Bioengineering Research

Comparison of Serologic Celiac Disease in Patients with Hypothyroidism and Healthy Controls: A Case-Control Study

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Abstract

Objectives: Celiac disease often accompanies by other endocrinologic diseases such as hypothyroidism. We aimed to determine the prevalence of celiac disease in autoimmune and non-autoimmune and clinical and subclinical hypothyroidism based on serological evaluation.

Methods: This case-control study was conducted in a referral clinic of Kurdistan University of Medical Sciences, Sanandaj Iran. The case group was assigned as patients who had clinical and subclinical hypothyroidism (based on TSH levels), and the control group included patients without any thyroid or gastrointestinal problems. The levels of anti-tissue transglutaminase antibody (anti-TTG) were assessed in all case and control patients.

Results: Two-hundred and fifty patients (150 in the control group) were included in the final analysis. The mean age of patients was 37.4 ± 10.4, and there were no significant differences for age and gender between the case and control groups (P-value > 0.05). The celiac serology was positive in five patients in the case group (5%) and two in the control group (1.3%). Celiac positive serology was significantly higher in the case group than the control group (P < 0.05).

Conclusions: While undiagnosed and untreated CD causes comorbidities in hypothyroid patients, timely CD diagnosis and treatment diminishes the complications that were caused. Considering the significant relation and growing prevalence, it seems logical to design a screening program to detect CD in hypothyroid patients, especially the clinical ones with autoimmune hypothyroidism, especially those who require higher doses of levothyroxine.

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1. Introduction

Celiac disease (CD) is an immune-related condition of the small bowel followed by over sensitivity and immune reaction to the gluten's dietary protein. [1] likewise, CD is increasingly associated with other endocrinological diseases, including hypothyroidism. [2] Its prevalence varies from less than 1% in the normal population to approximately 5% in patients with autoimmune thyroidal disease (ATD). Likewise, CD and thyroid disease's coincidence was associated with genetically determined due to the common detection of human lymphocyte antigen (HLA) in some reports. [3-6]

Clinical manifestations extend from a classic malabsorption syndrome to atypical presentation such as anemia, osteoporosis, and phycological disorders. Likewise, several involved patients never indicate any disease symptoms, and only 10–20% of the histologically diagnosed CD are identified through clinical findings. [7] Furthermore, previous studies reported several cases presenting with persistent hypothyroidism who did not respond to a determinate levothyroxine dose that CD was diagnosed for them eventually. Since the management of the mentioned patients with gluten-free diet followed by subclinical CD recognition in hypothyroidism patients not only helps prevent the long-term complication of the CD but also economically viable by reducing the needed dose of levothyroxine. Moreover, autoimmune thyroiditis frequently ensues in patients medicated with alpha interferons, such as hepatitis C, and reports of interferon-alpha therapy inducing CD suggesting the interpretation of mutual etiological mechanisms between CD and autoimmune thyroiditis. [8-10]

Although, small bowel biopsy and villous atrophy observation considering as accurate and gold diagnostic methods. Given the cost and invasive nature of the biopsy, genetic and serologic laboratory tests may be used to identify individuals with a high possibility of having celiac disease. [11] In terms of serology, celiac disease is associated with various autoantibodies, including tissue transglutaminase (tTG), deamidated gliadin antibodies, and endomysial. Anti-tTG is the first diagnostic step in suspected individuals. [12]

Previous studies usually reported the prevalence of CD in autoimmune thyroiditis. We designed a study to determine the relationship between the two diseases in autoimmune and non-autoimmune and clinical and subclinical hypothyroidism.

2. Materials And Methods

2.1. *Study design.* This case-control study was conducted on patients referring to the Tohid clinic of Sanandaj, Kurdistan province, Northwestern Iran. For this study, two groups of patients were enrolled based on the simple sampling method. The first group, assigned as the case group, had clinical and subclinical hypothyroidism. The second group, assigned as the control group, included patients without gastrointestinal problems such as diarrhea, weight loss, etc. Both groups of patients were matched based on age and gender. Furthermore, TSH levels were assessed in the control group to rollout clinical hypothyroidism. Pregnant patients and patients who received immunosuppressive or corticosteroid, and patients who had significant weight loss or a history of diabetes were excluded from our study.

2.2. *Disease Evaluation.* Patients presented to the clinic during the study period and suspected of hypothyroidism (case group) were evaluated based on TSH levels. A TSH level of more than 6.2 mU/L was assumed as hypothyroidism. Furthermore, the free T4 (normal range = 4.5-12 ng/dl) was evaluated in the hypothyroid patients for differentiation of sub-clinical hypothyroidism from clinical hypothyroidism. The anti-TPO levels were also assessed in hypothyroid patients, in which a value of more than 40 IU/ml was assumed as autoimmune hypothyroidism. TSH levels were also evaluated in the control group for excluding hypothyroidism. After selecting the case and the control patients, IgA of anti-tissue

Table 1: The baseline characteristics of patients

Variable		Case group *n=100*	Control group *n=150*	P-value
Gender	Male	33 (33%)	30 (20%)	0.39[a]
	Female	67 (67%)	120 (80 %)	
Age		36.8 ± 11.2	38.4 ± 9.6	0.43[b]
Type of Thyro*thyroidism*	*Autoimmune hypothyroidism*	60 (60%)	-	-
	non-autoimmune hypothyroidism	40 (40%)	-	
	Clinical hypothyroidism	22 (22%)	-	
	Sub-clinical hypothyroidism	78 (78%)	-	

[a] chi-square test , [b] independent sample t-test

Table 2: The prevalence of positive celiac serology in patients with hypothyroidism

Group		Celiac status; n (%)		P-value*
		Negative	Positive	
Case group	*Clinical hypothyroidism*	80 (95.2%)	4 (4.8%)	< 0.001
	Sub-clinical hypothyroidism	15 (93.7%)	1 (6.3%)	
	Autoimmune hypothyroidism	61 (93.8%)	4 (6.2%)	< 0.001
	non-autoimmune hypothyroidism	34 (97.1)	1 (2.9%)	

* Binomial test

Table3: The relation between hypothyroidism and celiac serology

Celiac serology	Study group		P-value*
	Case group *n=100*	**Control group** *n=150*	
Positive	5 (5%)	2 (1.3%)	< 0.001
Negative	95 (95%)	148 (98.7%)	

* Chi-square test

2.3. transglutaminase antibody (anti-TTG) was assessed in all patients using the ELISA method (kit: Euroimmun Kit, Nima Pooyesh Teb Company, Tehran, Iran) and the levels more than 18 IU/ml were assumed as positive for celiac disease. Selection and sample bias was the major issue since our subjects included the patients referred to our clinic, so many sub clinical hypothyroid individuals remain unrecognized; therefore, they may not represent the society.

2.4. *Statistical analysis.* The prevalence of hypothyroidism in celiac disease was assumed between 2.4% to 14.5% based on previous studies [13,14]. In addition, the prevalence of celiac in the case group and the control group were assumed 7% (P_1 = 0.07) and 0.5% (P_0 = 0.005) respectively. Therefore, the control group and case group's sample numbers were assumed about 150 patients and 100 patients, respectively, based on 0.05 of significance level (α = 0.05) and a power of 80% (β = 0.8). Controls were matched with cases in age and gender, therefore minimizing bias. After data collection, the information was entered into version 26 of SPSS software for statistical analysis. Chi-square test and binomial test were used for evaluating the relations between the two groups.

2.5. Ethical consideration. This study was conducted after obtaining permission from Kurdistan University of Medical Sciences, Sanandaj, Iran. Written informed consent was filled by all patients before, including in the study, and the researchers safeguarded patients' information. Also, the authors declare no conflict of interest in this study.

3. Results

3.1. *Demographics.* Three hundred and two patients were included in this study at the baseline. Thirty-two patients were excluded from the study for personal reasons, and 20 patients were excluded due to an underlying disease. Two-hundred and fifty patients were included in the final analysis, that 150 of them were in the control group. One-hundred and eighty-seven patients were female (74.8%), and there were no significant differences between genders (P = 0.39). The mean age of patients was 37.4 ± 10.4 (range between 18 to 64), and there were no significant differences for age between the case and control groups (P = 0.43). The baseline characteristics of patients are shown in table 1.

3.2. Celiac and hypothyroidism. Positive serology for celiac was observed in five patients of the case group (5%) and two control groups (1.3%). Also, 84 patients (84%) of the case group had clinical hypothyroidism, and 16 of them had sub-

clinical hypothyroidism. Furthermore, 65 patients had autoimmune hypothyroidism. The results of the case group are presented in table 2.

As seen in Table 2, positive celiac prevalence is significantly higher in autoimmune and clinical hypothyroidism than in subclinical and non-autoimmune patients ($P < 0.05$).

The prevalence of positive serology for celiac disease in case groups and control groups is presented in table 3.

As seen in Table 3, positive serology for celiacs is significantly higher in the case group than the control group ($P < 0.05$). It is worth mentioning that among the case group patients with celiac disease, 4 (80%) used a daily dose of 1 mcg/day levothyroxine or higher, while 1 (20%) used a daily dose of lower than 1 mcg/day; However, there was no statistical difference among the two groups (P=0.847)

4. Discussion

The association between CD and thyroid disorders such as hypothyroidism has been the subject of several studies. [15] Furthermore, although minor conflicts may exist in the results [16], most of these studies have focused on the relation between CD and autoimmune thyroid disease since they both have an autoimmune basis;[9] But CD can also be seen in other types of thyroid disease. This issue is especially of significance in the case of undiagnosed or subclinical celiac disease. In this study, we evaluated the prevalence of CD among specifically hypothyroid patients -and not only autoimmune thyroid disease - based on serological markers to address the question of whether it is necessary to rule out CD in hypothyroid patients.

As mentioned earlier, our results revealed that 5% of hypothyroid cases had positive serology for CD, yet the prevalence was only 1.3% in the control group, which was significantly lower than the case group hypothyroidism patients. Some variations may exist among studies regarding this issue; some reported that the prevalence of CD in hypothyroid patients is between 4-8%. [17,18] while others reported a lower incidence of this issue (1.5% to 2.5%). [14,19] These variations may have arisen from differences in the study subjects since some studies have chosen their subjects from clinical hypothyroid patients while others have restricted their research to autoimmune-hypothyroidism, congenital hypothyroidism, or those patients with only serological hypothyroidism. [20] Our study results alongside other studies show that celiac is more prevalent in all type of hypothyroid patients.

One of the important concern which follows is the higher dose requirements of levothyroxine in these patients, as our study demonstrated that 80% of celiac patients with hypothyroidism required a daily dose of 1mcg/day or more, however statistically insignificant, which may be due to the low sample size of celiac patients in our study. Different hypotheses exist, but the most important one is that celiac disease, as a gastrointestinal disease that is thought to present mainly in jejunum and ileum [18], reduces jejunal absorption of levothyroxine. [13] Therefore, an important matter to keep in mind is that in the co-existence of CD and hypothyroidism, the needed dose of levothyroxine has been shown to increase, and therefore further dose adjustments will be needed. Likewise, the subclinical and undiagnosed CD can play a role in wasting resources and increasing costs and drug-related side effects, which is problematic both for patients and the health care system. Since promising data exists about the positive effects of dietary treatment (gluten-free diet) on reducing levothyroxine dosing [7], it is critical to consider CD in hypothyroid patients, especially those resistant to the usual doses of levothyroxine. Our study results further highlight the importance of celiac screening in hypothyroid patients, although more studies with a larger sample size are required to assess the cost efficiency of this screening for all hypothyroid patients.

Additional evaluations and outcomes showed that a statistical relationship could be assumed between CD and clinical hypothyroidism in that only 20% of patients with positive celiac serology had subclinical hypothyroidism, and the rest (80%) were the cases diagnosed with clinical hypothyroidism. This means

that the prevalence of CD is 4 folds higher in cases with clinical hypothyroidism. In a similar study, Mehrdad et al. [14] reported that 54.5% of patients detected with positive results of celiac serology were overt hypothyroidism. This result prompts us to consider CD more thoroughly in clinical hypothyroidism, even with atypical presentation. However, existing data about this issue is insufficient, and more information is needed to support this idea.

Our results showed that positive serology in ATD is 4 times greater than this prevalence in non-ATD (prevalence: 4.69%). Results resemblance 0f 2-5% CD in ATD were found in other studies. [19] Roy et al. [9] also concluded that CD exists in 1.6% of the total number of ATD patients. The exact pathogenesis behind this co-occurrence is unknown, but evidence suggests that genetics may play a role, and HLA antigens are the possible culprits. [19,21] Therefore, further immunopathological studies are required to assess this correlation and establish a clearer explanation because a better explanation paves the way for the development of new treatments and reduces the comorbidities in these people.

. Our study results showed that neither age nor gender has a statistical relation with celiac disease prevalence. This is in accordance with other studies. [14,19] Also, Collins et al. [13], in an attempt to compare the required dose of levothyroxine in cases suffering from CD and hypothyroid disease compared to controls with hypothyroidism, found no significant difference in age and gender between cases and controls. This cannot be applied in the case of ATD since studies have shown that younger age is related to the higher prevalence of CD in ATD patients. [9] Demographic data about hypothyroid patients with concomitant CD is not yet satisfying and more researches can help to find an answer to this question that if screening for CD would be more critical in a defined group of hypothyroid patients

Our study is one of the few case-control studies conducted in Iran about this topic. Controls were matched with cases in age and gender, therefore minimizing bias. Selection and sample bias was the major issue since our subjects included the patients referred to our clinic, so many sub clinical hypothyroid individuals remain unrecognized; therefore, they may not represent the society. Although our sample size was determined by sample size analysis, the risk assessment required a much greater sample size, and a prospective cohort study with large sample size is suggested to overcome the insufficiencies and assess risks precisely.

5. Conclusions

While undiagnosed and untreated CD causes comorbidities in hypothyroid patients, timely CD diagnosis and treatment diminishes the complications that were caused. Considering the significant relation and growing prevalence, it seems logical to design a screening program to detect CD in hypothyroid patients, especially the clinical ones with autoimmune hypothyroidism, especially those who require higher doses of levothyroxine.

Data Availability

SPSS data of the participant can be requested from the authors. Please write to the corresponding author if you are interested in such data.

Conflict Of Interest

The authors declare that they have no competing interests.

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