Cardiovascular Risk Assesment of Subclinical Hypothyroid Patients by Using Framingham Risk Score

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ABSTRACT

Objectives: The aim of this study is to evaluate the variation of cardiovascular risks of subclinical hypothyroid patients with thyroid hormone replacement therapy by using Framingham Risk Scoring system.

Materials and methods: In this study 21 subclinical hypothyroid and 22 healthy volunteers, between the ages 37 to 68 were taken as case and control groups. Subclinical hypothyroid patients were given L-T4 replacement therapy for one year to keep the TSH values in normal ranges. Before and after the treatment clinical and laboratory parameters compared with each other for case and control groups.

Results: When we compared the pre and post treatment values of subclinical hypothyroid patients; The systolic and diastolic blood pressures, total cholesterol, LDL cholesterol levels and framingham risk scores obviously decreased ($p<0.05$). Although, at the begining of the study ten year cardiovacular risk of the case group was significantly higher than that of control group, after treatment no difference was found between the two groups ($p<0.05$ vs $p>0.05$).

Conclusion: By using Framingham Risk Score, its obviously seen that in subclinical hypothyroid patients, just by thyroid hormone replacement therapy a marked decrease of cardiovascular risk can be obtained.

Keywords: Framingham risk scoring, thyroxine treatment, subclinical hypothyroidism

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INTRODUCTION

Currently, the main risk factors for coronary artery disease on which a consensus has been reached include age, familial history of coronary artery disease, hypertension, low levels of high density lipoprotein and smoking (1,2).

It is known that clinical hypothyroidism increases cardiovascular risk especially by leading to hypertension and dislipidemia and its treatment contributes to a decrease in the risk. However, there are a limited number of studies investigating the association of subclinical hypothroidism with increased cardiovascular morbidity and mortality and the effects of its treatment on cardiovascular risks (3-6). Although there are many studies which have shown that subclinical hypothroidism and its treatment were primarily related with increased cardiovascular risks, almost all of the studies evaluates the cardiovascular risks seperately as blood pressure and lipid parameters. There is no study about subclinical hypothyroidism, which evaluates these data comprehensively together with other factors including age and smoking which are known to be related with cardiovascular risk.

In this study, we aimed to evaluate if thyroid hormone replacement treatment alone provides a decrease in cardiovascular risk in individuals with subclinical hypothyroidsm with "Framingham Risk Scoring" which uses the parameters of age, smoking, systolic blood pressure, total cholesterol and high density lipoprotein levels.

MATERİAL AND METHOD

The current study was carried out in the outpatient clinics of internal medicine and cardiology. 21 patients with subclinical hypothyroidism was taken as the case group and 22 euthyroid healthy individuals were included as the control group. The patients who had

diabetes mellitus, hypertension, chronic renal failure and coronary artery disease which are known to have effects on lipid profile were excluded from the study.

In all of the participants age, gender and smoking status were interrogated. Height, weight, systolic and diastolic blood pressures and lipid parameters were measured and recorded. The values of systolic and diastolic blood pressure were determined for two times at the beginning and end of the interview in accordance with the Joint National Committee (JNC) criteria and their aritmethical mean values were recorded.

Diagnosis of subclinical hypothyroidism was made with normal free T3 and T4 values and increased TSH concentrations. 21 individuals with subclinical hypothyroidism were followed up for one year with L-T4 replacement treatment. The clinical and laboratory parameters of the patients were compared with each other before treatment and after the one-year follow-up and with the control group. The blood samples were obtained after a fasting period of 10-12 hours and then centrifuged for 10 minute at 2500 xg: sera were stored at -20 °C until analysis. TSH, free T3 and free T4 were assayed with chemilluminescent enzyme immunometric methods, using commercial kits with automated hormone analyzers according to the manufacturer's instructions (Immulite One; DPC, Los Angeles 90045-5597). The normal values for thyroid function tests established in our laboratory are as follows: TSH: 0.4-4 IU/ml; freet T3: 2.1-4.7 pg/ml; free T4: 0.8-7.9 ng/ml. Subclinical hypothyroidism was defined as a TSH level of of 4-10 IU/ml with normal levels of fT3 and fT4.

Total cholesterol (TC), triglyceride (TG) and high density lipoprotein (HDL) values were measured after a fasting period of 12 hours in the blood samples obtained at 07:00-09:00 pm. LDL cholesterol values were calculated using the Friedwald formula (LDL-cholesterol = Total cholesterol-(triglyceride / 5) - HDL-cholesterol). Lipid parameters were evaluated using spectrophotometric methods with OLYMPUS AU 2700 device.

Framingham risk scoring system was used to calculate ten-year cardiovascular risk. The scoring table which was established with Framingham heart study is the revised form of the Framingham study performed in 1991 and shows the risk of having coronary artery disease in the future ten years. There are seperate risk tables for men and women and the factors which are considered in the assessment include age, total cholesterol, HDL cholesterol, systolic blood pressure and smoking status.

The study protocol was approved by the ethics committee of Abant İzzet Baysal University Duzce Medical Faculty and written informed consent was obtained from all participants.

Statistics

SPSS 11 for Windows statistical program was used for statistical analyses. The results of all parameters belonging to the control and case groups were given as mean ± standard deviation. x^2 (chi-square) test was used to analyse quantitative variables. Dependent T test was used for parametric data to analyse the values before and after treatment. Wilcoxon test was used for the data which were not compatible with parametric distribution. Mann-Whitney U test was used for parametric data to compare the values of the case and control groups. The statistical significance level of the data obtained was interpreted using "p" values. A p value of <0.05 was considered statistically significant. Kolmogorov smirnov test was used to determine parametric and non-parametric distributions of the data. The data with a p value of >0.05 were considered to have parametric distribution and the values below this were considered non-parametric values.

RESULTS

21 patients (4 male and 17 female) with subclinical hypothyroidism who presented to the outpatient clinics of internal medicine and cardiology of our hospital were included in this study as the case group and 22 (7 male and 15 female) euthyroid healthy individuals were included as the control group. Biochemical and hemodynamic parameters which could primarily affect the cardiovascular risk were evaluated before and after one-year thyroid hormone replacement treatment in the patients who were included in the study group and were compared with the data of the control group.

The mean age was found to be 51.48 ± 9.33 and 47.82 ± 6.32 years in the case and control groups, respectively; no statistically significant difference was found (p=0.219). When the body mass index values of the patients before and after the treatment were compared, no significant difference was observed (24.9 ± 2.7 and 24.52±2.9 p=0.162). There was also no statistically significant difference between the BMI values of the control group and the case group before and after treatment.

No statistically significant difference was found between the control and case groups in terms of smoking status which was another parameter that could affect the data in the study (3/19 and 4/17: p=0.689).

When the systolic and diastolic blood pressure values which were taken before and after the treatment were compared in the case group, it was observed that significant changes occured in both (p=0.033 and p=0.007) (Table-1).

While there was a significant difference between the systolic blood pressure values of the control and case group before and after treatment, no statistically significant difference was found between the diastolic blood pressure values (Table-2).

When the thyroid function values of the control group and the values of the case group before and after the treatment shown in Table- 1 were compared, the TSH values of the case

group before treatment was found to be significantly higher than the control group. Although the TSH values of the case group were within the normal limits after treatment, there was still a significant difference compared to the control group (Table-2).

When lipid paramters of case group were considered individually, total cholesterol and LDL values were found to be significantly decreased after treatment compared to the period before the study. No significant change was observed in HDL and triglyceride values after treatment (p=0.021 and p=0.001) (Table-3).

According to the Framingham risk scoring results in which the data of age, total cholesterol, HDL cholesterol, smoking status and systolic blood pressure were evaluated together in terms of development of coronary heart disease, there was a significant difference between the values observed before and after the treatment (p=0.004) (Table-3)

When the lipid parameters and ten-year cardiovascular risk between the control and case groups were compared before and after the treatment, altough a significant difference for cardiovascular risk was seen before the treatment, this difference disappeared after the treatment (p=0.004 and p=0.161) (Table-4).

DISCUSSION

In the literature, substantially controversial results have been reported for the association of subclinical hypothyroidism and its treatment with increased cardiovascular risks, morbidity and mortality. Since the results of previous studies were contraversial and there were almost no studies evaluating cardiovascular risks all together, we decided to perform this study.

In our study, the ten-year coronary artery disease risk was calculated in individuals with subclinical hypothyroidism by using Framingham risk scoring system and the effect of replacement treatment on the calculated risk was investigated. Conlcusively, it was shown

that thyroid hormone replacement treatment alone decreased the risk of coronary artery disease in these patients.

In some of the clinical studies, LDL levels have been found to be increased in patients with subclinical hypothyroidism (7,8). They have been found to be normal in some other studies (9-11). In some studies, LDL levels have been found to be decreased with thyroid hormone replacement treatment (7,12,13,14). In some other studies, no change has been observed in LDL levels (15,16). In our study, there was a difference between the control group and case group in LDL levels before treatment, but it was not statistically significant. In addition, the mean LDL levels after treatment showed a significant decrease compared to the period before treatment. The decrease in LDL levels with thyroid hormon replacement treatment may be explained with an increase in LDL receptor number with effect of L-thyroxine (17). In one study, it was reported that the incidence of coronary artery disease could be decreased 15% after a 7% decrease of LDL levels with thyroid hormone replacement treatment in patients with subclinical hypothyroidism (11). In our study, a decrease of 9.8 % occured in LDL levels after treatment. These results suggest that the decrease in LDL level had an important role in the decrease of the coronary artery disease risk, obtained in our study.

HDL fractions of blood lipids are protective lipoporteins which decrease the coronary artery disease risk. Controversial results related with HDL levels have been obtained in studies conducted with patients with subclinical hypothyroidism. HDL levels have been found to be decreased in some of these studies and normal in some others (7,9,11). While significant changes have not been observed after treatment in patients with subclinical hypothyroidism in some studies, significant increases have been found in some others (14,18,19). In our study, a mild increase was observed in HDL levels in patients with subclinical hypothyroidism after treatment, but this change was not statistically significant.

Controversial data have been reported for patients with subclinical hypothyroidism in relation with total cholesterol levels which are one of the main components of Framingham score. As with other lipid parameters, it has been reported that total cholesterol levels have been reported to be increased in some studies and normal in some others (9,11,20,21). In our study, the total cholesterol values of the patient group were slightly higher compared to the control group, but the difference was not statistically significant. In some studies, total cholesterol levels decreased markedly with L-T4 replacement treatment in patients with subclinical hypothyroidism, while the difference was not statistically significant in some other studies (11,22). In our study, although there was no difference between the case and control groups, a significant decrease was observed after treatment in the case group. In our study, despite the fact that there was no significant difference between HDL and triglyceride levels before and after treatment, the marked difference which occured in LDL levels may explain the change in total cholesterol values. In the Framingham study, total cholesterol was one of the risk factors for coronary artery disease. In the Multiple Risk Factor Intervention Study which was conducted total cholesterol values alone, the coronary artery disease risk increased with total cholesterol levels above 200 mg/dl, while it decreased below this value.

In our study, systolic and diastolic blood pressure values decreased significantly after treatment in patients with subclinical hypothyroidism. The systolic blood pressure value which is one of the elements of the Framingham scoring system decreased approximatley by 6 mmHg after treatment in the case group (145.00±15.15 mmHg before treatment and 139.47±7.2 mmHg after treatment). In our study, the patients with subclinical hypothyroidism were in the stage 1 hypertension class before treatment, whereas they regressed to pre-hypertension levels after treatment with mean values below 140 mmHg.

Smoking is one of the most important preventable risk factors in early deaths in developing countries. Development of subclinical hypothyroidism and related complications

increase in relation with smoking (23). In our study, 3 of 21 individuals with subclinical hypothyroidism were smoking and 4 of 22 individuals in the control group were smoking.

In our study Framingham risk scoring system was used, since it globally expresses all cardiovascular factors examined in detail above. According to the data obtained, the ten-year risk score was found to be higher in the control group than the patient group. After treatment, the risk score of the patient groups significantly decreased than the values before the treatment. As a result of the decrease in the coronary event risk after treatment in the patient group, the difference relative to the control group disappeared.

CONCLUSİON

Increased total cholesterol and blood pressure values accompanying the disease in subclinical hypothyroidism substantially explain the increased risk in the cardiovascular events. In this patient group, a marked decrease in the cardiovascular risk can be obtained by thyroid hormone replacement treatment alone. The cardiovascular risk should be determined in patients with hypothyroidism even if it is subclinical and risk factors should be modified. Smoking should be discontinued withouth losing time because it leads to subclinical hypothyroidism and has known harmful effects. The effect of thyroid hormone replacement treatment on these parameters should be evaluated before pharmacological approach directed to the other modifiable risk factors. The limited number of participants in our study can be considered as a limitation of our study, but we think that our study can be considered as a pilot study and larger prospective studies should be performed in this area.

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Table1: Comparison of thyroid hormone parameters and hemodynamic values before and after treatment in the patients with a diagnosis of subclinical hypothyroidism

(n=21)	Before treatment Mean ± SD	After treatment Mean ± SD	P
TSH (IU/ml)	9.24 ± 2.97	3.13±1.47	<0.001
fT4 (ng/dl)	1.11±0.41	1.18±0.39	0.094
fT3 (pg/ml)	2.69±0.81	2.51±0.73	0.770
BMI (kg/m^2)	24.90±2.7	24.52±2.9	0.162
SBP (mmHg)	145.00±15.15	139.47±7.2	0.033
DBP(mmHg)	87.81±12.37	84.53±10.05	0.007

Table 2: Thyroid hormone parameters and hemodynamic values in the control group and comparison of these with the values of the case group before and after treatment

	Control group(n=22) Mean ± SD	Before treatment Comparison with the case group (p)	After treatment Comparison with the case group (p)
TSH (IU/ml)	1.57 ± 1.01	<0.001	<0.001
fT4 (ng/dl)	1.17±0.26	0.071	0.346
fT3 (pg/ml)	2.76±0.50	0.721	0.193
MBI (kg/m^2)	25.45±2.92	0.526	0.452
SBP (mmHg)	125.00±8.94	<0.001	<0.001
DBP(mmHg)	82.5±7.07	0.176	0.444

Table 3: Comparison of lipid parameter values before and after treatment and ten-year coronary artery disease risks in the patients with subclinical hypothyroidism

(n=21)	Before treatment Mean ± SD	After treatment Mean ± SD	P
T-chol. (mg/dl)	206.38 ±37.92	196.90±31.11	0.021
LDL (mg/dl)	137.38±20.61	128.52±25.08	< 0.001
Triglyceride (mg/dl)	160.01±93.54	149.44±78.40	0.910
HDL-chol. (mg/dl)	40.99±7.04	42±6.29	0.128
Ten-year risk %	4.90±4.9	2.90±2.6	0.004

Table 4: Lipid parameters and ten-year coronary artery disease risks in the control group and comparison of these with the data of the case group before and after treatment

	Control group(n=22) Mean ± SD	Before treatment Comparison with the case group (p)	After treatment Comparison with the case group (p)
T-chol. (mg/dl)	192.86 ±38.8	0.255	0.709
LDL (mg/dl)	125.35±27.71	0.141	0.702
Triglyceride (mg/dl)	148.63±103.17	0.410	0.485
HDL-chol. (mg/dl)	45.70±13.17	0.156	0.252
Ten-year risk %	3.36±5	0.004	0.161