The effect of anti-TNF therapy on thyroid function in patients with inflammatory bowel disease

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Abstract. The aim of this study was to investigate for first time the thyroid function in patients with inflammatory bowel disease (IBD) and the potential effect of anti-TNF (tumor necrosis factor) therapy. We evaluated 41 patients with IBD (25M/16F, 36.5 ± 11.3 y, 27 with Crohn’s disease and 14 with ulcerative colitis), without any known thyroid disorder. Eighteen patients (9M/9F, 33.6 ± 8.8 y) were on anti-TNF therapy, while 23 patients (16M/7F, 38.7 ± 12.5 y) were treated with Azathioprine and Mesalazine (Aza/Mes) for more than 1 year. Twelve patients from the second group were then treated with anti-TNF and studied 6 months later. We assessed thyroid function by measuring thyroid stimulating hormone (TSH), free thyroxine (FT4), triiodothyronine (T3), thyroid peroxidase autoantibodies (TPOAb) and thyroglobulin autoantibodies (TgAb) levels. One patient presented with overt and one with subclinical hyperthyroidism. Thyroid auto-antibodies were positive in 12.2%. Patients from the anti-TNF group had lower levels of FT4 (1.09 ± 0.15 vs. 1.38 ± 0.9 ng/dL, p = 0.042), while TSH and T3 were comparable. The percentage of patients with positive thyroid auto-antibodies was lower in the anti-TNF group (5.6% vs. 17.4%). In the subgroup of patients who changed to anti-TNF, we found statistically significant reduction in FT4 after 6 months (1.26 ± 0.24 vs. 1.08 ± 0.15 ng/dL, p = 0.044), without changes in TSH and T3 levels. There was no change regarding thyroid auto-antibodies. In conclusion, patients with IBD showed a quite high percentage of thyroid autoimmunity. After treatment with anti-TNF, FT4 levels were found to be reduced, while no changes in TSH, T3 levels and thyroid auto-antibodies were noted.

Key words: Thyroid, Auto-antibodies, Inflammatory bowel disease, IBD, Anti-TNF

INFLAMMATORY BOWEL DISEASE (IBD) has been associated with a variety of endocrinopathies [1], but a clear causative relationship is not yet clarified. Functional and morphological thyroid abnormalities have been frequently reported in patients suffering from IBD [1-3]. Although there is no definite justification for concomitant IBD and thyroid diseases, autoimmune or immunologic factors could be hypothetically involved in the pathogenic machinery underlying both disorders.

Many of patients with IBD are now treated with biological agents targeting on the pro-inflammatory cytokine tumor necrosis factor alpha (TNF-a) [4]. The exact impact of anti-TNF therapy on thyroid biology is largely unknown, however, recent studies indicate a beneficial effect on hypothyroidism [5] and on autoimmune thyroiditis both clinically [6] and experimentally [7].

The aim of this study was to investigate for first time the thyroid function in patients with IBD and the potential effect of anti-TNF therapy on thyroid physiology.

Patients and Methods

Patients
We studied 41 patients with IBD (25M/16F, 36.5 ± 11.3 y, 27 with Crohn’s disease and 14 with ulcerative...
colitis), without any known thyroid disorder according to medical history. Eighteen patients (9M/9F, 33.6 ± 8.8 y) were on anti-TNF therapy for more than 1 year, specifically infliximab 5 mg/kg i.v. every 8 weeks or adalimumab 40 mg sc. every 1 or 2 weeks. Twenty three patients (16M/7F, 38.7 ± 12.5 y) were treated with Azathioprine and Mesalazine for more than 1 year (Aza/Mes), specifically Aza 2.5 mg/kg p.o. daily and Mes 2.4 gr p.o. daily. Twelve patients from the second group were then treated with anti-TNF and studied 6 months later. Consent has been obtained from each patient after full explanation of the purpose and nature of all procedures used. Clinical investigations have been conducted according to the principles of the Declaration of Helsinki.

**Assays**

We assessed thyroid function by measuring thyroid stimulating hormone (TSH), free thyroxine (FT4), triiodothyronine (T3), thyroid peroxidase autoantibodies (TPOAb) and thyroglobulin autoantibodies (TgAb) levels. TSH levels were measured by an electrochemiluminescent immunoassay (ECLIA, Elecsys 2010 Roche) with a precision of 1.8–8.7 (% CV) and detection limit <0.005 μIU/mL. FT4 levels were measured by a chemiluminescent microparticle immunoassay (CMIA, Architect 1000SR Abbott) with a precision of <10% (total CV) and a sensitivity <0.4 ng/dL. T3 levels were measured by a chemiluminescent microparticle immunoassay (CMIA, Architect 1000SR Abbott) with a precision of <10% (total CV) and an analytical sensitivity <0.38 nmol/L. TPOAb levels were measured by an electrochemiluminescent immunoassay (ECLIA, Elecsys 2010 Roche) with a precision of 7.1–24.4 (% CV) and a sensitivity <5.0 IU/mL. TgAb levels were measured by an electrochemiluminescent immunoassay (ECLIA, Elecsys 2010 Roche) with a precision of 5.9–8.7 (% CV) and a sensitivity <10.0 IU/mL.

**Statistical analysis**

The statistical analysis was performed with the software SPSS 16.0. Kolmogorov-Smirnov Test was used for the evaluation of distribution of continuous parameters. Differences between groups for continuous variables were tested with the independent t Test (age, TSH) or with the non-parametric Mann-Whitney U Test (FT4, T3, TPOAb, TgAb), as appropriate. Differences before and after intervention were tested with the paired t Test. Differences of categorical variables were tested using the Fisher’s exact test. A p value of <0.05 was considered statistically significant.

**Results**

The characteristics of the patients from the two therapy groups are presented in Table 1. From the Aza/Mes group one patient presented with overt and one with subclinical hyperthyroidism while none from the anti-TNF treatment group had thyroid dysfunction. Thyroid auto-antibodies were positive in 12.2%. Patients from the anti-TNF group had lower FT4 levels (1.09 ± 0.15 vs. 1.38 ± 0.9 ng/dL, p = 0.042), while there were no statistically significant differences in TSH (1.76 ± 0.8 vs. 1.58 ± 0.9 μIU/mL) and T3 levels (1.8 ± 0.28 vs. 2.02 ± 1.7 nmol/L). The percentage of patients with positive thyroid auto-antibodies was lower in the anti-TNF group, 5.6% (1/18) vs. 17.4% (4/23), but without statistical significance.

The thyroid status before and 6 months after the change to antiTNF therapy in the 12 patients of the Aza/Mes group patients are presented in Table 2. In

<table>
<thead>
<tr>
<th></th>
<th>Aza/Mes (n = 23)</th>
<th>Anti-TNF (n = 18)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>38.7 ± 12.5</td>
<td>33.6 ± 8.8</td>
<td>0.150</td>
</tr>
<tr>
<td>Gender</td>
<td>16M/7F</td>
<td>9M/9F</td>
<td>0.202</td>
</tr>
<tr>
<td>Thyroid functional disorders</td>
<td>2/23 (8.7%)</td>
<td>0/18 (0%)</td>
<td>—</td>
</tr>
<tr>
<td>TSH (μIU/mL)</td>
<td>1.58 ± 0.9</td>
<td>1.76 ± 0.8</td>
<td>0.534</td>
</tr>
<tr>
<td>FT4 (ng/dL)</td>
<td>1.38 ± 0.9</td>
<td>1.09 ± 0.15</td>
<td>0.042</td>
</tr>
<tr>
<td>T3 (nmol/L)</td>
<td>2.02 ± 1.7</td>
<td>1.8 ± 0.28</td>
<td>0.520</td>
</tr>
<tr>
<td>Thyroid auto-antibodies (+)</td>
<td>3/23 (17.4%)</td>
<td>1/18 (5.6%)</td>
<td>0.423</td>
</tr>
</tbody>
</table>

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patients who changed to anti-TNF, we found statistically significant reduction in FT4 levels (1.26 ± 0.24 vs. 1.08 ± 0.15 ng/dL, p = 0.044), while TSH (1.81 ± 1.24 vs. 1.69 ± 0.98 μIU/mL) and T3 (1.54 ± 0.42 vs. 1.81 ± 0.22 nmol/L) levels did no changed significantly. There was no change regarding thyroid auto-antibodies.

Discussion

This is the first study which evaluated the effect of anti-TNF therapy on thyroid function in patients with IBD. Patients with IBD showed a quite high percentage of thyroid autoimmunity, while the functional thyroid disorders presented were overt and subclinical hyperthyroidism. After 6 months treatment with anti-TNF, FT4 levels were found to be reduced, while no changes in TSH, T3 levels and thyroid auto-antibodies were noted.

Previous studies have shown increased prevalence of autoimmune thyroid diseases (Graves’ disease and Hashimoto’s thyroiditis) in patients with IBD [1, 2]. Similarly, in our study the occurrence of positive thyroid auto-antibodies in IBD counterparts was 12% in total (reaching up to 17% in Aza/Mes treated subgroup) reflecting an augmented autoimmune thyroid environment. One speculation for the coexistence of IBD with autoimmune thyroid diseases lies on inflammatory and autoimmune processes characterizing both disorders pathogenesis. It is possible that common mediators, yet unidentified, stimulate cellular inflammatory cascades that cause diverse effects both in the thyroid and gastro intestinal tract. That may explain the variety of endocrine and metabolic disorders frequently observed in individuals with ulcerative colitis and Crohn’s disease [8].

Regarding functional thyroid disorders, two incidences of overt and subclinical hyperthyroidism were documented in the Aza/Mes treated subgroup being in accordance with hyperthyroidism incidences in IBD individuals [9]. Due to small sample size from an epidemiological point of view, we cannot really reach any conclusions regarding differences in hyperthyroidism prevalence in IBD compared to the general population [10, 11].

Patients under anti-TNF treatment when compared to those receiving diverse therapies presented lower levels of FT4 and a trend towards lower thyroid auto-antibodies without reaching statistical significance probably due to the small sample size. Interestingly, after following 6 months anti-TNF treatment, the group of previously receiving Aza/Mes presented with a statistically significant reduction in FT4 levels. Combining the findings from both anti-TNF treated subgroups, there is some evidence that anti-TNF therapeutic intervention in patients with IBD has a plausible impact on FT4 production, through yet unclarified pathways. Of course, the clinical significance of such a small reduction in FT4 concentrations does not seem important enough to affect the clinical picture of the patients or to modify the therapeutic approach; however, the pathophysiological interactions are of interest. When Raterman et al. studied 138 consecutive patients with rheumatoid arthritis before and 6 months after treatment with adalimumab, they did not find any statistically significant decrease in FT4 levels in hypothyroid, euthyroid or hyperthyroid patients [5]. Of course, the different autoimmune background disease, as well as the different type of therapy may play an important role and should be taken under consideration when interpreting the results.

TNF-alpha, a cytokine involved in autoimmune and immune-mediated disorders, has been implicated in thy-
roid dysfunction pathophysiology as higher levels of this factor have been reported in patients with defective thyroid functioning [12]. Additionally, TNF infusion has been linked with deterioration of hypothyroidism [13] and induction of the sick euthyroid syndrome in humans [14]. Interestingly, inhibition of TNFα using anti-TNF agents in patients with ankylosing spondylitis results in amelioration of autoimmune thyroid status reflected by lower anti-thyroid peroxidase antibodies compared to counterparts following diverse therapies [6]. Furthermore, improvement of thyroid function in hypothyroid patients with rheumatoid arthritis was reported after 6 months of adalimumab treatment [5]. Similarly, in our study the percentage of patients with positive thyroid auto-antibodies was approximately three times lower in the anti-TNF group compared to Aza/Mes group. Though this differentiation did not reach statistical significance, it may indicate a beneficial impact of anti-TNF treatment on thyroid autoimmunity.

Furthermore, as mentioned above, a statistically significant reduction in FT4 levels was observed in the anti-TNF group and in the group following a 6 months anti-TNF treatment, without any other alterations in TSH or T3 levels. It is well-established from the literature that thyroxine is produced in the thyroid gland whereas triiodothyronine hormone mainly derives from peripheral conversion of T4 through deiodinase system [15]. One speculation is that anti-TNF treatment affects thyroid hormone production directly on the thyroid gland which explains the impact seen only on thyroxine levels. Besides, as T3 primarily exerts the negative feedback control to regulate TSH production [16], this mechanism could explain the unchanged TSH levels observed in those patients with lower FT4 levels. Moreover, a suppressive effect of TNFα on type 2 deiodinase has been previously reported [17]. T4 is converted to T3 by deiodinases in the periphery, in order to exert its biological activity. Type 2 iodothyronine deiodinase (D2) is present in human thyroid tissue, human skeletal muscle and other tissues, suggesting that D2 is involved in maintaining plasma T3 level in humans [17]. If TNFα suppress the action of D2, the anti-TNF treatment may lead to relative increase of its action and therefore to higher amount of conversion of T4 to T3, leading to decreased concentrations of T4 and FT4.

The main strength of the present study is the presence of three different IBD subpopulations; those already receiving anti-TNF treatments for at least a year at the time of the study, those receiving Azathioprine and Mesalazine therapy and a subcategory of the last group that followed a 6-month anti-TNF treatment. The analysis of the above populations provides sufficient evidence not only for thyroid dysfunction in IBD patients but also for the impact of anti-TNF therapy on thyroid biology. A limitation of the study is the absence of control, healthy population and the relatively small sample size, which probably did not allow results to reach statistical significance among some comparison parameters.

In conclusion, patients with IBD showed a quite high percentage of thyroid autoimmunity, while the functional thyroid disorders presented were overt and subclinical hyperthyroidism. After treatment with anti-TNF, FT4 levels were found to be reduced, while no changes in TSH, T3 levels and thyroid auto-antibodies were noted.

**Declaration of Interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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