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Original Article

Evaluation of ischemia-modified albumin levels and parametersof arterial stiffness in patients with hypothyroidism

Andac Komac[1], Utku Erdem Soyaltin[1], Hayrullah Durak[2], Ayfer Colak[2], Harun Akar[1]

[1]Tepecik Education and Research Hospital, Clinic of Internal Medicine, Izmir, Turkey
[2]Tepecik Education and Research Hospital, Clinic of Biochemistry, Izmir, Turkey

Abstract

Aim: The cardiovascular system is susceptible to thyroid hormones. Many studies show that hypothyroidism is associated with increased cardiovascular risk, functional abnormalities, atherosclerosis, and increased arterial stiffness. Pulse wave velocity (PWV) and augmentation index (AI) are regarded as indexes of arterial stiffness. Oxidative free radicals that occur during ischemic events cause certain chemical changes in the albumin molecules. The ischemia-modified albumin (IMA) has been suggested as an indicator of oxidative stress. Evaluation of oxidative stress markers and parameters of arterial stiffness can shed light on the mechanism of increased cardiovascular risk in patients with hypothyroidism.

Material and Methods: For this study, PWV, AI measurements, and IMA levels of 20 untreated patients with overt hypothyroidism (OH), 21 untreated patients with subclinical hypothyroidism (SH), and 30 healthy controls (control-CNT) were evaluated. Patients and the healthy controls' gender, age, weight, height, body mass index, waist circumference, smoking habit and blood biochemical results were recorded.

Results: PWV was found to be increased in patients with overt hypothyroidism; however, there was no difference in between subclinical hypothyroidism and control group(p=0,881). Also, PWV had a significant positive correlation with; age, BMI, waist circumference, blood glucose, uric acid, pulse pressure and systolic and diastolic blood pressures. IMA levels were not different in between the groups.

Conclusion: Hence the increased CV risk in patients with hypothyroidism is a multifactorial state; the interplay of many factors determines it. Future studies with larger sample sizes are needed to evaluate the possible relationship among IMA levels, arterial stiffness parameters and cardiovascular risk factors in patients with hypothyroidism.

Keywords: Ischemia Modified Albumin; Arterial Stiffness; Hypothyroidism.

INTRODUCTION

The cardiovascular system is known to be sensitive against thyroid hormones. Even in mild hypothyroidism, cardiovascular system can be affected (1). Many authors have reported that hypothyroidism is associated with increased cardiovascular risk, functional abnormalities, atherosclerosis and increased arterial stiffness. As a surrogate marker, arterial stiffness describes the expansion and contraction capability of an artery another word a parameter that shows the elasticity of an artery and can be measured with different methods such as pulse wave velocity and augmentation index. Pulse wave velocity and augmentation indexes are regarded as the indexes of arterial stiffness and they are in association with cardiovascular risk. (2). On the other hand, oxidative free radicals that occur during the ischemic events, cause certain chemical changes in the albumin molecule. Eventually, the new albumin molecule is called "ischemia-modified albumin - IMA "(3). In the previous studies, it has been reported that IMA was not specific for cardiac ischemia and also could be elevated in various diseases (4). Studies have shown that IMA can be affected by thyroid hormones which have serious effects on metabolism, cellular oxygen consumption and cardiac functions (4,5,6). Hypothyroidism was observed to be associated with elevated LDL and total cholesterol, diastolic hypertension, and endothelial dysfunction (7). The aim of this study

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Corresponding Author: Andac Komac, Tepecik Education and Research Hospital, Clinic of Internal Medicine, Istanbul, Turkey
E-mail: andac.d@hotmail.com

is to determine the possible relationships among IMA levels, arterial stiffness parameters and cardiovascular risk factors in patients with newly diagnosed, untreated hypothyroidism.

MATERIAL and METHODS

Patient recruitment and exclusion criteria: This study was conducted between May and October 2015 in the outpatient clinics of Internal Medicine and Endocrinology Departments of Izmir TepecikEducational and Research Hospital. The study was approved by the local ethical committee of the hospital. Informed consents of all the participants who agreed to join the study were obtained. The study was conducted prospectively after the formation of the patient groups. Patients were divided in to three groups according to the TSH, T3, and T4 levels as overt hypothyroidism(TSH>10 µlU/ml, T4 <0,93ng/dl, T3 <2pg/ml or normal) and subclinical hypothyroidism (TSH>5 µlU/ml, T3-T4 normal) and healthy controls (8). Twenty untreated patients with overt hypothyroidism and 21 untreated patients with subclinical hypothyroidism and 30 healthy controls were included in the study.

All the patients were newly diagnosed according to the thyroid function tests. Patients were divided into 3 groups as OH, SH, and CNT. Patients and controls with a previously diagnosed concomitant disease such as diabetes mellitus, hypertension, renal failure, cerebrovascular disease, liver failure, congestive heart failure, and coronary artery were excluded from the study.

Biochemical tests, anthropometric and arterial stiffness measurements: Patients and healthy controls' gender, age, weight, height, body mass indexes, waist circumferences, smoking habits and blood biochemical results were recorded. Body mass index is calculated by dividing a person's weight in kilograms by the square of his or her height. Laboratory test results including TSH (0,27-0,42 µlU/ml), fT3 (2-4,4 pg/ml), fT4 (0,93-1,71 ng/dl), Anti thyroglobulin antibody (Anti-T/0-115 IU/ml), Anti microsomal antibody (Anti TPO/0-35IU/ml), blood glucose (74-106 mg/dL), total cholesterol (110-199 mg/dL), LDL cholesterol (62-129 mg/dL), HDL cholesterol (40-60 mg/dL), triglycerides (30-200mg/dL), uric acid (2.6-6 mg/dL), albumin (3,5-5,5 g/dl) levels were obtained from the outpatient clinics' data retrospectively. Also, the pulse wave velocity, augmentation index, arterial blood pressure of patients were evaluated by using "Mobil-O-Graph® ARC solver algorithm" device from one arm prospectively. Besides, blood samples were obtained prospectively for the assessment IMA. IMA test was performed by the spectrophotometric method as described by David Bar-or et al. Cobalt chloride, dithiothreitol and 0.9% NaCl was used.

Thyroid doppler ultrasonography (USG) was performed in the radiology department on the patient group via Toshiba Aplio 300 Color Doppler Ultrasonography and 11-5 MHz linear probe.

Statistical methods:
SPSS v.20 software was used for statistical analysis. In descriptive statistics and categorical variables, numbers and percentages were used; for numeric variables; average, standard deviation, median, minimum and maximum values were used. ANOVA test was performed for the normal distribution of quantitative in multiple independent group comparisons; according to the homogeneity of the variance Bonferroni or Dunnett's T3 was used for the paired comparison test. Kruskal-Wallis test was used for the abnormally distributed variables; Mann Whitney U test was used for the comparison of abnormal distribution in dual independent groups. Cross-tables were created for the categorical data. Multilateral and bilateral Chi-square tests were used for group comparisons. Pearson correlation test was used for the relationship between the numerical data with normal distribution. In all analyzes, p- value< 0,05 was considered as statistically significant.

RESULTS

The demographic data of the groups and anthropometric measurements are given in Table1. There were no statistically significant differences among the three groups in terms of age, gender, and smoking habits. When the body mass indexes were compared, the OH group were found to have higher body mass indexes than the other groups (p<0,001). We also found significant differences between SH and OH group in terms of the waist circumference (p=0,004).

The laboratory findings and thyroid doppler ultrasonography results are given in Table 2. According to the data glucose, LDL, total cholesterol, uric acid levels (p = 0.93, p= 0.628, p= 0.630, p= 0.150) did not show any statistically significant differences among the groups; Compared to the CNT group triglyceride levels were significantly higher in OH group (p=0.027). There were significant differences in TSH, FT4 and FT3 levels among groups (p<0,001, p<0,001, p=0,005 respectively). Doppler ultrasound findings for thyroiditis did not reveal any differences between the overt and subclinical hypothyroidism group (p=0,062). In addition those two groups were not found to be different in terms of Anti-t and Anti TPO antibody positivity(p=0.146, p= 0.427). Correlation analysis revealed significant correlation between thyroid antibody positivity and thyroiditis existence in thyroid doppler ultrasonography as expected (p = 0,033, p = 0,020). There were no significant differences between the groups regarding IMA levels (p=0,811).

Arterial stiffness parameters of the groups are given in Table 3. When we compared the PWV among the groups, OH group had higher PWV values than the SH and CNT groups (p=0,05, p=0,036 respectively). Between SH group and CNT group, there was no statistically significant difference found in terms of arterial stiffness.

Comparative analysis is shown in Table 4. There were significant correlations between PWV and age, BMI, waist circumference, blood glucose, uric acid, pulse

pressure, systolic, and diastolic pressures. (p <0.001, p<0.001, p<0.001, p=0.003, p=0.001, p<0.001, p=0.008 and p<0.001 respectively). There was not any correlation between PWV and AI parameters (p=0,541). There were no significant correlations between IMA levels and PVW, AI, age, BMI, waist circumference, glucose, total cholesterol, triglycerides, LDL cholesterol, uric acid, thyroid function tests, thyroid antibodies, and blood pressures. There was a positive correlation between the IMA levels and female gender (p=0,028).

There were significantly positive correlations between age and BMI (p <0.001), waist circumference (p<0.001), glucose (p = 0.002), uric acid (p = 0.007), systolic blood pressure (p < 0.001) ,and pulse pressure (p = 0.011). There were significant negative correlations between age and T3 (p = 0.008), T4 (p=0.030), and albumin levels (p <0.001). There were significantly positive correlations between BMI and waist circumference (<0,001), total cholesterol (p=0,047), triglyceride (p<0,001), uric asid (p<0,001), systolic, diastolic and pulse pressure (p:<0,001, p=0,019, p=0,027).

Table 1. Demographic data of the groups and anthropometric measurements

	Control N:30	Subclinical hypothyroidism N:21	Overt hypothyroidism N:20	P value
Age (years)	Mean:42.62 SD:9.4	Mean:39.86 SD:13.078	Mean:50.5 SD:18.608	0.060
Gender (F/M)	%60 F %40 M	%76.2 F %23.8 M	%75 F %25 M	0.371
Smoking (yes/no)	%53.3 yes %46.7 no	%33.3 yes %66.7 no	%55 yes %45 no	0.280
Waist circumference (cm)	Mean: 86.23 SD:12.09	Mean: 80.10 SD:13.20	Mean:96.65 SD:21.310	0.004
BMI(kg/m^2)	Mean:24.63 SD:4.01ii	Mean:23.67 SD: 4.36ii	Mean:29.79 SD:6.32ii	<0.001

Table 2. Laboratory findings and Thyroid doppler USG results

	Control N:30	Subclinical hypothyroidism N:21	Overt hypothyroidism N:20	P value
TSH (u IU/ml)	Med:1.65 Min-Max:0.4-2.94	Med:5.74 Min-max:4.90-8,39	Med:15.95 Min-Max:10- >100	<0.001
T3 (pg/ml)	Mean:3.35	Mean:3.19	Mean:2.66	0.005
T4 (ng/dl)	Mean:1.18	Mean:1.12	Mean:0.779	<0.001
Anti-t (Positive/Negative)	-	% 47.6 P % 52.4 N	%70 P %30 N	0.146
Anti-TPO (Pozitive/Negative)	-	%47.6 P %52.4 N	%60 P %40 N	0.427
Thyroid doppler USG (thyroiditis/homogeneous)	-	%52.4 T %47.6 H	%80 T %20 H	0.062
Glucose (mg/dl)	Mean:89.17	Mean:88.1	Mean:88.3	0.93
Total cholesterol (mg/dl)	Mean:199	Mean:193	Mean:208	0.630
Triglycerides (mg/dl)	Med:925 Min-Max:39-496	Med:108 Min-Max: 42-324	Med:144 Min-Max:50-383	0.027
LDL (mg/dl)	Mean:125.87	Mean:118.10	Mean:130.7	0.628
Uric Acid (mg/dl)	Mean:5.09	Mean:4.32	Mean:5.16	0.150
Albumin (g/dl)	Mean:4.37	Mean:4.18	Mean:3.97	0.035
IMA (ABSU)	Mean:0.434 SD:0.060	Mean:0.428 SD:0.078	Mean:0.441 SD:0.038	0.811

Table 3. Parameters of Arterial stiffness

	Control N:30	Subclinical hypothyroidism N:21	Overt hypothyroidism N:20	P value
AIx	Mean:17.10 SD:10.623	Mean:22.90 SD:10.742	Mean:19.90 SD:13.226	0.210
PWV	Mean:6.06 SD:1.11 Min:4.7 Max:9.7	Mean:6.047 SD:1.54 Min:4.2 Max:10.3	Mean:7.67 SD:2.5 Min:5 Max:12.9	0.008
Systolic pressure (mm/hg)	Mean:115.13 SD:11.53	Mean:116 SD:10.78	Mean:121.75 SD:11.083	0.120
Diastolic pressure (mm/hg)	Mean:76.2 SD:10.56	Mean:81.29 SD:9.794	Mean:79 SD:11.055	0.243
Pulse	Mean:75.6	Mean:83.95	Mean:77.35	0.034
Pulse pressure	Mean:39.5	Mean:35.29	Mean:43.75	0.009

Table 4. Comparative analyses

	PWV		IMA		AIx	
	R	P	R	P	R	P
Age	0.946	<0.001	0.134	0.264	0.034	0.777
Gender	0.084	0.485	0.260	0.028	-0.229	0.054
Smoking	0.118	0.885	0.892	0.454	0.111	0.357
BMI	0.459	<0.001	0.085	0.483	0.057	0.634
Waist circumference	0.502	<0.001	0.099	0.410	-0.026	0.831
TSH	0.189	0.115	0.36	0.766	-0.037	0.760
Glucose	0.352	0.003	-0.54	0.653	0.111	0.357
Total cholesterol	0.109	0.364	-0.125	0.299	-0.029	0.808
Triglycerides	0.51	0.674	0.088	0.465	0.015	0.903
LDL	0.143	0.235	-0.084	0.435	-0.084	0.487
Uric acid	0.386	0.001	0.162	0.176	0.006	0.961
Systolic pressure	0.573	<0.001	0.147	0.221	0.098	0.418
Diastolic pressure	0.312	0.008	0.159	0.185	0.130	0.280
Pulse	0.44	0.714	-0.122	0.312	0.433	<0.001
Pulse pressure	0.406	<0.001	0.29	0.810	-0.015	0.899

DISCUSSION

Overt hypothyroidism condition is strictly in association with hypertension, hyperlipidemia, atherosclerosis, and cardiovascular risk. With thyroid hormone replacement therapy cardiovascular effects of hypothyroidism may be reversible (9). The measurement of arterial stiffness is predictive for cardiovascular events in the general population; Hansen et al., found a close association between the aortic PWV and cardiovascular endpoints (10). In the evaluation of cardiovascular risk factors in our study; waist circumference, BMI, and triglyceride levels were significantly higher in overt hypothyroidism group. This result was similar with the literature and we think that the measurements of BMI and waist circumference are meaningful anthropometric measurements that can be used for overt hypothyroid and subclinical hypothyroid patients.

In the study of Erdal et al. systolic and diastolic blood pressure measurements, triglyceride levels, and waist circumference were found significantly higher, and HDL levels were found significantly lower in patients with subclinical hypothyroidism compared to the controls (11). In our study, OH group had the highest mean PWV value among the groups. Between SH group and CNT group, no statistically significant difference was found concerning arterial stiffness. While there were no differences in between the groups in terms of the systolic blood pressure values but the increase of the PWV in overt hypothyroidism group, suggests that the increased arterial stiffness is independent from the blood pressure. In the study of Dagre et al., systolic pressure, pulse pressure, PWV and AI have been shown to correlate with TSH even in the subclinical stage of the disease (12). A significantly higher mean PWV value was found in patients with subclinical hypothyroidism than the controls by Toshiki et al (13). In our study, there was no increase in the arterial stiffness in

the subclinical phase of the disease, which may be due to the small sample size.

Anti-t and Anti-TPO are positive in 95-100% of the patients with autoimmune thyroiditis. In our study, there was a significant correlation between the antibody positivity and thyroiditis detection in thyroid USG. There was no correlation between the antibody positivity and PWV. Similarly, Toshiki et al did not report any significant correlation between the antibody positivity and PWV (13). These findings suggest that there is no difference in arterial stiffness between Hashimoto thyroiditis and antibody negative hypothyroidism.

There are studies showing that IMA levels may increase in untreated hypothyroidism patients and subclinical hypothyroidism patients as an indicator of oxidative stress (14,15,16). In our study; no significant difference was found between the groups in terms of IMA levels and there were no correlations between thyroid function tests, thyroid antibodies and IMA levels. IMA levels were found significantly higher in hypothyroidism and hyperthyroidism group and havebeen shown to decrease with treatment by Shao-gang et al. (5). Similarly, Reddy and Kıran et al. found increased IMA levels in subclinic hypothyroidism (4,6). Consistent with our study, Kerem et al. did not find any correlations between IMA levels and thyroid function tests (17).

In the study performed by Shao-gang Ma et al., CRP and homocysteine levels were evaluated as an indicator of inflammation and these values were found to be higher in the hypothyroid group when compared to the normal controls (5). In the study by Nagano et al. and the study by Mattace-Raso et al., there was a significant relationship between CRP values and PWV value (18,19). In our study, uric acid levels were examined as an indirect parameter of systemic inflammation. There was a significantly positive correlation between the PWV values and uric acid level ($p = 0.001$) and no statistically significant relation was found between IMA levels and uric acid level.

CONCLUSION

In conclusion; increased CV risk in patients with hypothyroidism is a multifactorial situation and the risk is determined by the interplay of many factors. The present work demonstrates the role of increased PWV in patients with overt hypothyroidism, but PWV were not different in between subclinical hypothyroidism group and the control group. PWV may be a significant predictor of cardiovascular risk in hypothyroid patients.

Arterial stiffness and IMA were evaluated separately in different studies in patients with hypothyroidism. These two parameters have not been evaluated together before. For this reason, we think that our work is original.

IMA levels did not show any difference different between groups. Hence the small sample size is the limitation of this study; with these results, it can be concluded that IMA may not be a significant indicator of hypothyroidism. Further researches and are needed to evaluate the possible relationship among IMA levels, arterial stiffness parameters and cardiovascular risk factors in patients with hypothyroidism.

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Andac Komac ORCID: 0000-0002-7973-1687
Utku Erdem Soyaltin ORCID: 0000-0003-0229-3452
Hayrullah Durak ORCID: 0000-0003-0300-6638
Ayfer Colak ORCID: 0000-0003-4910-0128
Harun Akar ORCID: 0000-0002-0936-8691

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