Inflammatory bowel disease severity and activity are correlated to thyroid gland nodularity, chronic nonthyroidal illness, and thyroid autoantibodies but not thyroid dysfunction

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Introduction
An association between inflammatory bowel disease (IBD) and autoimmune thyroid disease (AITD) exists. The aim of the present study was to evaluate thyroid nodules, function, and antibodies in patients with IBD.
Patients and materials
The study included 50 patients with established diagnosis of IBD either ulcerative colitis (UC) or Crohn's disease and 25 healthy controls. They were classified into two groups: group I included 25 patients with UC, and group II included 25 patients with Crohn's disease; the control group included 25 healthy individuals. They were subjected to history taking, complete physical examination, and laboratory investigations that included evaluation of erythrocyte sedimentation rate (ESR), C-reactive protein, fecal calprotectin, free T3, free T4, thyroid-stimulating hormone, antithyroid peroxidase (TPO), antithyroglobulin (TG), and TSH receptor antibodies. Ileocolonoscopic and histopathological examination with assessment of IBD activity and thyroid ultrasonography were carried out.
Results
There were no statistically significant differences between the three groups as regards anti-TG antibodies (P=0.075), anti-TPO (P=0.190), AITD assessed serologically or by means of ultrasound (P=1.000), or as regards thyroid status (P=0.528). IBD patients had significantly more thyroid nodules compared with controls (P<0.001), and there was a positive correlation between IBD markers of activity (ESR and fecal calprotectin) and the presence of nodules. A significant negative correlation existed between free T3 and fecal calprotectin, ESR, and C-reactive protein, as well as between free T4 and ESR and fecal calprotectin. A significant positive correlation between anti-TG antibodies and fecal calprotectin as well as between anti-TPO antibodies and histological activity assessment of UC patients also existed. We found a significant negative correlation between free T3 and free T4 and several indices of IBD activity/severity.
Conclusion
AITD and altered thyroid function were the same among IBD patients and controls. However, IBD patients had significantly more nodules; indices of activity/severity of IBD correlated negatively with free T3 and T4, and positively with anti-TPO, anti-TG, and nodularity.

Keywords:
autoimmune thyroid disease, chronic nonthyroidal illness, inflammatory bowel disease, thyroid dysfunction, thyroid nodules

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Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are the two major forms of idiopathic inflammatory bowel disease (IBD) [1]. Less common but increasingly recognized are the atypical microscopic colitis, primarily collagenous colitis, and lymphocytic colitis. The diagnosis of the two main forms is based on clinical presentations, endoscopic features, histological features, and radiological abnormalities [2–5].

Graves' disease (GD) and Hashimoto thyroiditis (HT) are the two major forms of autoimmune thyroid disease (AITD). AITD is characterized by the occurrence in the serum of antibodies against thyroid peroxidase (TPO) (the 'microsomal' antigen), thyroglobulin (TG), and the TSH receptor (TSHR) [6]. Case reports have suggested an association between IBD and AITD. Population studies have demonstrated a two-fold to four-fold increase in the prevalence of thyroid disease in patients with UC [7].

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Both AITD and IBD are associated with Th1/Th2 imbalance, with a dominance of Th2 responses [8]. However, this immunological imbalance also occurs in many other autoimmune conditions [9]. There are few research studies on possible common genetic factors in AITD and IBD [10,11]. Dysbiosis in the gut (altered composition of the gut flora), which has been reported in IBD could disturb the finely tuned immune balance and break tolerance to self-antigens and nonpathogenic non-self-antigens, leading to the development of autoimmune disorders [12,13].

Similar changes have interestingly been detected in patients with AITD, suggesting a pathogenic role of the leaky gut barrier in the development of AITD [14].

Chronic thyroiditis is well known as an extraintestinal complication of IBD [15]. Hyperthyroidism intensifies the systemic manifestations of IBD and renders its management difficult [16]. It is also possible that, as both IBD and thyroid disorder have a possible autoimmune etiology, treating IBD with corticosteroids and immunomodulating agents may prevent the manifestations of an AITD.

The aim of the present study was to evaluate the prevalence of thyroid autoimmunity, nodularity, and dysfunction in a group of patients with IBD.

Patients and methods

The study included 50 patients diagnosed as having IBD who were classified into two groups: 25 patients with UC as group I, and 25 patients with CD as group II. Twenty-five age and sex matched healthy individuals served as a control group.

All patients were subjected to history taking and physical examination, with emphasis on history of autoimmune diseases, extraintestinal manifestations of IBD, neck examination for goiter, symptoms, and signs of thyroid dysfunction.

Thyroid function was determined using thyroid-stimulating hormone (TSH), free T4, and free T3. Thyroid autoimmunity was assessed using anti-TPO antibodies, anti-TG antibodies, and TSHR antibodies using the enzyme-linked immunosorbent assay [17–19]. Overt and subclinical thyroid dysfunction was defined based on the criteria by US Preventive Services Task Force Recommendation Statement [20]. Nonthyroidal illness was diagnosed by identifying any of the six characteristic patterns postulated by Iglesias *et al.* [21].

Ultrasonography of the thyroid gland was performed for all individuals using a Kontron device (Kontron Medical, France; Plaisir) with a liner probe and a 7.5–10 MHz transducer to identify patients with ultrasonographic evidence of autoimmune thyroiditis (AIT) (diffuse hypoechogenicity or heterogenous echotexture or both) and also to detect thyroid nodularity [22].

IBD disease activity was assessed using erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and fecal calprotectin (Nova Tec immunodiagnostics GmbH, Dietzenbach, Germany) [23]. A number of IBD disease severity indices were used to assess disease severity: for CD, Simple Endoscopic Score in Crohn's Disease (SES-CD), Crohn's disease activity index, and histological assessment of CD; and for UC, Endoscopic Mayo Score in UC, Truelove and Witts' classification of severity of UC, and histological assessment of UC [24–28].

The protocol of this study was approved by the ethical committee of Alexandria Faculty of Medicine.

Statistical methods

Data were fed to the computer and analyzed using IBM SPSS software package (IBM US, New York), version 20.0. Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, SD, and median. Comparison between different groups as regards categorical variables was tested using the χ^2-test. When more than 20% of the cells have expected count less than 5, correction for χ^2 was conducted using Fisher's exact test or Monte Carlo correction. The distributions of quantitative variables were tested for normality using the Kolmogorov–Smirnov test, the Shapiro–Wilk test, and D'Agstino test. If it revealed normal data distribution, parametric tests were applied. If the data were abnormally distributed, nonparametric tests were used. For normally distributed data, comparison between two independent populations was made using the independent *t*-test, whereas more than two populations were analyzed using *F*-test (analysis of variance) and post-hoc test (least significant difference). For abnormally distributed data, comparison between two independent populations was made using the Mann–Whitney test, whereas the Kruskal–Wallis test was used to compare different groups and pair wise comparison was made using the Mann–Whitney test. To compare the different periods the Friedman test and Wilcoxon signed-rank test were applied. Correlations between two quantitative variables were assessed using Spearman coefficient. Significance of the obtained results was judged at the 5% level.

Results

The majority of our patients were male, but the differences between the three groups were nonsignificant (P=0.683): among UC patients, there were 56.0% male and 44.0% female patients; among CD patients, there were 52% male and 48% female patients; and in the control group 64.0% were male and 36.0% were female (Table 1).

Their ages in the three groups ranged between 19 and 77 years and differences between the three groups were nonsignificant (P=0.326) (Table 1).

An overall 44% of the UC patients took corticosteroids. Similarly, among CD patients, 44% of patients took corticosteroids. There were no statistically significant differences between the two groups (P=1.000).

None of the UC patients had concomitant autoimmune disorders, whereas among CD patients three patients (12%) had concomitant autoimmune disorders, one (4%) had type 1 diabetes mellitus, one (4%) had rheumatoid arthritis, and one (4%) had primary sclerosing cholangitis. As regards associated autoimmune disorders, there were no significant statistical differences between the two groups of patients (P=0.235).

Measures of disease activity

Erythrocyte sedimentation rate

Among UC patients it ranged from 6 to 128, with a mean of 40.44±34.32, whereas among CD patients it ranged from 3.0 to 111.0, with a mean of 43.80±35.34. In the control group it ranged from 3 to 39, with a mean of 10.32±8.97. There were significant statistical differences between the three groups as regards ESR (P<0.001) (Table 1).

C-reactive protein

Among UC patients it ranged from 3.0 to 80.0 mg/l with a mean of 24.48±22.61, whereas among CD patients the CRP ranged from 4.0 to 126.0 mg/l with a mean of 47.36±4.81. In the control group, it ranged from 4.0 to 100.0, with a mean of 16.44±20.62. There were no significant differences between the two groups as regards CRP (P=0.058) (Table 1).

Fecal calprotectin

As a measure of disease activity, there were significant statistical differences between the three groups (P<0.001). Among UC patients it ranged from 19.0 to 2628.0 with a mean of 474.48±631.65, whereas in CD patients it ranged from 31.0 to 4020.0, with a mean of 509.36±823.08. In contrast, in the healthy control group it ranged from 8.0 to 40.0, with a mean of 20.36±8.47 (Table 1).

Three indices for assessment of disease activity were used in categorizing UC patients. The first was Truelove and Witts' classification for assessing the clinical activity of the disease, in which 17 cases (68%) had mild disease activity, five cases (20%) had moderate disease activity, and three cases (12%) had severe disease activity.

The second index was Mayo score for assessing endoscopic activity of the disease: 11 cases (44%) achieved a score equal to 1, 10 cases (40%) achieved a score equal to 2, and four cases (16%) achieved a score equal to 3.

The third one was histological activity assessment of UC depending on the microscopic picture: eight patients (32%) had a score of 1, 14 patients (56%) had a score of 2, and three patients (12%) had a score of 3.

Three indices for the assessment of disease activity were used for categorizing CD patients. The first was SES-CD for assessing the endoscopic activity of the disease: 11 patients (44%) were grouped in score 1, eight patients (32%) were grouped in score 2, and six patients (24%) were grouped in score 3.

The second index was histological assessment to categorize microscopic pictures of patients' samples in four grades; eight cases (32%) in grade I, nine cases (36%) in grade II, four cases (16%) in grade III, and four cases (16%) in grade IV.

The third was Crohn's disease activity index for assessment of the clinical activity of the disease, which ranged from 119 to 700, with a mean of 258.84±194.72.

Thyroid autoimmunity

Among UC patients, the anti-TPO ranged from 1.0 to 83.0 IU/ml. Among CD patients it ranged from 0.14 to 106.0 IU/ml, whereas in the healthy control group it ranged from 0.40 to 321.0 IU/ml, with a mean of 6.71± 16.06, 7.82±20.67, and 27.09±82.89 in the three groups, respectively. There were no significant statistical differences between the three groups (P=0.190) (Table 1).

There were no statistically significant differences between the three groups as regards anti-TG antibodies (P=0.075): among UC patients it ranged from 4.70 to 153.0 IU/ml, with a mean of 25.45±28.93;

Table 1 Comparison between the three studied groups according to demographic data, thyroid function, thyroid autoantibodies, thyroid nodules, thyroid echogenicity, and IBD activity markers

	Patients		Controls (n=25) [n (%)]	Test of significance	P
	Ulcerative colitis (n=25) [n (%)]	Crohn's (n=25) [n (%)]			
Sex					
Male	14 (56.0)	13 (52.0)	16 (64.0)	χ^2=0.763	0.683
Female	11 (44.0)	12 (48.0)	9 (36.0)		
Nodules					
No	15 (60.0)	13 (52.0)	25 (100.0)	χ^2=15.952*	<0.001*
Yes	10 (40.0)	12 (48.0)	0 (0.0)		
Significant differences between groups	P_1=0.569, $^{FE}P_2$<0.001*, P_3<0.001*				
Multinodular goiter					
No	19 (76.0)	21 (84.0)	25 (100.0)	χ^2=7.128*	^{MC}P=0.031*
Yes	6 (24.0)	4 (16.0)	0 (0.0)		
Significant differences between groups	P_1=0.480, $^{FE}P_2$=0.022*, $^{FE}P_3$=0.110				
Hypoechogenecity					
No	21 (84.0)	23 (92.0)	20 (80.0)	χ^2=7.653	^{MC}P=0.065
Yes	4 (16.0)	2 (8.0)	1 (4.0)		
NA	0 (0.0)	0 (0.0)	4 (16.0)		
Age					
Minimum–maximum	20.0–77.0	19.0–63.0	19.0–55.0	$^{KW}\chi^2$=2.242	0.326
Mean±SD	39.04±13.11	39.72±13.51	34.56±11.92		
Free T3 (0.4–4.2 pg/ml)					
Minimum–maximum	0.70–2.80	0.50–2.73	1.80–26.0	F=1.574	0.214
Mean±SD	2.20±0.57	2.02±0.55	3.30±4.74		
Free T4 (0.8–2 ng/dl)					
Minimum–maximum	0.77–2.0	0.70–1.43	1.0–2.10	F=4.286*	0.017*
Mean±SD	1.12±0.25	1.11±0.17	1.29±0.30		
Significant differences between groups	P_1=0.910, P_2=0.016*, P=0.012*				
TSH (0.4–4.5 μIU/ml)					
Minimum–maximum	0.30–6.40	0.90–11.70	0.60–37.0	$^{KW}\chi^2$=8.582*	0.014*
Mean±SD	1.61±1.38	2.58±2.17	3.28±7.14		
Significant differences between groups	P_1=0.003*, P_2=0.165, P=0.128				
Anti-TPO (50 IU/ml)					
Minimum–maximum	1.0–83.0	0.14–106.0	0.40–321.0	$^{KW}\chi^2$=3.321	0.190
Mean±SD	6.71±16.06	7.82±20.67	27.09±82.89		
Anti-TG (100 IU/ml)					
Minimum–maximum	4.70–153.0	1.0–155.80	2.60–106.0	$^{KW}\chi^2$=5.185	0.075
Mean±SD	25.45±28.93	25.26±35.90	20.17±27.71		
TSH receptor antibody (>1.5 U/l)					
Minimum–maximum	0.16–1.10	0.10–2.0	0.70–1.20	$^{KW}\chi^2$=32.99*	<0.001*
Mean±SD	0.65±0.29	0.59±0.40	1.0±0.12		
Significant differences between groups	P_1=0.184, P_2<0.001*, P<0.001*				
ESR first hour (mm/h)					
Minimum–maximum	6.0–128.0	3.0–111.0	3.0–39.0	23.16*	<0.001*
Mean±SD	40.44±34.32	43.80±35.34	10.32±8.97		
Significant differences between groups	P_1=0.997, P_2<0.001*, P_3<0.001*				
CRP (mg/l)					
Minimum–maximum	3.0–80.0	4.0–126.0	4.0–100.0	5.685	0.058
Mean±SD	24.48±22.61	47.36±4.81	16.44±20.62		
Significant differences between groups	P_1=0.115, P_2=0.199, P_3<0.001*				

(*Continued*)

Table 1 (*Continued*)

	Patients		Controls (n=25) [n (%)]	Test of significance	P
	Ulcerative colitis (n=25) [n (%)]	Crohn's (n=25) [n (%)]			
Fecal calprotectin (mg/kg)					
Minimum–maximum	19.0–2628.0	31.0–4020.0	8.0–40.0	45.42*	<0.001*
Mean±SD	474.48±631.65	509.36±823.08	20.36±8.47		
Significant differences between groups	P_1=0.756, P_2=0.003*, P_3<0.001*				

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FE, Fisher exact for χ^2-test for comparing between two groups; IBD, inflammatory bowel disease; $^{KW}\chi^2$, χ^2 for the Kruskal–Wallis test, significant differences between groups was done using Mann–Whitney test; MC, Monte Carlo for χ^2-test; NA, not applicable; P_1, P value for comparing between ulcerative colitis and Crohn's; P_2, P value for comparing between ulcerative colitis and controls; P_3, P value for comparing between Crohn's and controls; TG, thyroglobulin; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone. *Statistically significant at $P \leq 0.05$.

among CD patients, it ranged from 1.0 to 155.80 IU/ml, with a mean of 25.26±35.90; and among healthy individuals it ranged from 2.60 to 106.0, with a mean of 20.17±27.71 (Table 1).

In our study, the presence of AITD was confirmed either by serology (thyroid autoantibodies) or by thyroid ultrasound (US) or by both together in addition to documented history of AITD.

Serological AITD included those who showed on investigation high thyroid antibodies titers. Among UC patients, only one case (4%) and among CD patients only three cases (12%) had serological AITD, whereas among healthy controls one case (4%) had serological AITD. There were no significant statistical differences between the three groups as regards serological AITD (P=0.516).

Sonographic AITD included those with evidence of AITD on thyroid US; there were four cases (16%) among UC patients, two cases (8%) among CD patients, and one case (4%) among healthy controls. There were no significant statistical differences between the three groups (P=0.091).

Thus, among UC patients, only five patients (20%) had AITD: two cases of GD and three cases of HT. However, among CD patients, there were only four (16%) patients with AITD: two with GD and two with HT. Among healthy controls, there were two cases of HT but no cases of GD. There were no significant statistical differences between the three groups as regards AITD (P=1.000).

Among UC patients, only two cases had a past history of multinodular goiter with thyroidectomy; among CD patients, there were only two cases of GD by history. None of the healthy controls had thyroid disease by history. There were no significant statistical differences between the three groups (P=0.333).

Altered thyroid function

Among UC patients, 20 patients had euthyroidism, three patients had nonthyroidal illness (NTI), one patient had hypothyroidism, and one patient had hyperthyroidism. Among CD patients, 21 patients had euthyroidism, one patient had NTI, three patients had hypothyroidism, and none with hyperthyroidism. Among controls, there were 22 cases of euthyroidism, two cases of hypothyroidism, and one case of hyperthyroidism. There were no significant statistical differences between the three groups as regards thyroid status (P=0.528).

Ten patients (40%) from the UC group, eight patients (32%) from the CD group, and eight individuals (32%) from the control group had altered thyroid status, with no significant differences between the three groups (P=0.869) (Table 2).

Thyroid ultrasonography 'nodularity and hypoechogenicity'

Among UC patients, 10 patients had nodules (40%), which ranged from 1 to 2 nodules with a mean of 1.70±0.48. Among CD patients, 12 patients (48%) had nodules, which ranged from 1 to 3 nodules with a mean of 1.42±0.67, whereas none of the controls had nodules. There were significant statistical differences between the three groups (P<0.001) (Table 1 and Fig. 1).

Among patients having more than one nodule, there were six cases (24%) among UC patients and four cases (16%) among CD patients. None of the controls had multinodular goiter. There were significant statistical differences between the three groups (P=0.031) (Table 1 and Fig. 2).

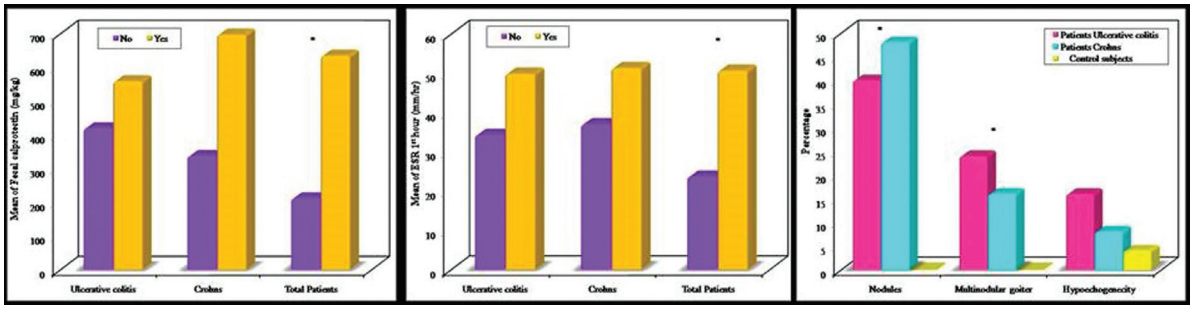
There were no significant statistical difference between the three groups as regards hypoechogenecity (^{MC}P=0.065): among UC patients, only four patients

Table 2 Comparison between the three studied groups according to altered thyroid status

	Patients		Controls (n=25) [n (%)]	χ^2	MCP
	Ulcerative colitis (n=25) [n (%)]	Crohn's (n=25) [n (%)]			
Altered thyroid status					
NTI	3 (12.0)	1 (4.0)	0 (0.0)	8.322	0.367
Hypothyroidism	1 (4.0)	3 (12.0)	2 (8.0)		
Hyperthyroidism	1 (4.0)	0 (0.0)	1 (4.0)		
Graves' disease	0 (0.0)	2 (8.0)	0 (0.0)		
Hashimoto thyroiditis	5 (20.0)	2 (8.0)	2 (8.0)		

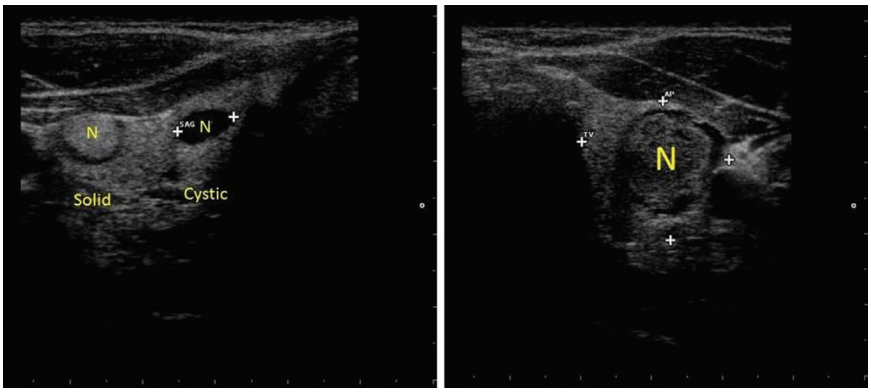
MC, Monte Carlo for χ^2-test; NTI, nonthyroidal illness.

Figure 1



Fecal calprotectin and ESR first hour showed a significant positive correlation with the presence of nodules in the total sample 'left and middle panels, respectively'. Patients exhibited statistically significantly more thyroid nodules compared with controls but not for thyroid gland hypoechogenicity 'right panel'. ESR, erythrocyte sedimentation rate.

Figure 2



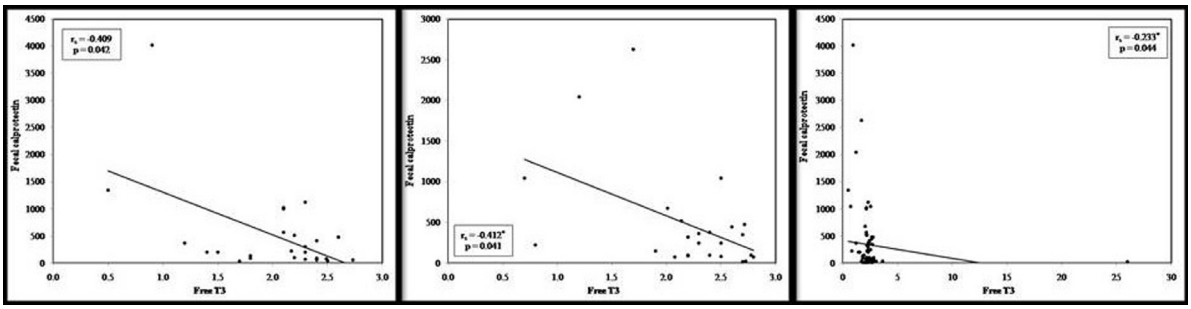
Patient 15, the CD group, showing two right lobe nodules and a left lobe nodule. CD, Crohn's disease.

(16%) showed hypoechogenecity on their thyroid US; among CD patients, only two cases (8%) showed hypoechogenecity; and among controls one case (4%) showed hypoechogenecity (Table 1 and Fig. 1).

Correlation between markers of activity of IBD (ESR, CRP, and fecal calprotectin) and thyroid function tests and autoantibodies

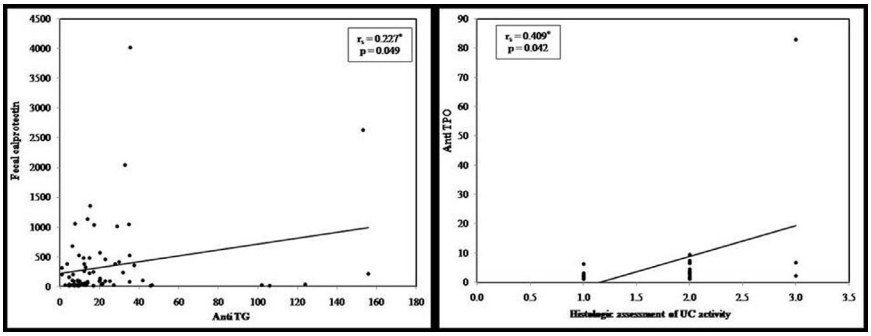
We noticed a significant negative correlation between free T3 and fecal calprotectin in both UC and CD patients and in the total sample of cases (P=0.041, 0.042, and 0.044, respectively) (Fig. 3). We also found a significant negative correlation between markers of activity of IBD (ESR and CRP) and free T3 in the total sample of cases. Moreover, a significant negative correlation was found between free T4 and IBD markers of activity (ESR and fecal calprotectin) in the total sample of cases (P=0.012 and 0.001, respectively). We also found a significant positive correlation between anti-TG antibodies and IBD marker of activity fecal calprotectin in the total sample of cases (P=0.049) (Fig. 4 and Table 3).

Figure 3



A significant negative correlation between free T3 and fecal calprotectin in Crohn's disease patients 'left panel', ulcerative colitis patients 'middle panel', and total sample 'right panel.

Figure 4



Left panel: a positive correlation between anti-TG antibodies and fecal calprotectin in the total sample. Right panel: a positive correlation between anti-TPO antibodies and histologic assessment of UC activity. TG, thyroglobulin; TPO, thyroid peroxidase; UC, ulcerative colitis.

Correlation between IBD indices of activity and thyroid function tests and autoantibodies

We noticed a significant negative correlation between free T3 and Truelove and Witts' classification of UC patients, SES-CD, and histological assessment for CD patients (P=0.014, 0.004, and 0.002, respectively) (Fig. 5). A similar negative correlation was found between free T4 and SES-CD (P=0.023). However, there was a significant positive correlation between anti-TPO antibodies and histological activity assessment of UC patients (P=0.042) (Fig. 4 and Table 4).

Correlation between markers of activity of IBD (ESR, CRP, and fecal calprotectin) and the presence of nodules

We noticed a positive correlation between IBD markers of activity (ESR and fecal calprotectin) and the presence of nodules in the total sample of patients (P=0.004 and $P \leq 0.001$, respectively) (Fig. 1 and Table 5).

Discussion

Idiopathic IBD comprises those conditions characterized by a tendency for chronic or relapsing immune activation and inflammation within the gastrointestinal tract. CD and UC are the two major forms of idiopathic IBD [29].

AITD is the most common category of autoimmune disease in humans. A prevalence of up to 10% is quoted, with a higher prevalence in women than in men. The two leading types are Hashimoto's type AIT, including the atrophic form, which presents as primary myxedema, and autoimmune hyperthyroidism, which is also known as GD (or Basedow's disease in a number of European countries). Rarer forms of AIT are silent thyroiditis, the iatrogenic thyroiditides, and postpartum thyroiditis [30].

Case reports have suggested an association between IBD and AITD. Population studies have demonstrated a two-fold to four-fold increase in the prevalence of thyroid disease in patients with UC [7].

In the present study, only three cases (12%) of CD, one patient (4%) with UC, and one (4%) healthy control who were noticed to have goiter on neck examination. Moreover, only two cases among the three CD cases

Table 3 Correlation between different studied parameters

	Free T3	Free T4	TSH	Anti-TPO	Anti-TG
Ulcerative colitis					
ESR first hour					
r_s	−0.338	−0.351	−0.290	0.125	−0.099
P	0.098	0.085	0.160	0.551	0.637
CRP					
r_s	−0.380	−0.246	−0.225	0.202	−0.005
P	0.061	0.236	0.281	0.333	0.982
Fecal calprotectin					
r_s	−0.412*	−0.336	−0.153	0.385	0.170
P	0.041	0.100	0.466	0.058	0.416
Crohn's					
ESR first hour					
r_s	−0.493*	−0.134	0.096	0.009	0.034
P	0.012	0.523	0.657	0.964	0.871
CRP					
r_s	−0.422*	−0.190	0.205	−0.027	0.016
P	0.036	0.364	0.337	0.900	0.941
Fecal calprotectin					
r_s	−0.409*	−0.070	−0.029	0.044	0.074
P	0.042	0.738	0.895	0.834	0.726
Controls					
ESR first hour					
r_s	−0.008	−0.114	0.205	−0.060	0.104
P	0.969	0.588	0.326	0.776	0.619
CRP					
r_s	0.186	0.074	0.004	0.072	0.295
P	0.374	0.724	0.986	0.732	0.152
Fecal calprotectin					
r_s	0.584*	−0.220	0.005	−0.160	−0.150
P	0.002	0.290	0.982	0.445	0.475
Total sample					
ESR first hour					
r_s	−0.312*	−0.289*	−0.032	0.125	0.130
P	0.006	0.012	0.786	0.284	0.268
CRP					
r_s	−0.295*	−0.196	0.024	0.114	0.076
P	0.010	0.092	0.836	0.328	0.516
Fecal calprotectin					
r_s	−0.233*	−0.375*	−0.016	0.208	0.227*
P	0.044	0.001	0.891	0.073	0.049

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; *r*, Spearman coefficient; TG, thyroglobulin; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone. *Statistically significant at $P \leq 0.05$.

with goiter presented also with eye signs of GD including exophthalmos, lid lag, lid retraction, and chemosis.

A study conducted by Cesarini *et al.* [31] on 909 IBD patients in Italy (2010) reported that the prevalence of goiter in IBD population was 42/909 (4.62%), 22/464 of CD patients (4.74%) and 20/445 of UC patients (4.49%).

In the present study, we used thyroid investigations, including both thyroid hormones and antibodies and thyroid ultrasonography to assess the thyroid status in both IBD patients and controls.

We found that the mean FT3 was not significantly different between the three groups. The mean FT4 was significantly lower in the patient versus the control group (P=0.017). Finally, the mean value of TSH was 1.61±1.38 in UC patients, 2.58±2.17 in CD patients, and 3.28±7.14 in controls, with significant difference between the three groups (P=0.014).

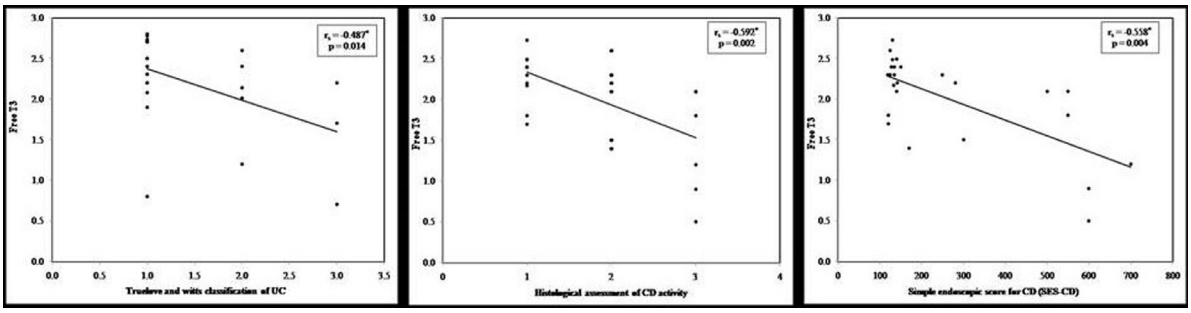
As regards thyroid antibodies, the mean value of anti-TPO antibodies was 6.71±16.06, 7.82±20.67, and 27.09±82.89 in the UC, the CD, and the control group, respectively, with no significant difference between the three groups. The mean value for anti-TG antibodies in UC patients was 25.45±28.93, 25.26 ±35.90 in CD patients, and 20.17±27.71 in the control group, with no significant difference between the three groups.

On thyroid ultrasonography, we had only four patients among UC patients, two patients among CD patients, and one control with sonographic AITD detected with evident hypochogenecity of the thyroid texture, denoting most probably HT. Although we had two patients with known GD by history, we had no evident signs on US. One of them was a 52-year-old female with CD who had subtotal thyroidectomy with recurrent Graves' on a biopsy of her thyroid remnant, and the other was a 61-year-old male with CD who was in a remission after long-term treatment with high corticosteroid doses and immunomodulatory drugs (infliximab) with regression of his goiter and improvement of his thyroid serology.

On interpretation of the previous serological and sonographic findings on screening for the presence of AITD, we found five patients (20%) in the UC group with HT but none with GD, whereas among CD patients there were only two patients (8%) with HT and also two patients (8%) with GD. In the control group, we found only two participants (8%) had HT. There were no statistically significant differences between the three groups as regards AITD.

However, we found a significant positive correlation between anti-TG antibodies and IBD marker of activity fecal calprotectin in the total sample of cases (P=0.049). However, there was a significant positive correlation between anti-TPO antibodies and histological activity assessment of UC patients (P=0.042). This finding may suggest that active/severe IBD may trigger or raise thyroid autoantibodies

Figure 5



A significant negative correlation between free T3 and Truelove and Witts' classification of UC 'right panel', histologic assessment of CD activity 'middle panel', and simple endoscopic score for CD SES-CD 'left panel'. CD, Crohn's disease; SES, Simple Endoscopic Score; UC, ulcerative colitis.

Table 4 Correlation between IBD indices of activity and thyroid investigations

	Ulcerative colitis patients			Crohn's disease patients		
	Truelove and Witts' classification of UC	Mayo score	Histologic assessment of UC activity	Simple endoscopic score for CD (SES-CD)	Histological assessment of CD activity	Crohn's disease activity index
Free T3						
r_s	–0.487*	–0.231	–0.363	–0.558*	–0.592*	–0.395
P	0.014	0.266	0.075	0.004	0.002	0.051
Free T4						
r_s	–0.236	–0.047	–0.233	–0.453*	–0.229	–0.052
P	0.257	0.824	0.263	0.023	0.271	0.805
TSH						
r_s	–0.021	–0.016	0.133	–0.016	0.015	0.163
P	0.922	0.939	0.525	0.940	0.946	0.446
Anti-TPO						
r_s	0.289	0.092	0.409*	–0.022	–0.110	–0.015
P	0.160	0.661	0.042	0.916	0.600	0.942
Anti-TG						
r_s	0.254	0.209	0.334	–0.007	–0.013	0.171
P	0.221	0.316	0.102	0.974	0.951	0.414

There is a correlation between free T3 and free T4 on one hand and some activity indices of IBD on the other hand. IBD, inflammatory bowel disease; r_s, Spearman coefficient; SES-CD, Simple Endoscopic Score in Crohn's disease; TG, thyroglobulin; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone; UC, ulcerative colitis. *Statistically significant at $P \leq 0.05$.

titers. Active IBD may compromise gut mucosal barrier in a way that facilitates the development of AITD, as suggested by Sasso *et al.* [14].

As regards the thyroid hormonal status, in the UC group we found three patients (12%) with NTI, one patient (4%) with hypothyroidism, and one patient (4%) with hyperthyroidism. In the CD group, we found one patient (4%) with NTI, three (12%) with hypothyroidism but none with hyperthyroidism. In the control group, we found two cases (8%) with hypothyroidism and one (4%) with hyperthyroidism. There were no statistically significant differences between the three groups as regards the thyroid status.

In accordance with our study, some studies concluded that the occurrence of thyroid disorders in IBD patients is reported to be at similar frequencies compared with normal population.

In a population-based study performed in Canada in which 8072 IBD patients were evaluated, thyroiditis rate was 0.23% in UC patients and 0.19% in CD patients (vs. 0.15–0.20% in controls) [32].

In a study performed in Italy in which 162 UC patients were evaluated, thyroid disorders (hyperthyroidism and hypothyroidism) were reported at a rate of 2.5%. In the same geographic region, the rate was reported as 7.5% in normal population [33].

Moreover, Snook *et al.* [34] reported that the prevalence of hyperthyroidism and hypothyroidism in UC patients was 1.5 and 0.9%, respectively. In

Table 5 Relation of ESR first hour, CRP, and fecal calprotectin with nodules

	Nodules					
	Ulcerative colitis		Crohn's		Total Patients	
	No (*n*=15)	Yes (*n*=10)	No (*n*=13)	Yes (*n*=12)	No (*n*=53)	Yes (*n*=22)
ESR first hour (mm/h)						
Minimum–maximum	6.0–90.0	10–128.0	3.0–111.0	9.0–109.0	3.0–111.0	9.0–128.0
Mean±SD	34.20±28.37	49.80±41.54	36.92±36.43	51.25±34.08	23.60±26.86	50.59±36.73
t	0.918		1.143		3.118*	
P	0.359		0.253		0.004*	
CRP (mg/l)						
Minimum–maximum	4.0–60.0	3.0–80.0	5.0–120.0	4.0–126.0	4.0–120.0	3.0–126.0
Mean±SD	20.40±18.39	30.60±27.71	46.46±45.33	48.33±46.23	24.92±30.30	40.27±39.11
t	0.779		0.518		1.830	
P	0.436		0.604		0.071	
Fecal calprotectin (mg/kg)						
Minimum–maximum	19.0–2628.0	90.0–2045.0	31.0–1025.0	55.0–4020.0	8.0–2628.0	55.0–4020.0
Mean±SD	418.66±662.44	558.20±606.90	336.38±350.21	696.75±1127.2	210.60±424.65	633.77±910.18
Z	1.415		0.952		4.143*	
P	0.157		0.341		<0.001*	

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; *Z*, *Z* for Mann–Whitney test. *Statistically significant at $P \leq 0.05$.

the same study, the prevalence of hyperthyroidism and hypothyroidism in CD patients was 0.3 and 0.5%, respectively, and 2.7% for both hyperthyroidism and hypothyroidism in the control group. Snook and colleagues suggested based on the findings of their study that the development of thyroid disorders did not show a clear temporal relationship with the onset or activity of IBD.

In studies conducted in Japan, the prevalence of chronic thyroiditis in UC patients was reported as 0.14% in the 1980s and 0.07% in the 1990s, and both rates were lower than those in normal population [35].

In another study conducted by Pooran *et al.* [36], the prevalence of hypothyroidism was lower in CD patients (3.8%; 8/210) than in controls (8.2%; 17/206), although the prevalence of hyperthyroidism was statistically similar between the groups.

In a study by Bardella *et al.* [37], the prevalence of HT in CD and UC patients was 4.4% (4/90) and 2.2% (2/90), respectively.

A cross-sectional multicenter study was performed by Boelaert *et al.* [38] on 3286 White participants (2971 with GD and 495 with HT) attending UK hospital thyroid clinics to identify the prevalence of coexisting autoimmune disorders in patients with AITD. They reported that 27 (0.97%) patients with GD and four (0.81%) patients with HT had IBD. IBD was the least prevalent autoimmune disorder among other studied six disorders coexisting with AITD.

In contrast to our study, some studies reported an increased prevalence of thyroid disorders in IBD patients.

In a recent study performed in Italy in which 909 IBD patients were evaluated, thyroid disorder rates were reported as follows: 6.6% in all IBD patients, 6.89% in CD patients, and 6.29% in UC patients. In this study, HT rates were reported as 1.98% in all IBD patients, 2.15% in CD patients, and 1.8% in UC patients. As a result of this study, it has been concluded that the prevalence of goiter was quite similar to that reported in the population in Europe (4.62 vs. 5%). However, the prevalence of HT is twice in IBD patients than that in healthy European population (1.98 vs. 0.8%) [31].

Powell *et al.* [16] and Nishimura *et al.* [39] reported that, although AITDs are well known to complicate chronic UC, the coexistence of hyperthyroidism and UC is very rare and that the incidence of thyrotoxicosis in patients with UC is 0.8–3.7% and the prevalence of UC in patients with hyperthyroidism is 1.3%. They have suggested only an incidental association of these two diseases.

Modebe [40] reported that hyperthyroidism intensifies the systemic manifestations of UC and renders the management difficult. The rapid metabolism of the drugs for treating UC or their rapid transit through the gut may prevent them from attaining effective concentrations. Hence, before UC can be effectively controlled, treatment of thyrotoxicosis is essential.

Moreover, an Italian study reported an increase in the volume of the thyroid gland and prevalence of anti-TG and anti-TPO antibodies in IBD patients compared with healthy controls; however, the study was limited to a small number of patients (14 UC and 27 CD patients) [41].

In a study by Järnoet *et al.* [42] in England, the frequency of thyroid disease was surveyed in 300 patients with UC (149 women and 151 men) and 600 controls. They found simple goiter in 6.3–8.7% of UC patients compared with 3.3–4.3% of controls, a difference which is significant. A history of thyrotoxicosis was obtained in 3.7% of the UC patients compared with 0.8% of the controls with significant difference ($P<0.01$). In more than half of the UC patients with hyperthyroidism, hyperthyroidism occurred years before the onset of colitis. It is therefore highly unlikely that hyperthyroidism is a complication of colitis.

Moreover, Edward and Truelove [43] reported thyroid disease in 2.4% of 624 UC cases. Goligher *et al.* [44] found hyperthyroidism in 2.2% of 465 UC cases.

Järnoet *et al.* [42] found increased radioactive iodine uptake by the thyroid gland and decreased urine iodine excretion in patients with UC or CD.

In a recent study in Warsaw by Szczeblowska and Wojtun [45], a group of 58 patients with diagnosed CD and research sample 45 cases with an affected abdominal cavity without any nonspecific inflammation diagnosed were examined for thyroid gland function disorders. The following investigations were made in the analyzed groups: TSH, anti-TPO, anti-TG, and TSHR antibodies. A statistically significant increase in the frequency of thyroid gland functional disorders in patients with CD compared with the random sample was found.

Simi *et al.* [46] reported an exaggerated response of thyrotropin to exogenous thyrotropin-releasing hormone in 13 patients who had previous intestinal resection for CD and in 42 healthy controls. An exaggerated and prolonged response curve was found in eight of the CD patients and one control ($P<0.01$), whereas baseline hormone levels were normal in all CD patients. CD is also characterized by malabsorption syndrome, and CD may be related to thyroid disorders through iodine malabsorption followed by iodine deficiency.

Microscopic colitis is also considered a variant of IBD of uncommon incidence predominantly affecting women and is considered a clinical and histopathological disease characterized by chronic watery diarrhea and a macroscopically normal or near normal colonic mucosa. Gustafsson *et al.* [47] conducted a study to examine the prevalence of thyroid dysfunction in 133 women with microscopic colitis compared with 737 women who served as controls. Anti-TPO antibodies were found in 10.6% of MC patients and 8.6% of controls. There were 25 patients with hypothyroidism, 15 with completed treatment of thyrotoxicosis, and four with completed surgery for nontoxic goiter. Thus, thyroid disorders were more frequent in MC patients than in controls.

In the present study, NTI was seen in three patients with UC and in one patient with CD. We also found a significant negative correlation between free T3 and fecal calprotectin in both UC and CD patients and in the total sample of cases. We also found a significant negative correlation between markers of activity of IBD (ESR and CRP) and free T3 in the total sample of cases as well as a significant negative correlation between free T3 and Truelove and Witts' classification of UC patients, SES-CD, and histological assessment for CD patients. Finally, free T4 showed a significant negative correlation with ESR and fecal calprotectin in the total sample of cases and SES-CD.

NTI syndrome is a state of adaptation or dysregulation of thyrotropic feedback control in which the levels of T3 and/or T4 are at unusual levels, but the thyroid gland does not appear to be dysfunctional. NTI has been assumed closely related with a series of diseases such as IBD [48].

Decreased triiodothyronine (T3) levels are most common. Patients with more severe or prolonged illness also have decreased thyroxine (T4) levels. Serum reverse T3 (r T3) is increased. Patients are clinically euthyroid and do not have elevated TSH levels. Pathogenesis is unknown but may include decreased peripheral conversion of T4–T3, decreased clearance of r T3 generated from T4, and decreased binding of thyroid hormones to thyroxine binding globulin (TBG). Proinflammatory cytokines (e.g. tumor necrosis factor-α and interleukin-1) may be responsible. Drugs such as corticosteroids are known to decrease pituitary secretion of TSH, resulting in low serum TSH levels and subsequent decrease in T4 secretion [49].

In a study by Järnerot *et al.* [50], the concentration of T3, thyroxine (T4), and TBG was measured in the

serum of 20 patients with UC or CD; the patients were compared with 20 healthy controls. The concentration of FT3 in the serum was lower in severely ill patients than in those who were mildly or moderately ill and the controls (whereas T4 and TBG were not affected by the severity of the disease). This finding confirms recent reports on low serum T3 concentrations in patients with severe chronic disease and severe liver cirrhosis. They also assumed that treatment with corticosteroids in severely ill patients seems to affect FT3 concentrations. The study indicated that corticosteroids exert a suppressing effect on the secretion of FT3 from the thyroid gland, another possible explanation that corticosteroids interfere with the conversion of T4–T3. An assessment of r T3 in our patients would have supported this explanation, but unfortunately it was not feasible.

There was a predominance of thyroid nodules in our IBD patients compared with the controls. Among UC patients, 10 (40%) patients had nodules, six patients had multinodular goiter, and four had a single nodule. Among CD patients, 12 (48%) had thyroid nodules, four had multinodular goiter and eight had a single nodule, whereas none of the controls had nodules. There was also a positive correlation between markers of IBD activity (ESR and fecal calprotectin) and the presence of nodules.

There is an obvious lack of studies investigating the prevalence of thyroid nodules in IBD patients, except for a study designed to assess the prevalence of abnormalities in the thyroid gland structure in IBD patients. The study was conducted in Poland by Nebauer and Wozniak-Stolarska [51] on 199 consecutive IBD patients (80 CD and 119 UC patients) and 42 healthy controls to report by means of thyroid ultrasonographic assessment that some morphological abnormalities of the thyroid gland may occur more often in patients with IBD. The most common focal lesions found in IBD patients were tumors: 13.1% of patients had tumors larger than 10 mm in diameter and 11.5% had tumors smaller than 10 mm in diameter. Small tumors occur more often in IBD patients as compared with the control group. In addition, enlargement of the thyroid gland is more frequent in UC patients compared with the control group.

In a recent study by Hou *et al.* [52], the different expression of ESR and CRP was studied on 341 patients with papillary thyroid cancer and 171 patients with nodular goiter. They demonstrated that there was a higher expression of activity markers (ESR and CRP) in patients with nodular goiter than in patients with papillary thyroid carcinoma, and that there is a positive correlation between ESR and CRP and the presence of nodular goiter, which is in accordance with the correlation between IBD activity markers (CRP and fecal calprotectin) and the presence of nodules in our study.

We mentioned before in the study conducted by Simi *et al.* [46] that the malabsorption syndrome characteristic for IBD may be related to thyroid disorders due to iodine deficiency.

Worldwide, iodine deficiency is the most common cause of nodular goiter. This may be due to low iodine content in water and food or due to failure of intestinal absorption as in case of IBD patients [53].

This can be explained as follows: the thyroid gland is controlled by TSH secreted from the pituitary, which in turn is influenced by thyrotropin-releasing hormone from the hypothalamus. TSH permits growth, cellular differentiation, and thyroid hormone production and secretion by the thyroid gland. Thyroid hormones are synthesized from iodination of tyrosine. The iodine is transported from plasma into the thyroid cell through a sodium–iodide symporter. This is an active process resulting in intracellular iodine level exceeding 20 times the plasma iodine level. The iodine transport activity is controlled by TSH. Serum thyroid hormones levothyroxine and T3 feedback to the pituitary, regulating TSH production [54].

A deficiency in thyroid hormone synthesis due to iodine deficiency (iodine malabsorption in IBD patients) leads to increased TSH production. Increased TSH causes increased cellularity and hyperplasia of the thyroid gland in an attempt to normalize thyroid hormone levels. If this process is sustained, a goiter is established and nodules can develop [54].

From the previous explanation, we can explain the predominance of nodules in IBD patients in our study, which achieved a significant statistical difference compared with the healthy controls. An assessment of iodine status in our patients would have supported this explanation, but unfortunately it was not feasible.

Some of the shortcomings of our study can be listed as follows: in the present study, the IBD patients were much fewer than those studied in the literature: only 50 IBD categorized as UC and CD. Also, many patients included in the study were on long-term corticosteroid therapy to control their activity and some were on

infliximab, which may negatively affect thyroid autoantibody assessment. Most of the patients in our study were male, whereas it is well known that AITD is more common in female sex. Lastly, we did not perform pathological examination of the nodules detected in our patients to determine their nature.

Conclusion

We found that thyroid nodular disease is more common in IBD patients compared with control, and that the presence of nodules correlated with markers of disease activity ESR and fecal calprotectin, probably due to associated iodine deficiency. Despite no difference being found in the prevalence of thyroid dysfunction, free T3 was significantly lower in patients with active and more severe disease (evidenced by higher fecal calprotectin and severity indices), a change consistent with chronic NTI probably caused by proinflammatory cytokines. Moreover, the expression of thyroid autoimmunity was correlated with activity and severity of IBD.

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Conflicts of interest

There are no conflicts of interest.

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