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Research Article

Evaluation of Micronutrient Deficiencies and Growth in Children with Celiac Disease

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ABSTRACT

Background: *Celiac Disease (CD)* is a serious autoimmune *disease* that occurs in genetically predisposed people where the ingestion of gluten leads to damage in the small intestine and its destruction leads to malabsorption. Impaired growth and micronutrient deficiencies are a well-known complication in celiac disease.

Objective: We aimed to analyze growth status of children with CD and to compare with healthy subjects and to evaluate frequency of micronutrient deficiency in children with CD.

Patients and methods: We reviewed the medical records of 70 children with CD and 57 age and sex-matched healthy controls. Age and sex specific height, weight and Body Mass Index (BMI) standard deviation scores were calculated with national reference data. Growth retardation was defined as the Height for Age Z score (HAZ)<-2, undernutrition as the Weight for Age Z score (WAZ)<-2, severe malnutrition as the Body Mass Index Z score (BMIZ)<-2, and obesity was defined as BMIZ more than +2. Age, gender, medical and physical examination findings, laboratory tests, upper GI endoscopy and biopsy results were recorded for each patient.

Results: Seventy children with CD and 57 controls were enrolled no significant differences were found between the two groups in terms of age or gender. The mean WAZ, HAZ and BMIZ scores of the CD group were -1.2 ± 1.13, -0.92 ± 1.19 and -1.0 ± 1.14 respectively (Table 1). The mean WAZ, HAZ and BMIZ scores were significantly lower in the CD group compared to the control group ($p<0.001$, $p<0.001$ and $p=0.005$ respectively). The prevalence of undernutrition, growth retardation and chronic malnutrition in the CD patients were 24.3% (n=17), 17.1% (n=12) and 14.3% (n=10) respectively. Vitamin D, zinc, iron and vitamin A deficiency were most commonly observed in the children with CD (60%, 44.1%, 41.2% and 37.5% respectively)

Conclusion: Children admitted with celiac disease should be evaluated for nutritional status and micronutrient deficiencies.

Keywords: Celiac disease; Nutritional status; Body mass index; Vitamins

INTRODUCTION

Celiac Disease (CD) is a systemic, immune-mediated, enteropathic disorder that is triggered by gluten in the diet in genetically-predisposed individuals. The prevalence of CD in children worldwide is about 0.5%-1%. The prevalence of CD in the Turkish population is 0.47%-0.99%. The disease can be seen in typical, atypical and silent forms. Clinical findings vary according to disease type.

Typical CD usually begins between 6 and 24 months of age, with symptoms such as chronic diarrhea, abdominal distension and weight loss. Apart from these findings, the disease may present with a wide spectrum extra intestinal manifestations [1]. Today, approximately 50% of the patients are diagnosed with non-gastrointestinal symptoms such as impaired growth and delayed puberty. Gluten Free Diet (GFD) is required to achieve remission and catch up growth.

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Study reports on growth of children with celiac disease on long-term GFD are not consistent. Therefore, it is important to monitor growth in children with celiac disease.

CD is characterized by malabsorption due to villous damage in the small intestine. This malabsorption results in a number of nutritional deficiencies that involve macronutrients and micronutrients. These deficiencies may cause changes in various physiological processes in patients. A strict GFD is the only treatment strategy available for CD in clinical practice. If a GFD is adhered to strictly, symptoms may resolve, histological and laboratory findings may return to normal. However, adhering to this type of restrictive diet is often challenging and it also can contribute to potential nutrition imbalance (eg, micronutrients deficiency) [2]. Currently, it is unclear which types of nutrient deficiencies are frequently present in CD patients during treatment with a GFD. Therefore, nutrition care is crucial for individuals with CD to improve the health of those patients. Previous studies have shown that nutritional deficiencies affect 20%-38% of CD patients. The nutritional deficiencies observed in celiac disease may be due to CD itself and/or be a consequence of the GFD.

We aimed to analyze growth status of children with CD and to compare with healthy subjects and to evaluate frequency of micronutrient deficiency in children with CD [3].

MATERIALS AND METHODS

In this retrospective observational cross-sectional study, we reviewed the medical records of 70 children with celiac disease followed in the pediatric gastroenterology department, Kecioren training and research hospital outpatient clinic during the period from June 2017 to December 2019 and 57 age and sex matched healthy controls. The study protocol was approved by the local ethics committee. Children were eligible if they were under 18 years of age in both two groups. Patients with a diagnosis of CD according to European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) 2012 criteria were included [4]. Modified marsh (Oberhuber) classification was used to histopathological evaluation of small intestine. Patients with gastrointestinal symptoms such as chronic diarrhea and malabsorption were regarded as classical CD, those with unusual intestinal complaints such as recurent abdominal pain and constipation or extraintestinal symptoms such, as anemia and short stature, were classified as atypical CD. Recurrent abdominal pain in children is defined as at least three episodes of pain that occur over at least three months and affect the child's ability to perform normal activities. Constipation was diagnosed according to Rome IV criteria [5].

Control subjects were included if they had no evidence of inflammatory or chronic disease. CD patients, who were known to have other diseases that might have an impact on height, weight and nutritional status, were excluded from this study. Control subjects were excluded if they had a diagnosis of any disease that affects growth, nutritional status, dietary intake or development. Data were collected from the database of our hospital's electronic medical record system. ICD-10 codes including K90.0 (Celiac disease) was used to identify the patients with CD.

Age and sexspecific height, weight and Body Mass Index (BMI) Standard Deviation Scores (SDSs) (z-scores) were calculated with national reference data.

The CD patients included in the study were divided into two groups: Newly diagnosed CD patients: Patients who were diagnosed with celiac disease between the study dates were included in this group. Follow-up patients with CD: Patients with celiac disease followed for at least one year were included in this group. If follow-up patients have negative tissue transglutaminase IgA and/or endomysial antibody after a GFD, they are classified as Gluten-Free Diet-Compatible (GFD^+) CD patients. If positive tissue transglutaminase IgA and/or endomysial antibody are present after a GFD, they are classified as gluten-free diet-incompatible (GFD^-) CD patients [6].

The following data were recorded for each patient: Age, gender, medical and physical examination findings, laboratory tests, Upper GI Endoscopy (UGIE) and biopsy results. Laboratory tests that were included are as follows: Complete blood count, biochemical panel (blood glucose level, liver and kidney function tests and electrolytes), vitamins (vitamin A, E, D, B_{12} and folic acid), trace elements and minerals (zinc, magnesium and iron). All blood samples were taken after at least 8 hours of fasting for vitamin, trace element and mineral evaluation. The Hemoglobin (Hb) and Mean Corpuscular Volume (MCV) levels of patients were evaluated according to their age and gender. Iron deficiency was defined if serum ferritin was <12 ng/ml, iron deficiency anemia was defined if Hb values were low for age and serum ferritin was <12 ng/ml.

The other laboratory test results were interpreted according to our hospital laboratory's reference intervals. Deficiency was defined as a concentration below the reference interval [7]. Growth Retardation (GR) was defined as the Height for Age Z score (HAZ)<-2, undernutrition as the Weight for Age Z score (WAZ)<-2, severe malnutrition as the Body Mass Index Z score (BMIZ)<-2 and obesity was defined as BMIZ more than +2.

Bone Mineral Density (BMD) was measured at the Lumbar Spine (L1-4) using Dual-Energy X-Ray Absorptiometry (DEXA). Osteoporosis was defined if the z score was less than -2 and osteopenia was defined if z score was between -1 and -2. Statistical analysis was performed with SPSS software version 23 (SPSS, Chicago, IL) and statistical significance was set at a P-value of <0.05. Descriptive tests, t-test, Mann-Whitney U test, and χ^2 test were used.

RESULTS

Seventy children with CD and 57 controls were enrolled no significant differences were found between the two groups in terms of age or gender (Table 1). In the CD group, the median age was 12 years (range; 2.5-18 years), 35 children were male (Table 1). The mean age at diagnosis was 9.42 ± 4.29 years (range 2-17 years). The median follow-up of CD patients was 13.5 months (range; 0-180 months). Among 70 patients with CD included in the study, there were 34 patients who were newly diagnosed. The demographic characteristics of the patients are shown in Table 1.

Thirty-one of the CD patients (44.3%) were atypical CD patients. The most frequent symptom was recurrent abdominal pain and/or abdominal distention (25.8%) followed by failure to thrive (24.2%), short stature (18.2%), diarrhea (12.1%), iron deficiency anemia (4.5%), constipation (3%), vomiting and nausea (1.5%) and recurrent oral ulcers (1.5%). Duodenum biopsy of 6 (9.4%) CD patients was compatible with Marsh 3a, 29 (45.3%) patients with Marsh 3b and 29 (45.3%) patients was compatible with marsh 3c of 34 patients followed-up with CD, 22 (61.1%) were in full compliance with their diet [8].

The mean WAZ, HAZ and BMIZ scores of the CD group were -1.2 ± 1.13 -0.92 ± 1.19 and -1.0 ± 1.14 respectively (Table 1). The mean WAZ, HAZ and BMIZ scores were significantly lower in the CD group compared to the control group (p<0.001, p<0.001 and p=0.005 respectively) (Table 1). The prevalence of under-nutrition, growth retardation and chronic malnutrition in the CD patients were 24.3% (n=17), 17.1% (n=12) and 14.3% (n=10) respectively. There were no patients who were obese.

Table 1: Demographic characteristics.

	CD group (n=70)	Control group (n=57)	P-value
Age (year)	11.54 (± 4.03)	11.96 (± 3.5)	0.54
Sex (male), n (%)	35 (50)	25 (43.9)	0.49
Prepubertal, n (%)	29 (41.4)	19 (33.3)	0.35
HAZ*	-0.92 (± 1.19)	-0.2 (± 0.05)	<0.001
WAZ*	-1.2 (± 1.13)	-0.18 (± 1.01)	<0.001
BMİZ*	-1.00 (± 1.14)	-0.3 (± 1.26)	<0.001

The mean WAZ, HAZ and BMIZ scores were significantly lower in the all follow-up CD patients compared to the control group (Table 2). There was no statistically significant difference the mean WAZ, HAZ and BMIZ scores of the control group and the GFD+ patients (p=0.07, p=0.14 and p=0.12 respectively).

The prevalence of under-nutrition, growth retardation and chronic malnutrition were not different from each other in newly diagnosed, GFD^+ and GFD^-, CD patients (p=0.81, p=0.95 and p=0.80 respectively).

Table 2: Comparison of anthropometric parameters.

	Newly diagnosed celiac patients (n=34)	Follow-up celiac patients (n=36)	Control group (n=57)	P-value	GFD^+ celiac patients	GFD^- celiac patients	Control group	P value
WAZ	-1.26 ± 1.12	-1.15 ± 1.16	-0.18 ± 1.01	<0.001	-0.85 ± 1.11	-1.64 ± 1.112	-0.18 ± 1.01	<0.001
HAZ	-1.05 ± 1.3	-0.80 ± 1.16	-0.02 ± 0.05	<0.001	-0.63 ± 1.2	-1.07 ± 0.91	-0.02 ± 1.05	<0.001
BMIZ	-0.90 ± 1.1	-1.10 ± 1.17	-0.30 ± 1.26	0.005	-0.97 ± 1.16	-1.03 ± 1.21	-0.30 ± 1.26	0.01

Mean Hb value of the CD patients was 13.26 (range: 7.5-16.3) mg/dl. Of the CD patients 8 (16.3%) had anemia and of these patients, were newly diagnosed celiac disease patients (p=0.26). Iron deficiency was detected in 41.2% (n=28) of the patients with CD [9].

All patients had normal serum albumin levels (mean=4.4 g/dl, range: 3.7-5 g/dl). Only 2 newly diagnosed CD patients has elevated ALT levels. Extensive transaminase elevation investigations were performed in the children with high ALT levels, but it did not reveal any autoimmune or other etiological causes.

DISCUSSION

The clinical manifestations of CD are extensive and varied and are no longer isolated to the gastrointestinal tract. The classic presentation with growth retardation, malnutrition, diarrhea, abdominal pain and distension within the first couple of years of life represents the tip of what is commonly referred to as the "celiac disease iceberg". Children and adolescents often present with short stature and nonspecific abdominal complaints. Similarly, approximately half of our patients were diagnosed with atypical findings [10].

Two to 10% of children and adolescents presenting for evaluation of short stature have evidence of celiac disease.

When other causes for short stature were excluded, the prevalence could rise up to 59%. In our study, CD presented with short stature as a manifestation in 18.2% patients. Therefore, in the diagnostic work-up of a short child investigation of CD is recommended.

It has been shown that majority of children with CD show rapid improvement in symptoms, normalization of nutrition and substantial improvement in height and attain road to health percentile curves on GFD. But, catch-up growth may not always catch up completely especially late-diagnosed CD patients; This could be due to the following: Catch-up in height in severely stunted children takes a relatively longer time even with a favorable environment, multiple alterations occur in the growth axis (growth hormone-binding proteins, insulin-like growth factor-1, insulin like growth factor binding protein) during the active phase of the disease, negative effects of CD on growth. In our patients, the rate of growth retardation was 17.6% in newly diagnosed CD patients and in 18.2% in GFD$^+$ patients. In our patients, this situation may be due to the late diagnosis and short follow-up [11].

The literature to date suggests that micronutrient deficiencies are common with CD and recent guidelines on the diagnosis and management of CD recommend testing for nutrient deficiencies regardless of presentation at diagnosis, and this assessment should include calcium, vitamin D, iron, folic acid, vitamin B_{12} and Zinc. Complications as a result of these nutrient deficiencies may affect a child's growth, development and overall well-being. A large study evaluating more than 1000 adult and pediatric CD patients found low ferritin in 50% of patients, low vitamin B_{12} in 6.6%, and low folate in 73.8%. Another study of 93 patients with CD in Turkey found 81.6% of patient's anemic, 64.1% with zinc deficiency, 8% with low vitamin B_{12} and 18.3% with low folate. Other micronutrients have been evaluated in the past, including low vitamin D seen in 33% of 93 patients with CD and low serum zinc was seen in 51% of patients with newly diagnosed CD and in 67% of patients with CD in another study. We determined that 75% of the newly diagnosed CD patients had vitamin D deficiency, 52.9% iron, 50% vitamin A, 37.5% zinc, 15.2% vitamin B_{12} and 10.3% of the newly diagnosed CD patients had folate deficiency. Our data were consistent with these previous studies.

In subjects undergoing GFD for a long time with good compliance, it has been described that micronutrient deficiencies may persist due to the following: Full reintegration of the mucous membrane is inadequate for a long time; gluten-free products are usually low in some micronutrients, such as magnesium and folic acid and gluten-free cereals found in nature have a lower magnesium content compared with gluten-containing ones; youth with CD tend to intake foods containing high sugar and saturated fat and low fibre, vitamin D, calcium, folate and potassium. Similarly, in our study, trace element and vitamin deficiencies were found to be high even among the patients with good compliance [12].

Iron deficiency anemia is a frequent finding in CD patients, as in our study. Iron deficiency anemia is itself an independent clinical manifestation of either well established celiac disease or may lead to its initial recognition, especially if other causes have been excluded and iron deficiency appears refractory to oral iron treatment.

As a result of disease localized in the proximal small intestinal mucosa, impaired duodenal iron absorption can be seen, even if there is provision of added oral iron of our CD patients 8 (16.3%) had anemia and of these patients, were newly diagnosed celiac disease patients. Iron deficiency was detected in 41.2% (n=28) of the patients with CD. In children, iron deficiency anemia in celiac disease is common and further screening with tissue transglutaminase antibodies has been strongly recommended.

CD is known as a cause of bone loss, mineral metabolism deterioration and metabolic osteopathy. Reduced bone mineral density has a prevalence as high as 75% in patients with CD and can occur in the absence of gastrointestinal symptoms. In a few studies classic presentation correlated more with severe bone loss and Gluten Free Diet (GFD) may increases the BMD in these cases. Increase in cytokines in lamina progeria and serum might have an important role in pathophysiological aspect of bone loss in CD cases. Low BMD make patients at risk of bone fracture and disability and even shorter height in CD. Low bone mineral density was reported in 58%-65% of children with newly diagnosed celiac disease. Prevalence of low bone mineral density was 75% in our study.

The limitations of our study include the small number of patients in both the study and control groups and the retrospective nature of the study. In conclusion, we recommend that children admitted with celiac disease should be evaluated for nutritional status and micronutrient deficiencies [13].

CONCLUSION

This study shows that problem solving and decision-making abilities in a game-based learning environment have an impact on the employees' problem solving and decision-making abilities. Thus, it is essential to design game-based testing and learning environment to scaffold employees' problem solving and decision making which were influenced through gamification, however not significantly on each other as different variables. Not all the games are necessarily designed as complex to engage employees in problem solving tasks and the time taken depends on their level of complexity and the employees' understanding of the rules, therefore gamification or game-based testing is not the only variable that enhances employees' higher order cognitions, but is challenged. The study reveals that there are complex interplay between gamification and higher order cognitions, the gamified tests can enhance or limit the employees' choices or decisions made while understanding and solving of complex problems, there exists some amount of effect of problem solving on decision making because of the order or gamified tests that were administered and however, there exists individual differences and other factors that play a role in determining the relationship between all the three variables. Therefore, in order to foster employee's problem and decision making abilities of the millennial employees, gamified tasks and real life simulations should be designed in a way that provides complexity for employees to go up the ladder and learn through their experiences of engaging in tasks that teach them problem solving and decision making through games, with sufficient autonomy for employees to make choices and attainable challenges to help them move closer to their intended goals.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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REFERENCES

1. Fasano A. Clinical presentation of celiac disease in the pediatric population. Gastroenterology. 2005;128(4):68-73.
2. Mustalahti K, Catassi C, ReunanenA, Fabiani E, Heier M, McMillan S, et al. The prevalence of celiac disease in Europe: Results of a centralized, international mass screening project. Ann Med. 2010;42(8):587-595.
3. Dalgic B, Sari S, Basturk B, Ensari A, Egritas O, Bukulmez A, et al. Prevalence of celiac disease in healthy Turkish school children. Am J Gastroenterol. 2011;106(8):1512-1517.
4. Gursoy S, Guven K, Simsek T, Yurci A, Torun E, Koc N, et al. The prevalence of unrecognized adult celiac disease in central Anatolia. J Clin Gastroenterol. 2005;39(6):508-511.
5. Bottaro G, Cataldo F, Rotolo N, Spina M, Corazza GR. The clinical pattern of subclinical/silent celiac disease: An analysis on 1026 consecutive cases. Am J Gastroenterol. 1999;94(3):691-696.
6. Soliman AT, Laham M, Jour C, Shaat M, Souikey F, Itani M, et al. Linear growth of children with celiac disease after the first two years on gluten-free diet: A controlled study. Acta Biomed. 2019;90(8):20-27.
7. Hallert C, Grant C, Grehn S, Midhagen G, Svensson H, Valdimarsson T, et al. Evidence of poor vitamin status in coeliac patients on a gluten-free diet for 10 years. Aliment Pharmacol Ther. 2002;16(7):1333-1339.
8. Leonard MM, Sapone A, Catassi C, Fasano A. Celiac disease and nonceliac gluten sensitivity: A review. JAMA. 2017;318(7):647-656.
9. Cheng FW, Handu D. Nutrition assessment, interventions and monitoring for patients with celiac disease: An evidence analysis center scoping review. J Acad Nutr Diet. 2020;120(8):1381-1406.
10. Di Nardo G, Villa MP, Conti L, Ranucci G, Pacchiarotti C, Principessa L, et al. Nutritional deficiencies in children with celiac disease resulting from a gluten-free diet: A systematic review. Nutrients. 2019;11(7):1588.
11. OberhuberG, Granditsch G, Vogelsang H. The histopathology of coeliac disease: Time for a standardized report scheme for pathologists. EurJ Gastroenterol Hepatol. 1999;11(10):1185-1194.
12. Reust CE, Williams A. Recurrent abdominal pain in children. Ame Fam Physician. 2018;97(12):785-793.
13. Neyzi O, Bundak R, Gokcay G, Furman A, Darendeliler F, Bas F, et al. Reference values for weight, height, head circumference and body mass index in Turkish children. J Clin Res Pediatr Endocrinol. 2015;7(4):280-293.