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Malabsorption of Thyroxine Occurs in Atypical Celiac Disease and Abates on a Gluten-Free Diet

Virili C, Bassotti G, Santaguida MG, Iuorio R, Del Duca SC, Mercuri V, Picarelli A, Gargiulo P, Gargano L, Centanni M. Atypical celiac disease as cause of increased need for thyroxine: a systematic study. J Clin Endocrinol Metab. January 11, 2012 [Epub ahead of print]. doi:10.1210/jc.2011-1851.

SUMMARY

Background

The dose of L-T_4 needed to treat hypothyroidism is unexpectedly high in over 10% of patients with hypothyroidism. Noncompliance is common, but once eliminated, causes of malabsorption should be considered; one possibility is celiac disease. This autoimmune enteropathy is found more commonly in patients with Hashimoto's thyroiditis (and vice versa) than in the general population. Higher-than-usual doses of L-T_4 have been required in several cases in which hypothyroidism has occurred in patients with active celiac disease, and their L-T_4 requirement has fallen after eating a gluten-free diet. However, patients with celiac disease who have severe gastrointestinal (GI) symptoms are much less common than patients with positive antibodies and biopsies but without notable GI symptoms. The current study systematically addressed the issue in patients with "atypical celiac disease," who do not have notable GI symptoms but have iron deficiency anemia, diminished stature, low weight, or recent weight loss.

Methods

The L-T_4 dose (Eutirox, Bracco, Italy) that was needed to treat 68 middle-aged patients with Hashimoto's thyroiditis (without GI symptoms) was compared to the TSH response in 35 patients who had Hashimoto's thyroiditis but also had tissue transglutaminase and/or endomysial antibodies plus biopsy-proven celiac disease. Patients who were pregnant or taking substances or drugs known to contain iodine or to interfere with L-T_4 absorption or action, eating a gluten-free diet, or had previously known celiac disease or other relevant GI disorders were excluded. All participants took their L-T_4 while fasting and waited at least an hour before eating. The TSH level achieved in the 68 patients who only had Hashimoto's thyroiditis was compared with the TSH achieved in the 35 patients who had both Hashimoto's hypothyroidism and atypical celiac disease. The 35 patients were then put on a gluten-free diet, but only 21 were judged to be compliant with the diet. The compliant patients were kept on their previous L-T_4 dose, whereas the 14 diet-noncompliant patients had their L-T_4 dose increased by 25 µg; thyroid-function tests were repeated about every 4 months. The statistical analysis was nonparametric, based on the median of the middle two interquartile ranges, excluding 25% at each end of the spectrum of data.

Results

The baseline studies before thyroxine therapy revealed the median TSH to be higher in the 68 subjects in the control Hashimoto's group, indicating that they had more subclinical hypothyroidism (7.26 µU/ml vs. 5.7 µU/ml). Their median weight was also 10% higher than that of the group with celiac disease (66 kg vs. 60 kg). On the other hand, the median baseline FT_4 was lower in those with celiac plus Hashimoto's disease (0.91 vs. 1.12 ng/dl), indicating that they had mild hypothyroidism more commonly. The median TSH fell to 1.02 µU/ml in the 68 control patients after they took L-T_4 for about 5 months (median dose, 1.3 µg/kg). In contrast, the median TSH fell only to 4.2 µU/ml after giving L-T_4 (median dose, 1.4 µg/kg) for about 6 months to the 35 patients with celiac plus Hashimoto's disease. Furthermore, the TSH of only one patient with celiac disease fell into the target range of 0.5 to 2.5 µU/ml. The 21 who were judged to be compliant with the gluten-free diet remained on their previous L-T_4 dose (median, 1.32 µg/kg), and in every case the TSH fell, with the median TSH reaching 1.25µU/ml after about-11months. In the 14 diet-noncompliant patients, the L-T_4 dose was increased by 25 µg, and after 4 months, their median TSH also fell (1.54 µU/ml) on a median dose of 1.96 µg/kg. The higher L-T_4 requirement did not correlate with the body-mass index.

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Conclusions

Patients with atypical celiac disease may need a higher dose of L-T_4, and this increased requirement may be reversed by a gluten-free diet. Some patients with evidence of malabsorption of L-T_4 may have atypical celiac disease.

ANALYSIS AND COMMENTARY

The authors do not indicate how noncompliance with the gluten-free diet was established. Up to 20% of patients who are considered diet-compliant can have recurrent or persistent symptoms. H. pylori infection is common in such patients, but the authors do not state that the diet-noncompliant patients were tested for H. pylori or atrophic gastritis. Wide variability in TSH levels can make nonparametric analysis appropriate, but it excludes 50% of the data, so it would have been useful if each outlier had been included on the "box-and-whisker plot." It is not clear why age, weight, and L-T_4 dose did not undergo regular parametric analysis. Regardless of these quibbles, it does seem clear that the dose of L-T_4 needed to normalize the serum TSH level in some patients with "atypical" celiac disease is reduced when they adhere to a gluten-free diet.

Should every patient requiring a "higher-than-normal" dose of L-T_4 be evaluated? First of all, L-T_4 absorption varies between individuals and between tablets/capsules from different manufacturers. Obviously, noncompliance, severe obesity, pregnancy, and dietary or drug factors that influence absorption, such as antacids, calcium, or long-term proton-pump inhibitor therapy need to be ruled out. However, in cases in which it proves difficult to maintain the TSH level in the target range with high dose of L-T_4, disorders of the GI tract need to be assessed.

Malabsorption of L-T_4 can reflect atrophic gastritis (1) or—more likely—H. pylori infection. H. pylori infection was found in 32 Turkish patients in whom celiac disease and small intestinal bacterial overgrowth had been excluded and who remained hypothyroid on doses of L-T_4 above 1.6 µg/day. Eradication of H. pylori with triple or quadruple therapy reduced the mean TSH from 30.5 µU/ml to 4.2 µU/ml, and 20% of the patients actually became hyperthyroid on the dose of L-T_4 that had previously been insufficient (2). Similar findings have been reported on the L-T_4 dose required to normalize TSH levels in patients with achlorhydria or with gastric parietal-cell antibodies, or to suppress the TSH in patients with multinodular goiter if they had H. pylori infection. In addition to celiac disease, malabsorption at the level of the small intestine can occur with the short bowel syndrome, from small intestinal bacterial overgrowth (which is also found more commonly in hypothyroidism), or from infections with certain parasites like Giardia, or even from severe lactose intolerance. Finally, in 28 Argentine patients in whom several GI causes of L-T_4 malabsorption were ruled out, administering 1 g of vitamin C in a glass of water along with the L-T_4 for 6 to 8 weeks increased L-T_4 absorption significantly (3).

— Stephen W. Spaulding, MD

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