

There is need a new insight for celiac disease

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Celiac disease is a lifelong, immune-mediated, systemic disorder induced by gluten, which is the major protein found in wheat, barley, and rye, in genetically susceptible individuals, resulting in a variety of clinical manifestations and antibodies and damage to the intestinal mucosa. Celiac disease occurs globally, but it is the most prevalent disease in Western Europe and North America, with reported incidence rates of up to 1% (1,2). Celiac disease prevalence is estimated to be approximately 0.47% in healthy school children in Turkey (3). The prevalence of celiac disease has been increasing in the past few decades. The recent higher incidence rates are a result of more widespread use of serologic tests in detection and screening; greater awareness of atypical and silent forms of the disease; and recognition of an increased incidence of celiac disease in patients with syndromic disorders, such as Down syndrome, IgA deficiency, and diabetes, and in first degree relatives of patients with celiac disease (4).

Active celiac disease can result in intestinal and extraintestinal manifestations of the disease. Since the past 10 years, attempts are being made to reach a consensus on the terminology of the clinical stages of celiac disease (2,5). A wide variety of clinical presentations have been described for celiac disease in children, including typical, atypical, silent, and potential forms. The most common presentation of celiac disease has shifted from the historically typical symptom of malabsorption in childhood to atypical symptoms, which can manifest in childhood or adulthood. Classic symptoms include gastrointestinal symptoms such as chronic diarrhea, weight loss, and failure to thrive (6). However, the atypical form is predominantly characterized by EI symptoms. The more common atypical symptoms include iron deficiency, bloating, constipation, chronic fatigue, headache, abdominal pain, and osteoporosis. Silent celiac disease describes asymptomatic patients with positive blood serology and characteristic intestinal inflammation on biopsy. Lastly, po-

tential celiac disease refers to individuals with positive blood serology who may or may not display symptoms, but show no apparent intestinal inflammation on biopsy (7,8). Currently, the only effective treatment for celiac disease is strict, lifelong adherence to a gluten-free diet. This usually results in the resolution of small intestinal inflammation. However, recently, it has become clear that many patients with celiac disease continue to suffer from persistent clinical symptoms, such as constipation and osteoporosis (9,10).

In this latest issue of the Turkish Journal of Gastroenterology, two well-designed and interesting studies investigated "the prevalence of celiac disease in patients suffering from chronic constipation" and "the bone mineral density (BMD) in children with celiac disease and the relationship between low BMD and vitamin K levels."

The first study indicated that the exclusion of celiac disease is not routinely obtained in patients with chronic constipation, and there is no general recommendation to routinely test for celiac disease despite the definition of functional diseases. Celiac disease occurs in children with chronic constipation in the ratio of 1:28. The conclusion section suggests that the use of screening tests for celiac disease should be considered in children with constipation resistant to conventional treatment. Sansotta et al. (9) found that abdominal pain, diarrhea, and failure to thrive are the most common GI symptoms, whereas short stature, fatigue, and headache were the most common EI symptoms in children. Children have significantly higher resolution rates of EI and GI symptoms than adults, with greater rates of improvement after >2 years in GI symptoms than in EI symptoms. Sansotta et al. (9) also found that constipation showed poor rates of improvement in children and adults (58% and 52%, respectively). Finally, it is suggested that early recognition of celiac disease and close attention to diet adherence may help in resolution of celiac disease symptoms. On the other hand, accord-

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ing to the guidelines published in 2012 by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition, there is no general recommendation regarding the screening of celiac disease in patients with chronic constipation (11). However, in daily practice, patients with chronic constipation may be screened for celiac disease. Consequently, despite the recommendation for screening celiac disease in the present study, new studies are needed on this subject, since there is no consensus regarding the screening of celiac disease patients with chronic constipation.

The second study investigated BMD in children with celiac disease and assessed the relationship between BMD and vitamin K levels. It highlighted that the previous studies of adults have proposed that vitamin K plays a beneficial role in bone mineral metabolism. BMD was measured, and serum anti-tissue transglutaminase IgA, ferritin, folate, vitamin B12, 25-hydroxyvitamin D, vitamin K2, calcium, phosphate, alkaline phosphatase, and parathormone were assayed in all patients with celiac disease. The results revealed lower BMD in patients with celiac disease compared with healthy participants; there was no difference in vitamin D or K2 levels between the celiac disease and control groups. There is no new explanation regarding the mechanism of osteoporosis in patients with celiac disease. Mager et al. (12) suggested that suboptimal vitamin D and K status may contribute to an increased risk of poor bone health in children with celiac disease despite compliance with a gluten-free diet. However, vitamin D and K status is not enough to explain the mechanism of osteoporosis, and there is a need for new insight to osteoporosis in patients with celiac disease.

Clinical studies suggested that autoantibodies have been increasingly implicated in the pathological bone loss, which is characteristic of conditions such as osteoporosis (13). Some studies have shown that the autoantibodies induce osteoclast differentiation and activation as well as bone mineral content alteration. Additionally, immunoglobulin IgA anti-endomysial autoantibodies have been implicated in the reduced BMD levels, characteristically observed in patients with celiac disease (14). The autoantibodies were reported to recognize bone tissue transglutaminase (TTG) as the autoantigen of interest; however, their titers subsided following the adoption of a gluten-free diet (13). Similarly, anti-TTG autoantibodies are also highly implicated in bone diseases. In a previous

study, anti-TTG autoantibodies were observed to be significantly associated with low BMD (15). Moreover, a prospective study showed that a positive anti-TTG autoantibody had a higher risk of osteoporosis later in life, which is independent of age, sex, body mass index, vitamin D, and smoking (16). This pathophysiological mechanism may explain the cause of osteoporosis in the aforementioned second study.

These two studies indicate that new studies are necessary for better understanding of pathogenesis and improved treatment of celiac disease patients with constipation and osteoporosis despite an increase in the prevalence of celiac disease and improved recognition and rate of diagnosis. Advances in the pathophysiology of celiac disease could enable preventive strategies in individuals who are at a high risk for disease development. Additionally, a careful follow-up is strongly recommended. New forms of treatment are currently under study and show promising results. Epitope-specific immunotherapy is one of the most promising potential therapeutic options for celiac disease in the future (17).

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