CLINICAL RESEARCH STUDY

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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 was 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-

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mendation has not been generally accepted. The pathogenesis of the association between celiac disease and hypothyroidism is unknown. However, the association appears independent of gluten exposure,[6] and is most likely related to a common genetic predisposition.

Levothyroxine absorption is thought to occur predominantly in the jejunum.[13] 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.[14,15] This suggests incomplete absorption of orally administered levothyroxine. It has been approximated that 63%-82% of levothyroxine is absorbed after oral administration.[13] 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.[16] Celiac disease has been identified as a potential disease that may require elevated levothyroxine doses to maintain a euthyroid state.[17] There have been case reports[18-21] 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 were 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.

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.

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