Celiac Disease and Hypothyroidism

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ABSTRACT

BACKGROUND: Celiac disease is more common in patients with hypothyroidism. Malabsorption of levothyroxine has not been studied in this population. We sought to determine if levothyroxine dosing was influenced by the presence and treatment of celiac disease.

METHODS: This retrospective study was conducted at an academic medical center. Cases had hypothyroidism and celiac disease. Controls had hypothyroidism alone and were selected randomly through the endocrinology clinic records. Celiac disease was defined as representative pathology with positive serology. Age, sex, height, weight, body mass index, creatinine, and medical comorbidity were assessed for cases and controls. The levothyroxine dose and weight-based levothyroxine dose necessary to maintain a euthyroid state were evaluated for controls, and before and after celiac disease therapy for cases.

RESULTS: Celiac disease was identified in 152 patients, and 22 patients had concomitant hypothyroidism (14.5%). Seven cases met inclusion criteria. Overall, 200 control patients were identified. The mean celiac disease pretreatment levothyroxine dose and weight-based levothyroxine dose needed to maintain a euthyroid state were higher in cases than in controls (154 μg vs 106 μg, P = .007, and 2.6 μg/kg vs 1.3 μg/kg, P < .001). Doses decreased significantly after treatment of celiac disease (154 μg vs 111 μg, P = .03; and 2.64 μg/kg vs 1.89 μg/kg, P = .04). All cases required at least 125 μg of levothyroxine initially to maintain a euthyroid state.

CONCLUSIONS: Levothyroxine malabsorption likely occurs with hypothyroidism and untreated celiac disease. Absorption may improve after celiac disease treatment. Screening for celiac disease in patients with hypothyroidism requiring elevated levothyroxine doses warrants further investigation.

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KEYWORDS: Celiac disease; Celiac sprue; Hypothyroidism; Levothyroxine; Malabsorption

Celiac disease is an immune-mediated disorder of the small intestine caused by sensitivity to the dietary protein gluten. It is estimated to occur in 0.75% (1:133) of the US population.1 Gluten exposure in susceptible patients typically causes an epithelial infiltration of lymphocytes, and blunting or atrophy of the villous architecture of the small intestinal mucosa. This damage can cause significant malabsorption, resulting in the common presenting symptoms of diarrhea, abdominal discomfort, and weight loss. Malabsorption of nutrients, vitamins, and minerals can occur.2 Iron-deficiency anemia and hypocalcemia in particular are encountered in this disorder. It is generally believed that malabsorption of medications also can occur in this disease;3 however, available data are conflicting for various medications.4,5

Autoimmune disorders associated with celiac disease include insulin-dependent diabetes mellitus and hypothyroidism.6 Hypothyroidism occurs in 5%-15%7,8 of patients with celiac disease. This is about 4 times greater than the risk of hypothyroidism in controls.6 Celiac disease occurs in 2%-5% of people with autoimmune thyroid disease, which is significantly more prevalent than controls.9-12 It has been suggested that patients with autoimmune thyroid disease should be screened for celiac disease; however, this recom-
Levothyroxine absorption is thought to occur predominantly in the jejunum. The average normal daily secretion of thyroid hormone to maintain a euthyroid state is lower than the oral maintenance dose needed to maintain a euthyroid state in an athyreotic patient. This suggests incomplete absorption of orally administered levothyroxine. It has been approximated that 63%-82% of levothyroxine is absorbed after oral administration. Certain patients treated for hypothyroidism require elevated doses of levothyroxine. Potential reasons for this include germ-line genetic variations, poor compliance, varying causes of the hypothyroidism, drug interactions, patient characteristics (age, body mass index), bioequivalence of levothyroxine between formulations, food interactions, or concomitant diseases. Celiac disease has been identified as a potential disease that may require elevated levothyroxine doses to maintain a euthyroid state. There have been case reports that have suggested elevated levothyroxine doses are necessary to maintain a euthyroid state in patients with celiac disease. Presumably, this is due to drug malabsorption. It has not been evaluated whether levothyroxine doses need to be adjusted in patients with hypothyroidism undergoing dietary treatment for celiac disease. Our hypothesis was that levothyroxine doses needed to maintain a euthyroid state in patients with concomitant hypothyroidism and untreated celiac disease was greater than controls with hypothyroidism alone. We also hypothesized that a dose reduction in levothyroxine would be necessary in patients with hypothyroidism and celiac disease who were undergoing dietary treatment for their celiac disease. If our hypothesis was correct, potentially these data would identify a high-risk population for screening for celiac disease and would help alert clinicians to adjust levothyroxine doses appropriately in a patient with hypothyroidism being treated for celiac disease.

**METHODS**

Patients were retrospectively included at the University of Vermont/Fletcher Allen Health Care. We initially searched our surgical pathology database (Cerner CoPath, Waltham, Mass) for the search terms “villous blunting” and “villous atrophy” from June 2000 to June 2010. The individual pathology reports identified were then reviewed. Patients who did not have villous blunting or atrophy were excluded. Serologic testing for celiac disease was reviewed using the electronic medical record (EPIC, Verona, Wis). Specifically, tissue transglutaminase and endomysial antibody were evaluated. Patients were considered to have celiac disease only if their biopsies showed villous atrophy or blunting, and if either their tissue transglutaminase or endomysial antibody were positive. The electronic medical records of these patients with celiac disease were reviewed for a history of hypothyroidism.

The cases included were patients with hypothyroidism present at the time of diagnosis of celiac disease. Information including levothyroxine dosing, thyroid-stimulating hormone (TSH) values, and celiac disease serology were evaluated both before and after dietary treatment of celiac disease. Controls were identified through University of Vermont endocrinology clinic records using the International Classification of Diseases, 9th Revision codes of 244.9 for unspecified hypothyroidism and 245.2 for chronic lymphocytic thyroiditis, which includes Hashimoto disease, struma lymphomatosa, and thyroiditis, including autoimmune and chronic lymphocytic. Two hundred controls were selected randomly from a cohort of endocrinology patients presenting to the endocrinology clinic over the course of 5 years, from June 2005 to June 2010.

Patients were excluded from the study if they had undergone prior surgical resection of their upper intestinal tract. Information identified from the electronic medical record of both cases and controls included age, sex, height, weight, body mass index, creatinine, and medical comorbidity. Weight-based dosing of levothyroxine (µg/kg) was calculated both for cases and controls. For cases, weight-based levothyroxine dosing was calculated both at the time of diagnosis of and post dietary treatment for celiac disease, when celiac disease serology normalized or significantly decreased. Weight-based levothyroxine dosing was calculated for controls when a euthyroid state was obtained. A euthyroid state was defined by a normal TSH level.

Statistical analysis was performed using SPSS software (IBM, Armonk, NY). Two-sided P values of <.05 were used to determine significance. The independent samples t test was used to evaluate whether the dose of levothyroxine needed to maintain a euthyroid state was greater in patients with concomitant hypothyroidism and untreated celiac disease than in those with only hypothyroidism. The paired-samples t test was used to determine if there was a significant decrease of levothyroxine dosing in cases subsequent to dietary treatment of celiac disease. These analyses were

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**CLINICAL SIGNIFICANCE**

- Levothyroxine is likely malabsorbed in patients with hypothyroidism and untreated celiac disease.
- Dose reduction of levothyroxine in hypothyroid patients undergoing dietary treatment for celiac disease may be required.
- Serologic evaluation for celiac disease in patients with hypothyroidism requiring elevated levothyroxine may be prudent.
done for both the total levothyroxine dose and weight-based dosing separately. For other comparisons, the chi-squared or Fisher’s exact tests were used for categorical data when appropriate, and the independent-samples t test was used for numeric data.

RESULTS

A total of 152 patients with celiac disease were identified through our pathology database. Concomitant hypothyroidism was identified in 22 patients (14.5%). Eight patients had hypothyroidism diagnosed before the diagnosis of celiac disease and had sufficient data for analysis. One of these patients had undergone gastric surgery and was excluded from analysis. Therefore, 7 patients with concomitant celiac disease and hypothyroidism were included as the cases in this study. The average age and weight of cases were 56 years and 139 pounds, and 71% were female. There were 200 control patients with hypothyroidism included in this analysis. The average age and weight of controls were 51 years and 178 pounds, and 82% were female. The Table represents demographic and clinical data of cases and controls. There was no significant difference in age, sex, TSH, or creatinine between groups. Patients with concomitant celiac disease and hypothyroidism weighed significantly less than patients with hypothyroidism alone.

Initial Levothyroxine Dosing

The mean initial dose of levothyroxine needed to maintain a euthyroid state was significantly higher in patients who had concomitant untreated celiac disease and hypothyroidism than in controls with hypothyroidism alone (154 μg ± SD 65 vs 106 μg ± SD 46; P = .007; 95% confidence interval [CI], 13-83). Weight-based dosing of levothyroxine also was considered in μg/kg. The initial weight-based dose of levothyroxine needed to maintain a euthyroid state was significantly higher in patients who had concomitant untreated celiac disease and hypothyroidism than in controls with hypothyroidism alone (2.6 μg/kg ± SD 1.3 vs 1.3 μg/kg ± SD 0.5; P < .001; 95% CI, 0.9-1.7). All cases required a total levothyroxine dose of at least 125 μg, and a weight-based dose of 1.5 μg/kg, to maintain a euthyroid state before dietary treatment of celiac disease. Overall, 31% of controls required 125 μg or more of levothyroxine, and 40% of controls required a weight-based dose of at least 1.5 μg/kg of levothyroxine, to maintain a euthyroid state. A boxplot of the weight-based dosing between cases and controls is illustrated in the Figure.

Post-therapy Levothyroxine Dosing

A reduction in levothyroxine dosing was required in all 6 cases subsequent to dietary treatment for celiac disease, for which post-therapy levothyroxine dosing was available. Dietary compliance was not directly measured. However, dietary compliance was indirectly assessed through post-therapy serologic testing for celiac disease (5 patients), and direct patient contact (1 patient). Post-therapy serologic normalization occurred in 4 patients, and reduced greatly in 1 patient. The directly contacted patient reported dietary compliance. The mean levothyroxine dose needed to maintain a euthyroid state in cases decreased significantly subsequent to dietary therapy for celiac disease (154 μg vs 111 μg; P = .03; 95% CI, 6.8-88.9). The levothyroxine dose needed to maintain a euthyroid state subsequent to treatment of celiac disease in cases was not significantly different from dosing in controls (111 μg vs 106 μg, P = .79). The mean weight-based dose of levothyroxine in cases decreased significantly subsequent to dietary treatment of celiac disease (2.6 vs 1.9; P = .04; 95% CI, 0.5-1.5). However, the weight-based dosing needed to maintain a euthyroid state in cases subsequent to therapy for celiac disease remained significantly greater than in controls (1.9 μg/kg vs 1.3 μg/kg; P = .01; 95% CI, 0.1-0.9).

**Table** Demographic Data of Cases and Controls

<table>
<thead>
<tr>
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<th>Celiac Disease and Hypothyroidism (%)</th>
<th>Hypothyroidism Alone (%)</th>
<th>P-Value</th>
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</thead>
<tbody>
<tr>
<td>Number</td>
<td>7</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>Average age (± SD)</td>
<td>56 years (±20)</td>
<td>51 years (±15)</td>
<td>.34</td>
</tr>
<tr>
<td>Average weight (± SD)</td>
<td>139 pounds (±30)</td>
<td>178 pounds (±50)</td>
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<tr>
<td>Female sex (%)</td>
<td>5 (71%)</td>
<td>164 (82%)</td>
<td>.62</td>
</tr>
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<td>TSH (± SD)</td>
<td>2.3 μIU/mL (±2.2)</td>
<td>1.9 (±1.4)</td>
<td>.49</td>
</tr>
<tr>
<td>Creatinine (± SD)</td>
<td>0.9 mg/dL (±0.4)</td>
<td>0.8 (±0.2)</td>
<td>.10</td>
</tr>
</tbody>
</table>

TSH = thyroid-stimulating hormone.
DISCUSSION

These data show that the dose of levothyroxine needed to maintain a euthyroid state in patients with concomitant untreated celiac disease and hypothyroidism is greater than patients who have hypothyroidism without known celiac disease. It also was shown that the dose of levothyroxine needed to maintain a euthyroid state in patients with celiac disease and concomitant hypothyroidism decreases after dietary treatment of celiac disease. This would suggest that malabsorption of levothyroxine occurs in patients with celiac disease, and it may identify a patient population that should be evaluated for celiac disease.

Malabsorption of nutrients and minerals occurs in patients with celiac disease. Absorption of medications appears to vary among individual medications, and has been less well studied. Gastrointestinal comorbidity that may alter medication absorption include altered gastrointestinal motility, gastrointestinal resection, and disorders of the intestine such as celiac disease. The proximal small intestine, which is usually damaged in celiac disease, is typically the site of maximum absorption for most compounds because of the presence of villi and microvilli. Evaluation of absorption of medications in celiac disease is potentially important because it may highlight the need for vigilance of patient monitoring and medication dose adjustments while celiac disease is being treated. Treatment of previously undetected celiac disease also may optimize uniformity of the therapeutic response to medications. Our data suggest that this is the case for the use of levothyroxine in patients with celiac disease. Failure to monitor these patients closely may lead to inappropriate dosing of levothyroxine while celiac disease is being treated and resultant symptoms of hyperthyroidism. Subsequent to treatment of celiac disease in this patient population, reduced doses of levothyroxine are needed to maintain a euthyroid state. Future study of the dosing of other medications such as medications for hypertension, diabetes, and depression in this patient population may be warranted.

The prevalence of celiac disease in a particular population and the benefits afforded by detecting undiagnosed celiac disease in that population, are important factors in determining whether a population should be screened. Multiple studies have shown that celiac disease is more common in patients with hypothyroidism. Overall, hypothyroidism was present in 14.5% of our patients with celiac disease. Patients with hypothyroidism who require higher doses of levothyroxine to maintain a euthyroid state may represent a population that should be screened for celiac disease. Detecting and treating celiac disease in this population may facilitate treatment of hypothyroidism with levothyroxine and prevent symptoms and complications of celiac disease. All cases included in our study required a total levothyroxine dose of at least 125 µg, and a weight-based dose of 1.5 µg/kg, to maintain a euthyroid state. It is therefore interesting to speculate that patients being treated for hypothyroidism, who require doses above these thresholds, should undergo serologic testing for the detection of celiac disease. A future study evaluating this question seems warranted.

Shortcomings of this article include its retrospective design and limited number of cases. A retrospective design was necessary because of the relatively infrequent clinical presentation of patients with untreated celiac disease who have concomitant hypothyroidism. Regardless, this design does not allow us to unequivocally conclude that levothyroxine is malabsorbed, or that the most appropriate cutoff levothyroxine dose that should prompt testing for celiac disease is 125 µg. However, our results did allow us to show significant differences between cases and controls in initial levothyroxine dosing, and a significant reduction of levothyroxine dosing after dietary treatment of celiac disease. This would seem very suggestive that levothyroxine malabsorption does occur in patients with hypothyroidism and untreated celiac disease.

In conclusion, levothyroxine is likely malabsorbed in patients with hypothyroidism and untreated celiac disease. Clinicians should be cognizant of the need for potential dose reduction of levothyroxine in hypothyroid patients undergoing dietary treatment for celiac disease. It is reasonable to perform serologic testing for celiac disease in patients with hypothyroidism requiring a total dose of at least 125 µg of levothyroxine or a weight-based dose of at least 1.5 µg/kg to maintain a euthyroid state.

References