



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

Vida Mohammad Parast; BSc¹, 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.

ARTICLE INFO

REVIEW ARTICLE

Article history:

Received: 5 Dec 2016

Revised: 30 Dec 2016

Accepted: 5 Jan 2017

*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

intestinal absorptive region and restrict absorption of micronutrients (Fasano, 2005, Pantaleoni *et al.*, 2014). In the general population, prevalence of CD was stated about 1% 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 have severely symptomatic or asymptomatic. Mostly CD patients have mal-absorption signs 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

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 signs such as indigestion, stomach ache, bloating inexplicable anemia, fatigue, hypertransaminasemia, sterility, neurologic disorders, short stature dermatitis herpetiformis, 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,

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

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 0.06g/cm^2 and 0.05g/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 1 year 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).

References

- Akobeng AK, Ramanan AV, Buchan I & Heller RF** 2006. Effect of breast feeding on risk of coeliac disease: a systematic review and meta-analysis of observational studies. *Archives of disease in childhood*. **91** (1): 39-43.
- Barera G, Beccio S, Proverbio MC & Mora S** 2004. Longitudinal changes in bone metabolism

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.

Acknowledgments

This research was funded by the Isfahan University of Medical Sciences, Isfahan, Iran.

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.

and bone mineral content in children with celiac disease during consumption of a gluten-free diet. *The American journal of clinical nutrition*. **79** (1): 148-154.

- Barera G, et al.** 2000. Body composition in children with celiac disease and the effects of a gluten-free diet: a prospective case-control study.

- The American journal of clinical nutrition.* **72** (1): 71-75.
- Bianchi M & Bardella M** 2002. Bone and celiac disease. *Calcified tissue international.* **71** (6): 465-471.
- Bioletti L, et al.** 2016. Celiac disease and school food service in Piedmont Region: Evaluation of gluten-free meal. *Ann Ig.* **28**: 145-157.
- Blume SW & Curtis JR** 2011. Medical costs of osteoporosis in the elderly Medicare population. *Osteoporosis International.* **22** (6): 1835-1844.
- Bonura F** 2009. Prevention, screening, and management of osteoporosis: an overview of the current strategies. *Postgraduate medicine.* **121** (4): 5-17.
- Calvo MS, Eyre DR & Gundberg CM** 1996. Molecular Basis and Clinical Application of Biological Markers of Bone Turnover*. *Endocrine Reviews.* **17** (4): 333-368.
- Camarota G, Cuoco L, Cianci R, Pandolfi F & Gasbarrini G** 2000. Onset of coeliac disease during treatment with interferon for chronic hepatitis C. *The Lancet.* **356** (9240): 1494-1495.
- Capriles VD, Martini LA & Arêas JAG** 2009. Metabolic osteopathy in celiac disease: importance of a gluten-free diet. *Nutrition reviews.* **67** (10): 599-606.
- Chand N & Mihas AA** 2006. Celiac disease: current concepts in diagnosis and treatment. *Journal of clinical gastroenterology.* **40** (1): 3-14.
- Chesnut 3rd C** 1989. Is osteoporosis a pediatric disease? Peak bone mass attainment in the adolescent female. *Public Health Reports.* **104** (Suppl): 50.
- Ciclitira PJ & Moodie SJ** 2003. Coeliac disease. *Best Practice & Research Clinical Gastroenterology.* **17** (2): 181-195.
- Exner G, Sacher M, Shmerling D & Prader A** 1978. Growth retardation and bone mineral status in children with coeliac disease recognized after the age of 3 years. *Helvetica paediatrica acta.* **33** (6): 497-507.
- Fasano A** 2005. Clinical presentation of celiac disease in the pediatric population. *Gastroenterology.* **128** (4): S68-S73.
- Giannotti A, et al.** 2001. Coeliac disease in Williams syndrome. *Journal of medical genetics.* **38** (11): 767-768.
- Gordon CM, Bachrach LK, Carpenter TO, Karsenty G & Rauch F** 2004. Bone health in children and adolescents: a symposium at the annual meeting of the Pediatric Academic Societies/Lawson Wilkins Pediatric Endocrine Society, May 2003. *Current problems in pediatric and adolescent health care.* **34** (6): 226-242.
- Green PH** 2005. The many faces of celiac disease: clinical presentation of celiac disease in the adult population. *Gastroenterology.* **128** (4): S74-S78.
- Hill ID, et al.** 2005. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *Journal of pediatric gastroenterology and nutrition.* **40** (1): 1-19.
- Holmes G, Prior P, Lane M, Pope D & Allan R** 1989. Malignancy in coeliac disease--effect of a gluten free diet. *Gut.* **30** (3): 333-338.
- James SP** 2005. National Institutes of Health consensus development conference statement on celiac disease, June 28-30, 2004. *Gastroenterology.* **128** (4): S1-S9.
- Johnson TC, et al.** 2004. Relationship of HLA-DQ8 and severity of celiac disease: comparison of New York and Parisian cohorts. *Clinical Gastroenterology and Hepatology.* **2** (10): 888-894.
- Kalayci AG, Kansu A, Girgin N, Kucuk O & Aras G** 2001. Bone mineral density and importance of a gluten-free diet in patients with celiac disease in childhood. *Pediatrics.* **108** (5): e89-e89.
- Kaukinen K, et al.** 2007. Persistent small bowel mucosal villous atrophy without symptoms in coeliac disease. *Alimentary pharmacology & therapeutics.* **25** (10): 1237-1245.
- Kavak US, et al.** 2003. Bone mineral density in children with untreated and treated celiac disease. *Journal of pediatric gastroenterology and nutrition.* **37** (4): 434-436.

- Kotze L & SRR U** 2011. Doença celaca e outros distúrbios na absorção de nutrientes. *Gastroenterologia essencial, 4th ed. Rio de Janeiro: Guanabara Koogan.* 294330.
- Larussa T, et al.** 2012. No evidence of circulating autoantibodies against osteoprotegerin in patients with celiac disease. *World Journal of Gastroenterology : WJG.* **18 (14):** 1622-1627.
- Lo W, Sano K, Lebwohl B, Diamond B & Green PH** 2003. Changing presentation of adult celiac disease. *Digestive diseases and sciences.* **48 (2):** 395-398.
- Lu PW, et al.** 1994. Bone mineral density of total body, spine, and femoral neck in children and young adults: a cross sectional and longitudinal study. *Journal of Bone and Mineral Research.* **9 (9):** 1451-1458.
- Margoni D, et al.** 2012. Bone health in children with celiac disease assessed by dual x-ray absorptiometry: effect of gluten-free diet and predictive value of serum biochemical indices. *Journal of pediatric gastroenterology and nutrition.* **54 (5):** 680-684.
- McGough N & Cummings JH** 2005. Coeliac disease: a diverse clinical syndrome caused by intolerance of wheat, barley and rye. *Proceedings of the Nutrition Society.* **64 (04):** 434-450.
- Molteni N, Bardella MT, Vezzoli G, Pozzoli E & Bianchi P** 1995. Intestinal Calcium Absorption as Shown by Stable Strontium Test in Celiac Disease Before and After Gluten-Free Diet. *American Journal of Gastroenterology.* **90 (11).**
- Mora S** 2003. Celiac disease: a bone perspective. *Journal of pediatric gastroenterology and nutrition.* **37 (4):** 409-411.
- Mora S** 2008. Celiac disease in children: impact on bone health. *Reviews in Endocrine and Metabolic Disorders.* **9 (2):** 123-130.
- Mora S, et al.** 2001. A prospective, longitudinal study of the long-term effect of treatment on bone density in children with celiac disease. *The Journal of pediatrics.* **139 (4):** 516-521.
- Mora S, et al.** 1999. Bone density and bone metabolism are normal after long-term gluten-free diet in young celiac patients. *The American journal of gastroenterology.* **94 (2):** 398-403.
- Mora S, et al.** 1998. Reversal of low bone density with a gluten-free diet in children and adolescents with celiac disease. *The American journal of clinical nutrition.* **67 (3):** 477-481.
- Mora S, et al.** 1993. Effect of gluten-free diet on bone mineral content in growing patients with celiac disease. *The American journal of clinical nutrition.* **57 (2):** 224-228.
- Murray JA, et al.** 2003. Trends in the identification and clinical features of celiac disease in a North American community, 1950–2001. *Clinical Gastroenterology and Hepatology.* **1 (1):** 19-27.
- Muzzo S, et al.** 2000. Effect of calcium and vitamin D supplementation on bone mineral density of celiac children. *Nutrition Research.* **20 (9):** 1241-1247.
- Niewinski MM** 2008. Advances in celiac disease and gluten-free diet. *Journal of the American Dietetic Association.* **108 (4):** 661-672.
- Pantaleoni S, et al.** 2014. Bone mineral density at diagnosis of celiac disease and after 1 year of gluten-free diet. *The Scientific World Journal.* **2014.**
- Passananti V, et al.** 2012. Bone mass in women with celiac disease: role of exercise and gluten-free diet. *Digestive and Liver Disease.* **44 (5):** 379-383.
- Ploski R, Ek J, Thorsby E & Sollid LM** 1993. On the HLA-DQ ($\alpha 1^* 0501$, $\beta 1^* 0201$)-associated susceptibility in celiac disease: A possible gene dosage effect of DQB1* 0201. *Tissue Antigens.* **41 (4):** 173-177.
- Plot L & Amital H** 2009. Infectious associations of Celiac disease. *Autoimmunity reviews.* **8 (4):** 316-319.
- Pratico G, et al.** 1997. Serum levels of osteocalcin and type I procollagen in children with celiac disease. *Journal of pediatric gastroenterology and nutrition.* **24 (2):** 170-173.
- Rampertab SD, Pooran N, Brar P, Singh P & Green PH** 2006. Trends in the presentation of celiac disease. *The American journal of medicine.* **119 (4):** 355.e359-355.e314.

- Rashtak S & Murray JA** 2012. Review article: coeliac disease, new approaches to therapy. *Alimentary pharmacology & therapeutics*. **35** (7): 768-781.
- Rea F, et al.** 1998. Effect of gluten-free diet on bone mineral metabolism of celiac children. *Nutrition research*. **18** (10): 1661-1666.
- Ribaldone D, Astegiano M, Fagoonee S, Rizzetto M & Pellicano R** 2011. Epilepsy and celiac disease: review of literature. *Panminerva medica*. **53** (4): 213-216.
- Scotta M, et al.** 1997. Bone mineralization and body composition in young patients with celiac disease. *American Journal of Gastroenterology*. **92** (8).
- Sdepanian VL, de Miranda Carvalho CN, de Moraes MB, Colugnati FAB & Fagundes-Neto U** 2003. Bone mineral density of the lumbar spine in children and adolescents with celiac disease on a gluten-free diet in Sao Paulo, Brazil. *Journal of pediatric gastroenterology and nutrition*. **37** (5): 571-576.
- Shaoul R & Lerner A** 2007. Associated autoantibodies in celiac disease. *Autoimmunity reviews*. **6** (8): 559-565.
- Stazi A** 2013. [Micronutrient deficiencies in osteoporosis]. *Minerva medica*. **104** (4): 455-470.
- Szathmári M, et al.** 2001. Bone mineral content and density in asymptomatic children with coeliac disease on a gluten-free diet. *European journal of gastroenterology & hepatology*. **13** (4): 419-424.
- Tack GJ, Verbeek WH, Schreurs MW & Mulder CJ** 2010. The spectrum of celiac disease: epidemiology, clinical aspects and treatment. *Nature Reviews Gastroenterology and Hepatology*. **7** (4): 204-213.
- Taranta A, et al.** 2004. Imbalance of Osteoclastogenesis- Regulating Factors in Patients With Celiac Disease. *Journal of Bone and Mineral Research*. **19** (7): 1112-1121.
- Tau C, Mautalen C, De Rosa S, Roca A & Valenzuela X** 2006. Bone mineral density in children with celiac disease. Effect of a gluten-free diet. *European journal of clinical nutrition*. **60** (3): 358-363.
- Vazquez H, et al.** 2001. Relation between cigarette smoking and celiac disease: evidence from a case-control study. *The American journal of gastroenterology*. **96** (3): 798-802.
- Zanchetta J, Plotkin H & Filgueira MA** 1995. Bone mass in children: normative values for the 2-20-year-old population. *Bone*. **16** (4): S393-S399.