

Celiac Disease in the Turkish Population

RENGIN ELSURER, MD,* GONCA TATAR, MD,† HALIS SIMSEK, MD,† YASEMIN H. BALABAN, MD,†
MUSA AYDINLI, MD,† and CENK SOKMENSUER, MD‡

Celiac disease (CD) is characterized by malabsorption of nutrients in the small intestine. The availability of highly specific and sensitive serologic tests has facilitated its diagnosis, increasing the disease prevalence. The aim of this study was to determine the clinical, laboratory, and histopathological features of CD in Turkish adults. Between 1968 and 2002, CD patients presenting to the Gastroenterology Unit were evaluated retrospectively. From 2002, newly diagnosed patients were prospectively followed up. Sixty patients (39 female, 21 male) were included in the study. Mean body mass index was 22.2 ± 5.4 kg/m². The most common symptoms were diarrhea, weight loss, and flatulence. Most common comorbidities were anemia, osteoporosis, type 1 diabetes mellitus, and steatohepatitis. Six (10.0%) patients had a family history of diabetes mellitus; one (1.7%) patient had a family history of CD. Plasma glucose and serum γ -glutamyltransferase levels were significantly higher in females than males. Most common histopathological findings were increased lymphocytes in the lamina propria (76.2%) and villus epithelium (59.5%). Over the years, the cumulative frequency of CD increased more in females than males. This is the first study in the literature showing the characteristics of CD in Turkish adults. In our previous recent study, the prevalence of tissue transglutaminase antibody positivity in Turkish healthy blood donors was 1.3%, indicating a high prevalence of CD in our population. In this study, the cumulative frequency of CD increased more in females than males. With the better understanding and increased suspicion of the disease, more patients are being diagnosed in our population.

KEY WORDS: celiac disease; symptom; comorbidity; endoscopy, histopathology.

Celiac disease (CD) is characterized by malabsorption of nutrients by the small intestine following the ingestion of wheat gluten or related proteins from rye, oat, and barley; characteristic villous atrophy of the small intestinal mucosa; clinical and histological recovery after a gluten-free diet; and clinical relapse after the reintroduction of gluten (1–3). Levels of antibodies against gliadin, endomysium, reticulín, tissue transglutaminase (tTG), and jejunum are high in the sera of CD patients (4). The availability of highly specific and sensitive serologic tests has facilitated the diagnosis of CD (3). The disease is common and can be diagnosed at any age (5, 6).

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From the Departments of *Internal Medicine, †Gastroenterology, and ‡Pathology, Hacettepe University Medical Faculty Hospital, Ankara, Turkey.

Address for reprint requests: Rengin Elsurer, MD, Department of Internal Medicine, Hacettepe University Medical Faculty Hospital, Kültür Mah. Galdiran Sok. Park Apt. 11/1, Ankara 06420, Turkey; renginels@hotmail.com.

The disease shows marked geographic variation, with the highest incidence in western Europe (1). In population-based screening studies, the disease prevalence is found to be between 2.3 and 5.57‰ (7–10). To estimate the prevalence of CD in the population, screening of the blood donors was carried out and the reported prevalence was 1.47–6‰ (11–15). In our recent study, the prevalence of tissue transglutaminase antibody positivity in Turkish healthy blood donors was 1.3%, indicating a high prevalence of CD in our population. In the present study, we evaluate the characteristics of the presentation of CD and determine the clinical, laboratory, and histopathological features of the disease in Turkish adults.

SUBJECTS AND METHODS

Between 1968 and 2002, the hospital records of 45 CD patients presenting to the Gastroenterology Unit were evaluated

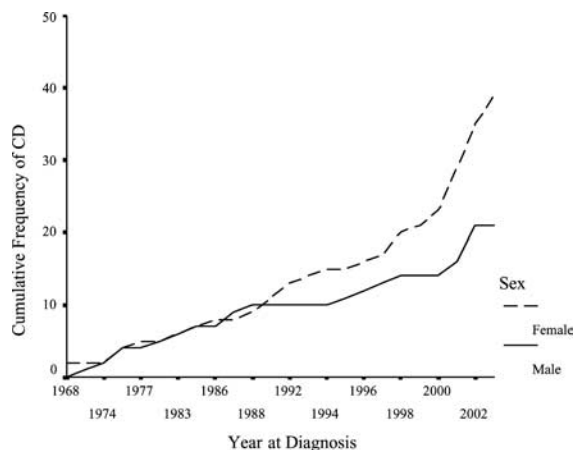


Fig 1. Cumulative frequency of CD over the years in females and males.

retrospectively. From 2002, 15 newly diagnosed patients were prospectively followed up. The age at diagnosis, weight, height, body mass index, hepatosplenomegaly and for females, years after menopause, if present, were noted. Symptoms at disease presentation, presence of associated diseases in CD patients and their relatives and serum biochemical parameters and 24-hr fat excretion in stool were recorded. Esophagogastroduodenographic findings, endoscopic mucosal changes, and histopathological findings were evaluated. Mortality due to CD in the hospital records was also noted.

Statistical Analysis. Independent-sample *t* test and Mann-Whitney *U* test were used to compare the two groups of patients, females and males.

RESULTS

Sixty patients were included in the study. Of these, 39 (65.0%) were female and 21 (35.0%) were male, with a predominance of females. The cumulative frequency of CD over years seemed to increase more in females than males (Figure 1).

The characteristics of female and male CD patients are listed in Table 1. Of 39 females, 28 were married (71.8%), and of 21 males, 13 (61.9%) were married. Although the mean age at diagnosis of females (39.7 ± 14.8 years) was higher than that of males (33.4 ± 13.6 years), the difference was not statistically significant. The mean body mass index (BMI) of the CD patients was 22.2 ± 5.4 kg/m². The

TABLE 1. CHARACTERISTICS OF FEMALE AND MALE CD PATIENTS*

	Females (n = 39)	Males (n = 21)
Mean age at diagnosis (yr)	39.7 ± 14.8	33.4 ± 13.6
Height (cm)	157.5 ± 8.9	168.7 ± 8.9
Body weight (cm)	54.5 ± 15.1	60.7 ± 14.2
Body mass index (kg/m ²)	21.7 ± 4.9	23.0 ± 6.3
Number of siblings	1.3 ± 0.5	1.4 ± 0.5

*All parameters are expressed as mean ± SD.

TABLE 2. SYMPTOMS AND SIGNS OF FEMALE (n = 39) AND MALE (n = 21) CD PATIENTS

	Females, no. (%)	Males, no. (%)
Diarrhea	26 (66.7)	14 (66.7)
Weight loss	20 (51.3)	11 (52.4)
Flatulence	18 (46.2)	7 (33.3)
Nausea	18 (46.2)	6 (28.6)
Aphthous oral lesions	4 (10.3)	3 (14.3)
Growth retardation	3 (7.7)	4 (19.0)
Eruptions	7 (17.9)	4 (19.0)
Infertility	0 (0.0)	1 (4.8)

mean BMIs of female and male CD patients did not differ significantly. Of nine females, six were postmenopausal and the mean number of years after menopause was 6.3 ± 5.13 years.

The most common symptoms of 60 CD patients were diarrhea (66.7%), weight loss (50.0%) and flatulence (48.3%). Five (8.3%) of 60 patients had a history of fracture; none of the CD patients had a history of infertility. The incidences of hepatomegaly and splenomegaly were 3.3 and 5.0% respectively. The symptoms and signs of female and male CD patients are listed in Table 2. The frequency of symptoms and signs of female and male CD patients did not differ significantly.

Of the 60 CD patients, 27 females (69.2%) and 8 males (25.8%) had accompanying comorbidities. The presence of comorbidities did not differ significantly between the sexes. The most common comorbidities (excluding parasite infestations) were anemia (33.3%), osteoporosis (16.7%), type 1 diabetes mellitus (DM) (6.7%), and steatohepatitis (6.7%). The frequencies of comorbidities in adult Turkish CD patients are listed in Table 3.

TABLE 3. FREQUENCIES OF COMORBIDITIES IN ADULT TURKISH CD PATIENTS (n = 60)

Comorbidity	Number of CD patients (%)
Anemia	20 (33.3)
Osteoporosis	10 (16.7)
Parasitic infestations	6 (10.0)
Steatohepatitis	4 (6.7)
Diabetes mellitus type 1	4 (6.7)
Hashimoto's thyroiditis	3 (5.0)
Osteomalacia	3 (5.0)
Hypocalcemia	2 (3.3)
Allergic rhinitis	2 (3.3)
Crohn's disease	1 (1.7)
Glomerulonephritis	1 (1.7)
Behçet's disease	1 (1.7)
Turner's syndrome	1 (1.7)
Asthma	1 (1.7)
Sjögren's syndrome	1 (1.7)
Discoid lupus erythematosus	1 (1.7)
Primary amenorrhea	1 (1.7)
Vitamin D deficiency	1 (1.7)

TABLE 4. FREQUENCIES OF DISEASES FOUND IN THE FAMILY HISTORY (*n* = 60)

Disease positive in family history	Number of CD patients (%)
Diabetes mellitus	6 (10.0)
Gastric cancer	3 (5.0)
Colon cancer	3 (5.0)
Colitis	1 (1.7)
Atopy	1 (1.7)
Anemia	1 (1.7)
Celiac disease	1 (1.7)

The most common disease in the family history of CD patients was DM, followed by gastric and colonic cancer. Of the 60 CD patients, 6 (10.0%) had a family history of DM. Only one patient (1.7%) had a family history of CD. The frequencies of diseases found in the family history are listed in Table 4.

The plasma glucose levels, serum transaminases, electrolytes, lipid profile and mean hemoglobin values were evaluated. The plasma glucose levels and serum γ -glutamyltransferase (GGT) levels were significantly higher in females than males ($P = 0.016$ and $P = 0.04$, respectively). The serum biochemical parameters and 24-hr excretion of fat in the stool are listed in Table 5. The amount of 24-hr fat excretion in stool did not differ significantly between the sexes.

Of the 60 CD patients, 23 had undergone radiological examination of the upper gastrointestinal system by means of esophagogastroduodenography. The most common finding was edema of the small intestinal segments, which was reported in 69.6% of 23 patients. Flocculation

TABLE 6. ESOPHAGOGASTRODUODENOGRAPHIC FINDINGS FOR 23 CD PATIENTS

	Number of CD patients (%)
Edema	16 (69.6)
Flocculation	4 (17.4)
Benign lymphoid hyperplasia	4 (17.4)
Dilatation of segments	4 (17.4)
Segmentation	2 (8.7)
Shortened passage	1 (4.3)
Nodular filling defects	1 (4.3)
Bulbar narrowing	1 (4.3)
Loss of contours	1 (4.3)
Mucosal thickening	1 (4.3)
Prominent valvula conniventes	1 (4.3)
Duodenitis	1 (4.3)
Others	2 (8.7)

and benign lymphoid hyperplasia were present in 17.4% of CD patients. Two (8.7%) of the 23 patients had normal radiological findings. The results of the radiological examination are listed in Table 6.

Thirty-three of 60 CD patients had available endoscopic findings in the hospital records. Three of the 33 CD patients had normal endoscopic findings. Two of the patients had roughening or loss of pili. Gastritis was the most common endoscopic finding. These changes were followed by hyperemia and nodularity of the mucosa. The endoscopic findings of the mucosal changes of CD are summarized in Table 7.

Of the 60 CD patients, 42 had duodenal biopsies available in hospital records. The histopathological changes in the biopsies were noted. The most common histopathological findings were increased lymphocytes in the lamina

TABLE 5. BIOCHEMICAL PARAMETERS AND 24-HR FAT EXCRETION OF CD PATIENTS IN MALE AND FEMALE CD PATIENTS*

	Females (n = 39)	Males (n = 21)
Plasma glucose (mg/dl)†	86.5 (66–163)	76.5 (52–102)
Alanine aminotransferase (U/L)	27.0 (10–167)	38.0 (10–88)
Aspartate aminotransferase (U/L)	30.0 (12–284)	35.0 (14–120)
Alkaline phosphatase (U/L)	177.0 (16–1845)	148.0 (6–519)
γ -Glutamyltransferase (U/L)‡	16.0 (9–479)	13.0 (8–24)
Total bilirubin (mg/dl)	0.46 (0.1–5.5)	0.52 (0.13–5.5)
Calcium (mg/dl)	8.9 (6.4–10.2)	8.7 (7.5–10.1)
Phosphorus (mg/dl)	3.5 (0.9–5.1)	3.45 (2.1–5.3)
Albumin (g/dl)	3.9 (2.0–4.8)	3.7 (1.8–4.3)
Parathyroid hormone (pg/ml)	43.3 (24.4–516.2)	48.1 (34.9–263.0)
25-Hydroxy vitamin D (ngr/ml)	21.9 (0.6–46.9)	15.5 (3.5–59.4)
Triglycerides (mg/dl)	76.0 (37–475)	80.0 (59–458)
Total cholesterol (mg/dl)	144.0 (68–196)	115.0 (84–167)
Hemoglobin (g/dl)	11.7 (7.0–15.1)	12.4 (4.4–16.5)
24-hr fat excretion in stool (g/day)	11.17 (2.0–58.0)	15.3 (9.1–56.9)

*All parameters are expressed as median (minimum–maximum) values.

† $P = 0.016$.

‡ $P = 0.04$.

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TABLE 7. ENDOSCOPIC FINDINGS FOR MUCOSAL CHANGES OF 33 CD PATIENTS

	<i>Number of CD patients (%)</i>
Gastritis	12 (36.4)
Hyperemia	11 (33.3)
Nodularity	9 (27.3)
Edema	8 (24.2)
Duodenitis*	7 (21.2)
Paleness	6 (18.2)
Atrophy	4 (12.1)
Roughness	2 (6.1)

*Grade I duodenitis in five patients, grade III in one patient, and grade IV in one patient.

propria (76.2%) and increased intraepithelial lymphocytes (IEL) in the villi (59.5%) (Table 8).

Of 60 CD patients, two (3.3%) patients died.

DISCUSSION

The interaction of gluten with the mucosa of the small intestine in susceptible persons is central to the pathogenesis of CD. In genetically susceptible individuals, an abnormal immunological response occurs to the gluten ingested in food. The local activation of CD4 + T lymphocytes results in mucosal damage (1, 3, 4). Various environmental, genetic, and immunological factors are involved in the disease progression (1, 4).

Antibodies against gliadin (AGA), endomysium (EMA), reticulín, tissue transglutaminase (tTG), and jejunum are found at high levels in the sera of CD patients. The serological tests used for diagnosis of the disease are IgA EMA and IgA tTG antibodies against tTG antigen and IgA AGA and IgG AGA antibodies against gliadin (1, 4). In a study by Dahele *et al.*, it was reported that more CD patients are diagnosed with the combined usage of the serological tests, with IgG AGA and IgA anti-tTG (93%) or IgA EMA (96%) combination having the highest sensitivity (16). There is no superiority of the IgA anti-tTG and IgA EMA tests in screening (16, 17). In our recent study, IgA anti-tTG and IgG anti-tTG were used to screen

TABLE 8. HISTOPATHOLOGICAL FINDINGS FOR 42 CD PATIENTS

	<i>Number of patients (%)</i>
Increased no. of lymphocytes in the lamina propria	32 (76.2)
Increased no. of IEL* in the villi	25 (59.5)
Subtotal villous atrophy	20 (47.6)
Mucosal flattening	18 (42.9)
Total villous atrophy	15 (40.5)

*Intraepithelial lymphocytes.

for CD in healthy blood donors and the prevalence of IgA anti-tTG or IgG anti-tTG positivity was 1.3%. The high antibody positivity prevalence showed that the prevalence of CD is high in our population (18).

Celiac disease is common in adults as well as in children and the diagnosis may be at any age (5,6). Most CD patients are diagnosed in childhood or early adulthood. Twenty percent of the CD patients are more than 60 years of age at the time of diagnosis (4). In our study, four patients (6.7%) were 60 years or older, indicating that the disease is diagnosed at relatively early ages in our population. The mean age at diagnosis was slightly higher in females than males. This difference may possibly be due to underestimation of some of the extraintestinal features of the disease (iron deficiency anemia, osteoporosis) seen in females. In this study, females seemed to have more comorbidities than males. Celiac disease is more common in women than men, but studies have shown that both sexes might be equally affected (1,3,4). This study shows that in our population, females with CD predominate. The cumulative frequency of CD over years increased more in females than males.

The incidence of CD in first-degree relatives of the CD patients is 8–18%. The incidence in monozygotic twins increases to 70% (1,19). Celiac disease is related to a specific HLA class II DQ haplotype (1). Celiac disease is primarily related to the HLA-DQ α 1*0501 and DQ1 β *0201 genes coding the DQ2 molecule (5,20). The HLA-DQ heterodimer (α 1*501, β 1*0201), known as HLA-DQ2, is found in 95% of the CD patients. In most of the remaining patients, the HLA-DQ heterodimer (α 1*0301, β 1*0302), known as HLA-DQ8, is found (1,3–5). Although CD is strongly related with HLA, only a small number of individuals expressing DQ develop the disease. The HLA-DQ, which is expressed in 25–30% of the normal population, contributes to the disease development in only 36%. Another gene(s), which is (are) probably inherited autosomal recessively at non-HLA loci, likely has (have) a role in the development of the disease (1, 4, 5). In this study, the incidence of CD in first-degree relatives of CD patients was found to be 1.7%. This is probably influenced by both HLA and non-HLA gene(s) expression in our population.

Celiac disease affects the mucosa, usually sparing the submucosa, muscularis mucosa and serosa. In untreated patients, mucosa is flattened and the normal villous architecture is lost. Mitotic activity and the number of undifferentiated cells are markedly increased and the crypts get longer (1, 19). Marsh first described the progression of the small intestinal lesions in 1992. Type 0 (preinfiltrative) lesion describes the normal small intestinal mucosal appearance. In type 1 (infiltrative) lesions, the normal mucosal structure is preserved and small, nonmitotic lymphocytes

(intraepithelial lymphocytes [IEL]) infiltrate the villous epithelium followed by lymphocytic infiltration of the lamina propria, which is not related to the increased permeability, malabsorption, and gastrointestinal symptoms. In type 2 (hyperplastic) lesion, crypts enlarge and small, nonmitotic IEL infiltration in the crypt epithelium is seen. Typically flattened mucosal lesions and villous atrophy are the hallmarks of the type 3 (destructive) lesion, which is found in most of the symptomatic individuals. The type 4 (hypoplastic) lesion is characterized by total villous atrophy, increased apoptosis, and crypt hyperplasia, which is irreversible (1, 21). Mucosal flattening may not be seen in all gluten-sensitive individuals; however, in individuals in whom mucosal flattening is seen, the above-mentioned lesions occur consequently (21). In our study, villous atrophy, either subtotal or total, was less frequent than the increase in the number of lymphocytes in the lamina propria and villi, which are seen primarily in early lesions.

The malabsorption due to the enteropathy may lead to various hematological and biochemical changes. Iron deficiency anemia (IDA) is common in both children and adults (1,3). Celiac disease is the most frequent malabsorptive disease leading to IDA and is seen in 10% of patients admitting to gastroenterology clinics for this reason (22, 23). Iron deficiency anemia may be the only major finding in 45% of subclinical CD patients (24). The decrease in the mucosal absorptive surface, changes in the brushed border and insufficiency of the transporters in the remaining enterocytes result in decreased absorption of iron. Rapid exfoliation of enterocytes and occult blood loss increase the iron deficiency (25). IDA patients who have accompanying CD are younger and have lower hemoglobin levels and a longer history of anemia (more than 3 years) than those without CD (26). In this study, anemia was the most common comorbidity, found in 33.3% of CD patients. This high incidence emphasizes that in patients with anemia, either refractory or not, CD must be excluded.

Hepatic damage is a frequently encountered finding in CD. Hypertransaminasemia is found in 10–54% of CD patients at the time of diagnosis (27). Idiopathic chronic hepatitis may occasionally be the initial finding. A gluten-free diet provides complete remission in all patients, reversing the biochemical and histological changes of hepatitis (28). In our study sample, steatohepatitis was found in 6.7% of CD patients and serum GGT levels were significantly higher in females than males.

Barium radiographs of the small intestine are most useful for the diagnosis of pathologies other than CD (Crohn's disease, scleroderma, diverticulosis). The findings of CD in barium radiographs are dilatation of the small intestine,

thickening or loss of the mucosal folds, flattening of the valvula conniventes, segmentation, and flocculation (1, 6). In this study, radiological examination was performed in 38.3% of CD patients. The most common radiographic findings were edema and dilatation of the small intestinal segments, flocculation, and benign lymphoid hyperplasia.

Upper endoscopy enables examination of the gastrointestinal system and multiple biopsy, sampling and is preferred to capsule biopsy, especially in older children and adults (1, 2, 4, 6). Endoscopic changes of CD seen in the duodenum are a decrease in the number of duodenal folds and scalloping, presence of fissures, micronodularity, and an increase in vascularity (29). In our study population of CD patients, the most pronounced mucosal changes were gastritis, hyperemia, and nodularity.

Bone mineral density is almost always low in untreated CD patients and routine screening of all CD patients with dual energy X-ray absorptiometry (DEXA) is recommended (2, 6). The incidences of osteopenia and osteoporosis in CD patients are 30–50 and 5%, respectively (30, 31). Osteopenia has also been found in individuals with latent gluten sensitivity, demonstrating that bone loss may precede any other symptoms of gastrointestinal disease. Bone mineral density may even be lower in clinically silent patients than in symptomatic CD patients (31). The bone mass of CD patients is inversely related to the age at diagnosis of the disease (32). In our study sample, the incidence of osteoporosis was 16.7%, which is a much higher incidence than in the literature. This may be due to a delay between the gastrointestinal disorder and the development of symptoms or between the onset of clinical manifestations and the correct diagnosis. In a study by Meyer *et al.*, it was reported that premenopausal women are least likely to have osteoporosis or low bone mass versus postmenopausal women and men. Men are more severely affected than either group of women; endogenous estrogen may protect against at least some of the bone loss associated with CD (32). The most important factor in the development of osteoporosis is the malabsorption of calcium (33). Long-lasting malabsorption of calcium may lead to secondary hyperparathyroidism, which worsens the osteopenia (2, 19). Secondary hyperparathyroidism may also increase the catabolism of vitamin D (31). Amenorrhea and early menopause, which are frequently encountered in women with CD, are other risk factors for the development of osteopenic bone disease (33). In our study sample, six females were postmenopausal; the incidence of osteoporosis did not differ significantly between males and females. The incidence of fracture is highest between the third–fourth and the sixth–seventh decades of life. The most common sites of fracture are the wrist and the radius. Early diagnosis and

treatment of CD is the most important issue in prevention of fractures (34).

In CD patients, menarche is delayed and menopause takes place in earlier ages, shortening the period of fertility (33). Amenorrhea is seen in one-third of women. Celiac disease is diagnosed in 4–8% of women without a known cause of infertility. It is common for infertile women with CD to become pregnant shortly after beginning a gluten-free diet (1, 2). Men with untreated CD may also present with infertility and impotence (19). In this study, none of the CD patients had accompanying infertility, which may be an indirect result of the low tendency of patients to undergo an infertility workup due to traditions.

Celiac disease is more common in children and adults with type 1 DM and their first-degree relatives. The prevalence of CD in type 1 DM patients is 1.4–3.5% and recent studies have shown that the prevalence has increased to 5.4–7.4% (33, 35). Type 1 DM is more frequent in untreated and undiagnosed CD patients (35). Both CD and type 1 DM share common genetic factors (HLA DR3-DQ2 and DR4-DQ8) involving the HLA region. The presence of organ specific antibodies, T-lymphocytic infiltration, and environmental factors in the etiology support the opinion that similar autoimmune pathogenic mechanisms are involved in both diseases (33, 35). In patients in whom both CD and DM are present, most of the CD patients (60%) are diagnosed at the time of the diagnosis of type 1 DM. In patients in whom autoimmunity of CD is not found at the time of the diagnosis, CD develops during follow-up (40%), usually in the following 4 years (36). There is no correlation between EMA positivity and age, sex, diabetic complications, duration of DM, or gastrointestinal symptoms (37). In our study, the incidence of type 1 DM in CD patients was 6.7%. One difference between both sexes was higher plasma glucose levels in female CD patients than in males.

Celiac disease may coexist with a range of autoimmune disorders. Long-standing CD, even clinically silent, predisposes for other autoimmune disorders. The prevalence of autoimmune disorders in CD is higher with increasing age at diagnosis of the patient and is directly related to the duration of exposure to gluten (38). Autoimmune diseases are more frequent (35.7%) in patients with both type 1 DM and CD than in those with DM alone (6.3%) (35). Autoimmune thyroid disease is more frequent in CD patients (men more than women) (33). Clinical and subclinical autoimmune thyroid diseases are detected in 13.9 and 10.1% of CD patients, respectively. Celiac disease is increased 5- to 10-fold in patients with autoimmune thyroid diseases than in the normal population. The development of manifest thyroid disease is not affected by the

duration of gluten exposure (39). Collagen tissue diseases (systemic lupus erythematosus, Sjögren's syndrome) are also more frequent in CD patients (1, 2). In our study, Hashimoto's thyroiditis and type 1 DM were the most commonly encountered autoimmune diseases.

The mortality is increased twofold in CD. The increase in mortality is more pronounced in the first 3 years and in patients presenting with signs of malabsorption. Mortality is not increased in patients presenting with minor symptoms or in patients in whom the disease is diagnosed by serological screening. Delayed diagnosis or in adherence to a gluten-free diet increases the mortality. The most important reasons for death are malignancies, mostly non-Hodgkin lymphoma. The mortality of CD in our study was 3.3%. A strict gluten-free diet decreases the mortality and improves the quality of life, even in asymptomatic patients (40).

In conclusion, CD has a wide spectrum of findings including both gastrointestinal and extraintestinal systems (2, 19). Atypical or extraintestinal features result from malabsorption of nutrients and involve virtually all organ systems (2). With better recognition of the disease presentation, it is expected that the number of diagnosed cases will increase, increasing the disease prevalence. This is the first study in the literature showing the presentations of CD in the adult Turkish population. The cumulative frequency of CD over the years seemed to increase more in females than in males in our population.

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