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Impact of Thyroid Dysfunction on Natural Course of Coronary Artery Disease

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1. Introduction

Cardiovascular diseases have similar pathophysiologic mechanisms which lead patient from risk factors, such as dyslipidemia, smoking, high blood pressure etc. to congestive heart failure and finally – to death (Fig. 1.). This global approach to the natural history of cardiac pathology has been proposed at the end of the twentieth century and remains current till now (Cheung, 2006). Thyroid dysfunction is a common clinical problem which plays a key role in the regulation of the cardiovascular system and can contribute to the clinical course of coronary artery disease (CAD). As it was shown on Fig.1 thyroid dysfunction can affect almost all chains of this continuum and its influence should be taken into account when treating patients with CAD.

In several studies the presence of predominantly adverse cardiac effects of thyroid dysfunction on the natural history of CAD has been shown (Iervasi et al., 2007). Thyroid diseases are associated with systolic and diastolic cardiac dysfunction, hypertension, heart rhythm disorders etc. Overt hypo- as well as hyperthyroidism affect outcomes in patients with CAD. As it has been recently shown in numerous studies, even subclinical hyperthyroidism can be an independent risk factor for all-cause and cardiovascular mortality (Sgarbi et al., 2010). Previously subclinical hypothyroidism was recognized as an independent risk factor for atherosclerosis and myocardial infarction in elderly women (Hak et al., 2000). But results of these studies are sometimes controversial (Biondi, 2010; Cappola et al., 2006; Iervasi et al., 2007; Ittermann et al., 2010)

Thyroid hormone excess causes a lot of cardiovascular changes due to both direct and indirect effects on the cardiovascular system (Table 1), and results in neurohormonal activation, including sympathetic nervous system activation. The latter determines increased heart rate and appearance of arrhythmia, especially atrial fibrillation. Hyperthyroidism is also associated with hypertension and CAD clinical manifestation.

With aging, physiological changes in thyroid homeostasis interact with different cardiovascular risk factors (Mariotti, 2008). Hypothyroidism is frequently found in the elderly, may cause several functional cardiovascular abnormalities and increases the risk of atherosclerosis and CAD manifestation (Mariotti & Cambuli, 2007). Hypothyroidism alters

lipid metabolism, which contributes to the natural course of CAD. Hypertension can be also a clinical sign of thyroid hypofunction. Hypothyroidism may result in diastolic and systolic cardiac dysfunction, i.e. heart failure. Other its potential cardiovascular risk factors are increased circulating C-reactive protein and homocysteine levels, increased arterial stiffness, endothelial dysfunction, and altered coagulation parameters (Mariotti & Cambuli, 2007). On the contrary, some investigators had found that hypothyroidism is not associated with an increased risk of carotid atherosclerosis (Chiche et al., 2009). On the other hand, Mazzeffi et al. (2010) confirmed the association between hypothyroidism and lower extremity arterial disease as an atherosclerosis display. So, after years of research there are still unexplored facts waiting to be resolved.

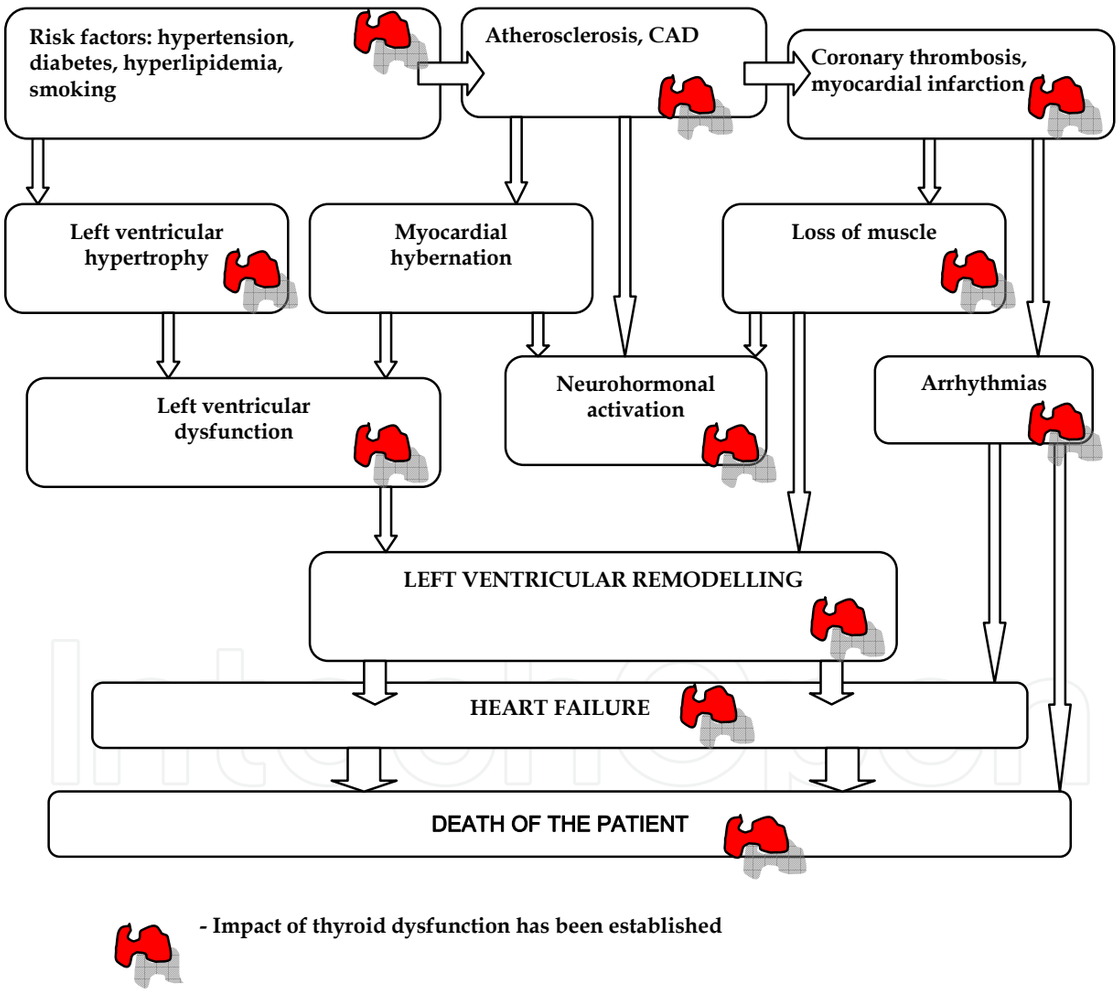


Fig. 1. Cardiovascular continuum and thyroid dysfunction (modified from Dzau & Braunwald, 1991).

Pathways	Clinical manifestations
Effects predominantly on cardiomyocytes:	
*1. **On the genome level (prolonged effects)**:* in the nucleus triiodthyronine interacts with specific transcriptional activators or repressors and alters the transcription modality of specific target genes (Brent, 1994). Triiodthyronine contributes to: -protein synthesis and thus transcriptional activation of α-isoform of myosin heavy chain, sarcoplasmic reticulum calcium-activated adenosine triphosphatase, β_1-adrenergic receptors, guanine-nucleotide-regulatory proteins, Na^+/K^+-adenosine triphosphatase, some of voltage-gated K^+ channels (Fazio et al, 2004; Kahaly & Dillmann, 2005) -transcriptional repression of β-isoform of myosin heavy chain, phospholamban, nuclear receptor α_1, adenylyl-cyclase types V & VI, Na^+/Ca^{2+} exchanger (Fazio et al., 2004; Kahaly & Dillmann, 2005)	
2. *Extranuclear cellular mechanisms (short-term effects):*	
Effects on membrane	
Augmented activity of the sinoatrial node (Sun et al., 2001) through increasing the conductance density of I(f)-channels (Renaudon et al., 2000)	Increased heart rate and myocardial oxygen demand
Activation of transmembrane transfer of sodium and potassium (Kahaly & Dillmann, 2005), calcium (Kiss et al, 1994) and glucose (Chidakel et al., 2005)	Activation of cardiomyocytes' metabolism
Effects on sarcoplasmic reticulum	
Activation of calcium reuptake during diastole, up-regulation of calcium-activated adenosine triphosphatase, down-regulation of phospholamban expression (Fazio et al., 2004; Kiss et al., 1994; Ojamaa et al., 2002)	Augmented contraction of cardiomyocytes, enhancing myocardial relaxation
Effects on mitochondria	
Activation of oxidative phosphorylation (Verhoeven et al., 1985)	Activation of cardiomyocytes' metabolism
Activation of adenine nucleotide translocase (Sterling, 1986)	Activation of cardiomyocytes' metabolism
Effects on heart:	
Increased density of cardiac β_1-adrenoreceptors (Kahaly & Dillmann, 2005) and, thus, response to catecholamines	Elevation of cardiac output
Effects on vascular wall:	
Relaxation effect on vascular smooth-muscle cells (Ojamaa et al., 1996)	Vasodilatation, decreased preload as well as afterload on the heart, decreased peripheral vascular resistance
Other effects of thyroid hormone, which have influence on the natural course of cardiovascular diseases:	
Activation of metabolism	Increased myocardial oxygen demand
Effects on lipid profile (Rizos et al., 2011)	Maintaining serum very low-, low- and high-density lipoprotein cholesterol, triglyceride and apo-B 100 levels within normal range
Modulation of glucose production and glycogen storage in the liver and heart (Boelen, 2009; Forhead et al., 2009; Klieverik et al., 2009)	Activation of cardiomyocytes' metabolism
Increase sodium reabsorbtion in the kidney (Capasso et al., 1999)	Increase circulation blood volume

Table 1. The most important effects of thyroid hormone on the cardiovascular system.

There are also several challenges of CAD treatment in patients with coexisting thyroid dysfunction. Usage (especially long-term, with high doses) of amiodarone *per se* can result in amiodarone-induced thyroiditis and thyroid dysfunction (Iervasi et al., 1997; Martino et al. 2001). Different β-blockers show dissimilar effects on thyroid hormone levels, and these responses should be taken into account when treating patients with CAD and coexisisting thyroid dysfunction. There is a wide discussion about safety of levothyroxine replacement treatment in patients with CAD. It is known that this therapy can improve results of cardiac function measurements in subjects with hypothyroidism, however in the presence of CAD levothyroxine replacement treatment may result in manifestation or worsening of the CAD symptoms (Mariotti & Cambuli, 2007).

New data emerged about association between thyroid dysfunction and CAD natural history, which will be discussed hereafter. During the last decades interest to the influence of subclinical thyroid dysfunction on CAD progression rises significantly, but findings are still too controversial to make definitive decision. By now even definition for normal serum thyroid hormone and thyrotropin range is still not completely established. This chapter will be dedicated to the main problems of coexisting CAD and overt thyroid dysfunction. Influence of subclinical thyroid dysfunction on CAD will not be discussed in this chapter because of the immensity and complexity of the issue.

2. Impact of hypothyroidism on the natural history of CAD

Hypothyroidism can influence the natural course of CAD in different ways. In patients with overt hypothyroidism hyperlipidemia, coagulation abnormalities, endothelial dysfunction, hypertension, hypertrophy and diastolic dysfunction of heart ventricles, and abnormalities of insulin resistance had been found. Most of these factors can alter atherosclerotic process and modify morbidity and mortality rates for CAD. But after decades of research implication of thyroid hypofunction in CAD progression is still unclear and needs to be reassessed.

2.1 Effects of overt hypothyroidism on the most important cardiovascular risk factors: hyperlipidemia and hypertension

2.1.1 Hypothyroidism and hyperlipidemia

The role of lipid metabolism disorders in pathophysiologic mechanisms of atherosclerosis, following CAD and its complications is well established. Hyperlipidemia is a first step of the cardiovascular continuum; it is widely known as an independent cardiovascular risk factor. Clear and exact recommendations addressed to the lipid levels control, especially in patients with CAD and those at high cardiovascular risk were developed. It is also generally accepted that hypothyroidism accelerates development of CAD by its impairment action on lipid metabolism (Jung et al., 2003; Rizos et al., 2011). Hyperlipidemia is more often observed in patients with serum concentration of thyrotropin more than 10 mIU/L (Biondi & Klein, 2004).

The most important mechanisms of thyroid hormone action on lipid metabolism are shown in Table 2.

Mechanism	**Result**	**Impact on the course of CAD in case of hypothyroidism**
Inducing the HMG-CoA reductase	Cholesterol biosynthesis	Theoretically depressed cholesterol production, but in practice increased total cholesterol and LDL cholesterol levels due to decreased catabolism of LDL and IDL cholesterol
Controlling the LDL receptor gene activation (for T_3) by: -the direct binding to specific thyroid hormone responsive elements (Rizos et al., 2011) -controlling the sterol regulatory element-binding protein-2 (Shin & Osborne, 2003)	Up-regulation of LDL receptors	Decreased catabolism of LDL and IDL cholesterol, increased total cholesterol and LDL cholesterol, acceleration of atherosclerosis and CAD
Controlling the TG levels by hypotriglyceridemic gene *APOA5* regulation (Prieur et al., 2005)	Inhibition of TGs production	Increased TG levels, acceleration of atherosclerosis and CAD
T_3 and its acetic derivative protect LDL from oxidation (Faureet al., 2004)	Protection from oxidation of LDL	Burden of oxidative stress, acceleration of atherosclerosis and CAD
Increased cholesteryl ester transfer protein activity	Increased exchange of cholesteryl esters from HDL_2 to VLDL and TGs to the opposite direction (Rizos et al., 2011)	Not definitely established, due to this mechanism plasma HDL levels may be elevated
Stimulation of lipoprotein lipase	Activation of TG-rich lipoproteins catabolism (Rizos et al., 2011)	Decreased clearance of TG-rich lipoproteins, hypertriglyceridemia, acceleration of atherosclerosis and CAD
Stimulation of hepatic lipase	Activation of hydrolyzation HDL_2 to HDL_3, conversion of IDL to LDL and in turn LDL to small dense LDL (Rizos et al., 2011)	Increased levels of HDL_2, IDL and LDL. Impact on the natural history of CAD is controversial
Up-regulation of apoAV	Decreased hepatic TGs, VLDL production, increased both plasma lipoprotein lipase levels and activity, enhanced affinity for the LDL receptor, greater clearance of lipoprotein core remnants (Rensen et al., 2005)	Increased plasma TG and VLDL levels; acceleration of atherosclerosis and CAD

Table 2. The most important mechanisms of thyroid hormone action on lipid metabolism and their impact on the course of CAD in case of hypothyroidism. HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; LDL = low-density lipoprotein; IDL = intermediate-density lipoprotein; T_3 = triiodthyronine; TG = triglyceride; HDL = high-density lipoprotein; VLDL = very low-density lipoprotein

Therefore overt thyroid hypofunction primarily leads to elevated plasma total cholesterol and low-density lipoprotein cholesterol levels. Elevation of triglyceride levels is also possible as well as increased concentration of high-density lipoprotein cholesterol (mainly because of increased concentration of high-density lipoprotein–2 particles). So, lipid profile in patients with hypothyroidism has atherogenic properties, and may be characterized by unusual condition with simultaneously elevated triglycerides and high-density lipoprotein cholesterol levels despite it is widely accepted that hypothyroidism is associated with decreased high-density lipoprotein cholesterol levels (Cappola & Ladenson, 2003) and that there is an inverse relation between these two measures. Thus, atherogenic lipid profile in patients with overt hypothyroidism may be partly diminished by this elevated plasma concentration of high-density lipoprotein cholesterol. It was also shown that patients with hypothyroidism have increased concentration of lipoprotein (a) – known by its atherogenic facilities and associated with atherosclerotic artery lesion, particularly CAD (Rizos et al., 2011; Tzotzas et al., 2000).

2.1.2 Hypothyroidism and hypertension

Hypertension is another strong cardiovascular risk factor and the starting point of the cardiovascular continuum. Hypertension has a great influence on the natural course of CAD resulting in an increase in cardiac afterload, ventricular hypertrophy, impairment of diastolic function of ventricles as well as endothelial dysfunction and neurohormonal activation (Dzau & Braunvald, 1991). Hypothyroidism prevalence among general population of patients with hypertension reaches 3-4%, and it was established that patients with hypothyroidism and hypertension represent higher blood pressure levels compared with those without thyroid dysfunction (Fommei & Iervasi, 2002; Saito, 1983). At the same time hypertension is more common in hypothyroid population – its prevalence reaches 20-40% (Klein & Ojamaa, 1995; Streeten et al., 1988). So, hypertension is a frequent symptom of hypothyroidism and independent risk factor for cardiovascular events, morbidity and mortality, particularly CAD-associated. As it was shown in several studies, thyroid hypofunction is associated with predominantly diastolic hypertension as a result of increased systemic vascular resistance, increased arterial stiffness and impaired endothelial function (Biondy & Klein, 2004; Dernellis & Panaretou, 2002; Kanbay et al., 2007; Obuobie et al., 2002).

Hypothyroid patients have significantly higher diastolic blood pressure levels in the fifth and sixth decades of life (time of CAD manifestation in most cases) compared with measures in euthyroid controls (Aronow et al., 2011). Iqbal et al. (2006) have shown in their study of 5,872 subjects (2,623 male subjects) without antihypertensive or replacement levothyroxine treatment, that even within the normal serum thyrotropin range (0.20–4.00 mIU/L) there was a modest, but significant and positive association between serum thyrotropin and both systolic and diastolic blood pressure levels. Serum thyrotropin levels were higher in the hypertensive subjects, but differences were significant only for diastolic hypertension. The same trend was found by group of Norwegian scientists (Åsvold et al., 2007a).

2.2 Hypothyroidism, atherosclerosis and CAD

In one of the recent reviews addressed to the problem of the association between CAD and hypothyroidism Cappola & Ladenson (2003) mentioned: "…today's clinicians managing

patients with hypothyroidism and atherosclerosis are still guided more by medical folklore than evidence-based medicine". It is widely accepted that hypothyroidism adverse contributes to the natural course of CAD (Miller & Gambert, 2008), but most of the studies, aimed to proof this postulate, are outdated, not large enough and have serious limitations. Most of them have been conducted in patients with subclinical hypothyroidism and/or predominantly in women. For example, findings of Vanhaelst et al. (1967) have been based on autopsy data of 25 patients with myxoedema and suggest that intensity of atherosclerotic disease was significantly higher in hypothyroid compared with euthyroid patients. But results of the Cardiovascular Health Study of 3,678 men and women didn't establish any prepotency of angina, myocardial infarction, transient ischemic attack, stroke and peripheral arterial disease in patients with subclinical hypothyroidism compared with such prevalence in euthyroid people (Ladenson et al, 1994). In the frequently cited study, performed by Perk & O`Neill and published in 1997, the authors found angiographic CAD progression differences for only 10 participants with hypothyroidism compared with those on adequate replacement therapy.

Interestingly, the evidence body of the association between overt hypothyroidism and CAD was proposed mostly by studies of not overt, but subclinical hypothyroidism, possibly because of its wider prevalence. The Wickham Survey, first large-scale examination of the relationship between thyroid function and cardiovascular outcomes, enrolled 2,779 men and women. Overt hypothyroidism was an exclusion criteria, 132 persons have subclinical thyroid hypofunction (Vanderpump et al., 1996). In a 20-yr follow-up of this population-based cohort study any relationship between incident CAD or mortality and composite variable of hypothyroidism on replacement therapy, presence of circulating antithyroid antibodies, and/or thyrotropin level more than 6 mIU/L was not established in both men and women. But replacement treatment was the most important limitation, which could cause shift in indexed results (Cappola & Ladenson, 2003). The Rotterdam Study of 1,149 women (age 55 years or older) was another study of subclinical hypothyroidism which proves the possibility of hypothyroidism to affect the natural course of atherosclerosis and to increase CAD-morbidity (Hak et al., 2000). It was shown after adjustment for age, smoking status, body weight index, blood pressure, and high-density lipoprotein cholesterol levels, that women with subclinical hypothyroidism had higher prevalence of aortic atherosclerosis on chest radiograms (odds ratio [OR] 1.9; 95% confidence interval [CI] 1.2-3.1) and higher prevalence of myocardial infarction (OR 2.3; 95% CI 1.3-4.2) compared with euthyroid ones.

Prevalence of obstructive CAD in patients with diabetes mellitus depending on the presence of hypothyroidism was shown in the study, conducted by Pierre-Louis et al. (2008). In this study totally 352 patients with diabetes mellitus underwent coronary angiography because of recent myocardial infarction or unstable angina or chest pain with a positive stress test. More than 50% narrowing of 1 or more major coronary arteries was present in 145 of 173 patients (84%) with diabetes mellitus and hypothyroidism and in 132 of 179 patients (74%) with diabetes mellitus without hypothyroidism (p<0.025). More than 50% narrowing of 3 major coronary arteries was present in 69 of 173 patients (40%) with diabetes mellitus and hypothyroidism and in 39 of 179 patients (22%) with diabetes mellitus without hypothyroidism (p<0.001). So, these findings represent evidence that patients with diabetes mellitus and hypothyroidism have higher prevalence and intensity of CAD compared with patients with diabetes mellitus without hypothyroidism.

One recent study provides some kind of confirmation of the association between hypothyroidism and lower extremity arterial disease as an atherosclerosis display (Mazzeffi et al., 2010). Six hundred fourteen patients and 529 control cases were enrolled, and gender was found to be a significant confounder. In men there was a positive independent association between hypothyroidism and lower extremity arterial disease (adjusted OR 2.65; 95% CI 1.19-5.89), whereas in women there was a negative independent association (adjusted OR 0.22; 95% CI 0.11-0.46).

Thus, despite of widely accepted opinion about ability of hypothyroidism to accelerate the natural course of CAD, carefully designed large controlled studies are still needed to prove this point of view conclusively.

3. Impact of hyperthyroidism on the natural history of CAD

Hyperthyroidism can alter the natural course of CAD in several ways. First of all it increases myocardial oxygen demand together with sinus and/or supraventricular tachycardia (as well as atrial fibrillation) – these factors can contribute to decompensation of underlying CAD and lead to manifestation of angina pectoris and heart failure (mostly with high cardiac output). Furthermore, systolic blood pressure is usually increased, while diastolic blood pressure – decreased in patients with hyperthyroidism. Due to this pulse pressure becomes wider and mean blood pressure – moderately decreased. These changes are associated with an increase in cardiac output and reduction in peripheral vascular resistance, resulting in the classic hyperdynamic cardiovascular status (Fazio, et al., 2004). Cardiac preload is increased and blood volume is enlarged in patients with hyperthyroidism, there are also conditions for diastolic dysfunction of heart ventricles due to above-listed factors and tachycardia. Hyperthyroidism affects one more chain of the cardiovascular continuum: renin-angiotensin-aldosterone system is activated in patients with thyroid hyperfunction (Resnick & Laragh, 1982). It was also shown that hyperthyroidism is associated with elevation of von Willebrand factor levels as well as enhanced platelet function and therefore shortened collagen-epinephrine-induced closure time (platelet plug formation measure) (Homoncik et al., 2007). The presence of CAD may compromise the ability of myocardium to respond to the metabolic demands of hyperthyroidism (Kahaly & Dillman, 2005). Hyperthyroidism may cause myocardial infarction even in subjects without coronary stenosis (Cowda et al., 2003; Jaber et al., 2010; Moliterno et al., 1992). There were also described such changes which can influence the natural course of CAD as necrosis of myocytes, small areas of fibrosis or round-cell infiltration in the hearts of patients with hyperthyroidism (Kahaly & Dillman, 2005).

The prevalence of cardiac decompensation in hyperthyroid patients with advancing age was established (Davis & Devis, 1975; Kahaly & Dillman, 2005; Trivalle et al., 1996). In patients over 50 years of age cardiovascular complications are the leading cause of death after treatment of hyperthyroidism (Franklyn et al., 1998). Supraventricular arrhythmias in older patients may contribute to some of the excess cardiovascular mortality as it was shown in several long-term follow-up studies (Franklyn et al., 1998; Parle et al., 2001; Osman et al., 2002). In one population-based study (Franklyn et al., 1998) of mortality with standardized mortality ratio (SMR) as a measure of relative risk in a cohort of 7,209 patients with hyperthyroidism treated with radioiodine it was shown, that during 105,028 person-years of follow-up, 3,611 subjects died; the expected number of deaths was 3,186 (SMR 1.1; 95% CI 1.1-1.2; $p<0.001$). The risk was increased for deaths due to cardiovascular disease (240 excess

deaths; SMR 1.2; 95% CI 1.2-1.3; p<0.001), and cerebrovascular disease (159 excess deaths; SMR 1.4; 95% CI 1.2-1.5; p<0.001). Rheumatic disease (46 excess deaths, SMR 3.2; 95% CI 2.5-4.2; p<0.001) and hypertensive heart disease (31 excess deaths, SMR 2.1; 95% CI 1.6-2.7; p<0.001) had the highest SMRs. On the other hand, SMR for ischemic heart disease was modest (SMR 1.1; 95% CI 1.0-1.1; p=0.03) with 55 excess deaths. Intriguingly, in this study after separate analyses for men and women the excess deaths due to the cardiovascular disease was established for women but not for men (women: SMR 1.3; 95% CI 1.2-1.4; men: SMR 1.0; 95% CI 0.9-1.2; p<0.001 for the comparison between men and women).

So, the most important confounders for cardiovascular morbidity and mortality of hyperthyroid patients are dysrhythmias (especially atrial fibrillation) with tromboembolic complications, and hypertension. Gender of the patient may also have some influence on the clinical course of cardiovascular diseases in patients with hyperthyroidism.

4. Cardiovascular risk factors in patients with different thyroid status: Our findings

Recently we conducted a retrospective study, which took place in two medical centres in Kiev (Ukraine), aimed to establish prevalence of the main cardiovascular risk factors in 464 consecutive patients with CAD depending on their thyroid status, stratified into 3 groups: euthyroid (n=115, mean age 57.4±0.8 years, 76.5% female, mean thyrotropin level 1.6±0.12 mIU/L), hypothyroid (n=108, mean age 56.8±1.1 years, 76% female, mean thyrotropin level 12±1.7 mIU/L), and hyperthyroid (n=241, mean age 55.4±0.6 years, 86.7% female, mean thyrotropin level 0.16±0.03 mIU/L). Medical records were estimated and all patients, who met inclusion criteria (registered CAD and/or prescribed antiischemic therapy together with defined thyroid status), were included in our study. During statistical analysis continuous variables were expressed as mean±error of mean, categorical variables were expressed as frequency and percentage. Comparison between variables was performed using analysis of variance and the Student t test. A p value less than 0.05 was considered statistically significant.

The prevalence of hypertension was high in all groups with the highest rate for hypothyroid group (Fig.2). For hyperthyroid patients there was a trend for the increased prevalence of grade 1-2 hypertension, and less prevalent (approximately 2.1 times) grade 3 hypertension compared with rates in the euthyroid group. There was also significantly increased rate of grade 1-2 hypertension in hypothyroid patients compared with rate in the euthyroid group (see Fig.2).

We didn't find any significant differences in lipid profile among these 3 groups: total cholesterol, low-density lipoprotein and triglyceride levels were somewhat elevated in all groups, the only difference was obtained for high-density lipoprotein level, which was 26.6% lower in hypothyroid compared with euthyroid group of patients (Fig.3), but still within the normal range. These findings are consistent to the results of several studies (Cappola & Ladenson, 2003), but disagree with statement of Rizos et al. (2011) about possibility of high-density lipoprotein levels increasing in hypothyroid patients, likely due to mild-to-moderate hypothyroidism in our study (mean thyrotropin level 12±1.7 mIU/L). On the other hand, our results didn't show any significant differences in lipid profile between patients with CAD depending on thyroid status. This finding suggests that these changes were determined by alternative mechanisms, and their consequences are almost irrespective of thyroid status when it comes to moderate but overt thyroid dysfunction.

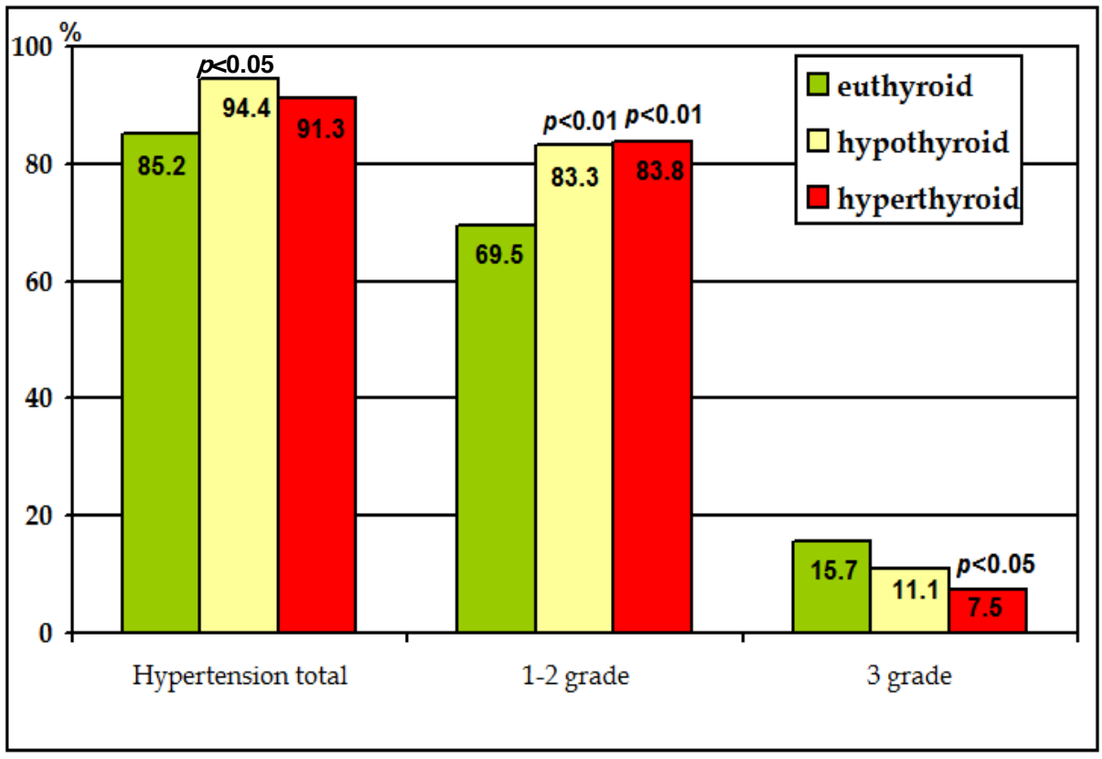


Fig. 2. Prevalence of hypertension in patients with CAD depending on thyroid status. *p* indicates statistical significance for comparison with euthyroid group.

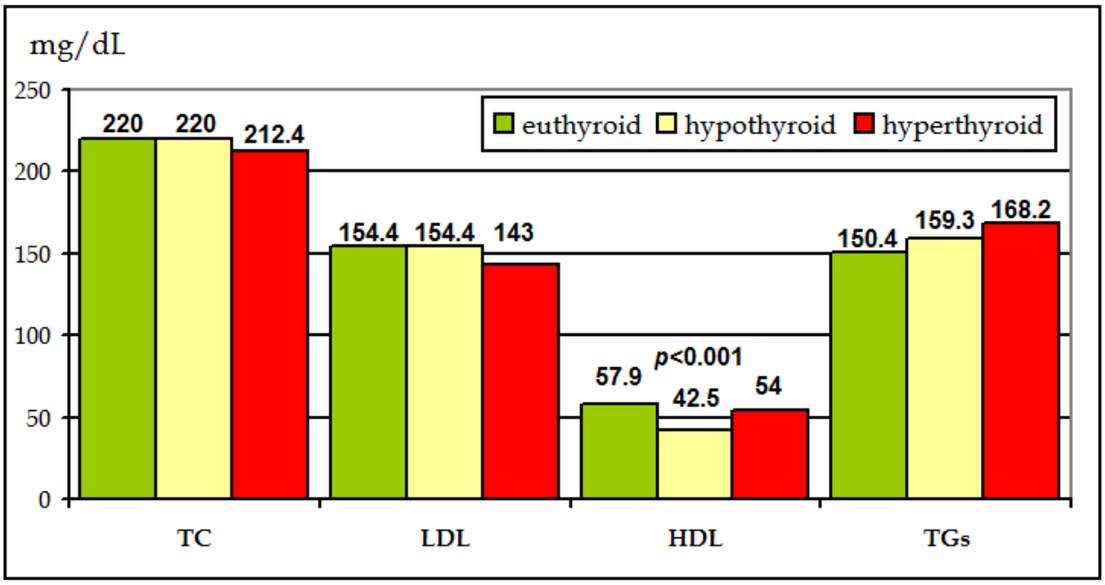


Fig. 3. Lipid profile in patients with CAD depending on thyroid status. *p* indicates statistical significance for comparison with euthyroid group. TC = total cholesterol, LDL = low-density lipoprotein, HDL = high-density lipoprotein, TGs = triglycerides.

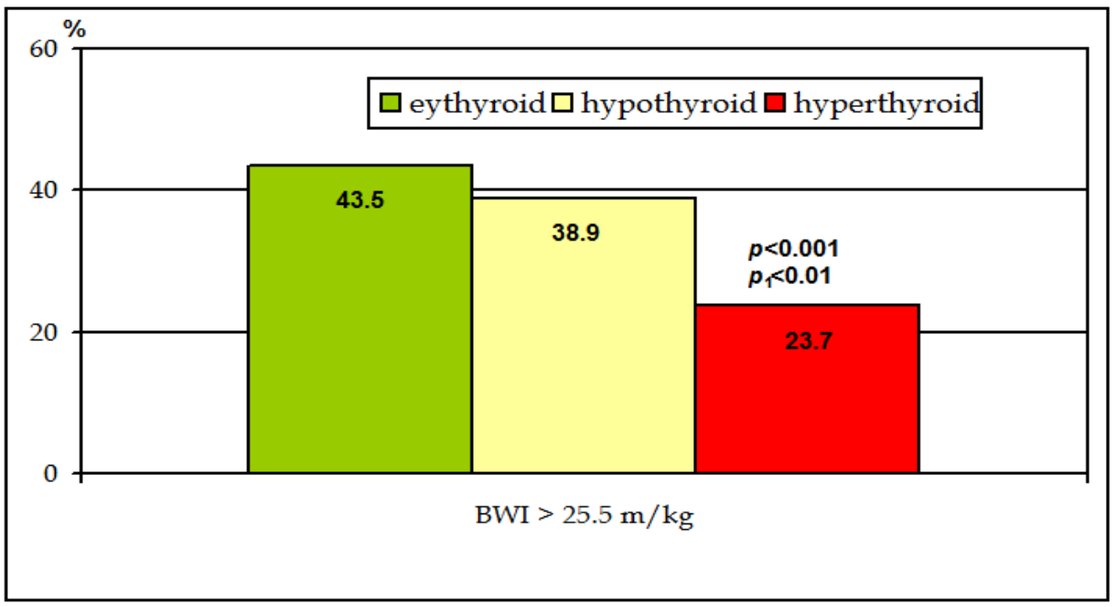


Fig. 4. Proportion of patients with body weight index more than 25.5 m/kg among those with CAD depending on thyroid status. *p* indicates statistical significance for comparison with euthyroid group, p_1 – statistical significance for comparison with hypothyroid group. BWI = body weight index.

In the course of body weight index estimation we had obtained expected results: patients with hyperthyroidism had better measures compared with other groups. Less than ¼ subjects of the hyperthyroid group had body weight index > 25.5 m/kg (Fig.4). In our study proportion of overweight patients in the hypothyroid group was more than ⅓ and in the euthyroid group – a little less than ½. We couldn't estimate waist circumference and waist-to-hip ratio, both the definite cardiovascular risk factors, because of the retrospective design of the study and lack of these data in medical records.

Our results regarding glycaemic status of the patients with CAD and thyroid dysfunction were surprising enough (Fig.5 & 6). Despite of being within normal limits, mean fasting plasma glucose level for patients in hyperthyroid group was significantly lower compared with such in euthyroid group (see Fig.5). This result was consistent to another one: in our study proportion of patients with fasting plasma glucose level > 102 mg/dL (5.6 mmol/L) was the smallest for hyperthyroid population (16.2%) compared with euthyroid (33%, $p<0.001$) and hypothyroid (25.9%, $p>0.05$) groups (see Fig.6). Fasting plasma glucose level >102 mg/dL is known cardiovascular risk factor influencing prognosis of the patients with hypertension (Mancia et al., 2007), and is important for patients with hyperthyroidism and CAD associated with increased prevalence of hypertension. This relatively lower level of fasting plasma glucose is probably linked to both activation of metabolism (particularly carbohydrate metabolism) and sensitivity to insulin, and reflects more intense glucose uptake by cells. There weren't any significant differences in diabetes prevalence between study groups (all $p>0.05$).

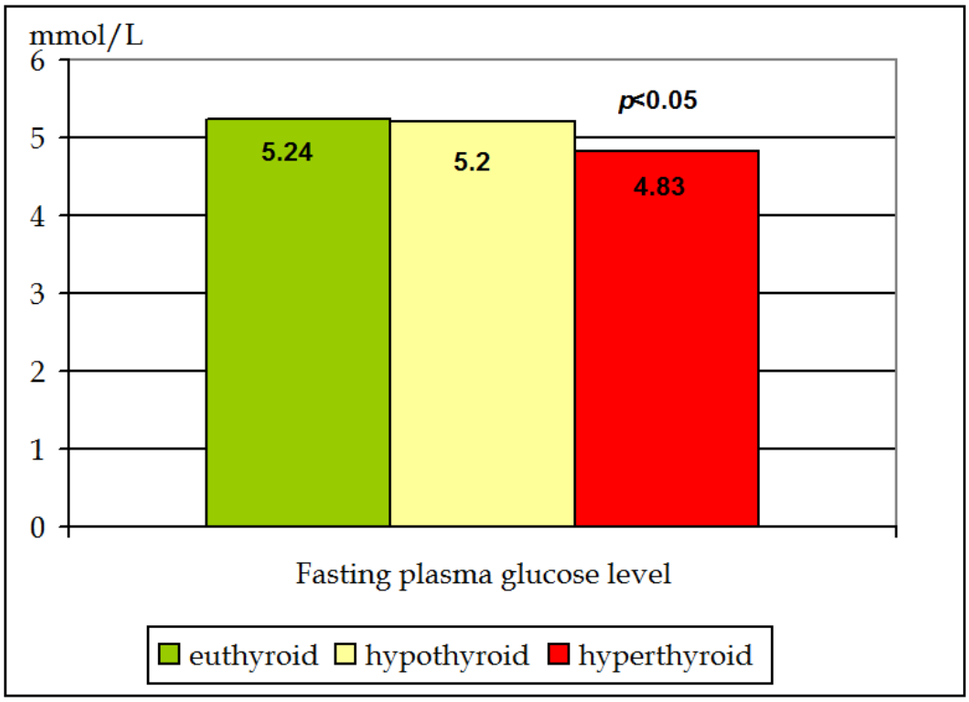


Fig. 5. Fasting plasma glucose levels in patients with CAD depending on thyroid status. *p* indicates statistical significance for comparison with euthyroid group.

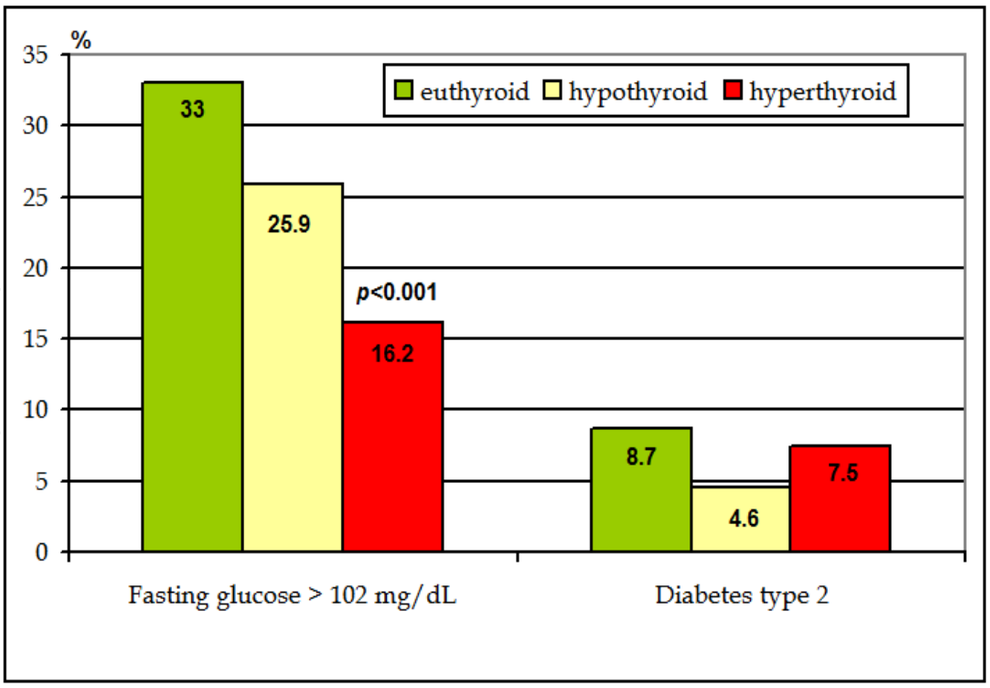


Fig. 6. Glycaemic status and prevalence of cardiovascular risk factors in patients with CAD depending on thyroid status. *p* indicates statistical significance for comparison with euthyroid group.

We also investigated the prevalence of previous main cardiovascular events: myocardial infarction and stroke in patients with CAD and different thyroid status (Fig.7). According to our data, in the euthyroid group prevalence of previous myocardial infarction was more than 2 times higher compared with such in hyperthyroid group (13.9% *vs*. 5%, respectively, $p<0.01$). In our study there weren't any statistically significant differences in the rates of stroke between study groups, which was really unexpected because of general opinion, that hyperthyroidism is strongly associated with stroke as a thromboembolic complication of atrial fibrillation (Franklyn et al., 1998). The lowest rate of previous myocardial infarction in this hyperthyroid group partly denies assumption that mild but not subclinical thyroid hyperfunction can definitely cause serious worsening of the natural course of CAD, and this hypothesis still needs careful and well designed investigation.

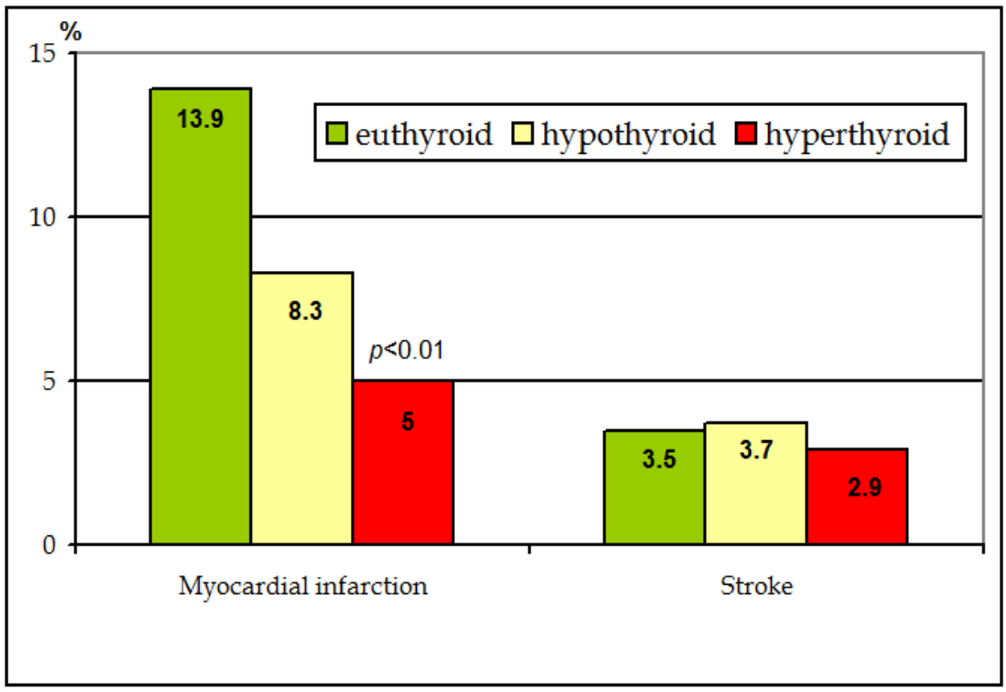


Fig. 7. Prevalence of previous cardiovascular events in patients with CAD depending on thyroid status. *p* indicates statistical significance for comparison with euthyroid group.

5. Conclusion

Despite numerous studies dedicated to the interaction between cardiovascular system and thyroid, a lot of issues are still unclarified. The results of different authors are often controversial first of all because of extreme difficulties in designing of such studies. The most problem of thyroid status identification and evaluation is its instability within the natural course of thyroid diseases. During years of illness thyroid function can be changed from activated to moderate activated, "normal" by results of several screening tests, and then - decreased. But if thyroid tissue is relatively preserved, it's absolutely possible, that thyroid function at times may become increased or "normal" again necessary amount of thyroid cells are available. This instability may cause selection bias during studies.

There is also a wide discussion about normal range of main markers of thyroid dysfunction: serum thyrotropin, triiodthyronine, thyroxine levels (Surks et al., 2004). Taking into consideration current complex classification of thyroid disorders, which is based on these marker levels, a new question arises: do we use the proper criteria for definition of thyroid dysfunction and dysfunction of different organs due to thyroid hormone changes, particularly cardiovascular system? What about tissue sensibility to thyroid hormone in patients with CAD? It is still unclear, how works thyroid hormone in people with cardiovascular diseases: atherosclerosis and CAD? Is this mechanism similar or not to such in healthy subjects? What are the differences? Can genetic features of the patients with cardiovascular disease, which predispose a person to atherosclerosis and CAD, influence normal or pathological thyroid?

Recently emerging evidence indicates that 45–65% of the inter-individual variation in serum thyroid hormone levels is due to genetic factors (Medici et al., 2011). In one study 68 genes (1512 polymorphisms) were studied in relation to serum thyrotropin and thyroxine levels in 1,121 Caucasian subjects. It was shown that for thyrotropin 8 *PDE8B* polymorphisms ($p=4\times10^{-17}$) and for thyroxine 2 *DIO1* ($p=8\times10^{-12}$) and 1 *FOXE1* ($p=0.0003$) polymorphisms remained significant in the meta-analysis (Medici at al., 2011). In the meta-analysis of 2,557 patients Taylor et al. (2011) have clarified associations between the rs4704397 single nucleotide polymorphism in *PDE8B* and thyrotropin, triiodothyronine and thyroxine levels. This meta-analysis confirmed presence of genetic variation in *PDE8B* associated with thyrotropin ($p=1.64\times10^{-10}$) and identified a possible new association with free thyroxine ($p=0.023$). Taylor et al. (2011) suggest that common genetic variation in *PDE8B* is associated with reciprocal changes in thyrotropin and free thyroxine levels that are consistent over time and lost in individuals on levothyroxine therapy. These both results are intriguing because they display possible genetic markers of variation in serum thyroid hormone levels that will be helpful in designing and carrying out epidemiological studies.

Treatment of both thyroid and cardiovascular diseases can contribute to pathways and outcomes, but till now we know little about this. Some studies were dedicated to the evaluation of influence of hyperthyroidism treatment strategies on cardiovascular outcomes (Hall et al., 1993; Franklyn et al, 1998), but precise mechanisms of their action are still unclear. One of the recent treatment approaches for hyperthyroidism is so called "suppress and replace" management with complete suppression of thyroid function (marker – thyrotropin levels) and simultaneously replacement therapy with thyroid hormone (Kahaly & Dillmann, 2005). This condition and its possibility to influence the cardiovascular system should be carefully established. In some cases of treatment with levothyroxine it is possible even in previously hypothyroid patients appearance of "tissue hyperthyroidism" on cardiac level (normal thyroxine and triiodthyronine and suppressed thyrotropin) (Banovac et al., 1989). The fact that euthyroid due to the replacement therapy hearts are not similar to those euthyroid without such therapy were discussed elsewhere (Bengel et al., 2000; Biondi et al., 1996), but we need more evidence.

It is also widely known that cardiovascular diseases may contribute to the thyroid function predominantly causing its down-regulation. In one study it was shown, that patients with CAD during acute phase of myocardial infarction demonstrated a rapid and sustained fall in serum total triiodothyronine concentration, a rise in reverse triiodothyronine concentration, and a transient fall in total thyroxine concentration. This observed fall in

triiodothyronine concentration wasn't accompanied by significant changes in basal thyrotropin concentrations (Franklyn et al., 1984). In another study of 47 consecutive euthyroid patients with acute myocardial infarction thyroid status also was evaluated (Friberg et al., 2002) with mostly similar results. The study had demonstrated that thyroid hormone was rapidly down-regulated with maximal development by 24-36 hours after onset of symptoms. The mean of serum total triiodothyronine concentration decreased by 19% (p=0.02), the mean of serum reverse triiodothyronine concentration increased by 22% (p=0.01), while serum thyrotropin concentration decreased by 51% (p<0.001) between the first 6-hour of myocardial infarction and 24-36-hour time interval. Notably, patients with severe heart dysfunction or more intense inflammatory reaction showed more pronounced down-regulation of the thyroid function. Interestingly, serum free thyroxine levels was predominantly unchanged in both studies (Franklyn et al., 1984; Frieberg et al., 2002). This adaptive reaction provides reduction of myocardial oxygen demand and relieves emerged mismatch between myocardial oxygen demand and oxygen delivery in patients with CAD. On the other hand, in several studies association between thyrotropin levels (even within reference range) and body weight index, the occurrence of obesity (Knudsen et al., 2005), and serum lipid concentrations (Åsvold et al., 2007b) was found. In 2008 Åsvold et al. had published their new results from the Nord-Trøndelag Health study (the HUNT study) about association between CAD mortality and relatively low thyroid function within the clinical reference range. Total 25,313 patients without history of thyroid disease, angina, myocardial infarction, stroke or diabetes mellitus at baseline were enrolled. At the end of follow-up (median 8.3 years) 228 women (1.3%) and 182 men (2.3%) died of CAD (192 women and 164 men of them had thyrotropin levels within the reference range). The presence of positive association of thyrotropin level within the reference range with risk of fatal CAD was shown (p for trend=0.01 in the total population and p for trend=0.007 in non-smokers), especially in women (p for trend=0.005). Compared with women in the lower part of reference range (thyrotropin level 0.5-1.4 mIU/L) hazard ratios were 1.41 (95% CI 1.02-1.96) and 1.69 (95% CI 1.14-2.52) for women in the intermediate (thyrotropin level 1.5-2.4 mIU/L) and higher (thyrotropin level 2.5-3.5 mIU/L) parts of the reference range, respectively (Åsvold et al., 2008). These results suggest that relatively low but clinically normal thyroid function may increase the risk of fatal CAD, especially in non-smoking women.

In Czech Republic Mayer et al. (2006) conducted a study aimed to ascertain the prevalence of hypothyroidism in 410 patients (303 men and 107 women) with manifest CAD and to establish its association with cardiovascular risk factors. The prevalence of hypothyroidism (overt & subclinical) in the total sample and among male and female patients was 11.2, 6.9 and 23.4%, respectively. Overt hyperthyroidism (thyrotropin level> 3.65 mIU/L and free thyroxine <9 pmol/L and/or levothyroxine substitution) in this study was detected in 4.1% of total sample, 2.6% male and 8.4% female patients. Interestingly, there weren't any differences in hyperthyroidism prevalence: for total sample and separately male and female patients it was 5.6%. On the other hand, in this study the high prevalence of diabetes type 2 was found for the total sample (was not shown) with mean of fasting plasma glucose levels ranged from 6.7 to 7.6 mmol/L in euthyroid and hypothyroid groups without statistical difference. This finding is somewhat controversial to our results, but it can be explained by differences in the study samples: Mayer et al. (2006) enrolled only those who had survived after acute coronary episode in their study, while we didn't use this selection approach.

A lot of issues must be investigated before we can understand all mechanisms of interaction between thyroid and cardiovascular system, especially the natural course of CAD. It seems there is a great influence of individual differences of our patients with CAD and thyroid dysfunction on cardiovascular outcomes, and we should determine them in new large carefully designed controlled studies.

6. References

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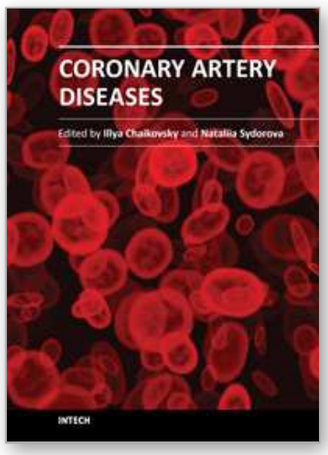
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This book has "wide geography" both literally and figuratively. First of all, this book brings together contributions from around the world, both from post-industrial countries and developing world. This is natural, because coronary artery disease is becoming pandemic worldwide. CAD is the single most frequent cause of death in developed countries, causes about 1 in every 5 deaths. Mortality from cardiovascular disease is predicted to reach 23.4 million in 2030. Moreover, in the developing world, cardiovascular disease tends to affect people at a younger age and thus could negatively affect the workforce and economic productivity. The morbidity, mortality, and socioeconomic importance of CAD make its diagnosis and management fundamental for all practicing physicians. On another hand, the book widely represents "geography" of CAD itself, i.e. many various aspects of its pathophysiology, epidemiology, diagnosis, treatment are touched in this book. This book does not pretend on complete and integral description of the Coronary artery disease. Rather, it contains selected issues on this complex multifactorial disease. Nevertheless, we hope that readers will find Coronary Artery Disease useful for clinical practice and further research.

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