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Hashimoto's thyroiditis is associated with elevated serum uric acid to high density lipoprotein-cholesterol ratio

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Background. Hashimoto's thyroiditis (HT) is an auto-immune condition characterized with lymphocytic and fibroblastic infiltration of the thyroid gland. The rate of uric acid and HDL cholesterol – so called as uric acid to HDL ratio (UHR) has been shown to be elevated in inflammatory conditions diseases. We aimed to compare UHR and other laboratory parameters of the patients with HT to those values in healthy controls.

Methods. The patients diagnosed with HT by medical history, physical examination, elevated thyroid autoantibodies in serum and characteristic sonographic findings in outpatient internal medicine clinics of our institution were enrolled to the present retrospective study. Age and sex matched healthy volunteers were enrolled as controls. UHR of the HT patients and control subjects were compared.

Results. The mean UHR of the HT group was 11% ± 4 %, while UHR of the control group was 8% ± 2% ($p<0.001$). UHR was significantly and positively correlated with thyroid stimulating hormone (TSH) ($r=0.26$, $p=0.01$) and negatively correlated with free T4 (FT4) ($r=-0.22$, $p=0.04$) levels. The sensitivity and specificity of the UHR level were greater than 8.3%: were 74% and 52%, respectively (AUC: 0.74, $p<0.001$, 95% CI: 0.64–0.84).

Conclusion. We suggest that UHR is a reliable and useful marker for HT. Therefore, it may be helpful in establishing the diagnosis of HT in addition to other diagnostic tools.

Key words: Hashimoto's thyroiditis, uric acid to HDL ratio, inflammation, autoimmune, diagnosis.

INTRODUCTION

Autoimmune thyroiditis is a common disease. This disease affects women more than men. The incidence in older women can reach up to 20% [1]. Autoimmune thyroiditis presents with 2 main clinics; Hashimoto's thyroiditis and Graves' disease. Both diseases are caused by lymphocyte infiltration of the thyroid gland. Graves' disease usually presents with thyrotoxicosis, and Hashimoto's thyroiditis with hypothyroidism [2].

There are publications in the literature showing that inflammation is associated with autoimmune thyroiditis [3]. Hashimoto's thyroiditis (HT) occurs with lymphocytic and fibroblastic infiltration. Hashimoto's thyroiditis is characterized by lymphocyte infiltration, lymphoid follicles, Askanazy cells and fibrosis [4]. Therefore, Hashimoto's thyroiditis is also an inflammatory condition.

The relationship of hypothyroidism with obesity and hyperlipidemia has been known since 1900s [5]. The prevalence of hypothyroidism in patients with hyperlipidemia is 1.4–13% [6, 7]. Thyroid hormones have a broad spectrum of physiological effects on lipoprotein metabolism. As a result, plasma lipid and lipoprotein levels are sensitive to changes in the concentrations of thyroid hormones [8].

Hyperuricemia has been thought to be one of the possible risk factors for atherosclerosis. Most patients with hyperuricemia are accompanied by metabolic comorbidity; diabetes, hypertension, and metabolic syndrome [9]. The rate of uric acid and HDL cholesterol – so called as uric acid to HDL ratio (UHR) – has been shown to be elevated in inflammatory conditions, including, metabolic syndrome [10], diabetes mellitus [11] and hepatosteatosis [12].

We hypothesized that UHR could be associated with Hashimoto's thyroiditis (HT). Therefore, we aimed to compare UHR and other laboratory parameters of the patients with HT to those values in healthy controls.

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MATERIALS AND METHODS

Study population

The patients diagnosed with HT in outpatient internal medicine clinics of our institution were enrolled to the present retrospective study. Ethical approval was obtained from the local ethics committee (approval no: 2020/55). The diagnoses of Hashimoto's thyroiditis were established with medical history, physical examination, elevated thyroid autoantibodies in serum and characteristic sonographic findings. Patients with other active inflammatory conditions, infectious disease, cancer, hematological disorders, type 2 diabetes mellitus, inherited dyslipidemic syndromes, and with a history of drug use which interfere with serum uric acid levels (i.e. allopurinol, etc…) were excluded from the study. Age and sex matched healthy volunteers who visited outpatient internal medicine clinics for routine check-up were enrolled to the study as control subjects.

Laboratory analyses

The results of the hemogram and serum laboratory parameters at the time of the diagnosis in initial hospital visit of the participants were used in present study. General characteristics such as age, gender were recorded from patients' files and from institutional computerized database. We also obtained and recorded laboratory parameters, such as white blood cell count (WBC), hemoglobin (Hb), hematocrit (Htc), platelet count (PLT), uric acid, fasting blood glucose (FBG), blood urea, serum creatinine, LDL-cholesterol, HDL-cholesterol, triglyceride, erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), thyroid stimulating hormone (TSH) and free T4 (FT4) hormone levels. Thyroid autoantibodies of the HT patients were also recorded. An UHR was calculated with simply division of serum uric acid by HDL-cholesterol levels. Data of the patients with Hashimoto's thyroiditis were compared to the control subjects.

Statistical analyses

Statistical analyses were held with a commercial statistics software (SPSS 15.0; SPSS Inc., Chicago, IL, USA). The fitness of the measurable variables to normal distribution was evaluated by Kolmogorov-Smirnov test. In data evaluation, continuous variables were expressed either as median (interquartile range) or mean ± SD, and frequency data were expressed as percentage (%). Comparisons of the variables with and without normal distribution were conducted with independent samples t test and Mann-Whitney U test, respectively. Pearson's correlation analysis was used in determining possible correlations between study variables. The sensitivity and specificity of UHR in predicting autoimmune thyroiditis were observed with ROC analysis. Significance level was considered as $p<0.05$ in all statistical tests.

RESULTS

Ninety-five individuals were enrolled to the study after exclusion criteria applied. There were 49 patients in Hashimoto's thyroiditis group and 46 in control group. Median ages of the HT and control groups were 40 (20.5) and 40.5 (16.3) years, respectively ($p=0.13$). 33 (67%) of the participants in HT group were women and 16 (33%) were men, while 29 (63%) were women and 17 (37%) were men in control group ($p=0.66$). Table 1 shows general characteristics and laboratory data of the study population.

Mean WBC ($p=0.23$), PLT ($p=0.06$), FBG ($p=0.95$), urea ($p=0.42$), creatinine ($p=0.42$), LDL ($p=0.26$), uric acid ($p=0.69$), and triglyceride ($p=0.96$) levels of the HT and control groups were not statistically different. Mean Hb ($p<0.001$), Htc ($p<0.001$), FT4 ($p<0.001$), CRP ($p<0.001$), ESR ($p<0.001$), and HDL ($p<0.001$) levels of the HT group were significantly lower than that of the control group. Median TSH of the HT group was decreased compared to the TSH of the control subjects ($p<0.001$). Mean UHR of the HT group was 11% ± 4 %, while UHR of the control group was 8% ± 2%. UHR of the HT group was significantly higher than the UHR of the control group ($p<0.001$).

In correlation analysis, UHR was significantly and positively correlated with TSH ($r=0.26$, $p=0.01$) and negatively correlated with FT4 ($r=-0.22$, $p=0.04$) levels. UHR was also positively correlated with CRP ($r=0.41$, $p<0.001$), and ESR ($r=0.31$, $p=0.002$).

The sensitivity and specificity of the UHR level greater than 8.3% were 74% and 52%, respectively (AUC: 0.74, $p<0.001$, 95% CI: 0.64-0.84, PPV: 61%, NPV: 64%). Figure 1 shows the ROC curve of UHR in detecting subjects with HT.

Table 1
General characteristics and laboratory data of the study population

		HT group	Control group	p
Sex	Men (n,%)	16 (33%)	17 (37%)	0.66
	Women (n,%)	33 (67%)	29 (63%)	
		Median (IQR)		
Age (years)		40 (20.5)	40.5 (16.3)	0.13
PLT (k/mm^3)		269 (110)	241 (97)	0.06
FBG (mg/dL)		90 (18)	93 (12)	0.95
Urea (mg/dL)		24 (9)	21 (9)	0.42
Creatinine (mg/dL)		0.73 (0.1)	0.75 (0.1)	0.42
LDL (mg/dL)		113 (52)	106 (25)	0.26
Uric acid (mg/dL)		4.5 (1.7)	4.9 (1.7)	0.69
Triglyceride (mg/dL)		98 (11)	114 (13)	0.96
HDL (mg/dL)		41 (17)	57 (10)	<0.001
TSH (uIU/mL)		5.2 (3.2)	2.2 (1.4)	<0.001
Anti TPO (kIU/L)		483 (239)	NA	-
Anti TG (kIU/L)		158 (99)	NA	-
		Mean ± SD		
WBC (k/mm^3)		7.1 ± 1.8	7.6 ± 2.8	0.23
Hb (g/dL)		12.9 ± 1.5	14.1 ± 1.7	<0.001
Htc (%)		39 ± 4	43 ± 5	<0.001
UHR (%)		11 ± 4	8 ± 2	<0.001
FT4 (ng/dL)		0.9 ± 0.23	1.2 ± 0.2	<0.001
CRP (mg/dL)		5.9 ± 1.6	0.79 ± 0.3	<0.001
ESR (mm/h)		24 ± 11	14 ± 5	<0.001

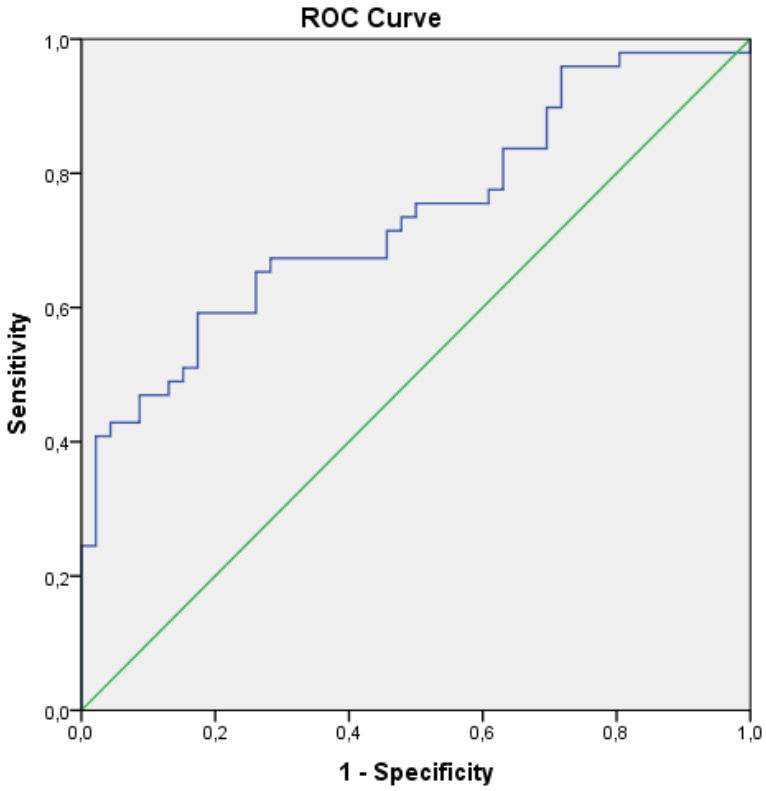

Figure 1. Sensitivity and specificity of the UHR in detecting HT.

DISCUSSION

The present study showed that UHR was a reliable predictor of Hashimoto's thyroiditis. Moreover, we also showed the significant correlation between UHR and TSH and negative correlation between UHR and FT4. To the best of our knowledge, this is the first study in the literature reporting significant association between HT and elevated UHR levels.

Hashimoto's thyroiditis is characterized with lymphocytic inflammation in thyroid tissue [13]. Inflammation plays important role in the clinical course of the disease in patients with HT. Increased uric acid levels are associated with inflammatory conditions, such as, type 2 diabetes mellitus [14], obesity [15], metabolic syndrome [16], and gouty arthritis [17]. Since HT is also an inflammatory condition, elevated UHR in patients with HT in present study might be a consequence of the underlying inflammation in this disease.

There are other studies in literature which reported association between increased UHR and various clinical conditions. Serum UHR has been suggested as a valuable predictor of diabetic control in men with type 2 diabetes mellitus [11]. Moreover, plasma glucose and glycated hemoglobin (HbA1c) levels were found to be correlated with UHR levels [11]. Continuous low grade inflammation is a characteristic of type 2 diabetes mellitus [18]. HT is also characterized by chronic inflammation. Therefore, similar elevation in UHR was reported in HT patients in our study.

The UHR of the patients with metabolic syndrome was reported to be higher than the UHR of the subjects without metabolic syndrome in a recent study [10]. In addition, authors showed that elevated UHR was superior to any other five criterion of the metabolic syndrome [10]. Alike with type 2 diabetes mellitus, metabolic syndrome is characterized by insulin resistance, too. Similarly, chronic inflammation plays an important role in metabolic syndrome [19]. Chronic inflammation is also a hallmark of HT which is revealed by lymphoplasmocytic infiltration of the thyroid tissue. Therefore, elevated UHR in HT patients which reported in our study is a finding that is consistent with literature knowledge.

Non-alcoholic fatty liver disease is another condition characterized by elevated UHR as reported in a study by Zhang *et al*. [12]. The authors also concluded that increased UHR was an independent risk factor for the presence of non-alcoholic fatty liver disease [12]. Non-alcoholic fatty liver disease is common in obese subjects. Obesity may also induce metabolic syndrome and type 2 diabetes mellitus. Inflammatory markers were reported to be increased in subjects with hepatosteatosis [20–22]. Thus, inflammation is a common feature both for HT and non-alcoholic fatty liver disease. Therefore, the elevated UHR reported in our study could be explained with the effects of inflammation in HT and similar inflammatory conditions; non-alcoholic fatty liver disease, type 2 diabetes mellitus, and metabolic syndrome.

Studies in the literature mention that elevation in UHR could be a consequence of increased inflammatory burden. Common feature of HT with those conditions, type 2 diabetes mellitus, hepatosteatosis and metabolic syndrome is elevated burden of inflammation. Recent studies confirmed the elevation of various inflammatory predictors in subjects with HT [23, 24]. Deteriorated metabolism is also a feature in type 2 diabetes mellitus, metabolic syndrome and hepatosteatosis. Interestingly, thyroid conditions were reported to be associated with metabolic alterations [25]. The therefore, increase in UHR levels in subjects with HT, could be explained with similar mechanisms with the UHR increase in such conditions.

Retrospective design and relatively low number of participants are two limitations of present work. However, to the best of our knowledge, this is the first study in literature reported significant association between UHR and HT.

CONCLUSION

We suggest that UHR is a reliable and useful marker for HT. Therefore, we think that it may be helpful in establishing the diagnosis of HT in addition to other diagnostic tools.

Introducere. *Tiroidita Hashimoto (HT) este o boală autoimună caracterizată prin infiltrate limfocitare și fibroblastice în glanda tiroidă. Raportul acidului uric cu HDL colesterol (UHR) s-a dovedit a fi crescut într-o varietate de patologii inflamatorii. Scopul studiului a fost de a compara UHR la pacienții cu HT comparativ cu martorii sănătoși.*

Materiale și metode. *Pacienții diagnosticați cu HT au fost incluși în studiu. Martori sănătoși, similari ca distribuție de gen și vârstă au fost incluși în studiu. A fost comparat UHR la pacienții cu HT și la martorii sănătoși.*

Rezultate. *UHR la pacienții cu HT a fost mai mare 11% ± 4 % versus 8% ± 2% (p<0,001). UHR s-a corelat pozitiv cu nivelurile TSH (r=0,26, p=0,01) și negative cu free T4 (r=-0,22, p=0,04). Sensibilitatea și specificitatea pentru UHR peste 8,3% au fost de 74%, respectiv 52%, cu o arie de sub curba ROC 0,74 (p<0,001, 95% CI: 0,64–0,84).*

Concluzii. *UHR pare să fie un marker folositor pentru pacienții cu HT. Așadar ar putea fi un marker util în diagnosticul HT, alături de alte metode diagnostice.*

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