. 1996). Application of T_3 elevated the burst activity of the sodium channel (Dudley & Baumgarten,1993).

A novel genetic link between inherited long QT interval and hypothyroidism has been proposed by Putrell and coworkers (2010). Mutations of the KCNQ1 and KCNE2 genes are related to long QT interval. hERC and KCNQ1, complexed with KCNE β, are the subunits of the voltage-gated potassium channels. They generate repolarisation currents I_{kr} and I_{ks}. I_{ks} is the slowly activated potassium current (generated by KCNQ1,-KCNE1 subunits) and I_{kr} is the rapidly activated potassium channel (generated by hERG-KCNE2 subunits). KCNQ1 mutations reduce ventricular muscle repolarisation capacity and prolong the QT interval. Furthermore, the KCNQ1-KCNE2 channel determines potassium influx to thyreocytes and correct accumulation of iodine ions. A mutation of KCNE could diminish the delivery of iodine ions to the thyreocytes, decreasing the substrate availability for thyroid hormone synthesis. Thus, two concomitant effects of KCNE dysfunction are observed: in the heart prolongation QT and possible arrhythmias, and in the thyroid gland inhibition of thyroid hormone synthesis and hypothyroidism formation. Hypothyroidism is associated by a molecular link with prolongation of QT (Purtell et al. 2010).

Life-threatening ventricular ectopic arrhythmias are rarely seen in hypothyroid patients (Schenck et al. 2006); additional factors triggering sustained or life-threatening ventricular arrhythmias are postulated (Galetta et al., 2008). Very few reports document ventricular arrhythmias in the course of hypothyroidism. The "torsade de pointes' (TdP) tachycardia was revealed in a few cases of women aged from 50 to 78 years affected with hypothyroidism with symptoms of hypometabolic crisis being commonly found. However, although different methods of treatment were applied, the authors stress that systematic therapy with thyroxine caused normalization of the electrocardiogram (Chojnowski et al. 2007, Shojaie & Eshraghian 2008, Schenck et al. 2006).

3. Heart contraction

Hypothyroidism causes a reduction of heart contractility, lowers the speed of myocardial relaxation (Jakab et al. 1994), decreases stroke volume, ventricular feeling and cardiac output. In hypothyroidism, the cardiac output is decreased by 30-50%. Thus, the hypodynamic status of the circulatory system can be diagnosed. In a hypothyroid subject while the expression of α isoform of myosin heavy chains (αMSH), sarcoplasmatic reticulum Ca^{2+} -ATPase (SERCa2) β1-adrenergic receptor genes is reduced due to a lowering of the triiodothyronine level (triiodothyronine is the factor which increases expression of these

genes), the expression of β isoform of myosin heavy chains (βMSH) and phospholamban genes is increased.

Both transcript and protein levels of β–MSH (known as slow myosin) are elevated in experimental animals with induced hypothyroidism (Haddad et al., 2003). β–MSH demonstrates low ATPase activity and works more economically (Harris et al., 1994). However, higher ATPase activity with a faster heart myofiber shortening velocity can be found in α-MSH, known as fast myosin (VanBuren et al., 1995). Domination of β–MSH in rodents impairs both diastolic and systolic heart functions. (Dillman et al., 1989, Morkin, 1993). This phenomenon could be seen mainly in laboratory animals because the β–myosin heavy chain isoform comprises 95% of the myosin molecule in human (Gorza et al., 1984) and is not markedly influenced by changes of thyroid hormone level. In a hypothyroid patient with dilated cardiomyopathy, the cardiac output was reduced to 16% and the α-myosin heavy chain mRNA level was found to be low in biopsy samples. After 9-month therapy with thyroid hormone, not only was the cardiac output elevated to 37%, but the level of α-myosin heavy chain mRNA was also increased (Ladenson et al., 1992). Myofibrillar ATPase activity in the heart of thyreoidectomized rats was found to be lower (Dowell et al., 1994)

The β–adrenergic receptors in the heart remain under the positive regulatory influence of the thyroid hormone. In rats with experimentally-induced hypothyroidism, a decreased β-receptor number was found on cell membranes but the agonists' affinity to the receptors was not changed. Isoproterenol-induced activation of adenylate cyclase was reduced (Dowell et al., 1994). Novotny and coworkers (1999) confirmed the reduced number of β-receptors in hypothyroid rats. Moreover, the positive inotropic effect of isoproterenol was reduced. These results were contrasted by Ariogla and coworkers (2009), who noted a reduced effect of isoproterenol and noradrenalin on heart contractility in hypothyroid animals, but saw increased expression of β 2 and β 3 receptors with no change in expression of β 1 receptors.

In animals with hypothyroidism, reduced pressure dvelopment (dP/dt) was linked with decreased phosphorylation of cardiac troponin I (cTnI) in the heart. Moreover, mRNA of cardiac troponin I was increased 3 fold in hearts of hypothyroid rats but mRNA of slow skeletal troponin I was initialy elevated but later was decreased to undedectable level in animals with hypothyroidism. (Averyhart-Fullard et al., 1994).

The reduction of heart contractility due to overt hypothyroidism decreases stroke volume and ejection fraction. In hypothyroid patients, prolongation of the pre-ejection period and decrease of ventricular ejection period were observed, however these values were normalized after replacement therapy (Crowley 1977). Moreover, these phenomena, as well as bradycardia, decreases cardiac output in hypothyroid patients.

The changes of calcium concentration in the heart are regulated by calcium activated ATPase and phospholamban during both systole and diastole periods. Calcium-activated ATPase is responsible for the calcium influx to the endoplasmatic reticulum and, in this way, influences the myocardial relaxation velocity (Dillman et al., 1990, Kiss et al., 1994). Phosholamban was found to inhibit the activity of the calcium-activated ATPase (Kiss et al. 1994). Cardiac contractility was increased in phospholamban-deficient mice and the thyroid

hormone treatment was not found to increase myocardium contractility (Kiss et al. 1998). Triodothyronin may determine the relaxation of the heart via regulation of gene expression through upregulation of calcium activated ATPase and downregulation of phospholamban. Thus, in hypothyroidism, the gene for calcium-activated ATPase expression is decreased but phospholamban gene expression is increased, which will affect the systo-diastolic function of the heart (Fazio et al. 2004). Impairment of the diastolic function in hypothyroidism patients by slow myocardial relaxation of the heart results in reduction of ventricular feeling. Furthermore, a decreased rate of active diastolic relaxation has been found in hypothyroid patients (Wieshammer et al., 1989). Echocardiographic studies of hypothyroid patients show the modifications of the acoustic properties and myocardial fiber velocity as well as regional myocardial deformations. Decreased intramyocardial contractility and the impairment of both the active and passive diastole phases have been observed (Di Bello et al., 2009). In women with subclinical hypothyroidism, magnetic resonance imaging revealed decreased end diastolic volume – preload and increased afterload causing impaired cardiac performance (Ripoli et al., 2005).

Exercise intolerance of the hypothyroid rats is related to decreased heart performance and increased total peripheral resistance. Lower blood flow to extensor muscles has been observed as well as reduced vasodilatator potential of isolated blood vessels (McAllister et al., 1995). Cardiac oxygen consumption measured by positron emission tomography is reduced in hypothyroid patients. This reduction is associated with decreased contractility and elevated total peripheral resistance (Bengel et al., 2000). Athea and coworkers (2007) investigated the effect of hypothyroidism on the cardiac energy metabolism. The maximal oxidative capacity of heart tissue was found to be markedly reduced, cytochrome oxidase and citrate synthase were inhibited and mitochondrial cardiolipin content was lower. Cardiolipin influences the activity of many inner membrane proteins and its amount increases in mitochondria with elevated metabolic rates. Utilization of 3 phospho-glycerol, malate and octanoate decreased in hypothyroid animals. Additionally, while the content or activity of creatine kinase is not changed, it was observed to have decreased efficacy in hypothyroid animals, leading to impairment of mitochondrial function. However, the mechanism of these changes remains to be elucidated. Expression of adenine nucleotide transferase is reduced in hypothyroidism. This effect is linked with impairment of mitochondrial permeability (Paradies et al., 1997; Chavez et al., 2008).

4. Connective tissue in the heart

The connective tissue of the heart remains under the regulatory influence of the thyroid hormones. Triiodothyronine increases the intracellular transport of amino acids, sugars and calcium and increases protein synthesis. However, interstitial fibrosis with excessive glycosaminoglycan accumulation was found on histological examination of a hypothyroid heart (Mohr-Kahaly et al. 1996). Additoinally, echocardiography showed changes of the heart structure in hypothyroid patients. The alterations could be the result of excessive accumulation of collagen, water retention or changes of the muscle fiber orientation (Monzani et al., 2001).

Ciulla and coworkers (2004) investigated the collagen content in the heart of hypothyroid patients with echocardiographical studies. The derived collagen volume fraction (dCVF% echocardiographical evaluation of the collagen content in the heart) was evaluated. Higher

values of dCFV% were found in hypothyroid hearts, but echoreflectivity was normalized after thyroid hormone treatment. Experiments performed on rats with induced hypothyroidism by thyroidectomy or 4-methyl-2-thiouracil application demonstrated increased accumulation of collagen and glycosaminoglycans in the hearts of two groups with experimental hypothyreosis (Drobnik et al., 2009). Moreover, an increased level of hialuronic acid was found in hypothyroid rats in the heart and the hindlimb muscle (Wiig et al., 2000). An elevated level of hyaluronan was also noted in human fibroblasts cultured in conditions without thyroid hormones (Shishiba et al., 1988).

The mechanism of the observed changes remains a matter of debate. The elevation of the extracellular matrix in the hypothyroid heart is supposed to be related to a low level of thyroid hormones and reduced catabolism of extracellular compounds. Decreased hydroxyproline levels, the marker of collagen, were noticed in the urine and serum of hypothyroid subjects; these changes were normalized by replacement therapy. Additionally, decreased collagen degradation was confirmed in hypothyroid subjects by experiments with radiolabeled proline. Most importantly however, the final effect of the thyroid status would seem to be dependent on the target organ; increased collagen content was noted in both the skin and liver of the hypothyroid animals as well as a decreased collagen level in the bones (Kucharz, 1992). Previous results showed decreased collagen catabolism in hypothyroid animals, and this effect may explain the elevation of collagen level in the heart.

However, in primary hypothyroidism, a low level of the thyroid hormone is accompanied with an elevation of TSH, which is thought to influence the regulation of the connective tissue matrix in the heart. Although an increased number of cells was found in myofibroblast cultures isolated from newborn rat heart after TSH application, the level of collagen or glycosaminoglycans in the culture was unchanged; this elevation of myofibroblast number in TSH-treated cultures raises the question of whether a TSH-dependent effect could be responsible for connective tissue accumulation in the hypothyroid heart (Drobnik et al., 2009). Application of immunoglobulin from the sera of patients with Graves' disease increases collagen biosynthesis, which is explained by immunoglobulin binding to the TSH receptors (Kohn & Winand, 1975). Experimental outcomes prove that the TSH receptor transcript is present in the human heart (Koshiyama et al., 1996). TSH receptor transcripts and receptor immunoreactivity were found in fibroblasts of different origins (Daumiere et al., 2002; Feliciello et al., 1993). Collagen accumulation in the heart is responsible for the increased stiffness of the heart wall and may contribute to diastolic heart failure development.

Excessive glycosaminoglycan accumulation in the skin is linked with myxedema formation (Smith et al., 1989). Wiig and coworkers (2000) found increased interstitial fluid pressure in the skin and muscle in hypothyroid rats. Thus, accumulation of glycosaminoglycans and proteins in the interstitial space is supposed to increase the edema of the interstitium.

While pleural or pericardial effusions are noted in 10% to 30% of the adult hypothyroidism patients, this complication is rare in children (Martinez-Soto et al., 2010). The main symptoms of cardiac tamponade in hypothyroid patients are increased or normal heart rate (after pericardiocentesis, the tempo is slowed) distant heart sounds, enlarged jugular veins, low P valves, T valves and QRS complex in the electrocardiogram and massive pericardial

effusion in echocardiography. The following mechanisms of the cardiac tamponade are possible: increased permeability in microcirculation, leakage of fluid with high protein concentration and disturbed lymphatic drainage. The cardiac tamponade is a rare complication of hypothyroidism because of the slow liquid accumulation and high distensibility of the pericardium (Lin et al., 2003).

5. Blood vessel

Low cardiac output and decreased blood pressure was noted in hypothyroid subjects however, increased total peripheral resistance was also noticed. On the other hand, diastolic hypertension was observed in 25% of the patients. Hypertension has been linked with increased systemic vascular resistance (Klein & Ojama, 2001; b). However, experimental hypertension could be reversed by hypothyroidism (Vargas et al., 1988).

The pressor response for vasoconstrictors and vasodilatators changes in the hypothyroid subject (Vargas et al., 2006). A reduced pressor response to noradrenalin has been proven in normotensive hypothyroid patients, suggesting a decreased sensitivity of blood vessels to noradrenalin, however, the response of blood vessels to noradrenalin become normal after thyroxin supplementation. Interestingly, in hypertensive hypothyroid patients, the sensitivity of blood vessel to noradrenalin was found to be normal (Bramnert et al., 1994). Similarly, aortic rings with an intact endothelium has been proven to demonstrate a reduced pressor response to phenylephrine (Pantes et al., 2006). The reduced sensitivity of blood vessels to α1 stimulators is thought to be due to a decreased number of α1-adrenoreceptors in tested samples (Vargas et al., 2006). Reduced arteries sensitivity to nitric oxide donors (sodium nitroprusside) has also been reported. Infusion of nitroprusside caused lower elevation of forearm blood flow in hypothyroid patients comparing with healthy subjects (Napoli et al., 2009). Moreover, both acetylcholine or histamine-induced vasodilatation was seen to be lower in hypothyroid rats but nitric oxide independent vasodilatation remained unchanged (Moreno et al., 2003).

Inhibited vasodilatation by endothelium dependent factors is thought to be responsible for the increased total peripheral vascular resistance seen in hypothyroid subjects (Vargas et al., 2006). Human smooth muscle cells are postulated to be targets for the thyroid hormones. The genomic and non-genomic mechanisms of thyroid hormones may well play a role in the regulation of smooth muscle cell contractility. However, the molecular targets are not known (Klein & Ojama, 2001; b). In hypothyroidism, a lower level of plasma renin concentration (Bouhnik et al., 1981) increased vasopressin level (Arnaout et al., 1992) and decreased concentration of atrial natriuretic peptide (Kohno et al., 1987) were observed.

Reduced activity of the thyroid gland was observed in subjects affected by hypertension. The inhibition of thyroid activity is supposed to be related to the thyroid-depressing factor found in the liver, spleen, kidney and plasma, which was released during hypertension development in rats. This thyroid-depressing factor reduces thyroid activity mainly by inhibiting the binding of ^{131}I and blocking thyrotropin-stimulated ^{131}I binding (Fregly & Threatte 1982; Vargas et al., 2006).

In hypothyroid patients elevation of total cholesterol, low-density lipoprotein (LDL) as well as the apo B levels was observed (Staub et al., 1992). These results could be explained by

lowered number of LDL receptors. Thus, decreased level of mRNA for LDL receptor in the liver of hypothyroid rats was found; however this effect was reversed by thyroxine treatment (Staels et al., 1990). In hypothyroid women the LDL catabolism was decreased (Thompson et al., 1981). The genomic effects of the thyroid hormones on LDL receptor expression were proved (Bakker et al., 1998). The gene coding of the LDL receptor is positively regulated by thyroid hormones.

Patients affected with overt hypothyroidism are influenced by several risk factors of atherosclerosis: elevated levels of low-density lipoprotein, total cholesterol, diastolic hypertension and elevated coagulability. Higher prevalence of atherosclerotic changes in aorta and myocardial infarction in women with subclinical hypothyroidism was observed (Hak et al., 2000). On the other hand, the thyroid hormone supplementation could be responsible for exacerbation of the ischemic heart disease due to positive chronotropic and inotropic effects (Roberts and Ladenson 2004)

6. Summary

The paper shows that hypothyroidism is responsible for profound disturbances in the structure and function of the cardiovascular system. The symptoms of hypothyroidism comprise heart arrhythmias (bradycardia, atrioventricular block, tachycardia, torsade de points) and disturbances in myocardium contraction and relaxation, as well as decrease of oxygen consumption. Molecular mechanism of symptoms has been described. Decreased thyroid hormone content influences the mechanisms of the development of hypothyroidism symptoms through both genomic and non-genomic effects. Elevation of TSH is thought to be involved in some of the peripheral effects observed in rats with primary hypothyroidism. In patients with heart disease, hypothyroidism should be considered as a possible cause.

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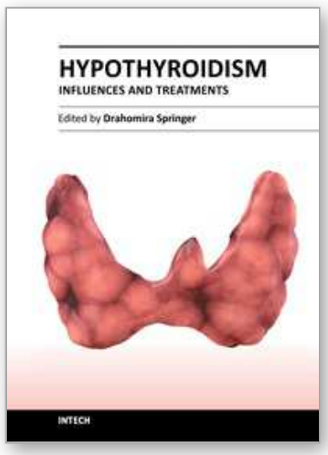

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Hypothyroidism is the most common thyroid disorder and it is significantly more frequent than presented - millions of people suffer from this disease without knowing it. People with this condition will have symptoms associated with slow metabolism. Estimates of subclinical hypothyroidism range between 3 to 8 %, increasing with age, whereas it more likely affects women than men. About 10% of women may have some degree of thyroid hormone deficiency. Hypothyroidism may affect lipid metabolism, neurological diseases or other clinical conditions. The book includes studies on advancements in diagnosis, regulation and replacement therapy, thyroid ultrasonography and radioiodine therapy for hypothyroidism. "Hypothyroidism - Influences and Treatments" contains many important specifications, results of scientific studies and innovations for endocrine practice.

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