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Original Article

Celiac disease detection in hypothyroid patients requiring elevated thyroid supplementation: A prospective cohort study☆,☆☆

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ABSTRACT

Background: Celiac disease (CD) is associated with hypothyroidism, but the disease prevalence is not thought to be great enough to warrant testing all hypothyroid patients. We hypothesized that hypothyroid patients with concomitant CD would require elevated doses of levothyroxine, and there is a threshold daily dose, above which, hypothyroid patients should be tested for CD.

Methods: Hypothyroid patients presenting to the endoscopy or endocrinology clinics at the University of Vermont Medical Center were included. Patients were categorized by whether or not they required ≥125 mcg/day of levothyroxine. A serum tissue transglutaminase (tTG) was performed on enrolled patients. Patients with an elevated serum tTG underwent endoscopy with duodenal biopsies. Symptoms were assessed by the Gastrointestinal Symptom Rating Scale.

Results: Overall, 500 patients were enrolled and 29% (144 patients) required ≥125 mcg/day of levothyroxine. CD was detected in 9 patients. The prevalence of CD ranged from 1.8% in our entire cohort to 12.5% in patients requiring ≥200 mcg/day of levothyroxine. Eight patients with CD (89%) required ≥125 mcg/day of levothyroxine. Patients who required ≥125 mcg/day of levothyroxine had a significantly increased risk of CD ($p < 0.001$). CD was detected in 5.6% of patients requiring ≥125 mcg/day of levothyroxine.

Conclusions: Hypothyroid patients requiring elevated daily doses of levothyroxine are more likely to have CD. Hypothyroid patients requiring ≥125 mcg/day of levothyroxine should undergo serologic testing for CD.

1. Introduction

Celiac disease (CD), a gluten sensitive enteropathy occurring in 0.2–1.0% of Americans [1–3], often goes undiagnosed [4]. Failure to diagnose CD may result in osteopenia, malabsorption, infertility, neurologic symptoms, intestinal malignancy, and intestinal symptoms [5]. The risk of osteopenia, infertility and intestinal malignancies in CD patients is reduced with a gluten free diet [6–9]. Improved serologic testing has facilitated disease diagnosis, and stimulated interest in screening [10,11]. Duodenal biopsy, however, remains the gold standard for diagnosis [12,13].

CD occurs in 2–5% of patients with autoimmune hypothyroidism [14], and is more prevalent in this group than in the general population [14,15]. Most experts feel the disease prevalence, in this population, is not high enough to justify generalized screening [13]. However, identification of subsets of patients with hypothyroidism at high risk for CD could identify groups that should be tested.

The American Gastroenterological Association and the British Society of Gastroenterology both recommend screening patients with iron deficiency anemia for CD regardless of gastrointestinal symptoms [13,16]. Studies leading to this recommendation [17–20] found a prevalence of CD in asymptomatic patients with iron deficiency anemia ranging from 2.3 to 5%. This 5% prevalence provides a reasonable threshold above which recommended screening of other populations seems reasonable.

Dose escalation of levothyroxine above standard daily dosing is necessary in about 10% of hypothyroid patients [21]. Potential causes of this include poor compliance, varied bioequivalence of supplemental thyroid preparations, specific health states (pregnancy, premenopausal women), drug or food interactions, altered surgical anatomy and concomitant diseases (helicobacter pylori infection, atrophic gastritis, parasitic infections, lactose intolerance, and celiac disease). There have been previous reports in the literature of patients with concomitant hypothyroidism and CD who required elevated daily doses of thyroid supplementation to maintain a euthyroid state [22–25]. These reports prompted our group to conduct a retrospective study [26], which found that all patients with concomitant hypothyroidism and untreated CD required ≥125 mcg of levothyroxine per day to maintain a euthyroid

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state. The prevalence of CD could not be determined with this study design, and it was concluded screening for CD in patients with hypothyroidism requiring elevated levothyroxine doses warranted further investigation. The hypothesis of this current prospective study is that hypothyroid patients requiring ≥125 mcg/day of levothyroxine are at increased risk for CD, and the prevalence is great enough in this population to warrant screening.

2. Materials and methods

2.1. Role of funding source

This study was funded by the Department of Medicine at the University of Vermont Medical Center. The funding source had no role in the design, conduct or reporting of the study.

2.2. General

This prospective cohort study, performed at a single academic institution, was approved by the Institutional Review Board at the University of Vermont Medical Center. Consecutive patients with hypothyroidism, and without CD, were enrolled from endoscopy and outpatient endocrinology clinics from March 2012 to November 2014. These patients were identified by daily review of the electronic medical record for the endoscopy ($n = 456$) and endocrinology ($n = 44$) clinics.

2.3. Design

A study schema is represented in Fig. 1. Serologic assessment for CD with an anti-tissue transglutaminase (tTG) was performed in enrolled patients. Serum tTG was performed at the Mayo Clinic laboratories. Patients who had normal tTG values had no further testing. Patients with a tTG above the upper limit of normal (normal <4.0 μ/ml) had upper endoscopy with four small bowel biopsies to confirm the diagnosis of CD. Enrolled patients were queried regarding their gastrointestinal symptoms using the Gastrointestinal Symptom Rating Scale (GSRS). They were also asked if they were diabetic, and if they had biologic children. The GSRS is a reliable and validated questionnaire [27] that has been used in multiple gastrointestinal disorders including CD [28,29]. It asks fifteen questions grouped into 5 gastrointestinal symptom categories including reflux, diarrhea, constipation, abdominal pain and indigestion. Demographic data including age and gender, physical data including weight, height and body mass index, and data on levothyroxine dosing were recorded. Patients were placed into groups depending on their daily dosing of levothyroxine. Grouping was performed and analyzed in two different ways. First patients were grouped by whether or not they required greater than ≥125 mcg/day of levothyroxine. Second patients were grouped by whether or not they required >1.5 mcg/kg/day of levothyroxine. Euthyroid status was determined in all patients by review of their most recent serum thyroid stimulating hormone (TSH).

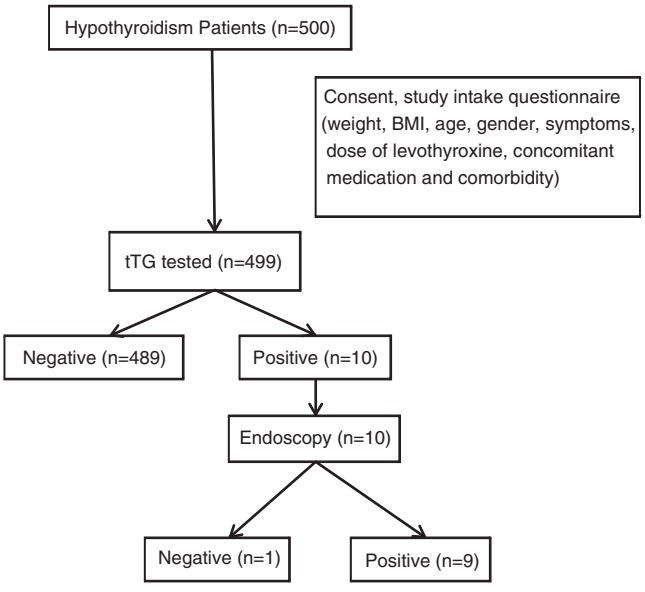

Fig. 1. Enrollment and study design flowchart.

2.4. Hypothyroidism

All patients enrolled were diagnosed with hypothyroidism. For the purposes of this study hypothyroidism was defined as the diagnosis of hypothyroidism in the electronic medical record and the need for thyroid supplementation. If a patient was taking a thyroid supplement other than levothyroxine the recorded dose of that supplement was converted to a levothyroxine equivalent. Patients were considered euthyroid if their TSH was within the normal range (0.35–5.00 uIU/ml). Hypothyroidism patients who had a pituitary tumor, prior thyroid surgery, neck irradiation, radioactive iodine therapy or had undergone prior treatment with lithium, methimazole, propylthiouracil or ethionamide were excluded.

2.5. Celiac disease

CD was defined as an elevated tTG with confirmatory villous blunting on small bowel biopsy (Marsh 3). At the time of upper endoscopy at least four small bowel biopsy specimens were obtained. Biopsies were reviewed by a single gastrointestinal pathologist in a blinded fashion. A gluten free diet was recommended for patients diagnosed with celiac disease. A repeat serum tTG, TSH, and symptom assessment with the GSRS was performed in these patients from 6 to 18 months after diagnosis. Patients who had prior serologic testing for CD with a tTG or who had previously been diagnosed with CD were excluded.

2.6. Statistical methods

2.6.1. Sample size calculations

It was assumed that the rate of CD in hypothyroid patients requiring ≥125 mcg per day of levothyroxine (or >1.5 mcg/kg/day) would be approximately 5%, and the rate of CD in patients with hypothyroidism requiring <125 mcg per day (or ≤1.5 mcg/kg/day) would mirror the general population at 0.7%. It was anticipated 50% of patients with hypothyroidism would require ≥125 mcg per day of levothyroxine. Therefore, with a power of 80%, and a significant 2-sided p value set at <.05, it was calculated that a total of 500 hypothyroid patients would be needed to adequately answer our primary question, and limit the possibility of incorrect rejection of the null hypothesis (type 1 error).

2.6.2. Methods of analysis

Descriptive statistics were used to report demographic data, euthyroid status, and prevalence rates of CD and associated disorders. Fisher's Exact test was used to compare the prevalence of biopsy proven CD between groups depending on their total (mcg/day) and weight-based (mcg/kg/day) daily levothyroxine dosing. Continuous variables including age, weight, height, and body mass index were compared using the Wilcoxon Rank Sum Test. The paired samples t-test was used to determine significant changes in symptoms subsequent to a gluten free diet in those patients diagnosed with CD. A stratified exact conditional logistic regression analysis was performed to reduce potential confounding. Cases and controls were derived from our cohort of patients. Cases were those patients with CD and controls were derived from those patients who did not have CD. Controls were matched to cases by gender and within 1 unit of BMI. If controls matched two