Celiac disease (CD) is an immune-mediated systemic disorder of the small intestine caused by the ingestion of dietary gluten in genetically susceptible individuals. In the past, the prevalence of CD had been underestimated, but it is now considered as one of the most common genetic disorders in the West. The overall CD prevalence is 1:133 in the not-at-risk groups, whereas in the at-risk group, prevalence is 1:22 in first-degree relatives, and 1:56 in symptomatic patients. The prevalence of CD in India is nearly similar to Western Caucasian populations.

CD also affects bone structure in children which manifests as low BMD and early onset osteomalacia. Alteration in bone mass has been recent subject of attention as bone mass acquired helps to predict future risk of fractures. Cause of metabolic disease in celiac is multifactorial, persistent activation of inflammation along with calcium and vitamin D malabsorption is also important cause of metabolic bone disease in these patients.

The current available treatment for CD is lifelong gluten-free diet (GFD). This study was done to see the effect of GFD on Vitamin D levels and bone mass density in celiac patients.

Objective: Celiac disease (CD) is a multifactorial immune-mediated enteropathy caused by a response to ingested gluten. The current available treatment for CD is lifelong gluten-free diet (GFD). This study was done to see the effect of GFD on Vitamin D levels and bone mass density in celiac patients.

Methods: A prospective interventional study on newly diagnosed celiac patients was conducted in the Pediatrics department of a tertiary care teaching institute in 2 stages viz. on presentation and after 6 months of GFD. Anthropometric measurements, biochemical investigations, Vitamin D levels, and DEXA scan was done at recruitment and after 6 months of GFD and was analyzed.

Results: In newly diagnosed 60 pediatric celiac patients, positive effect of GFD on anthropology, hemoglobin, Vitamin D levels, DEXA scan parameters was observed. Significant difference was found in Vitamin D levels which increased from baseline 14.85 ± 5.39 to 18.22 ± 5.67 ng/ml after 6 months of GFD (P < 0.05). Significant difference was found in BMD (mean Z-score) which increased from -0.941 ± 0.738 to -0.640 ± 0.60 after 6 months of GFD (P < 0.001).

Conclusion: Our study concluded that there is significant increase in vitamin D levels as well as Z-score, bone mass density (BMD) and bone Mass Content (BMC) after 6 months of GFD.

Keywords: Bone mass density, DEXA scan, gluten, vitamin D

Introduction

Celiac disease (CD) is an immune-mediated systemic disorder of the small intestine caused by the ingestion of dietary gluten in genetically susceptible individuals. In the past, the prevalence of CD had been underestimated, but it is now considered as one of the most common genetic disorder in the West. The overall CD prevalence is 1:133 in the not-at-risk groups, whereas in the at-risk group, prevalence is 1:22 in first-degree relatives, and 1:56 in symptomatic patients. The prevalence of CD in India is nearly similar to Western Caucasian populations.

Study of effect of gluten-free diet on vitamin D levels and bone mineral density in celiac disease patients

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ABSTRACT

Objective: Celiac disease (CD) is a multifactorial immune-mediated enteropathy caused by a response to ingested gluten. The current available treatment for CD is lifelong gluten-free diet (GFD). This study was done to see the effect of GFD on Vitamin D levels and bone mass density in celiac patients. Methods: A prospective interventional study on newly diagnosed celiac patients was conducted in the Pediatrics department of a tertiary care teaching institute in 2 stages viz. on presentation and after 6 months of GFD. Anthropometric measurements, biochemical investigations, Vitamin D levels, and DEXA scan was done at recruitment and after 6 months of GFD and was analyzed. Results: In newly diagnosed 60 pediatric celiac patients, positive effect of GFD on anthropology, hemoglobin, Vitamin D levels, DEXA scan parameters was observed. Significant difference was found in Vitamin D levels which increased from baseline 14.85 ± 5.39 to 18.22 ± 5.67 ng/ml after 6 months of GFD (P < 0.05). Significant difference was found in BMD (mean Z-score) which increased from -0.941 ± 0.738 to -0.640 ± 0.60 after 6 months of GFD (P < 0.001). Conclusion: Our study concluded that there is significant increase in vitamin D levels as well as Z-score, bone mass density (BMD) and bone Mass Content (BMC) after 6 months of GFD.

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Introduction

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as some of the complications are irreversible such as growth retardation, abnormal dentition, osteoporosis, etc.[9,10]

People in Haryana, where wheat is a staple food, may be having greater genetic as well as environmental predisposition for CD. Very few studies have been done to show effect of GFD on Vitamin D levels and bone structure in these patients. Keeping in view the above-mentioned facts, the present study was conducted to study the effect of GFD for 6 months on vitamin D levels and bone mineral density in CD patients.

**Material and Methods**

A prospective interventional study was conducted in the Pediatrics department of a tertiary care teaching hospital in 2 stages viz. on presentation and after 6 months of initial presentation. An informed written consent was obtained from the parents/legally Acceptable Representative (LAR) of all the enrolled children. Ethical clearance was obtained from Institutional Ethics Committee (IEC) before the commencement of study.

Newly diagnosed children between 1 and 14 years of age presented to Pediatrics OPD or admitted in ward with symptoms which were highly suggestive of CD such as chronic diarrhoea, abdominal distension, constipation, failure to thrive or growth retardation, features of malabsorption, refractory anemia, micronutrient deficiency, and other extra-intestinal sign and symptoms with IgA tissue transglutaminase level (IgA-tTG) 10 folds of normal level were taken as cases. Children of CD with other comorbid conditions like Type 1 Diabetes Mellitus, Hypothyroidism and who were non-compliant to GFD diet were excluded.

Baseline demographic profile, thorough history and clinical examination was recorded from all patients. Vitamin D level in serum was measured by using by Radioimmunoassay (RIA). DEXA scan was done to evaluate bone mineral density and bone mineral content in all patients. BMD was expressed in g/cm² and Z-score. Osteopenia was defined as BMD Z-score < -1.0 while severe osteopenia as BMD Z-score < -2.5.[11]

Vitamin D levels and DEXA scan was done at recruitment and after 6 months of GFD. All the data was entered in designed proforma including investigation findings and then results were analyzed statistically using appropriate statistical methods. For normally distributed data, Student t-test was employed for analysis. Chi-square test was employed for categorical and ordinal data. Statistical software SPSS version 21.0 was employed for analysis.

**Results**

Total of 392 patients with clinical symptoms suggestive of CD were screened for IgA-tTG and out of them 77 cases fulfilled the inclusion criteria and of which 60 cases which followed up for 6 months regularly were enrolled in study.

Mean age of presentation was 7.62 ± 3.1 years with male female ratio of 1.6:1. Majority of cases belonged to middle class (60%) followed by lower class (34%). Chief mode of presentation was non-gastro-intestinal (58.34%). Most of the patients were having short stature (46%), 40% patients had abdominal distension, 28% cases had diarrhoea, 24% had constipation, 24% had vomiting, and 22% patient had pain abdomen. Sixty percent children had weight less than 3rd centile for age and 46% had height less than 3rd centile for age. 82% patients were anemic. Out of 60 patients, 14 (23.3%) were deficient in vitamin D and 43 (71.6%) had insufficient levels. Out of 60 patients, 25 (41.66%) children had osteopenia with a BMD Z-score below -1 and 2 patients had severe osteopenia with BMD Z-score below -2.5 [Table 1].

Mean weight, height, body mass index (BMI) increased significantly after 6 months of GFD (P < 0.001). Mean hemoglobin and calcium values of patients increased significantly after 6 months. Mean IgA-tTG level also decreased significantly [Table 2].

Significant difference was found in Vitamin D levels which increased from baseline 14.8 ± 5.39 ng/ml to 18.22 ± 5.67 after 6 months of GFD. Significant difference was found in Vitamin D levels in patients with gastrointestinal and non-gastrointestinal symptoms individually after 6 months of GFD. Difference was significant in patients with Vitamin D deficiency, insufficiency, and sufficiency (P < 0.001).

After 6 months of GFD, 14 (23.3%) patients had BMD Z-score below -1 and none of the patient had BMD Z-score below -2.5. Significant difference was found in mean Z-score, mean BMD, and

**Table 1: Baseline characteristics of study subjects (n=60)**

| Parameters                  | n (%)         |
|-----------------------------|---------------|
| Age (years)                 | 7.62±3.10     |
| Sex                         |               |
| Male                        | 23 (38.34%)   |
| Female                      | 37 (61.66%)   |
| Presentation                |               |
| Gastrointestinal            | 25 (41.66%)   |
| Non-gastrointestinal        | 35 (58.34%)   |
| Sign and symptoms           |               |
| Abdominal distension        | 24 (40%)      |
| Pain abdomen                | 13 (21.6%)    |
| Diarrhea                    | 17 (28.3%)    |
| Pallor                      | 49 (81.6%)    |
| Short stature               | 28 (46.6%)    |
| Weight <3rd centile         | 36 (60%)      |
| Height <3rd centile         | 28 (46.6%)    |
| Vitamin D levels            |               |
| <10 ng/ml (Deficient)       | 14 (23.3%)    |
| 10-29 ng/ml (Insufficient)  | 43 (71.6%)    |
| 30-100 ng/ml (Sufficient)   | 3 (5%)        |
| BMD                         |               |
| Normal                      | 33 (55%)      |
| Z score below -1            | 25 (41.6%)    |
| Z score below -2.5          | 2 (0.03%)     |
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Table 2: Effect of Gluten free diet on various parameters

| Parameters          | At presentation Mean±SD (n=60) | After six months Mean±SD (n=60) | P    |
|---------------------|--------------------------------|---------------------------------|------|
| Height (cm)         | 111.09±19.18                   | 114.07±19.38                   | <0.001|
| Weight (kg)         | 18.60±7.30                     | 20.62±7.22                     | <0.001|
| BMI (kg/m²)         | 14.56±2.30                     | 15.47±2.11                     | <0.001|
| Hb (g/dl)           | 7.30±1.91                      | 8.58±1.16                      | <0.001|
| IgA-γtTG (U/ml)     | 196.03±68.52                   | 80.01±30.54                    | <0.001|
| Vitamin D levels    |                                |                                 |      |
| <12 ng/ml (Deficient)| 9.45±0.45                      | 13.53±1.52                     | 0.001 |
| <12-20 ng/ml (Insufficient)| 15.43±3.25                 | 18.53±3.89                     | 0.001 |
| > 20 ng/ml (Sufficient)| 31.66±0.57                   | 35.70±0.70                     | 0.001 |
| Total               | 14.85±5.39                     | 18.22±5.67                     | 0.001 |
| Z-SCORE             |                                |                                 |      |
| Gastrointestinal    | -1.098±0.754                   | -0.764±0.632                   | 0.001 |
| Non-gastrointestinal| -0.828±0.717                   | -0.551±0.569                   | 0.001 |
| Total               | -0.941±0.738                   | -0.640±0.60                    | 0.001 |
| BMD                 |                                |                                 |      |
| Gastrointestinal    | 0.531±0.104                    | 0.549±0.09                     | 0.05  |
| Non-gastrointestinal| 0.514±0.074                    | 0.540±0.076                    | 0.001 |
| Total               | 0.521±0.08                     | 0.544±0.08                     | 0.001 |
| BMC                 |                                |                                 |      |
| Gastrointestinal    | 16.92±6.57                     | 19.42±6.52                     | 0.001 |
| Non-gastrointestinal| 17.40±4.34                     | 19.81±4.64                     | 0.001 |
| Total               | 17.2±5.34                      | 19.65±5.45                     | 0.001 |

mean BMC which increased from baseline value after 6 months of GFD (P < 0.001). Significant improvement was found in Z-score, BMD and BMC in patients with gastrointestinal and non-gastrointestinal symptoms when compared at presentation and at 6 months of GFD (P < 0.05) [Table 2].

Discussion

A total of 60 newly diagnosed patients with CD were included in the study and were followed up for 6 months after starting of GFD. Compliance was ensured in all newly patients during follow-up and repeated counselling was being done.

In our study, mean age of population as well as sex distribution is similar to many reported studies in the literature.[12-15] Our study had more patients with non-gastrointestinal symptoms than those with gastrointestinal symptoms which was in concordance with other studies.[16-18]

The mainstay of treatment of CD is GFD. A recently done systematic review has shown that BMC as well as aBMD were lower in youth with CD, however most studies included were cross-sectional and there is dearth of data from longitudinal studies reporting change in bone health over time.[19]

In present study, after initiation of GFD weight, height, BMI and hemoglobin has also increased which was also seen in other studies.[16,20,21]

In our study, mean vitamin D level of the patients at the time of presentation increased significantly after 6 months of GFD. Similarly, El-Shaheed et al. reported that level of vitamin D increased significantly after GFD.[22]

In the present study, patients with vitamin D deficiency (<12 ng/ml) received 60,000 IU of vitamin D per week during the first 3 months of treatment, after which vitamin D was discontinued and they were advised to follow GFD. Vitamin D supplementation in deficiency cases may have influenced our results and part of the improvement may have been due to vitamin D reposition. Vitamin D supplementation was not given in patients with vitamin D insufficiency. However, vitamin D levels were increased in patients with vitamin D insufficiency and in sufficiency cases too. Hence, we can conclude that GFD for 6 months has significant effect on vitamin D levels. There are very few studies till date highlighting role of GFD on vitamin D levels in celiac patients.

Kalayci et al.[23] reported that bone mineral measurements of newly diagnosed patients were significantly increased after treatment for 1 year, 50% of patients with osteopenia still had BMD values 1 SD below the normal range. Similar results were found in our study but because of less duration of treatment, 23.3% patients still had osteopenia after 6 months of GFD.

Mean difference of BMD, Z-score, and BMC at presentation and after 6 months found to be statistically significant. Similarly, Tau et al.[24] in their prospective study concluded that BMD increased significantly from 0.46 ± 0.13 to 0.55 ± 0.13 g/cm², BMC increased from 10.04 ± 8.45 to 14.43 ± 10.83, and BMD Z-score improved from -1.36 ± 1.20 to -0.23 ± 1.20 after 1.17 ± 0.93 years of GFD. Mora et al.[20] reported that during
GFD period (1.4 ± 0.04 y), mean BMD value of lumbar spine changed from 0.683 ± 0.036 to 0.745 ± 0.042 g/cm², with a mean increment of 0.062 ± 0.010 g/cm². Kalayci et al.\textsuperscript{[23]} reported BMD in newly diagnosed celiac patients was 0.51 ± 0.11 g/cm², which was increased to 0.58 ± 0.16 g/cm², BMC increased from 13.66 ± 6.39 to 18.29 ± 8.72 g/cm, and Z score increased from -1.55 ± 1.36 to -0.67 ± 0.85 after one year of GFD.

Kalayci et al.\textsuperscript{[23]} found that patients without gastrointestinal symptoms had osteopenia of same degree as patients with these symptoms. There are only few studies that examined the annual BMD improvement in the patients with or without gastrointestinal symptoms in childhood.

GFD had a beneficial effect in our study, resulting in a significant increase in Z-score, BMD, and BMC in both the groups (gastrointestinal as well as non-gastrointestinal) separately. These findings are in concordance with previous studies,\textsuperscript{[23,24]} which also concluded that adherence to strict GFD alone is capable of increasing the bone mass values despite few patients out of them are having non-gastrointestinal symptoms.

Mora et al.\textsuperscript{[24]} also reported that GFD promotes a rapid increase of BMD that leads to a complete recovery of bone mineralization. These results emphasize the need for an early diagnosis and treatment in patients with CD to obtain an adequate peak bone mass at the end of puberty.

Kalayci et al.\textsuperscript{[23]} reported that strict gluten avoidance promoted a significant increase in BMD. However, values still remained markedly low after 1 year of follow-up in some patients. Hence these patients should be followed for longer periods of time with yearly BMD evaluation, as 6 months of diet therapy as was done in our study was found to be insufficient for osteopenia to be resolved.

This study suggests that GFD for 6 months has very beneficial effects on bone mass. Such studies will help to sensitize primary care physicians so that they can counsel parents regarding strict adherence to GFD. Repercussions of poor adherence on bone mass is the matter of concern which needs to be addressed during comprehensive management of CD by primary care physicians.

The main limitation of the index study is the relatively small number of cases, which may have reduced the power of the study to detect significant correlations. Another limitation is the relatively short duration of the study. Vitamin D supplement in deficient cases may have influenced our results and part of the improvement may have been due to vitamin D reposition. Adherence to GFD is also extremely difficult to evaluate because children may be involuntarily exposed to gluten.

**Conclusion**

The findings of the present study suggest that children with CD are at risk for vitamin D deficiency and decreased BMD. Hence routine monitoring of patients with DEXA scan is advisable so as to prevent further complications. Our study also concluded that there is significant increase in vitamin D levels as well as Z-score, BMD, and BMC after 6 months of GFD. As complete restoration of osteopenia was not obtained, hence longer follow-up may be needed for better results. Early diagnosis and treatment of CD by primary care physicians will lead to better bone mineralization and normal vitamin D levels which will ultimately help in attaining peak body mass thus preventing osteopenia in adult life.

**Key Points**

- Children with CD are at high risk for vitamin D deficiency and osteopenia.
- GFD for 6 months causes significant improvement in Vitamin D levels and Bone Mass density in children with celiac disease.
- Early diagnosis and treatment of CD by primary care physicians in form of GFD will improve bone mineralisation, thus preventing morbidities in later life.

**Key take home message**

GFD adherence for 6 months leads to substantial recovery in bone mass and vitamin D levels.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Husby S, Koletzko S, Korponay-Szabó IR, Mearin ML, Phillips A, Shamir R, et al. ESPGHAN guidelines for the diagnosis celiac disease in children and adolescents: An evidence-based approach. J Pediatr Gastroenterol Nutr 2012;54:136-60.
2. Fasano A, Berti I, Gerarduzzi T, Not T, Colletti RB, Drago S, 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.
3. Sher KS, Fraser RC, Wicks AC, Mayberry JF. High risk of coeliac disease in Punjabis. Epidemiological study in the South Asian and European populations of leicestershire. Digestion 1993;54:178-82.
4. Zanchi C, Di Leo G, Ronfani L, Stefano M, Not T. Bone metabolism in celiac disease. J Pediatr 2008;153:262-5.
5. Nestares T, Martin-Masot R, de Teresa C, Bonillo R, Maldonado J, Flor-Alemany M, et al. Influence of Mediterranean diet adherence and physical activity on bone health in celiac children on a Gluten-Free diet. Nutrients 2021;13:1636.

6. Di Stefano M, Bergonzi M, Benedetti I, De Amici M, Torre C, Brondino N, et al. Alterations of inflammatory and matrix production indices in celiac disease with low bone mass on long-term Gluten-free diet. J Clin Gastroenterol 2019;53:x221-6.

7. Hassan K, Kader AH. Celiac disease: The search for adjunctive or alternative therapies. Expert Rev Gastroenterol Hepatol 2014;8:313-21.

8. Makharia GK. Current and emerging therapy for celiac disease. Front Med (Lausanne) 2014;1:6-8.

9. Plugis NM, Khosla C. Therapeutic approaches for celiac disease. Best Pract Res Clin Gastroenterol 2015;29:503-21.

10. Freeman HJ, Chopra A, Clandinin MT, Thomson AB. Recent advances in celiac disease. World J Gastroenterol 2011;17:2259-72.

11. Binkovitz LA, Henwood MJ. Pediatric DXA: Technique and interpretation. Pediatr Radiol 2007;37:21-31.

12. Sahin Y. Clinical evaluation of children with celiac disease: A single-center experience. Arch Clin Gastroenterol 2020;6:26-30.

13. Bhattacharya M, Kapoor S, Dubey AP. Celiac disease presentation in a tertiary referral centre in India: Current scenario. Indian J Gastroenterol 2013;32:98-102.

14. Gomes RC, Maia JC, Arrais RF, Jatobá CAN, Rocha MAC, Brito MEF, et al. The celiac iceberg: From the clinical spectrum to serology and histopathology in children and adolescents with type 1 diabetes mellitus and Down syndrome. Scand J Gastroenterol 2016;51:178-85.

15. Khattib M, Baker RD, Ly EK, Kozielski R, Baker SS. Presenting pattern of pediatric celiac disease. J Pediatr Gastroenterol Nutr 2016;62:60-3.

16. Hota D, Bhalla K, Nanda S, Gupta A, Mehra S. Beneficial effects of gluten free diet on IgA tissue transglutaminase levels and various growth parameters in celiac disease patients. J Family Med Prim Care 2019;8:823-7.

17. Balamtekin N, Uslu N, Baysoy G, Usta Y, Demir H, Saltik-Temizel IN, et al. The presentation of celiac disease in 220 Turkish children. Turk J Pediatr 2010;52:239-44.

18. Saeed A, Assiri A, Assiri H, Ullah A, Rashid M. Celiac disease in Saudi children: Evaluation of clinical features and diagnosis. Saudi Med J 2017;38:895-9.

19. Fedewa MV, Bentley JL, Higgins S, Kindler JM, Esco MR, MacDonald HV. Celiac disease and bone health in children and adolescents: A systematic review and meta-analysis. J Clin Densitom 2020;23:200-11.

20. Mora S, Barera G, Ricotti A, Weber G, Bianchi C, Chiumello G. Reversal of low bone density with a gluten-free diet in children and adolescents with celiac disease. Am J Clin Nutr 1998;67:477-81.

21. Choudhary G, Gupta RK, Beniwal J. Bone mineral density in celiac disease. Indian J Pediatr 2017;84:344-8.

22. El-Shaheed AA, El-Arab AE, El-Kassas1 GM, El Wakeel MA, Abou-Zekri M, El-Banna M. An innovative effective nutritional therapy for vitamin D deficiency in children with celiac disease. Biomed Pharmacol J 2019;12:1481-90.

23. Kalayci AG, Kansu A, Gırgın N, Kucuk O. Bone mineral density and importance of a gluten-free diet in patients with celiac disease in childhood. Pediatrics 2001;108:89-91.

24. Tau C, Mautalen C, De Rosa S, Roca A, Valenzuela X. Bone mineral density in children with celiac disease. Eur J Clin Nutr 2006;60:358-63.

25. Valdmarsson T, Lofman O, Toss G. Reversal of osteopenia with diet in adult coeliac disease. Gut 1996;38:322-7.

26. Micic D, Rao VL, Semrad CE. Celiac disease and its role in the development of metabolic bone disease. J Clin Densitom 2020;23:190-9.