THYROID DYSFUNCTION AND ISCHEMIC HEART DISEASE – CLINICAL CORRELATIONS, PROGRESSIVE IMPLICATIONS AND IMPACT ON THE PROGNOSIS

Daniela Maria Tănase¹, Simona Daniela Ionescu², Anca Ouatu³, V. Ambăruş⁴, C. Rezuş², Cătălina Arsenescu-Georgescu²
University of Medicine and Pharmacy “Grigore T. Popa” - Iasi
Faculty of Medicine
1. Ph.D. student
2. Discipline of Internal Medicine - Cardiology

THYROID DYSFUNCTION AND ISCHEMIC HEART DISEASE – CLINICAL CORRELATIONS, PROGRESSIVE IMPLICATIONS AND IMPACT ON THE PROGNOSIS (Abstract): Thyroid dysfunctions are associated with systolic and diastolic heart dysfunction, hypertension, rhythm disorders, etc. Clinically significant hyperthyroidism and hypothyroidism may have an impact on the patients with ischemic heart disease. **Objectives:** Investigation of the risk of developing ischemic heart disease, of the evolution and prognosis in relation to the entire spectrum of thyroid dysfunctions. **Materials and methods:** All participants included in the study were selected from among subjects with heart disorders who were controlled with concern to the thyroid hormonal condition and who hadn’t been treated previously for thyroid functional disorders. Based on these criteria we defined a study group made out of 791 subjects, divided into five lots based on the level of thyroid hormones. Once the group was formed, we conducted evaluations of the cardiovascular and thyroid status at 6 and 12 months, respectively. **Results:** In the witness lot, during monitoring 49% of the patients showed an ischemic heart disease. The main risk factors were: heart frequency of over 80 beats/min (RR=1.83), age over 60 (RR=1.47), female sex (RR=1.21) and values of triglycerides over 160 mg/dl (RR=1.23). In the group of patients with overt clinic hyperthyroidism, during monitoring 46.1% showed ischemic heart disease. The main risk factors were: heart frequency over 80 beats/min (RR=2.41), age over 60 (RR=1.67), high level of LDL-cholesterol (RR=1.53) and female sex (RR=1.31). Among the patients with overt clinical hyperthyroidism, during monitoring 53.3% showed ischemic heart disease. The main risk factors identified were: heart frequency over 80 beats/min (RR=2.01), age over 60 (RR=1.42), high levels of triglycerides (RR=1.42) and LDL-cholesterol (RR=1.32), as well as the presence of hypertension in the health records (RR=1.31). **Conclusions:** Thyroid dysfunction is a common clinical condition with a key role in the regulation of the cardiovascular system and may contribute to the evolution of the ischemic heart disease and which should be taken into consideration when patients with heart disease are treated. In this light, thyroid function needs to be evaluated for all patients with a risk for ischemic heart disease. **Keywords:** HYPERTHYROIDISM, HYPOTHYROIDISM, ISCHEMIC HEART DISEASE.
significance at 0.3% and subclinical significance at 4.3%) (1).

Thyroids disorders are associated with systolic and diastolic heart dysfunction, hypertension, rhythm disorders, etc. Clinically significant hyperthyroidism and hypothyroidism may have an impact on patients with ischemic heart disease. As recently shown in numerous studies, even the subclinical hyperthyroidism may be an independent risk factor for the mortality caused by cardiovascular disorders (2). Previously, subclinical hypothyroidism was admitted as an independent risk factor for atherosclerosis and heart failure at older women (3). However, the results of these studies are sometimes controversial (4, 5, 6, 7).

The study tried to determine through a retrospective analysis (case study – control) and a subsequently prospective perspective the correlation between the thyroid status, the cardiovascular risk factors and mortality at adult patients.

**MATERIAL AND METHODS**

All participants included in our study were selected from among subjects with cardiovascular disorders who were subject to a control of thyroid hormone status in the 3rd Medical Clinic of “St. Spiridon” Emergency University Hospital, “Gr. T. Popa” University of Medicine and Pharmacy, Iași and who hadn’t been previously treated for thyroid functional disorders. The study lots were constituted from 2006 to 2012.

We included among the subjects men and women, with an age varying from 22 to 86, with an average of about 60 years old, based on the serum values of free triiodothyronine (FT3), free tetraiodothyronine (FT4) and the thyroid-thyrotropin stimulating hormone (TSH). All patients were subjected to a complete medical evaluation, laboratory exams, electrocardiogram and echocardiography. The exclusion criteria included: age < 18; hypophysary/hypothalamic disorders, pregnancy, administration of specific thyroid treatment prior to the inclusion in the study. Based on these criteria we defined a study lot made out of 791 patients who were divided into five groups based on the level of thyroid hormones: a) HYPER subclinic – 81 patients with subclinical hyperthyroidism (10.2%); b) HYPER – 165 patients with hyperthyroidism (20.9%); c) hypo subclinical – 75 patients with subclinical hypothyroidism (9.5%); d) hypo – 170 patients with hypothyroidism (21.5%); e) Witness group – 300 patients with cardiovascular modifications without thyroid dysfunction (37.9%). Once the study lot was formed we conducted evaluations off the cardiovascular status at 6 and 12 months.

The analysis was made by means of the **SPSS 13.0** package (SPSS Inc, Chicago, Illinois, USA).

**RESULTS**

At the witness group, during monitoring 49% of the patients showed ischemic heart disease. The main risk factors were: heart frequency of over 80 beats/min (RR=1.83), age over 60 (RR=1.47), female sex (RR=1.21) and values of triglycerides over 160 mg/dl (RR=1.23). The treatment with antiarrhythmic drugs (RR=0.88) and beta blockers (RR=0.79) administered prior to the inclusion in the study proved to be a protective factor (tab. I, fig. 1).

Among the patients with subclinical hyperthyroidism, 28.4% showed ischemic heart disease at the beginning of the study. The main risk factors identified were: the presence of hyperglycemia (RR=1.65) and
hypertension (RR=1.42) in antecedents and high values of triglycerides (RR=1.55). In the context of decompensation of thyroid disease, the treatment with beta blockers (RR=0.79), ACEIs (angiotensin converting enzyme inhibitors) (RR=0.61) and/or antiarrhythmic drugs (RR=0.48) shows a protective factor in the development of ischemic heart disease (tab. I, fig. 1).

In the group of patients with clinically overt hyperthyroidism, during monitoring 46.1% showed ischemic heart disease. The main risk factors were: heart frequency over 80 beats/min (RR=2.41), age over 60 (RR=1.67), high level of LDL-cholesterol (RR=1.53) and female sex (RR=1.31). The treatment with ACEIs, beta blockers and antiarrhythmic proved a protective factor for this group (tab. I, fig. 1).

The main risk factors leading to ischemic heart disease for the 52% of the patients with subclinical hypothyroidism included: heart frequency over 80 beats/min (RR=3.83), obesity (RR=2.55), presence of hypertension in the personal records (RR=1.97), age over 60 (RR=1.67), female sex (RR=1.61) and a high level of LDL-cholesterol (RR=1.57). In the case of the patients who, prior to the first evaluation, received beta blockers (RR=0.61) and/or antiarrhythmic drugs (RR=0.63), the medication proved to be a protective factor in the development of ischemic heart disease (tab. I, fig. 1).

Among the patients with clinically overt hypothyroidism, during monitoring 53.3% showed ischemic heart disease. The main risk factors identified included: heart frequency over 80 beats/min (RR=2.01), age over 60 (RR=1.42), high levels of triglycerides (RR=1.42) and LDL-cholesterol (RR=1.32), as well as the presence of hypertension in the personal records (RR=1.31). The treatment with ACEIs (RR=0.95), antiarrhythmic drugs (RR=0.68) and/or beta blockers (RR=0.42), administered prior to the admission in the group is a protective factor for the development of ischemic heart disease in this study group (tab. I, fig. 1).

### TABLE I

<table>
<thead>
<tr>
<th>Risk factors in the development of ischemic heart disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Witness (n=147/300)</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>RR</td>
</tr>
<tr>
<td>Female sex</td>
</tr>
<tr>
<td>Age ≥ 60</td>
</tr>
<tr>
<td>BMI ≥ 25 Kg/m²</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td>HF ≥ 80 beats/min</td>
</tr>
<tr>
<td>LDLc ≥ 130mg/dl</td>
</tr>
<tr>
<td>Tg ≥ 160mg/dl</td>
</tr>
<tr>
<td>ACEIs</td>
</tr>
<tr>
<td>Beta blocker</td>
</tr>
<tr>
<td>Antiarrhythmic</td>
</tr>
</tbody>
</table>
During the study, in the case of the witness lot, out of the 147 cases of ischemic heart disease, 2 fatal events are recorded (1.4%) and 37 non-fatal events (25.2%), statistically significant proportions (p=0.001). At the patients with antecedents of ischemic heart disease, the relative risk of developing an unfavorable event is 1.85 times higher (RR=1.85; IC95%: 1.38÷2.48) (tab. II, fig. 2).

At the lot with subclinical hyperthyroidism, 7 non-fatal events are recorded (17.9%) at the 39 patients with ischemic heart disease in the records (p=0.001). At this study lot, the relative risk of an unfavorable event in the context of the presence of heart disease in the records was 2.9 times higher (RR=2.90; IC95%: 1.43÷5.87) (tab. II, fig. 2).

Fig. 1. Relative risk of ischemic heart disease on study lots
Thyroid dysfunction and ischemic heart disease – clinical correlations, progressive implications and impact on the prognosis

TABLE II
Proportion of patients with ischemic heart disease

<table>
<thead>
<tr>
<th>Ischemic heart disease</th>
<th>Witness</th>
<th>HYPER subcl</th>
<th>HYPER</th>
<th>Hypo subcl</th>
<th>Hypo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Beginning of the study</td>
<td>147</td>
<td>49.0%</td>
<td>23</td>
<td>28.4%</td>
<td>76</td>
</tr>
<tr>
<td>End of the study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal events</td>
<td>2</td>
<td>1.4%</td>
<td>0</td>
<td>0%</td>
<td>0</td>
</tr>
<tr>
<td>Non-fatal events</td>
<td>37</td>
<td>25.2%</td>
<td>15</td>
<td>65.2%</td>
<td>28</td>
</tr>
<tr>
<td>p</td>
<td>0.001</td>
<td></td>
<td>0.002</td>
<td></td>
<td>0.229</td>
</tr>
</tbody>
</table>

Fig. 2. Proportion of fatal/non-fatal events during monitoring of ischemic heart disease

DISCUSSION

Hyperthyroidism, through the cardiac hyperkinetic status it determines and thus through the increased myocardium oxygen requirement may worsen or decompensate ischemic heart disease. This mechanism is most frequently met at older patients. However, acute myocardial ischemia is rarely met in hyperthyroidism, in the absence of an already developed heart disorder (8). There are nonetheless, numerous case off hyperthyroidism which determined coronary spasm with the production of an acute myocardial infarction (8, 9).

Taking into consideration the fact that at the patients with hyperthyroidism an increase of the flow-mediated vasodilatation dependent on the endothelium was demonstrated, it is somehow paradoxical that thyrotoxicosis may induce a vaso-spasm, given the peripheral vasodilatation effect of thyroxine. In vitro studies showed an increase of contractility of smooth muscle tissues upon stimulation with various vasoconstrictor agents in case of a hyperthyroid status (10). The hyperthyroid status is associated with an adrenergic hyper stimulation which may have as an effect coronary spasm. Myocardial infarction at hyperthyroid patients may appear if the
coronary spasm is maintained long enough. Generally, the prognosis of patients with coronary spasm associated to hyperthyroidism is favorable. Studied demonstrated the disappearance of anginous symptoms once the euthyroid status was reestablished at these patients (8).

The association between clinically overt hypothyroidism and ischemic heart disease was noticed in several studies (11). Less evident is the role of subclinical hypothyroidism, much more frequently met among patients with cardiovascular disorders. However, it was demonstrated that subclinical hypothyroidism is an independent risk factor which doubles the risk of myocardial infarction for women (12).

In a study that included patients with symptomatic ischemic heart disease, the prevalence of hypothyroidism was of 11.5%. Hypothyroidism was 4 times more frequent at women with ischemic heart disease than at men (23.4% vs. 6.9%) (11). At the level of the general population, out of which the study lot was selected, the prevalence of hypothyroidism was of 6.8% for men and of 13.8% for women. The prevalence of hypothyroidism for women was similar both under 55 years old and for above this age, which leads to a recommendation to investigate the thyroid function for all women with ischemic heart disease, regardless of their age (13).

The importance of hypothyroidism as a cardiovascular risk factor was assessed based on its association with high levels of total or LDL cholesterol. In the study conducted by Mayer O. (13), it was noticed that women with untreated hypothyroidism have higher levels of total or LDL cholesterol. Surprisingly, no similar association was found in case of men and this discrepancy couldn’t be explained based on the difference in the statin therapy.

Increased serum levels of homocysteine, an important predictor for coronary disorder, were found in both men and women with hypothyroidism. Wald and coll. showed that an increase of 4-5µmol/L of homocysteine determines an increase by 32% of the risk of coronary events and by 59% of the risk of cerebrovascular events (14). The increase of homocysteine in hypothyroidism is due to a reduction of the glomerular filtration rate and a decrease of the activity of methylenetetrahydrofolate reductase, a key enzyme in the remethylation of homocysteine at methionine.

As in the case of homocysteine, an association was found between hypothyroidism, both clinical and subclinical, and the increase of reactive C protein (CRP) as well as endothelial dysfunction, evaluated through the endothelium dependent vasodilation (15, 16). A very important aspect is that this endothelial dysfunction may be improved by the treatment of hormonal substitution with levothyroxine (16).

Taking into consideration this correlation between hypothyroidism and ischemic heart disease, the next question that arises is whether the treatment of hormonal substitution may reduce the coronary risk. Several placebo controlled trials, as well as a review showed that the levothyroxine administered to patients with hypothyroidism leads to a decrease of the total or LDL cholesterol level, failing to influence the HDL cholesterol or triglycerides (17, 18, 19).

In the recent years, several biomarkers, such as CRP and homocysteine gained an important role in the stratification of risk for patients with an alleged ischemic heart disease. However, we shouldn’t omit the importance of the thyroid function, which should be evaluated for the patients at risk.
Thyroid dysfunction and ischemic heart disease – clinical correlations, progressive implications and impact on the prognosis

for ischemic coronary disease. This could help to exclude secondary dyslipidemia. Taking into account the reverse association revealed between the serum level of FT3 and the prevalence of ischemic heart disease, as well as the correlations between the levels of FT4 and the mortality of any cause, their dosing is a rather inexpensive test which could prove useful in the stratification of coronary risk (20, 21).

CONCLUSIONS

Thyroid dysfunction is a common clinical issue with a key role in the regulation of the cardiovascular system and may contribute to the evolution of ischemic heart disease and should be taken into account when patients with coronary disorders are treated. In this light, the thyroid function should be evaluated for all patients with a risk of ischemic heart disease.

REFERENCES


---

**NEWS**

**DIABETES AND PERIODONTITIS**

Diabetes mellitus is emerging as a global epidemic, whose complications impact significantly on quality of life, longevity and healthcare costs. The escalating human and economic burden across both the developed and developing world necessitates a multidisciplinary approach, including adjunctive measures to managing diabetes and its complications. The onset of diabetes is preceded by inflammation, which leads to pancreatic beta-cell dysfunction and apoptosis, as well as impacting on the development of insulin resistance and ultimately diabetes. It is logical that comorbidities that contribute to systemic inflammation are likely to increase the risk of developing diabetes, and impact on diabetes control and the development of diabetes complications, ultimately affecting diabetes-associated morbidity and mortality.

Inflammatory periodontal diseases are the most common chronic inflammatory conditions of humans worldwide. Periodontal disease is a microbially initiated chronic inflammatory disease, in which dysregulated immune-inflammatory processes are responsible for the majority of host tissue destruction, and ultimately tooth loss. There is increasing evidence that systemic inflammation results from the entry of oral microbial agents and their virulence factors into the circulation. This is evidenced by elevated serum levels of C-reactive protein and other acute-phase reactants and raised biomarkers of oxidative stress. It is therefore biologically plausible that non-resolving chronic inflammation derived from periodontal disease impacts on diabetes control (elevated HbA1C) and complications, as well as beta-cell function, insulin resistance and development of type 2 diabetes. New researches are needed because a strong evidence base exists from epidemiological studies that periodontitis and diabetes are directly associated, and that periodontal interventions provide beneficial effects on diabetes outcomes (Iain L. C., Robert Genco. Diabetes and periodontal Diseases. *J Periodontol* 2013; 84(4 Suppl.): S106-S112).

*Doina Butcovan*