Atypical Celiac Disease as Cause of Increased Need for Thyroxine: A Systematic Study

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Objective: Replacement T4 dose in hypothyroid patients bearing both chronic autoimmune thyroiditis and atypical celiac disease (CD) has been analyzed.

Design: Replacement T4 dose has been analyzed in 35 hypothyroid patients with Hashimoto’s thyroiditis (HT) and atypical CD, as defined by the American Gastroenterological Association. We have evaluated the ability of the same dose of T4 to reach target TSH in 21 patients before and during gluten-free diet (GFD). In the remaining 14 patients, noncompliant with GFD, we analyzed replacement T4 dose and compared it with that in a similar group consisting of 68 patients with hypothyroid HT but no evidence of celiac sprue or other conditions interfering with T4 absorption.

Results: In patients with isolated HT, the desired serum TSH (median 1.02 mU/liter) was reached in all patients after 5 ± 2 months of treatment at a median T4 dose of 1.31 μg/kg·d. After a similar period and dose of T4, higher levels of TSH (median 4.20 mU/liter) were observed in patients with HT and CD. In 21 CD patients, target TSH (median TSH = 1.25 mU/liter) has been attained after 11 ± 3 months of GFD without increasing T4 dose (1.32 μg/kg·d). In the remaining 14 patients, who were noncompliant with GFD, target TSH has also been achieved but at a higher T4 dose (median = 1.96 μg/kg·d; +49%; P = 0.0002) than in hypothyroid patients without CD.

Conclusions: Atypical CD increases the need for T4. The effect was reversed by GFD or by increasing T4 dose. Malabsorption of T4 may provide the opportunity to detect CD that was overlooked until the patients were put under T4 therapy. (J Clin Endocrinol Metab 97: E419–E422, 2012)
pears to be approximately 1:100 (7, 9, 14). Celiac sprue and chronic autoimmune thyroiditis or Hashimoto’s thyroiditis (HT) are cognate diseases (15, 16), classified among the polyendocrine autoimmune syndromes (17). In fact, the prevalence of CD in patients with thyroid autoimmunity is 2 to 5%, and that of HT in celiac patients is up to 30%, both significantly higher than in the general population (16). CD is a paradigm of malabsorption of several nutrients and drugs (18), but there is evidence of an increased need for T4 in these patients only in few case reports (19, 20). Therefore, this study was aimed at analyzing the T4 requirement in patients bearing both HT and atypical CD.

**Patients and Methods**

**Patients and study design**

From 2003 to 2007, we studied a cohort of 1970 patients examined consecutively and referred to our Endocrinology Unit. Of these, 428 were in need for T4 treatment for hypothyroid HT. All of these patients were advised and agreed to take oral levothyroxine (starting dose about 1.3 μg/kg body weight/day) under fasting conditions, waiting at least 1 h before eating, according to recent evidence (3, 6, 21). Patients who were pregnant, those who recently used cosmetics and substances containing iodine and/or drugs interfering with levothyroxine sodium absorption and action, as listed by Liwanpo et al. (2), as well as those with known CD and/or other relevant gastrointestinal diseases or on a gluten-free diet (GFD) were excluded from the study. After this selection, the presence of an undiagnosed atypical CD was suspected in 69 patients with HT because of unexplained iron-deficiency anemia, short stature, and low weight or recent weight loss, according to the American Gastroenterological Association (AGA) (7). These patients were screened for the presence of celiac autoantibodies, which have been detected in 45 of them. The diagnosis of CD was finally confirmed by duodenal biopsy in 35 patients (31 females, four males; median age, 39 yr), mostly classified by a histopathologist as class II to class IIIb (7, 8). Of these, 428 were in need for T4 treatment for hypothyroid HT. The characteristics of the patients enrolled in the study are summarized in Table 1. At the time of the first examination, before the start of GFD (approximately every 3 months) and subsequently at the times indicated in Results. After completing the diagnostic workup for CD, all patients were advised to enter a GFD plan. Hence, we have checked the ability of the same dose of T4 to reach target TSH (0.5–2.5 mU/liter) in patients with atypical CD, before and during GFD. However, 14 patients refused to enter and/or were not compliant with a GFD, and therefore, we had to increase the T4 dose. To compare the T4 dose required in these non-GFD celiac patients, we used an internal reference group represented by 68 adult patients (61 females, seven males; median age, 41 yr) with isolated HT and comparable age and sex distribution. These patients had no evidence of gastrointestinal disorders and explicitly accepted and agreed to consume oral T4 with the same criteria as in the study group. The required dose of T4, normalized by patient’s body weight, was the outcome of this section. The study has been conducted upon written informed consent and as part of the diagnostic workup of the patients involved, according to the local ethical rules and to the guidelines in the Declaration of Helsinki.

**Methods**

The diagnosis of HT was based on a characteristic ultrasonographic pattern and the presence of high titers of anti-thyroid peroxidase antibodies (anti-TPOAb). Patients were considered subclinically hypothyroid when TSH was above 5.0 mU/liter and free T4 was in the normal range. Only one brand has been used in T4 treatment (Eutirox; Bracco, Milan, Italy). The diagnosis of atypical CD was suspected because of unexplained iron-deficiency anemia, short stature, and low weight or recent weight loss, supported by the presence of antitissue transglutaminase (tTG) IgG and IgA and/or anti-endomysial IgG and IgA antibodies and confirmed by multiple mucosal biopsies from duodenum and jejunum (10). CD was defined as “atypical” according to the National Institutes of Health Consensus Development Conference Statement on CD (12) and the AGA Institute Technical Review defining these patients as having little to no gastrointestinal symptoms, but coming to medical attention because of iron deficiency, osteoporosis, short stature, and infertility (7). The degree of intestinal atrophy and crypt hyperplasia was evaluated according to the Marsh classification, as modified by Oberhuber (8).

Levels of serum free T4 were detected by RIA (Radim, Pomezia, Italy) (range, 10.3–25.7 pmol/liter or 0.8–2.0 ng/dl). Serum TSH levels were assayed by immunoradiometric assay (Radim) (range, 0.2–4.0 mU/liter; intraassay variation, 5.1%; interassay variation, 7.8%). Serum anti-TPOAb were measured by quantitative immunoenzymometric assay (Radim).

Anti-tTG antibodies (IgA and IgG) were detected using an ELISA in which microtiter plate wells were coated with recombinant human tTG (Eu-tTG kit; Eurospital, Trieste, Italy). The lower limit of positivity of IgG and IgA antibodies was 29 and 7 AU/ml, respectively. IgA and IgG antiendomisial antibodies were screened by the direct immunofluorescent method on cryostat sections of monkey esophagus (Antiendomysium kit; Eurospital).

**Statistical analysis**

Data are expressed as median value and were analyzed by STATA 8.0 (StataCorp, College Station, TX).

**Results**

The characteristics of the patients enrolled in the study are summarized in Table 1. At the time of the first examination, most of the patients had subclinical hypothyroidism, but 13 patients with isolated HT and 14 patients with HT and CD had overt hypothyroidism. All these patients were then treated with levothyroxine as described above. In patients with isolated HT, the target serum TSH was reached in all patients after 5 ± 2 months of treatment [median TSH = 1.02 mU/liter; interquartile range (IQ1–IQ3) = 0.82–1.46 mU/liter], and the median T4 dose was 1.31 μg/kg · d (IQ1–IQ3 = 1.22–1.42 μg/kg · d). The median dose of T4 required to normalize TSH did not differ in patients with subclinical or overt hypothyroidism (P = not significant). At a similar T4 dose (1.47 μg/kg · d; P = 0.5311), the desired serum TSH has been obtained in
only one of 35 patients (Fisher’s exact test, \( P < 0.0001 \)) with HT and concomitant CD, after a similar period of treatment (6 ± 2 months) and pending the end of a diagnostic workup for CD. Hence, at that time, these patients showed higher levels of TSH (median = 4.20 mU/liter; IQ1–IQ3 = 3.69–5.87 mU/liter) than those with isolated HT (\( P < 0.0001 \)).

Once the diagnostic workup was completed, CD patients were soon advised to enter a GFD plan and, among them, only 21 patients accepted and were compliant with the prescribed diet. The patients who accepted the GFD (median TSH before GFD = 5.30 mU/liter) remained on previous T4 treatment (median dose of 1.32 \( \mu \)g/kg · d), and their thyroid function was checked approximately every 4 months. Target serum TSH (median TSH = 1.25 mU/liter; IQ1–IQ3 = 1.03–2.00 mU/liter) has been reached after 11 ± 3 months of GFD (Fig. 1A).

In each of the 14 patients noncompliant with GFD, after further hormone testing (median TSH = 3.78 mU/liter), T4 dose has been increased by 25 \( \mu \)g. Target serum TSH (median TSH = 1.54 mU/liter; IQ1–IQ3 = 0.98–2.60 mU/liter) has been finally achieved in all these patients after 4 additional months of treatment. Therefore, in this group of patients, the median replacement dose required was significantly increased (1.96 \( \mu \)g/kg · d; +49%; \( P = 0.0002 \)) compared with that in patients with isolated HT (Fig. 1B). Thyroid hormone was increased in these patients (1.49 pg/ml; IQ1–IQ3 = 1.28–1.64 pg/ml; \( P = 0.0147 \)) reflecting the increased dose of T4. Again, the median dose of T4 required to normalize TSH was similar in patients with subclinical or overt hypothyroidism (\( P = 0.8151 \)). Multivariate analysis revealed that a higher T4 requirement did not correlate with any analyzed variable (age, body mass index, baseline free T4 and TSH).

### Discussion

In this study, we have observed: 1) an increased need for T4 in patients with CD, even in its atypical presentation; 2) that this effect can be prevented by GFD; and 3) in patients with HT and CD not compliant with GFD, the therapeutic dose of T4 should be increased by almost 50%.

A malabsorption of T4 in celiac patients might have been expected, based on the few case reports describing an increased need for T4 in patients with overt or occult CD (19, 20). This is the first systematic study that analyzes T4 malabsorption in symptomless celiac patients. After the diagnosis of atypical CD, patients entered a GFD and the target TSH has been reached without changing the dose of T4. This is in keep-
ing with the observations in the case report (20). On the other hand, the target TSH has also been obtained in all patients who refused to enter GFD by increasing the dose of T₄ by 49%. This is of particular interest in patients with atypical CD because of their faint clinical symptoms. In fact, this is the most common form of CD and, because these patients are asymptomatic, a large number of them go undiagnosed (18) and some of them may be unwilling to enter GFD. So a screening for CD may be useful to improve therapeutic T₄ effectiveness, as already proposed, in patients with autoimmune thyroid disease (16). However, this does not appear to be cost-effective because the association of CD with autoimmune thyroid disorders is low anyway (15). Our findings may help to disclose these occult CD because the increased need for T₄ should trigger the search for an occult gastrointestinal disorder (Ref. 3 and http://www.hotthyroidology.com/editorial_169.html).

Whether an increased need for T₄ may represent true malabsorption is a matter for debate. In this study, the increased need for T₄ observed in all atypical celiac patients noncompliant with GFD may well be explained by mucosal damage (18). However, reduced absorption of T₄ in celiac patients may also be explained by the presence of undigested food and a net increase of water in the intestinal lumen (7). So far, this latter event, called adsorption of T₄, may contribute to explain the increased need for T₄, as already described for some nutrients and drugs (1, 2). Also, complete mucosal recovery seems to be absent in a significant portion of patients with CD during GFD, despite clinical improvement (22). In our patients compliant with GFD, however, target TSH levels have been achieved without increasing T₄ dose, suggesting that even partial recovery of the mucosal structure may be sufficient to improve T₄ absorption.

In conclusion, CD, even in its atypical form, is a further cause of increased need for T₄. In addition, malabsorption of T₄ may help to reveal occult CD in patients with autoimmune thyroid disease.

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