ORIGINAL ARTICLE

Ultrasonographic Assessment of Intima-Media Thickness (IMT), as a Surrogate of Future Atherosclerosis and Cardiac Diseases in Patients with Hashimoto's Thyroiditis and Concomitant Celiac Disease: A Case-Control Study

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Abstract

Purpose: Intima-Media Thickness (IMT), which is frequently evaluated by B-mode ultrasound study, has been proved to be a reliable surrogate marker for atherosclerosis progression and a predictor of upcoming cardiovascular risks. Sonographic changes of intima-media thickness of carotid artery in Hashimoto's thyroiditis and Celiac disease have been investigated separately. In this study we aimed to evaluate the changes in sonographic appearance of the carotid artery and its mural thickness in patients with Hashimoto's thyroiditis and concomitant Celiac disease, as a surrogate marker of atherosclerosis and a predictor of cardiovascular diseases.

Materials and Methods: A total of 191 patients including 89 patients with only Hashimoto's thyroiditis, 11 patients with Hashimoto's thyroiditis and concomitant Celiac disease, and 91 healthy control subjects underwent ultrasound evaluation of intima-media thickness of carotid artery. High resolution B-mode images with a multi-frequency linear probe, were utilized for assessing the IMT.

Results: IMT in the Hashimoto with celiac disease group was 0.72 ± 0.11 and was 0.69 ± 0.09 in the Hashimoto without celiac disease group and was 0.63 ± 0.10 in the control group. IMT showed significant difference between the three groups and was higher in the Hashimoto patients compared to the control group (P-Value = 0.039 and 0.028). Moreover, IMT was marginally higher in the Hashimoto patients with celiac disease compared to the Hashimoto patients without celiac disease (P-Value = 0.046).

Conclusion: Patients with Hashimoto's thyroiditis suffering from concomitant Celiac disease, showed a more increased IMT values compared to other subjects. This can indicate the potential importance and predictive value of ultrasonic IMT evaluation in Celiac disease and Hashimoto's thyroiditis as a marker of atherosclerosis progression as well as future risk of cardiovascular insults.

Keywords: Ultrasonography; Intima-Media Thickness; Carotid Artery; Hashimoto's Thyroiditis; Celiac Disease.

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1. Introduction

Hashimoto's thyroiditis is the most prevalent autoimmune disease [1]. Pernicious anemia, adrenal insufficiency, Celiac disease, and type 1 diabetes mellitus are among numerous associations that have been attributed to Hashimoto's thyroiditis [2]. Many studies reported separate impacts of Hashimoto's thyroiditis and Celiac disease on patients' cardiovascular outcomes [3, 4]. It has been claimed that either hypo or hyper thyroidism, as well as a positive anti-TPO (Thyroid Peroxidase) antibody can result in increased cardiovascular risks [5, 6]. Moreover, studies have revealed an appreciable relationship between Celiac disease and certain cardiovascular conditions, including cardiomyopathy, myocarditis, arrhythmias, and premature atherosclerosis compared to individuals without the disease [7-9]. Intima-media thickness has been proved to be a reliable surrogate marker for atherosclerosis progression and a predictor of upcoming cardiovascular risks [10, 11]. In the current study, we aimed to investigate the effect of Celiac disease on the intima-media thickness in patients with Hashimoto's thyroiditis independent of the thyroid hormones' status.

2. Materials and Methods

2.1. Patients

A total of 194 subjects were enrolled in this case-control study which was implemented in Valiasr Hospital, Tehran, Iran. 103 subjects with proven euthyroid Hashimoto's thyroiditis (normal FT3, FT4, and TSH≤4.5μU/ml) were recruited for serological assessments of anti-EMA (Endomysial antibody), Immunoglobulin (Ig)A and IgG for diagnosis of Celiac disease [12]. Seropositive patients were then enlisted to undergo duodenal biopsy for confirmation of the diagnosis of Celiac disease [13]. Out of 22 patients with positive serologic findings, 19 patients admitted to participate and underwent duodenal biopsy and 11 of them showed positive histopathologic results for Celiac disease.

Also, 91 age and gender-matched participants, who were referred to radiology ward for performing FAST assessment following trauma, were selected as the healthy control group. Subjects with a history of abnormal thyroid function tests, as well as concomitant known cardiovascular risk factors such as diabetes mellitus, hypertension, dyslipidemia, smoking, and history of vascular disease or Cerebrovascular Disease (CVD) were excluded from the study. BMI was calculated for all subjects [14]. The lab data were extracted from patients' recent documents.

For assessing the blood pressure, a digital blood pressure monitor (Withings, Issy-les-Moulineaux, France) was employed in a calm situation. Patients with systolic and/or diastolic blood pressure ≥ 135mmHg and ≥85mmHg were supposed as hypertensive [15, 16]. Type 2 diabetes diagnostic criteria by the ADA (American Diabetes Association) were applied to excluding diabetic patients [17]. The objectives of the study were explained to the research participants, and the patients were included in the study after obtaining written informed consent about the outlined sampling method. Also, all ethical considerations of Helsinki were observed.

2.2. IMT Ultrasound Measurements

High resolution, two Dimensional (2D), B-mode, gray scale, longitudinal images obtained by Mindray Resona I9 ultrasound scanner (Mindray Medical International Limited, Guangdong, China) equipped with an L9-4 MHz linear transducer were utilized for assessing the IMT. Ultrasound examination was performed by an expert radiologist with 5 years of experience in a supine position with mild neck extension and minimal tilt of the head to the opposite side toward the radiologist. A 10mm-long segment of the arterial wall, 20mm proximal to the carotid bulb, was selected to be investigated for IMT (Figure 1). Atherosclerotic plaques were ignored if the aforementioned segment contained any of them, and the IMT was measured regardless of the plaques. IMT, as the interval between the innermost two layers of the arterial wall, was evaluated considering the guideline approved by Mannheim Carotid Intima-Media Thickness and Plaque Consensus [18]. A horizontal position and far wall of the lumen were preferred, since in longitudinal images the far wall of the artery depicts a better distinction of the lumen-intima interface. An optimized angle of insonation (90° to the vessel wall) was also applied to achieve a desirable

delineation of the intima-media thickness. It should be mentioned that with all aforesaid considerations, the actual thickness of the intima cannot be precisely measured due to its thin internal elastic lamina which is below the resolution of transcutaneous B-mode ultrasound. The maximum values of measured IMT were recorded for each patient and were analyzed statistically.

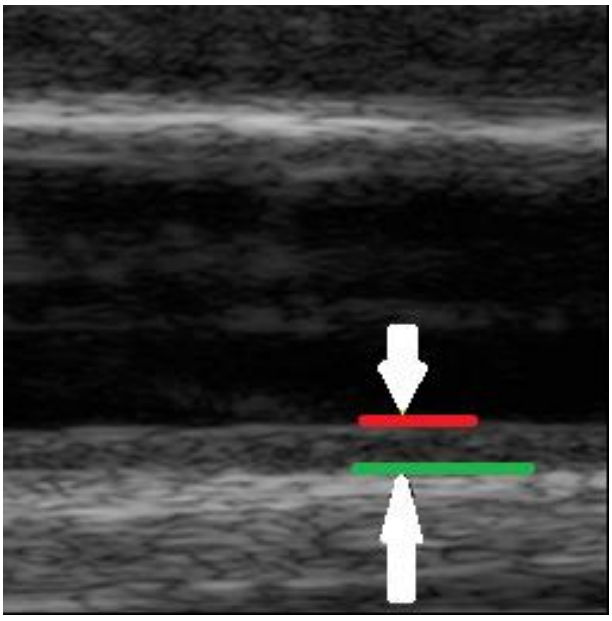

Figure 1. Longitudinal view of the common carotid artery. Intima-media thickness is measured as the distance between the two arrows and is defined as the distance between the outer-most margin of intima (red line) and the outer-most margin of media (green line)

2.3. Serological Examination

Generic assays (Blankenfelde-Mahlow, Germany), a test kit for identifying IgA and IgG autoantibodies to human EMA, was employed for evaluating Anti-EMA IgA and IgG presence. Conventional approved methods were used for investigating other lab data.

2.4. Duodenal Biopsy

Subjects with positive serological results for Celiac disease were recruited for obtaining endoscopic biopsies to establish the diagnosis. Biopsies were obtained from the second portion of the duodenum and the duodenal bulb, under moderate sedation induced by Midazolam (0.5-1mg) and Fentanyl (12.5-75µg) (Figure 2) [19]. Modified Marsh classification was employed for pathological assessments [20].

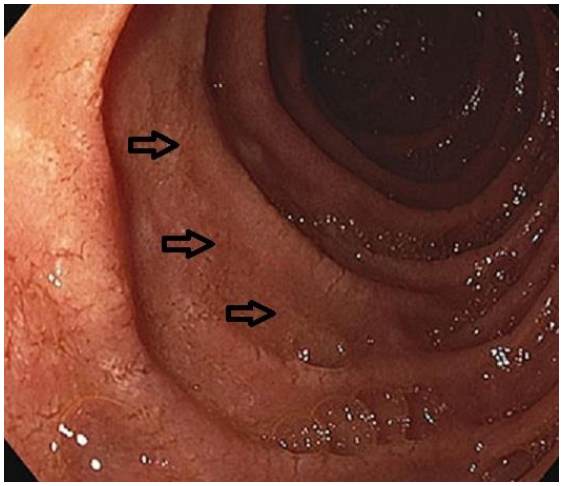

Figure 2. Endoscopic evaluation of a patient with Celiac disease illustrates fissures on the folds and the absence of mucosal villi (arrows)

2.5. Statistical Analysis

The data were analyzed employing SPSS v26 (SPSS Inc., Chicago, Ill., USA) for Windows (Microsoft Corporations, Washington D.C, USA) with a significance level considered less than 0.05. Quantitative data were recorded as numbers and percentages and subsequently were compared by student t-test.

3. Results

A total of 194 subjects were selected to enroll in the current study. Of the total subjects, 103 subjects were proved cases of Hashimoto thyroiditis with normal FT3 and FT4 levels and TSH≤4.5µU/ml.

All patients with Hashimoto thyroiditis underwent a serological study for evaluating Celiac disease, and 22 subjects (21.3%) showed positive results for Celiac disease. 19 patients from the 22 serology-positive patients admitted to continue participation in the study. Therefore, duodenal biopsies were obtained and a histopathological study confirmed Celiac disease in 11 (57.8%) of them.

Subjects of the study were divided into three subgroups: Patients with Hashimoto's thyroiditis and Celiac disease (N=11), Patients with Hashimoto's thyroiditis without Celiac disease (N=89), and a healthy control group (N=91).

Demographic characteristics as well as the laboratory and ultrasound study variables are depicted in Table 1. As the groups were gender and age-matched, no significant difference was noticed between the groups. Also, no significant difference was detected in BMI and FT4 levels between the groups.

TSH levels were significantly higher in both groups with Hashimoto's thyroiditis compared to the control group (P-Value = 0.032 and 0.041), but no significant differences were revealed between Hashimoto's thyroiditis patients with and without Celiac disease. Likewise, FT3 levels were significantly lower in both groups with Hashimoto's thyroiditis compared to the control group (P-Value = 0.012 and 0.021), but no significant differences were detected among Hashimoto's thyroiditis patients with and without Celiac disease.

IMT measured by ultrasound in Hashimoto with Celiac disease group was 0.72 ± 0.11and 0.69 ± 0.09 in Hashimoto without Celiac disease group and 0.63 ± 0.10 in the control group. As presented in Tables 2 and 3, IMT measurement showed significant difference between the three groups and was higher in Hashimoto patients compared to the control group (P-Value = 0.039 and 0.028). Moreover, IMT was significantly higher in patients with Celiac disease compared to Hashimoto patients without Celiac disease (P-Value = 0.046) (Tables 2, 3, 4).

4. Discussion

The diagnosis of Hashimto's thyroiditis is based on the presence of anti-thyroid peroxidase antibody as well as supportive ultrasound findings [21]. Concordant autoimmune diseases, like Celiac disease, are of the dominant features of Hashimoto's thyroiditis [1]. The culprit of increased future risk of cardiovascular diseases in patients with either Hashimoto's thyroiditis or Celiac disease is claimed to be the atherosclerotic process [22, 23]. IMT is reported to be the most valuable surrogate marker of atherosclerosis. Therefore, in the current study, we investigated the impact of Hashimoto's thyroiditis and Celiac disease on IMT values and we found that patients with Hashimoto's thyroiditis have higher IMT values in the ultrasound study compared to the control group.

Due to the fact that impaired thyroid hormone status has a distinct effect on the process of atherosclerosis and can be an important confounding factor in the evaluation of the effects of Hashimoto's disease [23], we restricted our subjects to euthyroid patients. Also, with the same logic, we excluded patients with other known risk factors of atherosclerosis.

Our study revealed that TSH levels were significantly higher in patients with Hashimoto's disease compared to the control group, regardless of concomitant Celiac disease. The same fact was true about FT3 levels which were of lower values in patients with Hashimoto's thyroiditis. This can potentially be a clue that Hashimoto's thyroiditis can contribute to increased IMT even in euthyroid subjects who might be hard-wired to the decline in thyroid function.

We also compared the aforementioned variables in Hashimoto patients with and without concomitant Celiac disease. The only significant difference in the groups was higher IMT values in patients with concomitant Celiac disease suggesting the additive effect of Celiac disease on the progression of the atherosclerosis process in patients with Hashimoto's thyroiditis.

Table 1. Demographic characteristics, laboratory findings, and IMT in groups

	HT with CD (Mean±SD)	HT without CD (Mean±SD)	control (Mean±SD)
Quantity	11	89	91
Sex (Female)	8	76	77
Age (years)	38.65±11.31	39.21±9.93	41±10.06
BMI (kg/m^2)	29.49±5.52	31.46±6.11	27.07±8.24
TSH (μU/ml)	2.48±1.18	2.51±1.20	1.65±1.03
FT3 (pg/ml)	3.12±0.46	3.14±0.39	3.42±0.33
FT4 (pg/ml)	10.33±1.31	10.52±1.19	10.49±1.36
IMT (mm)	0.72±0.11	0.69±0.09	0.63±0.10

Table 2. Comparison of variables between HT patients with and without Celiac disease

	HT with CD (Mean±SD)	HT without CD (Mean±SD)	P-Value
Quantity	11	89	-
Sex (Female)	8	76	0.562
Age (years)	38.65±11.31	39.21±9.93	0.872
BMI (kg/m^2)	29.49±5.52	31.46±6.11	0.429
TSH (µU/ml)	2.48±1.18	2.51±1.20	0.125
FT3 (pg/ml)	3.12±0.46	3.14±0.39	0.767
FT4 (pg/ml)	10.33±1.31	10.52±1.19	0.332
IMT (mm)	0.72±0.11	0.69±0.09	0.041*

HT (Hashimoto's Thyroiditis), CD (Celiac Disease), BMI (Body Mass Index), TSH (Thyroid Stimulation Hormone), FT3 (Free T3), FT4 (Free T4), IMT (Intima-Media Thickness)

Table 3. Comparison of variables between HT patients with Celiac disease and the control group

	HT with CD (Mean±SD)	control (Mean±SD)	P-Value
Quantity	11	91	-
Sex (Female)	8	77	0.839
Age (years)	38.65±11.31	41±10.06	0.063
BMI (kg/m^2)	29.49±5.52	27.07±8.24	0.241
TSH (µU/ml)	2.48±1.18	1.65±1.03	0.032*
FT3 (pg/ml)	3.12±0.46	3.42±0.33	0.012*
FT4 (pg/ml)	10.33±1.31	10.49±1.36	0.447
IMT (mm)	0.72±0.11	0.63±0.10	0.039*

HT (Hashimoto's Thyroiditis), CD (Celiac Disease), BMI (Body Mass Index), TSH (Thyroid Stimulation Hormone), FT3 (Free T3), FT4 (Free T4), IMT (Intima-Media Thickness)

Table 4. Comparison of variables between HT without Celiac disease and the control group

	HT without CD (Mean±SD)	control (Mean±SD)	P-Value
Quantity	89	91	-
Sex (Female)	76	77	0.459
Age (years)	39.21±9.93	41±10.06	0.211
BMI (kg/m^2)	31.46±6.11	27.07±8.24	0.164
TSH (µU/ml)	2.51±1.20	1.65±1.03	0.041*
FT3 (pg/ml)	3.14±0.39	3.42±0.33	0.021*
FT4 (pg/ml)	10.52±1.19	10.49±1.36	0.412
IMT (mm)	0.69±0.09	0.63±0.10	0.028*

HT (Hashimoto's Thyroiditis), CD (Celiac Disease), BMI (Body Mass Index), TSH (Thyroid Stimulation Hormone), FT3 (Free T3), FT4 (Free T4), IMT (Intima-Media Thickness)

To the best of our knowledge, to date, no other studies have assessed Celiac disease and concomitant Hashimoto's thyroiditis with regard to their impact on the IMT. Furthermore, studies focused on the effects of Hashimoto's disease and Celiac disease, separately, on IMT values are scarce.

Ciccone *et al.* conducted a study, the result of which showed increased IMT levels in patients with Hashimoto's thyroiditis [24]. In our study, the IMT comparison in patients with and without Hashimoto's thyroiditis was in the same line with Ciccone's. In that study, only obese female subjects were involved. Also, cerebrovascular risk factors such as hypertension or dyslipidemia were not restricted in the sample selection; yet in our study, we have done our best to reduce the confounding effects of the aforesaid

factors. In Ciccone's study, no subdivision with regard to the presence of Celiac disease was made.

In another study completed by Demir *et al.* [25], carotid artery IMT was evaluated in Celiac disease and a comparison was made with a healthy control group. They demonstrated that patients with Celiac disease show higher IMT which was concordant with our results and this can empower the relationship between Celiac disease and higher IMT.

The association between Celiac disease and Hashimoto's disease is from the most widely-investigated issues. In a study completed by Farahid *et al.*, the seroprevalence of Celiac disease in patients with Hashimoto's thyroiditis was 12.8% (117 out of 914 patients), but in our study, 21.3% of patients with Hashimoto's thyroiditis was seropositive for Celiac disease [26]. This might be due to the sample size difference and also the ethnic/genetic background of the participants.

In 1999, Velentino *et al.* completed a clinical trial, investigating the prevalence of Celiac disease in patients with varied types of autoimmune thyroid diseases [27]. Their data suggested a prevalence (3.3%) of Celiac disease in patients with autoimmune thyroid diseases. This lower prevalence can be due to the fact that they included subjects with different autoimmune thyroid diseases, contrary to ours which has just included patients with Hashimoto's thyroiditis. Other possible justifications can potentially be the escalating prevalence of Celiac disease through decades.

In this study we encountered limitations. This was a single-centered study and the selection bias was inevitable. Regarding the need for confirmation of Celiac disease by endoscopic biopsy, some of the participants refused to pursue their enrolment. We could not sufficiently evaluate the effect of medication on our patients; hence, there was an alteration in treatment dosage and it was not feasible to be assessed by a single questionnaire and needed a focused investigation and time-consuming interviews. Therefore, we suggest studies be conducted with a larger sample volume and consideration of medications the patients receive. Also, evaluating other concomitant autoimmune diseases (i.e. lupus, rheumatoid arthritis) that can lead to pivotal impacts on cardiovascular status is of a great importance.

5. Conclusion

IMT was of higher values in patients with Hashimoto's thyroiditis compared to the control group; hence, it might be concluded that they are at a higher risk of future cardiovascular diseases. Patients with Hashimoto's thyroiditis suffering from concomitant Celiac disease showed increased IMT values compared to the other subjects. This can indicate the potential additive impact of Celiac disease on atherosclerosis progression as well as the future risk of cardiovascular insults. This entity can prove the potential role of ultrasonographic assessment of IMT in predicting upcoming cardiovascular outcomes in patients with Hashimoto's thyroiditis and concomitant Celiac disease.

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