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Celiac Disease, Gluten-Free Diet, and Bone Mass Density

Vida Mohammad Parast; BSc [1], Zamzam Paknahad; PhD [*2]

[1] *Department of Nutrition, School of Nutrition and Food Sciences, Isfahan University of Medical Sciences, Isfahan, Iran.*
[2] *Department of Clinical Nutrition, School of Nutrition and Food Sciences, Isfahan University of Medical Sciences, Isfahan, Iran.*

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*Corresponding author:
Department of Clinical Nutrition, School of Nutrition and Food Sciences, Isfahan University of Medical Sciences, Isfahan, Iran.
Paknahad@hlth.mui.ac.ir

Postal code: 81745
Tel: +98 313 7923166

ABSTRACT

Background: Celiac disease (CD), as an autoimmune disease has initiated since ingestion of food containing gluten. Constant intolerance to gluten causes damages of the small intestinal mucosa. One reason of mal-absorption in children and infants is CD. Additionally, about 75% of newly identified patients with CD have low bone mineral density (BMD). Many factors have role in metabolic bone diseases, such as disturbance in calcium absorption, consumption of endogenous calcium, fecal loss, damaged to vitamin D absorption, and inflammatory mediators. The gluten free diet (GFD) is the only efficacious treatment for CD. Low BMD which is a prevalent problem of untreated CD may be restored by GFD. **Methods:** Databases of PubMed, Web of science, Google scholar, Scopus and Embase were searched by the following keywords: CD and GFD, CD and BMD, GFD and children up to July 2016. **Results:** Most children with CD already have reduced bone mass density before treatment with GFD. GFD caused normal bone mineral density in most of celiac children and adolescent. The treatment duration for restoration of bone mass was not obvious. There were no similar time points for all patients, thus the duration of treatment was different. There was a relationship between age of patients at diagnosis and therapeutic intervention and recovery of BMD; older children may have slower grades of improvement. **Conclusions:** GFD has an important role in bone health. If CD is diagnosed and managed before adolescence, children with CD may achieve normal bone mass.

Keywords: *Celiac; Gluten free diet; Bone mineral density*

Introduction

Celiac disease (CD) is a chronic autoimmune disorder related to the small intestines, individuals with such disease are genetically susceptible to dietary gluten due to disease stimulation. Main characteristic of CD is subtotal or total atrophy of intestinal villi disease and intestinal mal-absorption, which was improved by gluten-free diet (GFD) (Fasano, 2005). Prolamine polypeptides or gluten is found in wheat, rye, barley, and other closely-related grains (Ribaldone *et al.*, 2011). In genetically susceptible individuals, gluten causes an inflammatory reaction in the jejunum predominantly. Small intestinal mucosa damage induced by gluten will ultimately decrease the

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intestinal absorptive region and restrict absorption of micronutrients (Fasano, 2005, Pantaleoni *et al.*, 2014). In the general population, prevalence of CD was stated about1% at any age (Blume and Curtis, 2011, Rampertab *et al.*, 2006). Classical symptoms, such as diarrhea and mal-absorption are common in childhood but there are a wider spectrum of symptoms in adults than children (Pantaleoni *et al.*, 2014). Strict adherence to GFD makes the nutritional status better (Stazi, 2013).

Clinical manifestations of CD are on a wide spectrum, immune response is mainly targeted at the intestinal mucosa; but it also affects other tissues or organs. One of the main extra-intestinal manifestations of CD is low bone mineral density (BMD) which decreases bone mass while raises bone frailty and risk of breaks (Kotze and SRR, 2011). Inflammation and intestinal mal-absorption influence the pathophysiology of bone in CD (Molteni *et al.*, 1995). Several reports have confirmed that patients with untreated CD have BMD (Barera *et al.*, 2004, Kalayci *et al.*, 2001, Kavak *et al.*, 2003, Mora, 2003, 2008, Mora *et al.*, 2001). Metabolic bone disease has a multifactorial etiology, including damage in absorption and consequently fecal loss of vitamin D and calcium. It also causes disruption of normal bone turnover since inflammatory moderator influences bone cell (Barera *et al.*, 2004, Mora, 2008, Taranta *et al.*, 2004). Osteopenia as a typical public health problem in adults can be identified and stopped in childhood. Maximum of the bone mass is attained throughout the first two decades of life, therefore, early identification of CD and adherence to the gluten-free diet (GFD) has an important role in obtaining sufficient bone metabolism in such patients (Chesnut 3rd, 1989, Lu *et al.*, 1994).

Early treatment in pediatric CD patients has been proved to cause considerably greater bone metabolic rates. So, remedy switches the inflammatory process and stops damage of bone mass gaining during the most important period of its growth (Kavak *et al.*, 2003, Mora, 2003, Mora *et al.*, 1999).The aim of the present review was to investigate the gluten free diet and BMD in children with CD.

Materials and Methods

The following databases of PubMed, Web of science, Google scholar, Scopus and Embase were searched by using these keywords: CD and GFD, CD and BMD, as well as GFD and children up to July 2016.

Results

Pathogenesis: CD is a multi-gene disorder that is related with human leukocyte antigen (HLA) genes. Alleles encoding HLA-DQ2 were inherited in 90% to 95% of celiac patients and remaining of patients have HLA-DQ8 (Johnson *et al.*, 2004, Ploski *et al.*, 1993). In pathogenesis of CD, expression of HLA-DQ2 or HLA-DQ8 is essential but not enough. Furthermore, environmental factors such as infections (Plot and Amital, 2009), some drugs (Cammarota *et al.*, 2000), smoking (Vazquez *et al.*, 2001),breastfeeding, and the beginning time of gluten intake (Akobeng *et al.*, 2006) may influence disease incidence. Most of cases diagnosed with widespread serological testing (James, 2005, Lo *et al.*, 2003, Murray *et al.*, 2003). This disease is common in adults more than pediatric and it is predominate in females. Young adults and patients older than 60 years are the most newly diagnosed CD patients. Only in severe illness, ileum and colon are damaged. CD mostly influences the mucosa of the proximal small intestine so that the severity of injury is slowly reducing towards the distal small intestine (Ciclitira and Moodie, 2003). The clinical appearance of CD is widespread and thus influenced by patients' age, period and degree of disease, as well as existence of extra-intestinal signs(Chand and Mihas, 2006). These patients may haveseverely symptomatic or asymptomatic. Mostly CD patients have mal-absorption sings related to concomitant symptoms of autoimmune disorders. Symptoms such as diarrhea, constipation, abdominal emphysema, vomiting, weight loss, infirmity, short stature, flatus, muscle losses and hypotonia, as well as usual irritability and depression were observed in children, adolescents, and adults with CD (Fasano, 2005, Green, 2005). There are usual symptoms including hypocalcemia, vitamin D deficiency, low bone foundation, boosted bone resorption signs, and

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low BMD in children and adolescents with untreated CD. Gastrointestinal (GI) symptoms in minor CD patients may not be present or not distinguished, but patients might state irrelevant sings such as indigestion, stomach ache, bloating inexplicable anemia, fatigue, hypertransaminasemia, sterility, neurologic disorders, short stature dermatitis herpetiforms, and osteoporosis (Rampertab *et al.*, 2006).

Intestinal mucosal abnormalities are characteristics of the silent form of CD that are apparently asymptomatic but majority of patients have positive serologic test (Rashtak and Murray, 2012). The relationship among autoimmune and immune-mediated diseases, such as autoimmune thyroiditis, morphea, and type 1 diabetes mellitus, with CD has been investigated (Tack *et al.*, 2010). In addition, Down, Turner, or Williams syndromes increased the risk for incident of CD (Shaoul and Lerner, 2007). Elimination of gluten from the diet is a basis of CD management (Giannotti *et al.*, 2001).

In a GFD, it is generally accepted that barley, wheat, and rye must be evaded because of their prolamines (gliadin, hordein, and secalin) which are the initiating factors of CD (Rashtak and Murray, 2012). Most celiac patients can tolerate 50 mg of gluten per day. Amounts equal to or more than 100 mg per day can cause appearance of symptoms. Gluten free food have less than or equal to 20 mg/kg (20 ppm) of gluten (Bioletti *et al.*, 2016).

Children and low BMD: CD children are at risk for decreased BMD. Decreased BMD and bone mineral content (BMC) have been frequently observed in children and adolescents with untreated CD (Barera *et al.*, 2004, Mora *et al.*, 1998). Clinical presentations such as reduced BMD, significantly upper parathormon (PTH), and reduced serum calcium were reported in untreated children with CD in comparison with treated and control groups (Mora *et al.*, 1999).In this regard, reduced BMD was reported in untreated CD children (Barera *et al.*, 2004), also a study on young children (mean age of 4.9 years) with CD indicated reduced BMD and severe osteopenia in 17% of CD children at the time of diagnosis (Tau *et al.*, 2006). In another study, bone status in CD children was evaluated; it was observed that BMD reduced significantly even after 1 or at least 2 years of GFD than the control population.

CD children are at risk for less-than-optimum peak bone mass gaining and a delayed growth. The peak quick acquisition of bone mass happens throughout adolescence. Peak value of bone mass is achieved at the end of puberty. The patient is at a higher risk of osteoporosis increase if normal peak bone mass is not achieved. Therefore, individual's future resistance to fractures can be predicted by the amount of bone mass increased throughout the pediatric years (Gordon *et al.*, 2004). Biochemical tests performed on blood or urine samples can demonstrate the bone metabolism rate and bone metabolic processes (Calvo *et al.*, 1996). But, there are a few studies that have examined the bone metabolism rate in CD young patients (Mora *et al.*, 1999, Pratico *et al.*, 1997). It was also found that the alteration rate of bone metabolism in children with untreated possibly can cause osteopathy (Barera *et al.*, 2004).

Gluten free diet: The best way for management of bone disorder and calcium deficiency in CD patients is still contradictory. Nutritional status of these patients is affected by length of time that the disease has been undiagnosed, the amount of injury to the GI tract, and the grade of mal-absorption (Niewinski, 2008). A constant and strict GFD in children and adolescents with CD can help them to improve normal bone density (Mora *et al.*, 1999, Mora *et al.*, 1993), but there is no evidence that the highest point of bone mass level can be attained or preserved for many years, just similar to healthy population. Early diagnosis and treatment of CD children changes inflammatory process and stops bone-mass-gaining damage, therefore, the best treatment period is within childhood. In a longitudinal study (Barera *et al.*, 2000) on children with CD, after 1 year of observing GFD, their BMD became similar to those of healthy control group. Also another study (Kavak *et al.*, 2003) in CD children demonstrated that following a strict GFD has increased bone mineralization even after a year. It was also reported in another study (Szathmári *et al.*, 2001) that after being on a GFD for 3 years,

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children and adolescents with CD had normal or even upper radius BMD level than controls, but the bone size stayed low. In a study (Sdepanian *et al.*, 2003) on BMD in young CD patients who followed GFD, it was demonstrated that BMD of the control children was higher than adolescents with CD but no difference was observed between that of the control group and children with CD. These findings indicated that in adolescents the time between appearance of symptoms and diagnosis was longer than the detection time of children, this made them experience more bone injury and more malnutrition. In adult CD patients bones disease treatment with GFD is a rational approach (Bonura, 2009, Hill *et al.*, 2005). However, GFD seldom can have normal BMD in adulthoods (Bianchi and Bardella, 2002, Capriles *et al.*, 2009). In another study (Larussa *et al.*, 2012)it was demonstrated that after adherence to a strict GFD for a long-term, 74% of patients showed low BMD; 76% osteopenia, and 24% showed osteoporosis.

At present, the only effective treatment for CD is a strict and constant GFD, however, it is still unknown whether only GFD is sufficient to correct the bone alterations and whether these metabolic bone diseases are reversible. Searching the literature about the effects of GFD on bone modification in CD reveals conflicting consequences. In other words, some studies indicated that the risk of low BMD in CD patients on a GFD has significantly reduced (McGough and Cummings, 2005, Passananti *et al.*, 2012). But, the results of other studies (Kaukinen *et al.*, 2007)represented that patients with constant small-intestinal mucosal villous atrophy, even with following a strict GFD and absence of symptoms, had an elevated risk for osteoporosis. Certainly, CD patients' bone metabolism modifications and bone mineral loss require appropriate management (Holmes *et al.*, 1989).

Age and BMD improvement in children with CD: In a study, Zanchetta et al. reported that 93% of children who began treatment with GFD before the age of 4 years, attained normal spine BMD values. However, only 50% of patients who were older at the time of diagnosis and treatment reached normal BMD. The authors reported that children older than 4 years suffered a longer period between symptoms and diagnosis compared with younger infants (Zanchetta *et al.*, 1995). In another study, Sdepanian et al. indicated that BMD was significantly higher in children with CD compared with the control group but BMD in adolescent with CD on GFD was significantly lower than that of the control participants; these findings demonstrated that longer time interval between signs and diagnosis in adolescents caused them suffer more from malnutrition and bone damage than children (Sdepanian *et al.*, 2003).

Frequently, literature confirmed existence of a relationship between patients' age at the time of intervention and the observed improvements. The results are different, some studies agree that children start GFD at a younger age (Scotta *et al.*, 1997, Tau *et al.*, 2006); but other studies explained that BMD also increased in older children in comparison with the control group after one year of receiving GFD (Kavak *et al.*, 2003, Tau *et al.*, 2006). Mora et al. (Mora *et al.*, 1999), in a study compared children and adolescents with CD and determined that independent from GFD, starting the long-standing diet before or during puberty has caused normal BMD. Also, Scotta et al. (Scotta *et al.*, 1997), stated that the age of diagnosis and the period of GFD extensively affect spine BMD.

The length of treatment needed to restore bone mass in CD children: Several studies evaluated bone mass in celiac children. Numerous authors reported reduced total body BMD and spine before treatment with GFD (Exner *et al.*, 1978, Mora *et al.*, 1999, Mora *et al.*, 1998, Muzzo *et al.*, 2000, Scotta *et al.*, 1997). Szathmari et al. stated that after adherence of GFD for three or more years, adolescent and children with CD have normal or even upper radius mineral density rates than controls (Szathmári *et al.*, 2001). In a longitudinal study bone mass of very young celiac children was assessed, it was reported that increase of BMD was two-fold greater than its increase in the area, demonstrating that GFD

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therapy raises bone mineralization in addition to the increment due to bone growth (Tau *et al.*, 2006). In the very young patients, it was 0.10g/cm^2 during the approximately 14 months period of observation, but in normal cases, increase of the spine BMD was respectively 0.05g/cm^2 and 0.02g/cm^2 at 2 and 10 years of age during 1 year period (Zanchetta *et al.*, 1995). Mora et al. reported a respectively increase of 0.06 g/cm^2 and 0.05 g/cm^2, after 1.4 years on GFD in spine and whole-body BMD of children with CD, BMD was reported as normal at the end of the study (Mora *et al.*, 1998). The duration of cure needed to repair bone mass has not been clear yet. Rea et al. reported that 1year of GFD is enough to gain whole restoration of BMD (Rea *et al.*, 1998). In another study(Bianchi and Bardella, 2002), it was found that some patients recovery of bone mass happened after only 3–7 months on GFD, while others' recovery occurred after 1.5 years therapy. They reported that patients with a shorter symptomatic period (5.3 months between first symptoms and diagnosis) recover more completely in comparison with patients suffering longer periods of untreated CD. Possibility of full recovery of the genetically predisposed peak bone mass and minimum period of getting GFD needed for normalization of BMD is not clear. Some studies have demonstrated that 1 year is enough for the increment of the bone mass values to levels similar to those found in the normal population (Kavak *et al.*, 2003, Mora *et al.*, 1998), however other researchers have shown that there was a significant increase within 1 year, although the normal standards were not attained (Kalayci *et al.*, 2001, Margoni *et al.*, 2012).

Conclusions

Several studies have reported that low BMD is present in patients with untreated CD. Decreased BMD and BMC have been frequently observed in children and adolescents with untreated CD. Early beginning to cure CD children caused significantly greater bone metabolism rates. The best management of bone disorder and calcium deficiency in CD patients is controversial. Length of time through which the disease is undiagnosed, the amount of injury to the GI tract, and the grade of mal-absorption affect nutritional status of these patients. A constant and strict GFD in children and adolescents with CD can help improve normal bone density, but there is no evidence that an optimum highest point of bone mass level can be attained or that it can be preserved for many years similar to healthy population. Further, the age and duration of intervention needed to repair bone mass are still not clear.

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Author contributions

Paknahad Z contributed in the conception of the work. Mohammad Parast V searched data bases and extracted findings. Mohammad Parast V and Paknahad Z wrote the manuscript. Paknahad Z revised the manuscript. All authors approved the final version of the manuscript, and agreed for all aspects of the work.

Conflicts of Interest

The author declares no conflict of interest.

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