







■ Original Article

The Invisible Part of "ICEBERG": Extraintestinal Findings and Celiac Disease

Buzdağının Görünmeyen Yüzü: Ekstraintestinal Bulgular ve Çölyak Hastalığı

Serdar Karakaya*¹ , İbrahim Karadag² , Aslihan Mete Yıldırım³ , Oktay Bulur⁴ , Metin Uzman⁵ ,
Esin Beyan⁶ 

¹Sanatorium Atatürk Chest Disease and Thoracic Surgery Education and Research Hospital, Department of Medical Oncology, Ankara/ TURKEY

²Hittite University Erol Olcok Education and Research Hospital, Department of Oncology, Çorum / TURKEY

³Malatya Education and Research Hospital, Department of Internal Medicine, Malatya/ TURKEY

⁴Cumhuriyet University Faculty of Medicine, Department of Gastroenterology, Sivas/ TURKEY

⁵Kecioren Education and Research Hospital, Department of Gastroenterology, Ankara/ TURKEY

⁶Kecioren Education and Research Hospital, Department of Internal Medicine, Ankara/ TURKEY

ABSTRACT

Aim: Clinical manifestations of celiac disease (CD) can be quite different and varying. The number of CDs presenting with atypical symptoms is increasing day by day. Hence, we aimed to determine how many patients with CD were atypical celiac through examining their admission complaints, clinical characteristics, laboratory results, endoscopic findings, and pathological findings.

Material and Methods: Eighty-nine patients with CD aged over 18 years who were followed-up in Ankara Kecioren Training and Research Hospital Internal Medicine Clinic between 2007 and 2014 were included in the study. The files of the patients were reviewed retrospectively. Sex, age, hospital admission complaints, clinical characteristics, laboratory results, endoscopy findings, and pathology results of the patients were recorded.

Results: The median age of the patients in the study was 36, and 68.5% of them were female. The most common symptoms of the patients were fatigue (49.4%), anorexia (33.7%), and dyspepsia (22.5%), while diarrhea (19.1%), which is among the classical symptoms, was less common. 7.8% of the patients had no complaints at the time of admission, whereas 47.1% of them had only extraintestinal symptoms. At admission, 47% of the patients had anemia, 73.4% had iron deficiency, and 55.4% of them had vitamin B12 deficiency. When hemoglobin, ferritin, and vitamin B12 levels were compared before and after a gluten-free diet, a significant increase was determined. Transaminase elevation was detected in 25.3% of our patients at the time of diagnosis. When pre-treatment and post-treatment values were compared, a significant decrease was determined in those with high transaminase levels. In the pre-treatment serological test results of the patients, Ig A EMA positivity was the most common finding with a rate of 90.2%, followed by IgG EMA with 88.9%. In terms of pre-treatment endoscopy findings, 50.2% of our patients had normal appearance, 25.4% had a mosaic pattern, 12.6% had effacement of the duodenal folds, 12.6% had a nodular appearance, and 9.5% had a scalloping of the duodenal folds. When the pathology results of our patients were examined, 83.4% of them were at the advanced stage and with Marsh Type 3.

Conclusion: CD may present with atypical complaints such as extraintestinal findings, as in more than half of the patients in this study. Celiac disease should be taken into consideration, particularly in conditions such as iron deficiency, osteoporosis, and transaminase elevations, which are prevalent in the community. The prevalence of CD in our country is estimated to be around 1-2%; however, it is considered that there are more asymptomatic patients with atypical celiac disease. When diagnosing CD, the most crucial step is to consider the potential presence of CD during pre-diagnoses. Thus, CD should be included in the differential diagnosis, specifically in patients presenting with atypical symptoms.

Keywords: celiac disease; diagnosis; anemia.

Corresponding Author*: Serdar Karakaya, Sanatorium Atatürk Chest Disease and Thoracic Surgery Education and Research Hospital, Department of Medical Oncology, Ankara/ TURKEY

E-mail: drserdarkarakaya@gmail.com

ORCID: 0000-0002-2111-7131

Received: 21.12.2021 accepted: 24.12.2021

Doi: 10.18663/tjcl.1039075

ÖZ

Amaç: Çölyak hastalığı (ÇH) kliniği oldukça farklı ve değişken olabilir. Atipik semptomlarla başvuran ÇH sayısı gün geçtikçe artmaktadır. Bu nedenle ÇH tanısı alan bireylerin hastaneye başvuru şikayetleri, klinik özellikleri, laboratuvar bulguları, endoskopik bulguları, patolojik bulguları inceleyerek hastaların ne kadarının atipik çölyak olduğunu saptamayı amaçladık.

Gereç ve Yöntemler: Çalışmaya Ankara Keçiören Eğitim ve Araştırma Hastanesi İç Hastalıkları kliniğine 2007-2014 tarihleri arasında takip edilen 18 yaş üstü tüm ÇH tanısı alan 89 hasta dahil edildi. Hastaların dosyaları retrospektif tarandı. Hastaların cinsiyetleri, yaşları, hastaneye başvuru şikayetleri, klinik özellikleri, laboratuvar tetkikleri, endoskopi bulguları, patoloji sonuçları kaydedildi.

Bulgular: Çalışmadaki hastaların median yaşı 36 ve % 68.5'i kadındı. Hastalarda en sık halsizlik (%49.4), iştahsızlık (%33.7) ve dispepsi (%22.5) görülürken klasik semptomlardan diare (%19.1) daha az sıklıkla görüldü. Hastaların %7.8'inde başvuru anında herhangi bir şikayeti yokken %47.1'inde yalnızca ekstraintestinal semptomlar mevcuttu. Başvuruda hastaların %47'sinde anemi, %73.4'ünde demir eksikliği, %55.4'ünde vitamin B12 eksikliği vardı. Glutensiz diyet öncesi ve sonrası hemoglobin, ferritin, vitamin B12 değerleri karşılaştırıldığında istatistiksel anlamlı artış saptandı. Hastalarımızın tanı anında %25.3'ünde transaminaz yüksekliği saptandı. Tedavi öncesi ve sonrası karşılaştırıldığında transaminaz seviyesi yüksek olanlarda istatistiksel anlamlı düşüş gözlemlendi. Hastaların tedavi öncesi serolojik testlerinde en sık Ig A EMA %90.2, Ig G EMA %88.9 pozitifliği vardı. Hastalarımızın tedavi öncesi endoskopi bulguları %50.2 normal görünüm, %25.4'ünde mozaik patern, %12.6'sında foldlarda silinme, %12.6'sında nodüler görünüm ve %9.5'inde tarak sırtı görünümü mevcuttu. Hastalarımızın patoloji raporları incelendiğinde %83.4'ü ileri evre olup Marsh Tip 3'tü.

Sonuç: Sonuç olarak ÇH bu çalışmadaki hastaların yarısından fazlasında olduğu gibi extraintestinal bulgular gibi atipik şikayetlerle başvurabilir. Özellikle toplumda sık görülen demir eksikliği, osteoporoz, transaminaz yükseklikleri gibi durumlarda çölyak hastalığı göz önünde bulundurulmalıdır. Ülkemizde ÇH prevalansının %1-2 civarında olduğu tahmin edilmekte ancak bundan daha fazla atipik çölyak hastalığı asemptomatik hastaların olduğu düşünülmektedir. ÇH tanı koyarken en önemli aşama ön tanılarda akılda bulundurmalıdır. Bu yüzden özellikle atipik semptomlarla başvuran hastalarda ÇH ayırıcı tanılar arasında bulundurulmalıdır.

Anahtar Kelimeler: çölyak hastalığı; teşhis; anemi.

Introduction

Celiac disease (CD) is a chronic inflammatory illness of the small bowel that can progress with gastrointestinal and/or extra-gastrointestinal symptoms and occur in genetically predisposed individuals with the impact of environmental factors [1]. It can occur at any age, from early childhood to adulthood. The gold standard in the diagnosis of the disease is small bowel biopsy. It is diagnosed with intraepithelial lymphocyte increase, crypt hyperplasia, and villous atrophy findings in the small intestine (SI) mucosa [2]. Yet, before having SI biopsy, antigliadin antibody (AGA), anti-tissue transglutaminase antibody (anti-tTG), and/or anti-endomysium antibody determination, which is the first step in the diagnosis, is of great importance [3]. After diagnosis, these antibody levels are expected to decrease or disappear completely with a strict gluten-free diet, which is crucial for follow-up.

The clinical manifestation of CD may be remarkably diverse and

variable. The disease is categorized as classic celiac, atypical celiac, silent celiac, and latent celiac. In classical celiac disease, findings related to malabsorption are prominent. Atypical CD includes only minor gastrointestinal symptoms. These patients may have symptoms such as anemia, dental enamel dysplasia, osteoporosis, arthritis, elevated transaminases, neurological symptoms, and infertility [4,5]. Albeit sometimes minor symptoms such as fatigue occur in silent celiac disease, no major symptoms occur. In latent celiac disease, there is normally small intestinal mucosa and no symptoms. In recent years, it has been understood that types other than classical celiac disease are much more common than previously thought.

It is well-documented that CD, which was previously considered to be a rare disease of north-western Europe, is very common across the world, and occurs in various societies at an average prevalence of 0.3-1% [6,7].

Although population-based screening is conducted in limited groups of adults in our country, there is no comprehensive study. The prevalence of CD has ranged from 1% to 2% in studies [8]. The majority of the studies rather reflect classical celiac outcomes. Hence, we aimed to analyze the admission complaints, clinical characteristics laboratory findings requested during routine examinations, endoscopic findings, and pathological findings of patients diagnosed with CD who presented to our clinic with different complaints and to find out how much of the patients had atypical celiac disease.

Materials and Methods

Of the 145 patients over the age of 18 who were followed up in Ankara Kecioren Training and Research Hospital between 2007 and 2014 with a diagnosis of CD, 89 patients whose data could be accessed were included in this retrospective study. To carry out the study, ethical approval was obtained from the Ankara Kecioren Training and Research Hospital Ethics Committee with the decision numbered B.10.4.ISM.4.06.68.49 on April 08th, 2015. Patients with positive serology and pathology were considered celiac. In addition to that, patients whose diagnoses were supported serologically and pathologically in external centers and followed up in our hospital were included in our study. The files of the patients were reviewed retrospectively. Demographic data, hospital admission complaints, clinical characteristics, laboratory tests, endoscopy findings, and pathology results of the patients were noted down. Pathology reports were classified based on the Modified Marsh staging. The collected data were analyzed by frequency analysis. Statistical analysis was conducted via the software of SPSS 15.0.

Results

The median age of the patients in the study was 36 (18-85 years) and 68.5% (n=61) were female. The complaints of the patients are summarized in Table 1, and the most common symptoms were fatigue with 49.4% (n=44), anorexia with 33.7% (n=30), dyspepsia with 23.6% (n=21), and nausea with 22.5% (n=20). 15.7% (n=14) of the patients were diagnosed with celiac disease when investigating the etiology of osteoporosis, 2.2% (n=2) of the patients were diagnosed with celiac disease when investigating the etiology of growth and developmental retardation, and 15.7% (n=14) when investigating the etiology of elevated transaminases. Only extraintestinal symptoms were present in 47.1% (n=42) of the patients.

Table 1. Hospital admission complaints

Complaints	Percent (%)
Weakness	49.4 (n=44)
Decreased appetite	33.7 (n=30)
Dyspepsia	23.6 (n=21)
Nausea	22.5 (n=20)
Diarrhea	19.1 (n=17)
Transaminase Elevation	15.7 (n=14)
Constipation	12.4 (n=11)
Vomiting	10.1 (n=10)
Muscle Weakness	1.1 (n=1)
Patients With Only Extraintestinal Symptoms	47.1 (n=42)

Anemia was present in 47% of the patients at the time of admission (n=42). Anemia was detected in 20% of the 70 patients whose follow-up hemoglobin values could be reached after their treatment was regulated and dietary recommendations were made (n=14). When 70 patients with pre-treatment and post-treatment hemoglobin values were compared, a significant increase was determined in hemoglobin level ($p < 0.0001$). Thrombocytosis was detected in 14.6% (n=13) of the patients before the gluten-free diet, while thrombocytopenia was found in 4.5% (n=4). After the treatment, thrombocytosis was detected in 4.5% (n=4) of the patients, whereas thrombocytopenia was not detected. When the pre-treatment and post-treatment values were compared, a significant decrease was observed in high platelet levels ($p = 0.04$).

Ferritin level was found to be lower in 73.4% (n=58) of 79 patients who had ferritin values before the gluten-free diet, and when 49 patients with post-gluten-free diet data were analyzed, ferritin levels were found to be lower in 28.6% (n=14). A significant increase was determined in ferritin level after a gluten-free diet ($p < 0.0001$). When 74 patients with vitamin B12 levels at the time of admission were analyzed, vitamin B12 deficiency was detected in 55.4% (n=41) of them. Besides, when 56 patients who had a folate level at the time of admission were analyzed, folate deficiency was found in 8.9% (n=5) of the patients. Vitamin D levels were found to be lower in 96.1% (n=49) of the 51 patients whose pre-gluten-free diet data were available. When 24 patients with vitamin D data before and after the gluten-free diet were evaluated, an increase was observed in vitamin D levels of all patients ($p < 0.0001$). Moreover, osteoporosis was detected in 15.7% (n=14) of 89 patients included in the study. Pre gluten-free diet coagulation parameters of the patients were reviewed. INR (international normalized ratio > 1.2) was found to be higher in 16.2% (n=6) of 37 patients whose data could be accessed from their files.

Corrected calcium levels of the patients before gluten-free diet were analyzed. Hypocalcemia (Ca<8.8 mg/dl) was detected in 22.7% (n=15) of the 66 patients whose data were available before the diet. Hypocalcemia was detected in only 3.1% (n=1) of 32 patients whose follow-up calcium value was reached after a gluten-free diet. When 32 patients with pre-and post-treatment data were compared, an increase in calcium levels in 26 patients, a decrease in calcium levels in 4 patients, and no change in 2 patients were found (p<0.0001). The pre-treatment albumin levels of the patients were analyzed. Hypoalbuminemia (albumin<3.5 g/dl) was detected in 15.1% (n=11) of 73 patients whose data could be accessed. On the other hand, after the gluten-free diet, it was observed that the hypoalbuminemia status of these patients completely improved.

The pre-gluten-free diet transaminase levels of the patients were analyzed. Of these patients, 25.3% (n=22) had elevated AST (>35 U/L), while 26.1% (n=23) had elevated ALT (>35 U/L) and 25.3% had elevated ALT and AST values together. Of the patients whose data could be accessed after a gluten-free diet, 12.3% (n=8) had elevated AST, 9.2% had elevated ALT, and 9.2% (n=6) had elevated ALT and AST values together. A significant decrease was observed after a gluten-free diet in patients with elevated ALT and AST levels (p < 0.0001) (Table 2). When the serological tests performed for the diagnosis before the gluten-free diet were analyzed, IgA AGA was studied in 76 patients and it was positive in 81.6% (n=62). IgG AGA was studied in 76 patients and it was positive in 83% (n=63). IgA EMA was studied in 82 patients and it was positive in 90.2% (n=74). IgG EMA was studied in 81 patients and IgG EMA was positive in 88.9% (n=72). IgA tTG was studied in 75 patients and it was detected to be positive in 72% (n=54) of the patients. IgG tTG was studied in 75 patients, and it was detected to be positive in 82.7% (n=62) of the patients.

Table 2: Transaminase levels before and after treatment

	Before Treatment Number of patients	After treatment Number of patients	P value
Elevated ALT	23(26.1)	6(9.2)	<0.0001
Elevated AST	22(25.3)	8(12.3)	<0.0001
Elevated both ALT+AST	22(25.3)	6(9.2)	<0.0001

Abbreviations: ALT: Alanine transaminase AST: Aspartate transaminase

Endoscopy findings before the gluten-free diet were analyzed. On endoscopy, 50.8% of the patients had normal appearance, 25.4% had mosaic pattern appearance, 12.6% had nodular

appearance, 12.6% had effacement in folds, and 9.5% had ridge appearance. Pathology reports of 78 patients were reached. Median 4 biopsies had been taken from the patients. According to the Modified Marsh staging, 16.6% (n=13) of the patients were type 1, 28.2% (n=22) type 3a, 21.8% (n=17) type 3b, and 33.3% (n=26) type 3c, type 0, type 2 whereas type 4 were absent. In other words, 83.4% (n=65) of the patients were advanced stage type 3 (Table 3). Celiac patients who had been stained for Helicobacter pylori were evaluated. Of 63 patients with data, 50.8% (n=32) had negative H.pylori, 27% (n=17) had weakly positive(+) H.pylori, 17.5% (n=11) had moderately positive (++) H.pylori and 4.8% (n=3) of them had strongly positive(+++) H.pylori. Put it differently, the presence of H.pylori was detected in 49.2% (n=31) of the patients (Table 4). Moreover, atrophy and metaplasia were detected in 1.6% (n=1) of the patients who underwent biopsy.

Table 3: Distribution of patients according to Modified Marsh Staging

Stage	N	%
Type 0	0	0
Type 1	13	16.6
Type 2	0	0
Type 3a	22	28.2
Type 3b	17	21.8
Type 3c	26	33.3
Type 4	0	0
Total	78	100

Table 4. The frequency of H.pylori in our patients

H.pylori	N	%
Negative	32	50.8
+	17	2.7
++	11	17.5
+++	3	4.8
Total	63	100

Discussion

In this study, the median age was 36 years and the female to male ratio was 2.1/1. In a study carried out in the USA on 1032 celiac patients, the mean age was determined to be 55 in males and 50 in females [9]. In a study in which 59 celiac patients were analyzed in our country, the mean age was determined to be 40, and in another study, it was determined to be 39 [10,11]. These studies indicate that celiac disease occurs at an earlier age in our country. It can be predicted that this situation might have been caused by environmental,



dietary, and racial differences. In a study conducted in our country, female predominance was found with a female-male ratio of 3.2/1 [11]. Similar to other studies, there was a female predominance in our study.

The most common complaints of our patients at the time of admission were fatigue, anorexia, and dyspeptic complaints. While diarrhea, one of the classic symptoms of celiac disease, was present in 19.1% of the cases, interestingly, constipation was present in 12.4%. In a study conducted in the USA, fatigue was the most common complaint, similar to our study [9]. Again, in the same study, abdominal pain was the second most common complaint with 77%, while dyspeptic complaints were observed in 37% of the patients, and constipation was observed in 7% [9]. Likewise, in our study, similar rates of dyspeptic complaints and constipation were determined. 7.8% of our patients were asymptomatic. Similarly, in another study conducted in our country, the rate of asymptomatic patients was found to be similar (11%) [11]. In our study, celiac patients with only extraintestinal symptoms comprised 47.1% of our patients. In addition to that, when our asymptomatic patients are included, it is noticed that more than half of our patients actually present with atypical symptoms. In fact, it was revealed in this study that there were more patients presenting with atypical symptoms than expected. The less frequent occurrence of classical symptoms may be due to the increasing incidence of atypical celiac disease and increasing awareness of a wide spectrum for the clinical manifestation of celiac.

15.7% of our patients were diagnosed with the disease while investigating the etiology of elevated transaminases. At the time of admission, 25.3% of our patients had elevated transaminase levels. In another study, transaminase elevation was reported at the rate of 42% at the time of admission [12]. As in our study, improvement in transaminase levels was observed in the patients in this study after the gluten-free diet. Moreover, elevated creatine phosphokinase is also a condition that can be seen in these patients. While elevated creatine phosphokinase is often seen together with elevated transaminases, it was revealed in a study that it was elevated alone at a rate of 7.1% [13]. In one of our patients who presented with the complaint of generalized muscle pain, celiac disease was detected while investigating the etiology of isolated creatine phosphokinase elevation.

Anemia is very common at presentation in celiac disease. The duodenum, which is the part most affected by mucosal injury, is the place where iron absorption is highest. Thus, it is well-known

that these patients are prone to iron deficiency. Vitamin B12 deficiency may develop due to impaired absorption of vitamin B12, particularly in severe cases with ileal involvement. For these reasons, anemia is common in celiac disease. In previous studies, the prevalence of anemia at the time of diagnosis in celiac patients was reported to be 12-69% [14]. Similarly, in a study conducted in our country, the prevalence of anemia was determined to be 46% [15]. In our patient group, the frequency of anemia at the time of diagnosis was 47%, which is consistent with the literature. In a study, vitamin D deficiency was detected in 54% of celiac patients [16]. In studies conducted in our country, vitamin D deficiency was determined to be 69-84% [10,11]. However, in our study, vitamin D deficiency was found with a rate of 96.1%. This difference may be due to the difference in the exposure of our patients to sunlight, geographical conditions, the way they dress, and the low consumption of milk and dairy products. Hypocalcemia due to malabsorption and vitamin D deficiency is seen in celiac patients before treatment. In a study of 42 patients, hypocalcemia was detected in 10% of celiac patients [17]. In our study, hypocalcemia was detected in 22.7% of the patients. This might have been caused by the dietary patterns, the inclusion of only symptomatic hypocalcemia in the other study, and the difference in the number of patients. Hence, it is necessary to evaluate hypocalcemia and symptoms of celiac patients at the time of admission. Osteoporosis is a common condition in celiac patients. While osteoporosis was found at a rate of 40% in a study conducted in our country, it was found at a rate of 44% in another study [10,11]. On the other hand, in our study, osteoporosis was detected in 15.7% of the patients. Detecting less osteoporosis than expected may be due to the difficulty in reaching the bone mineral density measurement data of our patients as well as due to the measurement methods.

Serology has a very important place in the diagnosis and screening of celiac disease. The serological parameters with the highest sensitivity and specificity have been reported to be IgA tTG and IgA EMA [18-20]. Yet, the most sensitive parameter was IgA EMA in our patients, whereas IgA tTG was found to be the least sensitive parameter on the contrary. One of the reasons for the low IgA tTG sensitivity may be that there is no study in our hospital in some periods as well as because of the kit differences. However, in our patient population, consistent with the literature, the use of IgA EMA suggests that it may be more helpful in diagnosis.

In a study conducted in our country, abnormal findings were

detected in 73.3% of celiac patients who underwent endoscopy before diagnosis [21]. In this study, it was reported that 28% of the patients' endoscopies had a mosaic appearance, 24% were characterized by fold deletion, 20% had a comb-back appearance, and 11% had a nodular appearance [21]. In this study, abnormal findings were detected in 49.2% of the patients. Similar to this study, the most common endoscopic finding in our patients was the mosaic pattern and fold deletion. The presence of endoscopic abnormal findings is a situation that brings the diagnosis closer; however, the absence of these abnormal findings does not indicate that there will be no celiac disease. As in 50.8% of the patients in our study, it has been reported that there may be varying rates of endoscopically normal patients in other studies in the literature [22,23].

As it is well-known, the gold standard in the diagnosis of celiac disease is pathological examination via biopsy. In the study, 83.4% of the patients were Marsh Type 3 and advanced stage. On the other hand, 16.6% of the patients were Marsh Type 1 and were low-stage. In studies conducted in our country, the majority of patients, with a rate of 76.3% and 87.8%, were detected to be in advanced stages [10,11]. Furthermore, in a study conducted in the USA, findings compatible with advanced celiac disease were found in 98% of adult patients, and in this study, it was demonstrated that there is a relationship between advanced histopathological changes and increased IgA tTG (24). Similar to the literature, the pathology of the patients was predominantly Marsh Type 3. However, a definite relationship could not be found between this staging and the severity of the disease.

During the analysis of the biopsies of celiac patients, *Helicobacter pylori* positivity was also examined, and *Helicobacter pylori* positivity was detected in 49.2% of the patients. In a study, *Helicobacter pylori* positivity was found to be 12.5%-36% in celiac patients [25-26]. This difference may be due to environmental, racial, and regional differences. In addition, the higher prevalence of *Helicobacter pylori* in our country may have caused this.

The limitations of our study are that it is a retrospective study and it reflects the data of a single center. Thus, further comprehensive studies are needed on this issue.

In conclusion, celiac patients may present with a great variety of complaints. In particular, celiac disease should be considered in cases such as iron deficiency, osteoporosis, and transaminase elevations, which are common in the population.

The prevalence of the celiac disease is predicted to be around 1-2% in our country, but it is considered that there are more asymptomatic patients with atypical celiac disease. The most important step in diagnosing celiac disease is to keep the celiac disease in mind in the preliminary diagnosis. Hence, celiac disease should be included in the differential diagnosis, especially in patients presenting with atypical symptoms. After the diagnosis, all signs and symptoms improve with a gluten-free diet, as in our study. The prognosis for patients on a lifetime gluten-free diet is quite favorable. However, in cases of dietary non-compliance, the prognosis is variable.

References

1. Rubin CE, Branborg LL, Phelps PC, et al. Apparent identical and specific nature of the duodenal and proximal jejunal lesion in celiac disease and idiopathic sprue. *Gastroenterology* 1960; 38: 28-49.
2. Arranz E, Ferguson A. Intestinal antibody pattern of celiac disease: occurrence in patients with normal jejunal biopsy histology. *Gastroenterology*. 1993; 104: 1263-72.
3. Sulkanen S, Halttunen T, Laurila K, et al. Tissue transglutaminase autoantibody enzyme-linked immunosorbent assay in detecting celiac disease. *Gastroenterology* 1998; 115: 1322-8.
4. Sanders DS, Carter MJ, Hurlstone DP, et al. Association of adult coeliac disease with irritable bowel syndrome: a case-control study in patients fulfilling ROME II criteria referred to secondary care. *Lancet*. 2001; 358: 1504-8.
5. Corazza GR, Di Sario A, Cecchetti L, et al. Bone mass and metabolism in patients with celiac disease. *Gastroenterology* 1995; 109: 122-8.
6. West J, Logan RF, Hill PG, et al. Seroprevalence, correlates and characteristics of undetected coeliac disease in England. *Gut* 2003; 52: 960-5.
7. Fasano A, Berti I, Gerrarduzzi T, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. *Arch Intern Med* 2003; 163: 286-92.
8. Ertekin V, Selimoglu MA, Kardas F, et al. Prevalence of celiac disease in Turkish children. *J Clin Gastroenterol* 2005; 39: 689-91.
9. Reilly NR, Fasano A, Green PH. Presentation of celiac disease. *Gastrointest Endosc Clin N Am*. 2012; 22: 613-21
10. Harmancı Ö. Erişkin yaş grubunda çölyak hastalığının klinik özellikleri (Yan dal uzmanlık tezi). Ankara: Hacettepe Üniversitesi; 2008.
11. Merter M. Erişkin çölyak hastalarının klinik ve laboratuvar özellikleri (uzmanlık tezi). Bursa: Uludağ Üniversitesi ; 2013.

12. Bardella MT, Fraquelli M, Quatrini M. Prevalence of hypertransaminasaemia in adult coeliac patients and effect of gluten-free diet. *Hepatology* 1995; 22: 833-6.
13. Selimoglu MA, Ertekin V, Altinkaynak S, Hyper-CK-emia in pediatric celiac disease: prevalence and clinical importance. *J Clin Gastroenterol.* 2007; 41: 667-70
14. Harper JW, Holleran SF, Ramakrishnan R, et al. Anemia in celiac disease is multifactorial in etiology. *American Journal of Hematology.*2007; 82: 996-1000.
15. Keskin Ç. Çölyak hastalarında anemi parametrelerinin değerlendirilmesi ve serum hepsidin düzeyleri ile ilişkisi (uzmanlık tezi). Ankara: Gazi Üniversitesi ; 2013.
16. Kempainen T, Corazza GR, Di Sario A, et al. Osteoporosis in adult patients with celiac disease. *Bone* 1999; 24: 249-55
17. Ross JR, Gibb SP, Hoffman DE, et al. Gluten enteropathy and skeletal disease. *JAMA* 1966; 196: 270-4
18. Sulkanen S, Halttunen T, Laurila K, et al. Tissue transglutaminase autoantibody enzyme-linked immunosorbent assay in detecting celiac disease. *Gastroenterology* 1998; 115: 1322-8.
19. Stern M. Comparative evaluation of serologic tests for celiac disease: A European initiative toward standardization. *J Pediatr Gastroenterol Nutr* 2000; 31: 513-9.
20. Dieterich W, Laag E, Schopper H, et al. Autoantibodies to tissue transglutaminase as predictors of celiac disease. *Gastroenterology* 1998; 115:1 317-21.
21. Savas N, Akbulut S, Saritas U, Koseoglu T, . Correlation of clinical and histopathological with endoscopic findings of celiac disease in the turkish population.2007; 52: 1299-1303
22. Bardella MT, Minoli G, Radaelli F, Quatrini M, et al. Reevaluation of duodenal endoscopic markers in the diagnosis of celiac disease. *Gastrointest Endosc* 51: 717-720
23. Magazzu G, Bottari M, Tuccari G, et al. Upper gastrointestinal endoscopy can be a reliable tool for celiac sprue in adults. *J Clin Gastroenterol.* 1994; 19: 255-9.
24. Donaldson MR, Book LS, Leiferman KM. Strongly positive tissue transglutaminase antibodies are associated with Marsh 3 histopathology in adult and pediatric celiac disease. *J Clin Gastroenterol* 2008; 42: 256-60.
25. Simondi D, Ribaldone DG, Bonagura GA, et al. Helicobacter pylori in celiac disease and in duodenal intraepithelial lymphocytosis: Active protagonist or innocent bystander? *Clin Res Hepatol Gastroenterol.* 2015; 2270-7401
26. Lasa J, Zubiaurre I, Dima G, et al. Helicobacter pylori prevalence in patients with celiac disease: results from a cross sectional study. *Arq. Gastroenterol.* 2015; 52: 1678-4219