Cerrahpaşa Med J 2023; 47(2): 123-128 ORIGINAL ARTICLE

Irritable Bowel Syndrome in Women with Euthyroid Hashimoto's Thyroiditis: Is There Any Relationship Between Thyroid Autoimmunity and Irritable Bowel Syndrome?

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Abstract

Objective: The relationship between euthyroid Hashimoto thyroiditis and irritable bowel syndrome is not well elucidated. The objective of this study is to estimate the rates of irritable bowel syndrome using Rome IV diagnostic criteria in both Hashimoto thyroiditis and control participants and to evaluate the relationship between thyroid autoimmunity and irritable bowel syndrome.

Methods: We conducted a cross-sectional study including a total of 480 women; 260 women with Hashimoto thyroiditis and 220 age-matched controls. We evaluated comprehensively the rates of irritable bowel syndrome in Hashimoto thyroiditis patients and controls. We also investigated the features likely to influence the presence of irritable bowel syndrome in women with euthyroid Hashimoto thyroiditis and healthy controls.

Results: The frequency of irritable bowel syndrome was 30.7% (n = 80) in Hashimoto thyroiditis patients and 29.5% (n = 65) in controls with no statistically significant differences between the groups (P = .428). Although thyroid antibody titers were higher in Hashimoto thyroiditis with irritable bowel syndrome than in Hashimoto thyroiditis without irritable bowel syndrome, this difference did not reach statistical significance (P = .056). The presence of asthma and depression was associated with increased rates of irritable bowel syndrome in both Hashimoto thyroiditis patients (P = .001 and P = .001) and controls (P = .001and P= .037).

Conclusions: In this study, we found that there was no association between euthyroid Hashimoto thyroiditis and irritable bowel syndrome. Although not statistically significant, thyroid antibody titers were higher in Hashimoto thyroiditis with irritable bowel syndrome, and their implications for irritable bowel syndrome development in HT patients remain to be elucidated.

Keywords: Thyroiditis, anti-TPO, autoimmunity, autoimmune disease, irritable bowel syndrome

Introduction

Disorders in thyroid function associated with both deficiency or excess of thyroid hormones affect gastrointestinal system (GIS) presenting with various clinical manifestations.[1] Knowledge about the interaction between intestine and thyroid disorders beyond the altered thyroid function is limited. Hashimoto's thyroiditis (HT) is an example of organ-specific autoimmune disease (AD) that, irrespective of thyroid hormone levels, can overlap with some autoimmune intestinal diseases including celiac disease (CD) or non-celiac wheat sensitivity (NCWS) supporting the general concept of susceptibility for AD.[2,3] But the data on the relationship between functional intestinal disorders such as irritable bowel syndrome (IBS) and euthyroid HT are not well elucidated. Irritable bowel syndrome is a disorder characterized by abdominal pain associated with changes in bowel habits without detectable structural abnormalities, which on the other hand would also be associated with some AD.[4,5] The evaluation of the relationship between HT and IBS is of interest for several reasons. Both HT and IBS are frequent diseases, have female predominance, and are associated with concurrent unexplained syndromes such as fibromyalgia and chronic fatigue. Although there is no common single etiology explaining these associations, evidence exists as to some common phenomena such as local low-grade inflammation or infectious and hormonal events being involved in their pathogenesis.[4,6] Recently, dysbiosis was shown to be a common finding in both diseases, suggesting the existence of a thyroid–gut axis.[7-9] Thus, clarifying the presence and direction of relationships between HT and IBS is necessary to determine the need for screening and raise awareness among clinicians in routine practice.

The aim of the current study was to evaluate the frequency of IBS in patients with euthyroid HT compared to controls and characteristics associated with the presence of IBS in women with euthyroid HT and controls.

Methods

This was a cross-sectional, comparison study conducted between January and December 2019 at the Prof. Dr. Cemil Taşçıoğlu City Hospital, Department of Internal Medicine.

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Participants

Patients with well-documented HT at euthyroid state were included consecutively among patients attending the medical outpatient clinic. The inclusion criteria were age ≥ 18 years, having the diagnosis of HT before the study, having all clinical and laboratory data available, being at euthyroid state regardless of levothyroxine replacement therapy, and absence of other florid inflammatory disease and malignant diseases. The control group consisted of apparently healthy volunteers matched for age and gender who were selected among persons attending the outpatient clinic for routine checkups who have available laboratory results confirming the absence of any thyroid abnormalities including autoantibodies. Individuals previously diagnosed with GIS diseases such as inflammatory bowel diseases (IBD), and gall bladder diseases, who had alarm symptoms such as weight loss or rectal bleeding, who had a history of treatments that interfere with intestinal motility, and pregnant or breastfeeding women were excluded.

Measurements

The sociodemographic characteristics of the participants (age, education and employment status, monthly income), smoking, body mass index (BMI), and comorbidities (hypertension, prediabetes/diabetes—DM/IGT, except long-standing diabetes, depression, and asthma) were recorded. Medication data were obtained from electronic medical records, including the use of levothyroxine replacement therapy. All available data about previous procedures or investigations including abdominal ultrasonography or endoscopic procedures were reviewed in order to exclude IBD, malignancy, and other causes for gastrointestinal symptoms. Serum levels of thyroid-stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), C-reactive protein (CRP), antithyroperoxidase antibody (anti-TPO) and antithyroglobulin antibody (anti-TG), the whole blood count, neutrophil to lymphocyte ratio (NLR) were all recorded. We considered the following reference values: TSH: 0.27-4.2 μIU/L, FT4: 0.93-1.6 ng/L, FT3: 2.0-4.4 ng/L; anti-TPOAb: upto 34 IU/mL, and anti-TGAb: upto 115 IU/mL.

All participants were inquired about the presence of symptoms specific to IBS. We used the most recent Rome IV criteria for the diagnosis of IBS. Type of IBS was classified based on stool patterns, that is IBS with constipation, diarrhea, or mixed stool pattern. In patients who had previously received a diagnosis of IBS, the diagnosis was reviewed based on the Rome IV criteria. These patients were also evaluated for prior medication history for IBS and whether they had been consulted by a gastroenterologist.

We compared the frequency of IBS among HT patients to that among controls. We also compared the characteristics of patients with and without IBS within the HT and control groups separately. In a subgroup analysis of patients with euthyroid HT, we compared thyroid antibody titers in subgroups of HT with or without IBS to assess whether autoimmunity might influence the presence of IBS.

Ethics Approval

This study was conducted in accordance with the Declaration of Helsinki. The study was approved by the institutional ethics committee of Prof. Dr. Cemil Taşçıoğlu City Hospital (Date: March 14, 2017, Number: 48.670.771-514.10). All participians were informed about the study, and their informed consent was obtained.

Statistical Analysis

Descriptive statistical methods were used to describe the main characteristics of the study population. We used the Student's

Table 1. Socio-Demographic and Laboratory Data of the Participants

Variables	Patients with HT (n = 260)	Control Participants (n = 220)	*P*
Age; years (SD)	39.53(9.28)	38.79 (10.38)	.420
Educational status (n, %)			
Illiterate	30 (11.5)	20 (9)	.047
Primary school	148(57)	110 (49.5)	
High school	57 (22)	58 (26.5)	
University	25 (9.5)	32 (15)	
Employment status (n, %)			
Employed	79 (30.3)	60 (27.2)	.213
Smoking (n, %)	71 (27)	48 (21)	.319
BMI (kg/m²)	28.51 (5.87)	28.30 (6.41)	.739
Co-morbidities (n, %)			
Hypertension	37 (14.2)	28 (12.7)	.689
DM/IGT	25 (9.6)	21(9.5)	.553
Depression	17 (6.5)	15 (6.8)	.425
Asthma bronchial	24 (9)	10 (4.5)	**.03**
Presence of IBS (n, %)	80 (30.7)	65 (29.5)	.428
IBS prior to study (n, %)	21 (8)	12 (5.5)	.5
IBS type (n, %)			
IBS-constipation	43 (53.7)	29 (44.6)	.509
IBS-diarrhea	15 (18.8)	13 (20)	
IBS-mix	22(27.5)	23 (35.4)	
Anti TPO IU/mL (SD)	275.73(243.26)	11.79 (5.83)	**.000**
Anti TG IU/mL (SD)	475.67(766.98)	22.83 (21.75)	**.000**
TSH (mIU/L)(SD)	2.88 (1.47)	2.10 (1.06)	**.000**
Free T4 (ng/L)(SD)	1.18 (0.21)	1.205 (0.22)	.409
Free T3 (ng/L) (SD)	3.13 (0.44)	4.94 (0.12)	.264
CRP(SD)	4.05 (2.24)	4.09 (2.11)	.811
WBC (/10^3/mm^3) (SD)	7.08 (1.58)	6.91 (1.57)	.252
Neu (/10^3/mm^3) (SD)	4.04 (1.13)	3.88 (1.11)	.104
Ly(/10^3/mm^3) (SD)	2.29 (0.61)	2.36 (0.57)	.241
NLR (SD)	1.87 (0.66)	1,69 (0.51)	**.001**
Plt (/10^3/mm^3) (SD)	271.68 (68.24)	265.04 (59.23)	.263

P-value <.05 is statistically significant. BMI, body mass index; DM/IGT, diabetes mellitus/impaired glucose tolerance; Anti-TPO, antithyroperoxidase antibody; Anti-TG, antithyroglobulin antibody; TSH, thyroid-stimulating hormone; FT4, free thyroxine; FT3, free triiodothyronine; CRP, C-reactive protein; IBS, irritable bowel syndrome; HT, Hashimoto thyroiditis; SD, standard deviation; NLR, neutrophil to lymphocyte ratio; WBC, white blood cell; Neu, neutrophil; Plt, platelet; Ly, Lymphocyte.

t-test to compare the continuous variables and the chi-square test to compare the categorical variables. Continuous values were presented as mean ± standard deviation. Spearman's correlation was used to assess the relationship between IBS rates and factors probably able to affect the IBS. A *P*-value <.05 was considered statistically significant. Data were analyzed using Statistical Package for the Social Sciences (IBM SPSS Corp., Armonk, NY, USA) for Windows, version 20.0.

Results

We evaluated 260 women with HT and 220 age-and gender-matched controls. All patients with HT were women in euthyroid state and anti-TPO and anti-TG antibodies were increased above the normal limits. Demographic and laboratory test results of the groups are given in Table 1.

Overall, 145 study participants (30.2%) fulfilled the Rome IV criteria for IBS including 80 HT patients (30.7%) and 65 healthy controls (29.5%). There was no statistically significant difference in the rates of IBS between the HT and control groups (chi-squared *P* = .428). In the subgroup analysis of patients with HT with or without concomitant IBS, the levels of anti-TPO in HT + IBS subgoup were higher than in HT without IBS subgroup, but this difference did not reach a statistical significance (*P* = 0.056).

Around 81 (56%) out of 145 participants with IBS had seen a physician because of IBS symptoms, but 33 (22.7%) patients had received a diagnosis of IBS (14.4% for HT group and 8% for control) before the study and only 16 (11%) patients had consulted a gastroenterologist for IBS (Figure 1).

In the subgroup analysis of patients with HT, the presence of asthma [22 (27.5%) vs. 2 (1%), odds ratio (OR): 33.75 (95% CI,7.75-147.93); *P* = 0.001] and depression [13 (16.2%) vs. 4 (2.3 %), OR: 8.53 (95% CI, 2.68-27.19), *P* = .001] was strongly associated with IBS. Anti-TPO levels were numerically higher in IBS patients than those without a diagnosis of IBS but did not reach statistical significance. In controls, subgroup with IBS had higher rates of depression [9 (13%) vs. 5 (3%), OR: 4.22 (95% CI, 0.97-18.22); *P* = .037] and asthma [7 (10.7%) vs. 3 (2%), OR: 6.11 (95% CI, 1.52-24.4); *P* = .001] than controls without these diseases (Table 2).

The IBS rates were not associated with age, education, employment status, monthly income, smoking habits, BMI, comorbidities such as hypertension and DM/IGT, the laboratory results of NLR, TSH, FT3, FT4, and CRP in both HT and control groups. Neutrophil to lymphocyte ratio levels were higher in HT with IBS and control with IBS subgroups, but these differences were not statistically significant.

Discussion

This study is the first to evaluate the relationship between euthyroid HT and IBS as defined by Rome IV criteria in Turkish female patients. Although HT is known to be associated with particular intestinal diseases, we did not observe an increased frequency of IBS in euthyroid patients with HT.[2,3] There was also no relationship between thyroid antibody titers alone and the frequency of IBS among euthyroid HT patients.

The interaction of intestine and thyroid was neglected for decades, but the recent demonstration of microbiota representing an endocrine network that impacts the metabolism of many organs has brought about a rise in attention on gut–thyroid–endocrine axis.[7] Accumulating data have revealed that commensal intestinal microorganisms have beneficial effects on the immune system and dysbiosis may play a role in the development of some autoimmune and autoinflammatory diseases (A/AD) including IBD, type 1DM, and rheumatological diseases.[8]

Irritable bowel syndrome patients show alterations in microbiota that impair mucosal defense mechanisms and unfavorable immune activation hypothesized to cause a loss of tolerance to self-antigens that predisposes them to AD.[9] An altered microbiota is also reported in HT which, through these hypothetical mechanisms, might be involved in the development of IBS.[7]

To date, few studies have evaluated the coexistence of IBS and A/AD, especially HT. Some studies reported an increased prevalence of rheumatological AD in patients with IBS, while others observed an increase in the prevalence of A/AD only in combination with multiple functional intestinal disorders but not in IBS alone.[10-14] Also, IBS displays a strong association with CD and NCWS.[15,16] Numerous specific antibodies including anti-enteric neuronal antibodies, anti-tissue transglutaminase, tissue transglutaminase antibodies, and gonadotropin-releasing hormone (GnRH) IgM antibodies have been found to be increased in IBS patients, especially in constipation type IBS, suggesting disturbances of self-tolerance associated with the entity.[15-18] Antibodies against various microbial antigens are reported in IBS, especially development after GIS infection.[19]

In contrast to studies showing the association of IBS with A/AD, we did not observe a relationship between IBS and HT at euthyroid state. In our study, the higher titers of anti-TPO and anti-TG were not clearly associated with the presence of IBS. Thus, our

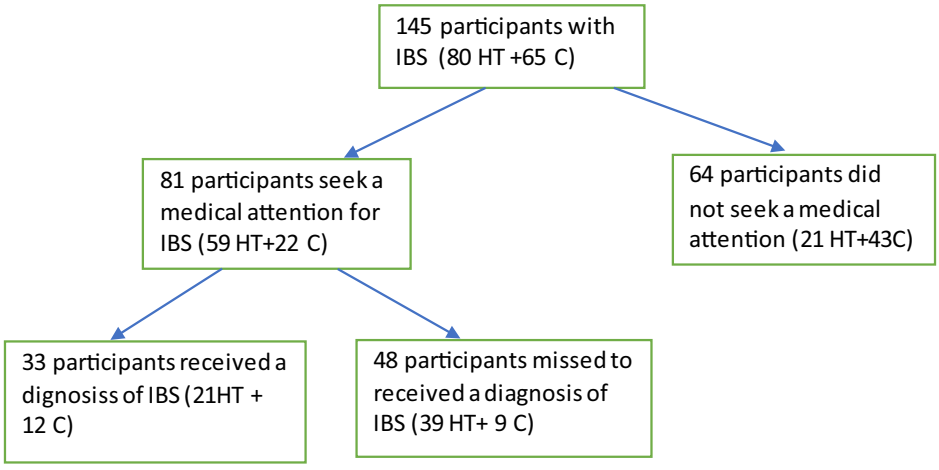

Figure 1. The behavior of IBS patients in seeking medical attention for the symptoms of IBS. IBS, irritable bowel syndrome.

Table 2. Distribution of Socio-Demographic, Laboratory, and Clinical Factors Among HT and Control Participants Subdivided According to Presence of IBS and Association of These Factors with the Presence of IBS

Variables	HT with IBS (n = 80)	HT with no IBS (n = 180)	*P*	Control with IBS (n = 65)	Control with no IBS (n = 155)	*P*
Age, years (SD)	39.64(8.95)	39.48(8.48)	.902	39.60(9.63)	38.45 (10.45)	.453
Education						
No education	8 (10%)	27 (15%)	.5	4 (6%)	16 (10%)	.729
Primary school	48 (60%)	104 (58%)		35 (54%)	75 (49%)	
High school	15 (19%)	37 (20%)		16 (25%)	42(27%)	
University	9 (11%)	12 (7%)		10 (15%)	22 (14%)	
Employment						
Employed	26 (32%)	53 (29%)	.5	19 (29%)	41 (26%)	.673
At least MW	21 (81%)	38(72%)	.16	5 (26%)	11 (27%)	.972
Twice the MW	4 (15%)	13 (24%)		12 (63%)	27 (66%)	
Three times MW	1(4%)	2 (4%)		2 (11%)	3 (7%)	
Smoking (n, %)	24 (30)	47 (26)	.8	14 (21.5)	34 (22)	.998
BMI(kg/m²)	28.54(6.43)	27.92(5.54)	.14	28.81 (6.45)	28.09 (6.40)	.449
Co-morbidities (n, %)						
Hypertension	12 (15)	25(14)	.4	9 (14)	19 (12.2)	.747
DM/IGT	8 (10)	17 (9.4)	1	6 (9)	15	.918
Depression	13 (16.2)	4 (2.3)	**.001**	9 (13)	5 (3)	**.037**
Asthma	22 (27.5)	2 (1)	**.001**	7 (10.7)	3 (2)	**.001**
Anti TPO (SD)	294.3(301.2)	236.1(198.5)	.056	11.5 (5.5)	11.9(5.9)	.634
Anti TG (SD)	519.6 (860.4)	456.6 (720.6)	.556	19.7 (16.5)	24.09(23.53)	.182
TSH (mU/L) (SD)	2.99(1.38)	2.83(1.52)	.410	2.11(1.07)	2.09 (1.06)	.891
Free T4 (ng/L) (SD)	1.16(0.17)	1.19(0.22)	.317	1.18 (0.15)	1.21(0.24)	.471
FreeT3 (ng/L) (SD)	3.17(0.46)	3.12 (0.42)	.433	3.89(0.43)	3.22(0.76)	.135
CRP**(SD)**	3.97(1.43)	4.091(2.07)	.720	4.31 (2.13)	3.78(2.10)	.182
WBC ($10^3/mm^3$)	7.41(1.54)	6.93(1.59)	.024	6.93 ±(1.62)	6.90 (1.56)	.915
Neu ($10^3/mm^3$)	4.24 (1.09)	3.95(1.13)	.70	3.94(1.08)	3.73 (1.12)	.191
Ly($10^3/mm^3$)	2.40(0.67)	2.25(0.58)	.66	2.3(0.51)	2.48(0.67)	.044
NLR	1.91(0.75)	1.85±(.61)	.481	1.71(0.49)	1.62(0.57)	.073
Plt ($10^3/mm^3$)	277.5(67.6)	269.0(68.7)	.357	258.4(54.8)	267.3(61.3)	.364

MW, minimum wage; DM/IGT, diabetes mellitus/impaired glucose tolerance; Anti-TPO, antithyroperoxidase antibody; Anti-TG, antithyroglobulin antibody; TSH, thyroid-stimulating hormone; FT4, free thyroxine; FT3, free triiodothyronine; CRP, C-reactive protein; IBS, irritable bowel syndrome; HT, Hashimoto thyroiditis; SD, standard deviation; NLR, neutrophil to lymphocyte ratio; WBC, white blood cell; Neu, neutrophil; Plt, platelet.

study results did not support the notion of autoimmunity, particularly which was associated with low-grade systemic inflammation as in HT, to be a causal or the only causal link, if any, between these 2 diseases. As HT is an organ-specific AD where local, subclinical inflammation is predominant, it may be argued that the positive relationship found between some A/AD and IBS could be related to florid systemic inflammation (as in rheumatological diseases) or the heterogeneity in immune responses inherent to A/AD. For example, García Carrasco et al[11] reported a higher frequency of IBS in SLE patients with higher disease activity (systemic lupus erythematosus disease activity index (SLEDAI)> 4) and in those treated with biologic agents that actually supported this idea. Furthermore, the diversity of the relationship between certain antibodies and the presence of IBS might reflect, on the other hand, the variety of the IBS cases and would be beneficial in identifying specific IBS cases developed after different etiopathogenetic pathways.

Similar to our study results, Ford et al[10] in their large sample of primary care patients (n= 23 471) did not observe an association between IBS and endocrine autoimmune disorders including HT. Khadka et al[20] investigated the presence of thyroid dysfunction in the cohort of IBS patients diagnosed with Rome III criteria, methodologically different from our study, and showed an increased prevalence of thyroid dysfunction in IBS. But the thyroid dysfunction found in this study was associated with abnormal thyroid hormone levels, especially subclinical hypothyroidism; however, the underlying reasons for subclinical hypothyroidism were not elucidated. Hashimoto thyroiditis at hypothyroid state is known to be accompanied by motility disorders presenting as IBS or IBS-like syndrome including abdominal pain and discomfort.[1] Therefore, the IBS and IBS-like symptoms developed in the course of HT are likely to result from the direct effects of altered thyroid hormones on motility instead of impact of autoimmunity alone in the euthyroid state. However, it should be kept in mind

that in HT patients who progress to hypothyroidism, autoimmunity proceeds more severely and also dysbiosis, which could be either the cause or consequence of autoimmunity, is more severe as well.[7]

The prevalence of the IBS in general population varies between different countries and is reported in rates from 1.1% to 45% depending on diagnostic criteria, study methodology, and sampling cohort used.[21-23] Western communities are reported to have lower IBS prevalence rates than non-Western countries.[21,23] In Turkey, the rate of IBS in general population is estimated to be around 6.3%-19.1% with a 2-3 : 1 female prevalence.[24,25] In our study, the rates of IBS in both HT patients and controls using Rome IV criteria were higher than those from other national or international studies conducted on general population. When we looked at the rate of IBS only in the HT patients in our study, we observed that these rates were higher than those in the general population but lower, albeit to different degrees than the rates in numerous A/AD. For example, the frequency of IBS according to Rome IV in patients with inactive IBD, PSS and SLE were found to be 32%, 34.61% and 48.6% respectively.[11-13] The differences in IBS frequencies between A and AD indicated that the severity of the systemic inflammation involved in the pathogenesis of A/AD might correspond with the presence of IBS. Therefore, it is expectable that IBS would occur to a lesser extent in euthyroid HT than systemic A/AD.

But the higher rate of IBS in controls found in our study was contradictory to the results obtained from case–control studies addressing A/AD (13.8%-18.7%) or those conducted on general population.[11-13,21-24] The discrepancy between study results may be explained by the fact that our participants consisted primarily of women in middle age and IBS shows a female predilection with an age-dependent decrease. In this instance, women aged 45-50 years or older have significant lower rates of IBS than those aged younger than 45 years.[21] The epidemiological data on general population from previous 15-20 years in Turkey showed a lower prevalence of IBS compared to data reported in Western communities.[24] In recent years, Turkey and some developing countries have adopted a Western diet and lifestyle. Westernization is discussed in the literature to be a behavior that might justify the increase in the rates of IBS in developing countries and we speculated that it might affect the rates of IBS in controls in our study. Another important point is that in contrast to some population-based studies where the data on IBS were collected using electronic health records, we have interviewed our participants "face to face'' with an awareness about the condition allowing participants time to answer questions. If we assume that our data had been extracted from electronic health records only, the rates of IBS in HT and controls would have been 8% and 5.5%, respectively (Table 1).

Irritable bowel syndrome is now recognized as a heterogeneous group of conditions and multiple factors might contribute to increased rates of IBS such as age, educational status, economic status, obesity, smoking, and NLR.[21-24] However, studies have reported conflicting results on the association between IBS and socioeconomic status, obesity, NLR; some of the studies confirmed them as risk factors, whereas others did not.[21-24] In this study, we did not find an association between the rates of IBS and age, education status, employment status and monthly income, BMI, HT, DM/IGT, NLR, TSH, FT3, FT4, and CRP. Higher levels of NLRs in both HT+IBS and control+IBS subgroups did not reach statistical significance in terms of presence of IBS. The presence of asthma and depression displayed a strong association with IBS in both HT and control groups, findings that were consistent with previous studies.[25,26]

Antibodies against TPO and TG are useful markers of thyroid autoimmunity. There were no relevant data assessing the effects of thyroid antibodies on the GIS. Higher levels of anti-TPO were found in HT patients with IBS than in those without IBS, but this difference did not reach statistical significance.

The limitations of this study are misclassification of significant organic diseases. There might be some misclassification of significant organic diseases; however, it is reported to be at low rates (1.03%).[27]

We did not find an association between IBS and autoimmunity related to euthyroid HT. Thus, the routine screening of IBS among euthyroid patients with HT is not warranted, except in selected cases, with concomitant depression and asthma.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Prof. Dr. Cemil Taşçıoğlu City Hospital (Date: March 14, 2017, Number: 48.670.771-514.10).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.B., A.Y., M.A.; Design – A.Y., M.A., M.B., Y.G.; Supervision – M.A., Y.G., A.Y.; Funding – A.Y., M.B.; Materials – A.Y., M.B., Y.G.; Data Collection and/or Prosessing – A.Y., M.B., Y.G.; Analysis and/or Interpretation – A.Y., Y.G., M.A.; Literature Review – A.Y., Y.G., M.A.; Writing – A.Y., M.B., M.A.; Critical Review – M.A., Y.G.

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