Effects of Treatment with L-thyroxin on Glucose Regulation in Patients with Subclinical Hypothyroidism

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Aims: We examined effects of treatment with L-thyroxin on glucose regulation in patients with subclinical hypothyroidism. Methods: The study included 100 patients, ages 51.75±13.23 years, BMI=27.97±4.52 kg/m², with SH (TSH>4.2 mU/L and with normal level of T3 and T4). Laboratory evaluation included serum free T3, free T4, TSH, thyroid antibodies, TGL, insulin, C-peptide and glucose during OGTT, HbA1c, CRP and level of lipids. Percentile, average and correlation analysis have been utilized in statistical analysis. Twelve patients with SH had GI and 38 patients had DM. All patients were treated with low dose of L-thyroxin (25-50ug) and high physical activity. Results: After 6 months treatment with L-thyroxin, patients had normal or limited TSH (5.85±0.92 vs. 3.54±0.55 mU/L), level of fasting insulin (114.64±24.11 vs. 96.44±17.26 pmol/l) significantly decreased, HbA1c (6.74±1.01 vs. 6.26±1.12) decreased as well. The level of CRP significantly decreased as well (2.27±0.8 vs. 3.32±1.1 mg/l). The changes were and in level of total cholesterol (5.39±0.57 vs. 6.10±0.67 mmol/l), triglyceride levels (1.69±0.37 vs. 2.22±0.49 mmol/l), HDL cholesterol (1.16±0.14 vs. 1.03±0.15mmol/l) and LDL cholesterol (3.79±0.64 vs. 4.37±0.77 mmol/l). The correlation between TSH and HbA1c was positive and significant (r=0.46). Conclusion: The normalization of TSH resulted in decrease of level of fasting insulin, fasting and postprandial glucose, CRP and lipids. Higher CRP associated with fasting hyperinsulinemia before insulin resistance has been evidenced in most patients with SH. These data support an important role of treatment of SH in support of glucose regulation. Key words: subclinical hypothyroidism, L-thyroxin, glucose regulation.

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1. INTRODUCTION

Hypothyroidism is one of the most common diseases of the endocrine system (1, 2, 3, 4, 5). Most hypothyroidism cases are subclinical. The prevalence of subclinical hypothyroidism is 8-10%, even 15% for women and 3% for men. Already slight subclinical hypothyroidism can cause disorders of sensitive functions-left ventricular diastolic dysfunction, lack of ovulation and the expression of LDL receptors which cause increase in LDL and decrease HDL-cholesterol while total cholesterol still remains normal (6, 7, 8, 9, 10). The slowdown of all processes at the same time leads to the loss of their mutual balance of thyroid hormones which regulate metabolic processes throughout the body and affect the supply of sugar in the blood. In hypothyroidism is slowed reabsorption of carbohydrates from the digestive system, slower the gastric emptying but increased sensitivity to insulin. The prevalence of thyroid disease in patients with diabetes mellitus is approximately 10-15% (1).

Absence of symptoms in patients with subclinical hypothyroidism and the serious health consequences, including cognitive disorders, imposes the importance of timely diagnosis of subclinical hypothyroidism and adequate treatment of patients with small doses of L-thyroxine (11, 12, 13).

In addition, subclinical hypothyroidism can progress to manifest, especially in patients with circulating anti-body thyroid gland. Since the determination of TSH is accurate, accessible, safe and inexpensive test to diagnose subclinical hypothyroidism, in the future we can expect that determination of the TSH level can be used to define the risk of the occurrence of various complications (osteoporosis, cardiovascular disease, depression) for different TSH levels.

As a result, the decision on the introduction of substitution therapy shall
be taken, not only by the levels of TSH, but based on additional factors, such as gender, age, smoking, hypertension, cholesterol levels and diabetes. Analogous approach is now used in making decisions about the treatment of hypertension and dyslipidemia.

Modern research has shown a link between type 1 diabetes and autoimmune thyroid disease. Type 1 diabetes is more common in young people, especially in puberty. Even at the very beginning of the development of diabetes by 15 to 30% of children were positive anti TPO antibodies and antithyrogeglobulin. Antibodies are more often present in girls than boys. For half of the children in the further course of disease will develop clinically manifested autoimmune thyroid disease. In children with diabetes rapidly increasing level of antibodies leading to subclinical hypothyroidism. Then the child has no symptoms. The laboratory will detect elevated TSH and thyroid hormones (T3 and T4) are normal. Disease progression is towards development of manifest hypothyroidism, except when reduced thyroid hormones, there are problems. This disease usually develops gradually and insidiously. Patients usually have fatigue, malaise, lethargy, cold intolerance, and get fat if you often have increased appetite, then they can have stomach bloating and constipation, sweating and weak often feel pain in the chest.

Subclinical hypothyroidism independently increases the risk for impaired insulin sensitivity, especially in the adipose tissue and muscle. Post receptors disorder of insulin signal seems to be the main reason for hyperinsulinemia. Almost all persons with excessive body weight have insulin resistance. The concept of insulin resistance in patients with subclinical hypothyroidism has been further complicated by selective tissue sensitivity and selective activity within the tissue that is resistant to its effect.

On the other hand there is an evident correlation between subclinical hypothyroidism and hyperinsulinemia and insulin resistance, so that subclinical hypothyroidism and insulin resistance via its numerous mechanisms involved in disorders of diabetes control, are described in many recent studies. It is therefore of utmost importance to identify the influence of L-thyroxine treatment on glucose regulation in patients with subclinical hypothyroidism.

2. GOAL

Determine the influence of L-thyroxine treatment on glucose regulation.

Determine whether between TSH and HbA1c there is a statistically significant correlation. To determine the prevalence of glucose intolerance and diabetes mellitus in patients with subclinical hypothyroidism.

3. MATERIAL AND METHODS

This study was a retrospective, clinical, comparative and descriptive. For the analysis were used the history of all the patients with subclinical hypothyroidism who were hospitalized or treated as outpatients in period from January 1st 2007 until December 31st 2009 at the Clinic of Endocrinology, Diabetes and Metabolic Diseases, Clinical Center University of Sarajevo. The study included 50 patients referred to the Clinic who were hospitalized or treated in outpatient department if period from January 1st 2007 until December 31st 2009 with subclinical hypothyroidism (TSH >4.2 mIU/l and normal levels of T3 and T4) and who were treated with low doses of L-thyroxine.

The average dose of L-thyroxine therapy of was 25-50 ug. All the tests were repeated 6 months after the L-thyroxine therapy was introduced. The control group consisted of 50 patients with subclinical hypothyroidism that was treated with L-thyroxine. Excluded from the study were the subjects with subclinical hypothyroidism of iatrogenic origin (all states after surgical intervention on the thyroid gland or after treatment with radioactive iodine). For each patient a detailed history was taken with clinical and laboratory parameters.

4. RESULTS

Statistical analysis of data was performed using the computer software specific to this type of problem. The results are presented graphically. Testing of significance in differences of quantitative variables was done using the Student t-test with the statistical package SPSS.

In our sample glycemic control disorders was present in 58 (58%) of patients with subclinical hypothyroidism. In our sample, there were 20 patients with prediabetes (20%) and 38 patients with diabetes (38%).

The results shown in Figure 1 indicate that there was a significant decrease of TSH after treatment with L-thyroxine in both groups, or in the group of patients with prediabetes (6.0±0.01 vs. 3.74±0.45, p=0.02), as well as in the group of patients with diabetes (6.92±0.76 vs. 3.85±0.56, p=0.01).

Figure 2 presents the average values of TSH in all patients treated and not treated with L-thyroxine

Student t-test with the statistical package SPSS.

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Figure 2 presents the average values of TSH in all patients treated and not treated with L-thyroxine. It is evident that in the group of patients who were treated with L-thyroxine was significantly decreased TSH in relation to a group of patients who were not
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The results shown in Figure 3 show that there has been a reduction in HbA1c values after the treatment with L-thyroxin in both groups of patients, or in those with prediabetes (6.46±0.13 vs. 5.99±0.13, p=0.01), as well as in patients with diabetes (7.94±0.59 vs. 7.11±0.45, p=0.006).

Figure 4 presents the average values of HbA1c in patients treated and not treated with L-thyroxin. It is evident that in the group of patients who were treated with L-thyroxin significantly reduced HbA1c compared to a group of patients who were not treated with L-thyroxin (6.74±1.01 vs. 6.26±1.12, p=0.001).

The Figure 5 presented the mean values of fructosamine in the group of subjects with prediabetes and the patients with diabetes. Results show that there was a significant reduction of fructosamine after treatment with L-thyroxin in both groups, or in the group with prediabetes (2.95±0.23, p<0.05), as well as in the group of patients with diabetes (3.22±0.31 vs. 3.06±0.27, p<0.05).

The results shown in Figure 6 show that the mean value of fructosamine in patients treated with L-thyroxin was significantly lower than in the control group (6.74±1.01 vs. 6.26±1.12) which was statistically significant (p<0.05).

The results of lipid profile in the two groups are shown in Figure 7. From the obtained results it is evident that the decreased value of all the lipids or values of total cholesterol (6.10±0.67 vs. 5.39±0.57, p=0.003), triglycerides (2.22±0.49 vs. 1.69±0.37, p=0.03), LDL-cholesterol (4.37±0.77 vs. 3.79±0.54, p=0.01) and an increase in HDL-cholesterol (1.03±0.15 vs. 1.16±0.14, p=0.09) in the group of patients who were treated with L-thyroxine.

The results shown in Figure 8 show that there was a significant reduction of CRP after treatment with L-thyroxin in both groups of patients, or in those with prediabetes (3.34±0.41 vs. 2.56±0.42, p<0.05) and in the group of diabetes patients with (4.36±0.92 vs. 2.55±0.67, p<0.05).

### Table 1: Mean values of lipids and fructosamine before and after L-thyroxine therapy

<table>
<thead>
<tr>
<th>Group</th>
<th>Triglycerides</th>
<th>HDL-cholesterol</th>
<th>LDL-cholesterol</th>
<th>Total cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before therapy</td>
<td>2.22±0.49</td>
<td>1.03±0.15</td>
<td>4.37±0.77</td>
<td>6.10±0.67</td>
</tr>
<tr>
<td>After therapy</td>
<td>1.69±0.37</td>
<td>1.16±0.14</td>
<td>3.79±0.54</td>
<td>5.39±0.57</td>
</tr>
</tbody>
</table>

5. DISCUSSION

Comparing the results obtained in this study with the results reached by other authors, leads to similar and even identical conclusions.

However it should be noted that this problem only over the past few years, capturing the attention of the world's endocrinologist, and therefore do not need to mention that in the region of our country as well as neighboring countries in the region still has no major projects on this topic.

Based on studies by a group of authors, in certain groups of the population, the incidence of subclinical hypothyroidism reaches 10-12% (8). Prevalence of thyroid disease in patients with diabetes mellitus is about 10-15% (9).

According to the data of most authors subclinical hypothyroidism is a disease that in most cases affecting women at 40-60 years of age. Our results have just confirmed the results above claim, because a hundred of the patients with subclinical hypothyroidism, as many as 80% were members of the female gender, mean age, 51.75 years. Group of authors did a study that included 583 women, aged 40-78 years, different occupations, which previously did not have any problems with the thyroid gland. Patients were divided into two age groups: the first group consisted of women from 40-55 years. (44±1.3) a total of 298, and another group of women aged 56-78 years (61±2.3) 294. To all is determined the level of TSH, T4, T3. Frequency of subclinical hypothyroidism in women in the first group amounted to 7.9%, and 17.1% in the second groups. From this stems the conclusion that the high frequency of subclinical hypothyroidism is associated with older age groups (10).
terol and LDL-cholesterol were significantly elevated in patients with subclinical hypothyroidism. However, between the levels of triglycerides and HDL-cholesterol there were no statistically significant differences in the study and control group. Also, the level of CRP showed no statistically significant difference in the study and control groups (p>0.05). Insulin level was significantly elevated in patients with subclinical hypothyroidism compared to the control group (p<0.05) (11).

Thyroid hormones affect the cardiovascular system by direct action on the heart and blood vessels, as well as the influence on lipid profile and atherogenesis. In overt hypothyroidism, cardiovascular function is characterized by increased vascular resistance and heart rate.

In subclinical hypothyroidism there is a disorder of systolic and diastolic function of the left and right ventricles. Recent studies have shown a positive correlation between serum TSH and total and LDL-cholesterol. It is also shown that subclinical hypothyroidism is a risk indicator for atherosclerosis and coronary heart disease.

The results showed a decrease in levels of total cholesterol (5.39±0.57 vs. 6.10±0.67), a reduction in triglycerides (1.69±0.37 vs. 2.22±0.49), HDL cholesterol (1.16±0.14 vs. 1.03±0.15) and LDL cholesterol (3.79±0.64 vs. 4.37±0.77). Then, our results clearly showed that the concentration of CRP in the serum of patients who were not treated with L-thyroxine increased compared to the group of patients who were treated with L-thyroxine (2.27±0.8 vs. 3.32±1.1). Also, changes were found in the level of postprandial glucose (7.45±2.0 vs. 8.48±2.35) in basal insulin levels (96.44±17.26 vs. 114.64±24.11) and the level of the basal C-peptide (883.58±213.14 round. 1120±299.17).

Clinical studies in the last decade have shown that chronically elevated CRP levels also indicates the existence of long-term subclinical inflammation that exposes an individual’s risk of developing hypertension and other cardiovascular damage, which leads to loss of elasticity of the arterial wall. Some authors believe that CRP is not only a marker of risk for hypertension, but it actually induces the development of arterial hypertension.

It is well known that cardiovascular disease is closely associated with diabetes. Bahcece et al. (16) believe that inflammation, insulin resistance and hyperglycemia jointly contribute to cardiovascular risk in patients with diabetes. It is still not known whether poor glycemic control leads to inflammation and inflammation causes a higher concentration of glucose in the blood, or some third factor affects both. Possible link between inflammation and hyperglycemia may represent oxidative stress, which, on one hand, increased in conditions of hyperglycemia, on the other hand promotes inflammation. Vascular endothelial dysfunction is considered an important factor in the pathogenesis of micro- and macro-angiopathy of patients with diabetes. It has been shown that hyperglycemia and its immediate biochemical sequel directly alter endothelial function. However, it is also possible their indirect impact by encouraging the synthesis of growth factors, cytokines, and vasoactive agents in other cells. Still not sufficiently investigated whether the impaired function of endothelial cells only caused hyperglycemia or other factors. It was found that endothelial dysfunction may contribute to insulin resistance independent of the presence of diabetes.

We also demonstrated a correlation between CRP and markers of endothelial dysfunction in patients with diabetes mellitus. These data suggest a link between the activation of the endothelium and chronic inflammation in these patients. At the same time, and subclinical chronic inflammation is considered important for the initiation and/or progression of atherosclerosis in patients with diabetes mellitus (16).

Studies have shown that elevated CRP levels are associated with insulin resistance (15). Also, an increase in triglyceride concentrations with CRP may explain the appearance of insulin resistance. The most important reason for insulin resistance is abdominal obesity. The real cause was a larger increase visceral of subcutaneous adipose tissue. Triglycerides are fat, the compounds of glycerol and fatty acids, which accumulate in fatty tissue as vis-
cereal fat, and in the case of the energy needs, are broken down into glyceral which is converted to glucose, which can be used for energy or other building materials, and fatty acids are broken down to simpler, thereby producing power. In obese people, or if we bring too much food that contains carbohydrates, excess is converted by glyceral into triglycerides and stored in fat tissue as body fat. As a result of excessive accumulation of body fat, especially when the upper body fat, increase in insulin resistance and therefore increase and concentrations of CRP.

It is well known that type 2 diabetes is a major risk factor for cardiovascular disease. Prediction about the rising incidence of type 2 diabetes will cause a significant increase in the incidence of cardiovascular disease. Prevention of type 2 diabetes with the aim of prediabetes regression to normal glucose tolerance is a very attractive target. Diabet Prevention Program (DPP) and the Finnish studies to prevent diabetes have demonstrated that changes in lifestyle can prevent or delay the onset of new cases of type 2 diabetes in subjects with prediabetes by 58%. However, some participants still developing diabetes. In addition, lifestyle changes are ineffective on a long term basis, as shown in the EUROASPIRE study increased occurrence of diabetes by 60% in patients with cardiovascular disease over a ten-year follow-up (17).

Statistically significant correlation was obtained for TSH and HbA1c values in patients treated with L-thyroxine (r=0.46, p<0.05), TSH and fasting glucose (r=0.39, p<0.05), TSH and postprandial glucose (r=0.41, p<0.05). Subclinical hypothyroidism is difficult to diagnose and is often overlooked. Adequate diagnosis requires: conducting more extensive laboratory tests in relation to the performance of routine TSH test from time to time should be practiced by monitoring the temperature of the body, and careful monitoring of clinical signs and history of the disease (1, 18, 19, 20, 21).

6. CONCLUSIONS

Hypothyroidism is one of the most common diseases of the endocrine system. Most cases are subclinical hypo-

thyroidism. Subclinical hypothyroidism is a disease that in most cases affects women at age from 40-60 years. Normalization of TSH levels leads to a reduction in postprandial glucose levels, CRP, HbA1c and lipids. This indicates a significant effect of treatment with L-thyroxine on glucose regulation in patients with subclinical hypothyroidism. The correlation between TSH and HbA1c is positive and statistically significant. Disturbance of glycemic control was present in 58% of patients with subclinical hypothyroidism. Patients with subclinical hypothyroidism exhibited elevated levels of atherogenic parameters (hyperinsulinemia, total cholesterol, LDL-cholesterol).

With regard that the determination of TSH is accurate, accessible, safe, and inexpensive test for the diagnosis of subclinical hypothyroidism in the near future we expect that determination of TSH level can be used to determine the risk of the occurrence of various complications (osteoporosis, cardiovascular disease, depression) for different intervals TSH levels.

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