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The Relationship Between The Presence of Gastrointestinal Symptoms and Anemia, Thyroid Functions and Bone Mineral Density In Celiac Patients

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ABSTRACT

The prevalence of typical celiac patients decreases gradually with the investigation of patients presenting with non-gastrointestinal symptoms (non-GIS) like anemia, thyroid dysfunction, liver function test anomalies and dermatitis herpetiformis. The diagnosis of atypical and subclinical celiac has also increased due to the development of immunological and genetic tests. The aim of our study is to determine the relationship between the presence of GIS and anemia, thyroid functions, and bone mineral density in celiac patients.
The study included 230 celiac patients who were diagnosed and followed-up in our clinics between 2015-2019. The demographic and anthropometric characteristics, initial presentation complaints, disease durations, dietary compliance of the patients were documented. Presence of anemia, thyroid functions, bone mineral density were documented and its relationship with presence of GIS was analyzed.
The age range of the patients was 18-65 years, and the mean age was 33,4±10,6 years. A total of 170(73.9%) patients were female and the duration of disease follow-up was 4,8±3,5 years. Osteoporosis/osteopenia was found in 146(63,5%) patients, anemia was found 65(28.3%) and thyroid dysfunction was found 58(25.2%). Patients without GIS were significantly more anemic than patients with GIS (39.1%, 24.1% respectively) ($p<0.05$). In terms of thyroid function tests, the rates were similar in both groups and there wasn't significant difference ($p>0.05$). Osteoporosis was significantly higher in patients with GIS ($p<0.05$).
The number of patients with atypical celiac disease is increasing. Celiac disease should be considered in patients presenting with unexplained anemia, a history of thyroid disease, and abnormal bone density.

Key Words: Celiac Disease, Gastrointestinal Symptoms, Anemia, Thyroid Dysfunction, Bone Mineral Density

Introduction

Celiac disease (CD) is an autoimmune disease affecting about 1% of the population worldwide (1). The disease is usually atypical or subclinical, therefore many cases are not diagnosed and there are significant delays in the time of diagnosis (2). Clinical, immunological and genetic studies of celiac disease show that despite small bowel villous atrophy, disease may be subclinical or atypical without symptoms of malabsorption (3). Subclinical celiac patients may present with few symptoms. Even patients may present with only one of the diseases such as tetany, low bone mineral density, peripheral neuropathy, permanent tooth enamel defects and autoimmune diseases (3). CD is likened to "an iceberg" model because patients with no clinical symptoms are more diagnosed than patients with clinical symptoms (4,5). The prevalence of typical celiac patients decreases gradually with the investigation of patients presenting with non-gastrointestinal symptoms (non-GIS) like anemia, thyroid dysfunction, liver function test anomalies and dermatitis herpetiformis. The diagnosis of atypical and subclinical CD has also increased due

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to the development of immunological and genetic tests (1).

Studies have shown that patients with non-GIS have significantly higher anemia and thyroid dysfunction than patients with GIS (6). The main aim of this study is to determine the relationship between the presence of GIS and anemia, thyroid functions and bone mineral density in celiac patients. The secondary aim of the study is to determine the factors associated with the presence of GIS in celiac patients.

Materials and Methods

Study Design: The patients who were diagnosed and followed-up in the clinics of Gastroenterology were included in the present study. The study was designed as retrospective screening. For all patients who were diagnosed with CD, the inclusion criteria for the study were having positive results of the Antibody level test (Anti-Endomysium and Tissue Transglutaminase Antibody (anti-TTG)), which is carried out in clinical and laboratory suspicion, and having consistent results of the tissue samples taken in endoscopy in histopathological examination according to the Marsh classification. The patients who did not continue follow-ups in our clinic, whose data could not be obtained or who had missing data and who were pregnant were not included in the study. The study included 230 celiac patients, who were followed-up in our clinics between 2015-2019, and whose data were fully accessible and who were regularly followed up.

Immunological, Endoscopic and Histopathological Evaluation in Celiac Patients: Because of its high specificity and sensitivity, only anti-TTG positivity was observed in patients. At the last visit antibody levels were evaluated again in order to evaluate the immunological remission of patients. Patients with negative antibody levels were accepted in immunological remission. In patients with antibody positivity endoscopic examination was performed using a video endoscope and biopsies were taken from the second / third part of the duodenum. All biopsies were examined by a specialist pathologist and histopathology was performed according to the Marsh classification (7).

Evaluation of Demographic and Clinical Features: The demographic and anthropometric characteristics (ages, genders, onset of disease, duration of disease, Body Mass Index (BMI)) of the patients who included in the study were documented. Height (meter) and weight (kg) measurements were made to calculate the BMI of the patients. The BMI was calculated with the following formula: Weight/Height x Height. The waist circumference, hip circumference, waist/hip rates were also documented. In men, 0.9 waist/hip rate was considered to be risky for abdominal obesity and chronic diseases in men, and 0.85 in women (8). The symptoms of the participants at admission were documented. Diarrhea, constipation, reflux, bloating, abdominal pain, nausea and vomiting were evaluated as GIS (9). In addition to the GIS, the presence of thyroid diseases, anemia, growth retardation, presence of weight loss, presence of skin lesions, infertility, bone disorders and bleeding were documented and were evaluated as non-GIS. Dietary compliance was classified into two categories: strict diet (complete diet compliance) and normal gluten-containing diet.

Evaluation of Anemia, Thyroid Functions and Bone Mineral Density: Iron, total iron binding capacity, ferritin, folate, vitamin B12, mean corpuscular volume (MCV), hemoglobin level, thyroid function tests (Free T4, T3, Thyroid stimulating hormone) were evaluated in all participants. Hemoglobin value was <12.0 g / dL in women and <13 g / dL in men was evaluated as anemia. The patients were evaluated as hypothyroid, hyperthyroid and normal in terms of thyroid hormone functions. Bone densitometry was performed to measure bone mineral density. Bone mineral density was measured by DEXA (dual energy x-ray absorptiometer) device in radiology department and the results were recorded. L1-L4 lumbar vertebrae and femur neck's lowest T score was evaluated. Bone mineral density was defined as being between -1 and -2.5 osteopenia, and being below -2.5 was defined as osteoporosis (11).

Ethics Declaration: To conduct this study, ethical approval was obtained from the Ethics Committee of our hospital. All the applied procedures were complied with the ethical standards of human testing committee of our institution and the Helsinki Declaration. Written informed consent forms were received from all participants.

Data Analysis: The results of our study were analyzed with "the Statistical Package for Social Sciences 24.0 (SPSS Armonk, NY: IBM Corp.)" program. The data that had continuous values were given as (mean±standard deviation), and the categorical data were given as frequency and percentage (n, %). The data were tested for compliance to normal distribution with the Kolmogorov-Smirnov Test, Histogram and ± SD. The nonparametric data of the groups were compared by using the Mann Whitney U-test; and the parametric data were compared with the Parametric T-test. The Chi-square Test was employed to test the categorical data. A P value <0.05 was considered to be statistically significant.

Results

A total of 230 patients who were followed-up with CD were included in the study. A total of 172 (74.8%) of the patients were female, and the mean age was 33,4±10,6 years (range between 18-65 years). Although the mean BMI level of the patients was 22,6±4,2; only 146 (63.5%) patients had normal BMI. The waist-hip rate of the patients ranged between 0.63 and 0.98 with a mean of 0.81±0.07 (0.87±0.06 in males, and 0.8±0.06 in females). In 54 (%24,5) of the patients, it was determined that the waist-hip rate was above normal. The histopathological findings of the patients were evaluated as grade 2 and 3a mild, grade 3b, 3c and 4 advanced disease. 126 (54.8%) patients were mild and 104 (45.2%) patients were in severe stage. When the first presentation symptoms of the patients were evaluated; 166 (72.2%) patients had GIS, 64 (27.8%) patients had non-GIS.

The factors associated with the presence of GIS are examined in celiac patients; It was found that patients with non-GIS group were younger (34.6 ± 11.1 vs 30.4 ± 8.9, respectively), disease onset age was earlier (29.6 ± 10.9 vs 25.1 ± 9.6, respectively), and that the patient group was weaker (22.9 ± 4.2 vs 21.7 ±). 4.2 respectively) than GIS group (p <0.05). In addition, it was found that female gender was significantly higher in patients with GIS (80.7% versus 56.3%) and immunological remission was lower (50.6% versus 71.9%) than in patients without GIS (p<0.05) (Table 1).

The relationship between the presence of GIS and anemia, thyroid functions and bone mineral density in celiac patients was evaluated. Patients without GIS had significantly more anemia (24.1% vs. 39.1%) (p <0.05). In terms of thyroid function tests, the rates were similar in both groups and there was no significant difference (p> 0.05). While 74.7% of patients with GIS have osteopenia/osteoporosis, this rate was found to be 65.6% in patients with non-GIS. There was no significant difference in osteopenia in both groups but osteoporosis was significantly higher in patients with GIS (29.5% versus 12.5%) (p <0.05) (Table 2) (Figure 1).

Discussion

In our study, 72.2% of the patients presented with GIS, while 27.8% had non-GIS. The factors associated with GIS were evaluated; In both groups, thyroid dysfunction is similar and there was significant difference in osteoporosis and anemia. In a

Table 1. Factors associated with the presence of gastrointestinal symptoms ın celiac patients

Variables	Celiac Disease with GIS N:166	Celiac Disease without GIS N:64	Total N:230	P value
Age (years ± Sd)	34.6±11.1	30.4±8.9	33.4±10.6	0.007*
Gender				<0,001**
Female	134(%80.7)	36(%56.3)	170(%73.9)	
Male	32(%19.3)	28(%43.8)	60(%26.1)	
Onset age of the disease (years)	29.6±10.9	25.1±9.6	28.5±10.7	0.002*
Disease duration (years)	4.7±3.2	5.3±4.1	4.8±3.5	0.201*
Waist/hip rate				0.302
Below the limit	130(%78.3)	46(%71.9)	176(%76.5)	
Above the limit	36(%21.7)	18(%28.1)	54(%23.5)	
BMI (kg/m²)	22.9±4.2	21.7±4.2	22.6±4.2	0.035*
Dietary Compliance				0.647
Strict	62(%37.3)	26(%40.6)	88(%38.3)	
None	104(%62.7)	38(%59.4)	142(%61.7)	
Immunologic Remission				0.004*
Yes	84(%50.6)	46(%71.9)	130(%56.5)	
No	82(%49.4)	18(%28.1)	100(%43.5)	
Disease stage				0.385
Mild (Stage 2-3a)	88(%53)	38(%59.4)	126(%54.8)	
Severe (Stage 3b,3c,4)	78(%47)	26(%40.6)	104(%45.2)	

BMI: Body Mass Index, **Sd:** Standard Deviation, **GIS:** Gastrointestinal symptoms Statistically significant *(p<0.05) **:(p<0.001)

Table 2. The relationship between the presence of gastrointestinal symptoms and anemia, thyroid functions and bone mineral density in celiac patients

Variables	Celiac Disease with GIS N:166	Celiac Disease without GIS N:64	Total N:230	P value
Presence of anemia				0.024*
Yes	40(%24.1)	25(%39.1)	65(%28.3)	
No	126(%75.9)	39(%60.9)	165(%71.7)	
Thyroid functions				0.499
Normal	126(%75.9)	46(%71.9)	172(%74.8)	
Hypothyroidism	38(%22.9)	18(%28.1)	56(%24.3)	
Hyperthyroidism	2(%1.2)	0(%0)	2(%0.9)	
Thyroid functions				0.528
Normal	126(%75.9)	46(%71.9)	172(%74.8)	
Abnormal	40(%24.1)	18(%28.1)	58(%25.2)	
Bone mineral density				0.025*
Normal	42(%25.3)	22(%34.4)	67(%29.1)	
Osteopenia	75(%45.2)	34(%53.1)	109(%47.4)	
Osteoporosis	49(%29.5)	8(%12.5)	54(%23.5)	
Bone mineral density				0.169
Normal	42(%25.3)	22(%34.4)	82(%35.7)	
Abnormal	124(%74.7)	42(%65.6)	148(%64.3)	

GIS: Gastrointestinal symptoms Statistically significant *($p<0.05$)

study of 101 patients with celiac disease by Paez et al., 52 patients had GIS and 49 patients had non-GIS. While the duration of diagnosis is 2-3 months delay in celiac patients with GIS, this period is 42 months in the non-GIS group (6). Green et al. reported that the mean age at diagnosis was 11 years delayed in 1138 people with CD who presented with GIS of 85% (11). In our study, patients with CD without GIS were found to be significantly younger and the disease onset age was earlier. Patients are consulted earlier to the doctor because of diseases such as anemia, thyroid dysfunction, liver function test anomalies and dermatitis herpetiformis. We think that this is effective in early diagnosis of CD. Patients with a GIS indirectly consult to the doctor later therefore, the delay in diagnosis can be said to be more. In addition, male gender was significantly higher and immunological remission was higher in patients with non-GIS. Although immunological remission is achieved in CD following dietary adaptation, HLA-DR3, HLA-DQ2 and other genetic locus that plays a role in the development of extraintestinal manifestations are involved. For this reason, other findings are thought to continue despite immunological remission in patients with non-GIS.

Anemia is one of the most common symptoms of CD. In recent studies, approximately 85% of celiac patients have been found to be anemic (12,13). Paez et al. found that the rate of anemia was 69.4% in the non-GIS group and 21.2% in the GIS group in their study. Similarly, the rate of anemia in our study was significantly different between the two groups; the rate of anemia was 39.1% in the non-GIS group and 24.1% in the GIS group. In many studies, the incidence of low bone mineral density has been increased in celiac patients compared to healthy population (14,15). Stenson et al. (15) reported that the prevalence of CD in osteoporotic individuals is high enough to require serological screening. Paez et al. found low bone mineral density prevalence in 68% of patients with non-GIS and 41% in patients with GIS, but not statistically significant (6). In our study, 74.7% of patients with GIS had osteopenia/osteoporosis, while this rate was found to be 65.6% in patients with non-GIS. In our study, osteoporosis was significantly higher in the patient group with GIS. It is known that adherence to strict diet increases bone mineral density. Although the lack of dietary adaptation was similar in both groups, and it was found to be high. However, we think that the patients with non-GIS are diagnosed earlier and the adherence of diet, even in partial, plays an important role in the development of bone disorders less frequent.

Autoimmune thyroid disease is a common disease in CD. Collin et al. (16) found that 5.4% of 335 adult celiac patients had autoimmune thyroid disease. In their study, Ventura and Viljama showed that the prevalence of autoimmune disease was 34% and 31% in celiac patients and they were frequently

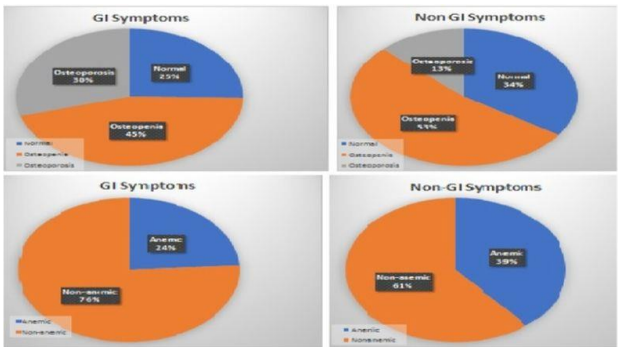

Fig. 1. The relationship between the presence of GIS symptoms with anemia and bone mineral density

accompanied by thyroid diseases (17, 18). Cosnes et al. show that found a significant relationship between the development autoimmune disease and diagnosis age of celiac disease is <36 years, presence of non-GIS, presence of autoimmune disease in the family (19). Paez et al. reported that thyroid dysfunction was significantly higher in patients with non-GIS (7). Many environmental factors play a role as well as genetic characteristics in the development CD and accompanying the other autoimmune diseases (19-21). Since the environmental characteristics and genetic characteristics of different geographic locations may vary, we did not find a significant relationship between thyroid dysfunction and presence of GIS in our study.

In conclusion, in our study, we found that celiac patients without GIS were significantly more anemic and osteoporosis was significantly higher in the patient group with GIS. As observed in our study, clinical presentations of CD changed over time and patients with atypical CD rather than malabsorption symptoms started to increase. Patients with unexplained anemia, a history of thyroid disease and abnormal bone density should be suspected of having CD. This highlights the need for accurate screening in celiac patients.

Declaration of Conflicting Interests: The authors declare that they have no conflict of interest.

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References

1. Green PH, Cellier C. Celiac disease. N Engl J Med 2007; 357: 1731-1743.
2. Nejad MR, Rostami K, Emami MH, Zali MR, Malekzadeh R. Epidemiology of celiac disease in Iran: a review. Middle East J Dig Dis 2011; 3: 5.
3. Farrell RJ, Kelly CP. Diagnosis of celiac sprue. Am J Gastroenterol 2001; 96: 3237-3246.
4. Ravikumara M, Tuthill DP, Jenkins HR. The changing clinical presentation of coeliac disease. Arch Dis Child 2006; 91: 969-971.
5. Lindfors K KO, Kaukinen K. An update on the diagnosis of celiac disease. Int Rev Immunol 2011; 30: 96.
6. Paez MA, Gramelspacher AM, Sinacore J, Winterfield L, Venu M. Delay in diagnosis of celiac disease in patients without gastrointestinal complaints. Am J Med 2017; 130: 1318-1323.
7. Marsh MN. Gluten, major histocompatibility complex, and the small intestine: a molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). Gastroenterology 1992; 102: 330-354.
8. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes care 2015; 38: 140-149.
9. Revicki DA, Wood M, Wiklund I, Crawley J. Reliability and validity of the Gastrointestinal Symptom Rating Scale in patients with gastroesophageal reflux disease. Qual Life Res 1997; 7: 75-83.
10. Lewiecki EM, Gordon CM, Baim S, et al. International Society for Clinical Densitometry 2007 adult and pediatric official positions. Bone 2008; 43: 1115-1121.
11. Green PH, Stavropoulos SN, Panagi SG, et al. Characteristics of adult celiac disease in the USA: results of a national survey. Am J Gastroenterol 2001; 96: 126.
12. Harper JW, Holleran SF, Ramakrishnan R, Bhagat G, Green PH. Anemia in celiac disease is multifactorial in etiology. Am J Hematol 2007; 82: 996-1000.
13. Javid G, Lone SN, Shoukat A, et al. Prevalence of celiac disease in adult patients with iron-deficiency anemia of obscure origin in Kashmir (India). Indian J Gastroenterol 2015; 34: 314-319.
14. Kemppainen T, Kröger H, Janatuinen E, et al. Osteoporosis in adult patients with celiac disease. Bone. 1999;24(3):249-255.
15. Stenson WF, Newberry R, Lorenz R, Baldus C, Civitelli R. Increased prevalence of celiac disease and need for routine screening among patients with osteoporosis. Arch Intern Med 2005; 165: 393-399.
16. Collin P, Reunala T, Pukkala E, Laippala P, Keyriläinen O, Pasternack A. Coeliac disease--associated disorders and survival. Gut 1994; 35: 1215-1218.
17. Ventura A, Magazzù G, Greco L. Duration of exposure to gluten and risk for autoimmune disorders in patients with celiac disease. Gastroenterology 1999; 117: 297-303.

18. Viljamaa M, Kaukinen K, Huhtala H, Kyrönpalo S, Rasmussen M, Collin P. Coeliac disease, autoimmune diseases and gluten exposure. Scand J Gastroenterol 2005; 40: 437-443.
19. Cosnes J, Cellier C, Viola S, et al. Incidence of autoimmune diseases in celiac disease: protective effect of the gluten-free diet. Clin Gastroenterol Hepatol 2008; 6: 753-758.
20. Counsell C, Taha A, Ruddell W. Coeliac disease and autoimmune thyroid disease. Gut 1994; 35: 844-846.
21. Fallahi P, Ferrari SM, Ruffilli I, et al. The association of other autoimmune diseases in patients with autoimmune thyroiditis: review of the literature and report of a large series of patients. Autoimmun Rev 2016; 15: 1125-1128.