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Research Article

Anthropometric Indices and Clinical Manifestations After Gluten Free Diet Therapy and Nutritional Education in Pediatric Patients with Celiac Disease

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Abstract

Celiac disease (CD) is an immune enteropathy with wide heterogeneous symptoms which can affect children's growth. Since gluten-free diet (GFD) is the only treatment available for CD, the aim of the present study was to evaluate anthropometric indices and symptoms recovery in children with CD after treatment with a GFD. Seventy-four children with age of 2-18 years old and diagnosed with CD recruited from XXX specialized clinic in a quasi-experimental retrospective study. Height, weight, Body Mass Index (BMI), malnutrition based on WHO growth charts, and clinical symptoms were collected from patients' records. A GFD was prescribed by a nutritionist and patient's nutritional needs including the amount of calories and the percentage of macronutrients were calculated. The results indicated a significant difference in height ($p < 0.001$), weight ($p < 0.001$), and height z-score ($p = 0.003$) before and after the intervention. No difference was seen in number of patients in different height z-scores. However, number of patients with low body weight and BMI for age had decreased at the end of study compared to the beginning. There was a remarkable reduction in clinical symptoms including diarrhea, flatulence, abdominal pain, constipation, hair loss, skin dryness and weight loss ($p < 0.05$). However, the number of patients with abdominal distention increased significantly. To sum up, adherence to GFD may lead to improvements in body weight and height in underweight children. Moreover, GFD have beneficial effects in reduction of CD manifestations. Further prospective trials are warranted.

Keywords: Celiac Disease; Gluten; Height; Body Weight

Introduction

Celiac disease (CD) as a gluten sensitive immune disorder is triggered by protein complex in wheat, rye, and barley in genetically predisposed individuals with HLA-DQ alleles [1,2]. The gliadin fraction in wheat, along with hordeins and secalins in barley and rye are responsible for intestinal mucosa damage [3]. Based on recent epidemiological evidences, globally 1.4% of general population suffer from CD [4]. Nevertheless, CD is still widely under-recognized [5].

The clinical manifestations of CD vary from asymptomatic or silent with lack of features, to symptomatic or classic form. Classic features include malabsorption, chronic diarrhea, abdominal pain and fatigue. However, some extra-intestinal symptoms such as osteoporosis, anemia, elevated liver enzymes, neurologic problems and short stature become more dominant in last decades [6,7].

Among children, CD has wide spectrum and heterogeneous symptoms, with prevalent occurrence of delayed puberty, failure to thrive and short stature. These complications might be due to a long duration of the disease, growth hormone (GH) deficiency and chronic malabsorption of nutrients [8]. On the other hand, CD might also accompany by other autoimmune disorders in childhood, including thyroiditis and type 1 diabetes mellitus. Some

investigators insist on the early diagnosis and treatment of CD to prevent its related complications [9].

Although some scientific efforts have been made to prevent or cure the manifestations of CD, up to now the only treatment is permanent, strict adherence to the gluten-free diet (GFD) [10,11]. Compliance with GFD may modulate CD related complications in adults and return normal growth and development in children [12].

It has been found that 10-47.5% of pediatric celiac patients have short stature as the first extra-intestinal presentation at the time of diagnosis [13,14]. Also 19-59% of the non-endocrinologic causes of short stature are reported to be celiac disease. Poor growth has been more often observed in children with a more severe celiac disease onset [13,14].

Since short stature and growth retardation is prevalent in children with CD, correcting this condition through diet therapy should be considered in the treatment regimen. As there is limited evidences about the effects of GFD on mentioned complications [15,20], the aim of the present study was to evaluate symptoms recovery and malnutrition indices improvement in children with CD after treatment with a GFD. Accordingly, by reducing the complications of the disease, the quality of life of the patients will be increased.

Methods

Study design

The present retrospective Quasi Experimental study performed between the years 2016 and 2019. The subjects were referred to XXX Specialized Clinic for CD. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects/patients were approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1398.1153). Written informed consent was obtained from all patients. A comprehensive database of 361 patients' information in past 3 years was available and after ethical code approval, we were referred to the clinic to extract the desired data. It should be noted that since leaving the patient without treatment is not ethical, patients cannot be left as a control group without diet. Therefore, this study lacks a control group. Moreover, our study lacked blindness because it was designed based on diet therapy and nutrition education. Informed consent was also obtained from the parents/legal guardians of the patients involved in the study after explaining the aim, method, and goal of the research.

The patients recruited in this study were children with positive serologic test and biopsy-proven of CD based on the diagnosis of a gastroenterologist. Children in the age range of 2-18 years old and having at least two visits with a record of height, weight and body mass index (BMI) were included in the study. It should be noted that in order to eliminate the effect of time, only those individuals who had referred to the clinic with an interval of 3 months were included in the study. Patients who did not have records with an interval of 3 months were excluded. Totally, 74 patients were eligible to participate in the study and their records were reviewed retrospectively. Sex, age of diagnosis, height, weight, BMI, and clinical symptoms were collected from patients' records. The height was measured by a portable stadiometer without shoes and an accuracy of 0.1 cm and weight was assessed by a calibrated scale (Omron, Korea) with light dressing and to the nearest 0.1 kg [21]. BMI was calculated by dividing weight (kg) by height squared (m) before and after the GFD [21]. Based on World Health Organization (WHO) criteria, values less than -2 z-score, between -2 to + 2, and higher than +2 are classified as low, normal and high amounts of height, weight and BMI for age [22].

All the patients were monitored by a nutritionist, received educational package including booklets having pictures of gluten containing foods and celiac recipes, DVDs containing training clips, and brochures. A group class (groups of 9-10 patients with their parents in a two-hour session) aiming at enhancing the interaction between the dietitian and the pediatric patients was held, and each individual received nutrition counseling and training. Each patient's nutritional needs was calculated by a nutritionist, including the amount of calories and the percentage of macronutrients and an individualized GFD was prescribed for pediatric patients with CD. Patients were followed for three months by weekly phone calls, and monthly clinical assessments by the nutritionist through face-to-face visit in which all the symptoms and anthropometric measurements were evaluated. GFD adherence was evaluated by a trained nutritionist through five point Likert rating system [23]. Patients were classified into two groups of adequate compliance (1 or 2) and inadequate compliance (3-5). In addition, self-reported adherence rate was also measured among participants. This rate was classified as (A: 60-100%, B: 30-60%, C: 0-30% adherence).

Statistical analysis

SPSS software, version 21.0 (SPSS Inc., Chicago, IL, USA) was used to perform statistical analysis. Kolmogorov-Smirnov test were used to measure the normality of variables. Frequency and frequency percentage were reported to describe qualitative variables and mean and standard deviation (SD) was used for quantitative variables. To compare anthropometric indices (height, weight, and BMI) before and after treatment regimen, paired sample t-test was used. Also to assess the presence or absence of clinical symptoms before and after treatment regimen, McNemars test was used. P value < .05 was considered to be statistically significant.

Results

Of the 361 pediatrics with known celiac disease, 74 (20.4%) had recorded anthropometric data and GFD adherence from at least two separate visits in this retrospective study. 59.5% of included participants were rated as adequate GFD adherence. The patients' baseline characteristics is illustrated in table 1. Seventy-four children including 24 (32.4%) boys with the mean age of 9.4 (3.5) years and 50 (67.6%) girls with the mean age of 8.4 (3.3) years recruited in this research. No significant difference was seen between the age of girls and boys. Subjects were followed for 3.03 (0.3) months. The mean of height, weight and BMI of participant were 129.03 cm, 27.04 kg and 15.5 kg/m^2 respectively. 21.6% and 5.4% of subjects had other associated complications including diabetes mellitus type 2 and hypothyroidism respectively. Based on serological assessment, the anti-tissue transglutaminase (TGA-IgA) level was 125.5 (176.7) (U/ml).

Variables	Celiac patients (n = 74)
Demographics	
Male	*24.0 (32.4)
Female	50.0 (67.6)
Age (yrs)	†9.38 ± 3.51
Age of diagnosis (yrs)	8.43 ± 3.27
Duration of disease (yrs)	0.95 ± 1.81
Anthropometrics	
Height (cm)	129.03 ± 20.68
Weight (kg)	27.04 ± 10.81
BMI (kg/m2)	15.52 ± 1.99
Associated disorders	
Diabetes mellitus type 1	16.0 (21.6)
Hypothyroidism	4.0 (5.4)
Serologic marker	
TGA-IgA (U/ml)	125.55 ± 176.68

Table 1: Baseline characteristics of children with celiac disease.

BMI: Body Mass Index; TGA-IgA: Anti-Tissue Transglutaminase

*Number (%); † Mean ± SD.

Based on presented results in table 2, there was a significant difference in height (P < .001), weight (P < .001), and height z-score (P = .003) before and after the intervention.

Height, weight and BMI of patients at the beginning and at the follow-up, based on WHO categorization, was given in table 3. No difference was seen in number of patients with different height z-score before and after the intervention. However, number of patients with low body weight for age (Z-score < -2) at the end of intervention were lower (16 vs 12 patients) and those with normal weight (-2 < z-score < +2) increased (58 vs 62 patients) compared to the beginning. Number of subjects with normal BMIs was increased compared to study initiation (60 vs 61).

Variable	Before intervention		After intervention		P-value
	Mean	SD	Mean	SD	
Height	129.03	20.68	130.84	20.25	P < 0.001*
Weight	27.04	10.81	27.95	11.23	P < 0.001*
BMI	15.52	1.99	15.56	2.10	P = 0.71
Height for age z-score	-0.88	1.05	-0.80	1.00	P = 0.003*
Weight for age z-score	-1.23	0.95	-1.16	0.94	P = 0.15
BMI for age z-score	-0.95	1.03	-0.96	0.97	P = 0.97

Table 2: Characteristics of participants before and after intervention.

BMI: Body Mass Index; Z-Scores Based on World Health Organization (WHO). P < 0.05 considered significant.

*Paired sample t-test used to compare anthropometric indices.

Variable	Height for age N (%)		Weight for age N (%)		BMI for age N (%)	
	Before	After	Before	After	Before	After
<-2	8.0 (10.80)	8.0 (10.80)	16.0 (21.60)	12.0 (16.20)	14.0 (19.00)	13.0 (17.60)
-2_2	66.0 (89.20)	66.0 (89.20)	58.0 (78.40)	62.0 (83.80)	60.0 (81.00)	61.0 (82.40)
≥2	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)

Table 3: Nutritional status of children with CD before and after GFD based on WHO criteria.

BMI: Body Mass Index

Comparison of the frequency of common manifestations of CD among children presented in table 4. The results showed that there was a statistically significant reduction in patients suffered from clinical symptoms including diarrhea, flatulence, abdominal pain, constipation, hair loss, skin dryness and weight loss (P < .05), but skeletal pain (P = .19) and nausea (P = .06) didn't change remarkably.

The most common symptom at the beginning of the study was abdominal pain (67.6%) which reduced to 9.5% at the final assessment after GFD. In contrast, the number of patients with abdominal

Clinical manifestations	Before n (%)	After n (%)	P-value
	Yes	Yes	
Diarrhea	16.0 (21.6)	3.0 (4.1)	<0.001*
Flatulence	12.0 (16.2)	4.0 (5.4)	0.04*
Abdominal pain	50.0 (67.6)	7.0 (9.5)	<0.001*
Abdominal distention	1.0 (1.4)	11.0 (14.9)	0.006*
Constipation	22.0 (29.7)	5.0 (6.8)	<0.001*
Nausea	6.0 (8.1)	1.0 (1.4)	0.06
Skeletal pain	19.0 (25.7)	12.0 (16.2)	0.19
hair loss	12.0 (16.2)	3.0 (4.1)	0.02*
skin dryness	15.0 (20.3)	3.0 (4.1)	<0.001*
Weight Loss	14.0 (18.9)	0.0 (0.0)	<0.001*

Table 4: Clinical symptoms of pediatric patients with CD before and after GFD.

P < 0.05 considered significant.

* McNemars test was used.

distention increased from 1 to 11 after the intervention. Moreover, the percentage of children suffered from weight loss reached 0 at the end of study (P < .001).

Discussion

The results of present study demonstrated that GFD improved malnutrition in terms of body weight and BMI in children with CD. In addition, GFD modulated manifestations of the disease, except for skeletal pain, nausea and abdominal distention. Although the majority of the participants in our study had normal height, weight and BMI and no change in height values were detected, an incremental trend in body weight and BMI was observed.

CD is known as one of the most common lifelong diseases and may manifests with atypical or silent symptoms. If the disease remains undiagnosed, without a proper intervention, the risk of long-term complications would increase [11,24,25]. Since more than 10 mg per day gluten content of diet may lead to intestinal mucosa damage [26], GFD is the only option for patients with CD which might reverse destructive effects of the disease on children growth [11,24,27]. GFD is effective in alleviating CD in pediatric patients and could cause remarkable catch up growth [28]. Compliance to GFD is associated with intestinal lesion recovery and improvement of body composition [29]. In addition, in children with CD growth hormone response is disturbed which disappears after adherence to GFD [30]. Based on Boersma., *et al.* study, following GFD, gradual increase in Insulin Growth Factor-1 (IGF-1) and Insulin Growth Factor-2 (IGF-2) levels was seen [28]. It should be noted that nutritional education and frequent evaluation by an expert dietitian in patients with CD results in good compliance with GFD [10]. Compliance rate to GFD is considered as an important factor affecting results. This rate was about 60% in this study which was somehow near to the adherence rate to GFD in the studies done by Kabbani., *et al*. [18]. (66.7%) and Reilly., *et al.* [19]. (63%). While higher adherence rates to GFD were reported in investigations conducted by Dehghani., *et al*. [17]. and Ukkola., *et al.* [20]. (73.3% and 89% respectively), comparing the findings might be somehow difficult. In this regard, available data about the effect of GFD on growth and nutritional status in patients suffering from CD is controversial. Yachha., *et al*. investigated the effect of GFD on growth of children with CD. 76% of patients had height standard deviation scores (HSDS) < -2, while 60% of them were undernourished at diagnosis. Results obtained from follow up showed that HSDS significantly improved and 84% of pediatric patients achieved normal weight for height as an indicator of good nutrition [22]. In addition, Comba., *et al*. indicated that adherence to GFD in children and adolescents positively affected weight and BMI but not height values [31]. As Amin and associates claimed in their study on children with CD, GFD led to BMI improvement [32]. In a study conducted by Dehghani., *et al*. with the aim of evaluating a gluten-free diet on BMI; 44 children aged 3-12 years were on GFD for 2 years. Pediatric patients with celiac disease had lower BMI than the general population at the time of diagnosis. After following a GFD, body mass index increased significantly in all weight groups [17]. Also in 2010, a study by Cheng., *et al.* conducted to evaluate effect of GFD on body mass index in celiac patients; 369 celiac patients went on a GFD for 2.8 years. Patients who were underweight at the beginning of the study gained weight, and patients with overweight and obesity lost weight. The researchers cited specialized nutrition advices as the key factor in the beneficial effects observed [16]. In Ukkola., *et al*. study, 698 adults with celiac disease followed a GFD for one year. 69% of underweight patients became overweight, 18% of overweight people and 42% of obese people lost weight. BMI remained constant in the remaining individuals. According to this study, the desired changes in BMI were related to an individuals' skill and talent in following GFD and younger age at the time of diagnosis and was not related to the dietary advices received [20]. It's important to note that, adherence to GFD is not always satisfactory due to incorrect compliance with gluten restriction and lack of complete recovery of intestinal mucosa. In this regard, Bardella., *et al.* showed that adherence to GFD in adults with CD, was associated with lower BMI, lean mass and fat mass compared to healthy subjects. They emphasized on the lower energy intake and unbalanced energy sources, lower carbohydrate and a higher fat intake, in patients with CD than control participants [33]. In contrast, Saukkonen and colleagues investigated the effect of GFD on adults and children with CD, accompanied by diabetes mellitus type 1 (DMT1) [34]. The results showed a significant increase in weight-for-height compared to the beginning [34]. As we see in our results, high percentage of patients were well-nourished at the beginning and after

intervention, GFD led to a significant increase in weight and height. Thus nowadays, increased prevalence rate of CD in pediatrics with normal weight or even overweight might be a reflector of shift in disease manifestations [19].

Since CD causes a wide range of gastrointestinal (GI) symptoms, another aim of the present research was evaluating recovery from clinical complications. Based on our results several manifestations recovered, except for abdominal distention. In the present study, the increase in the number of children with abdominal distention might resut from change in dietary pattern and fiber intake. For instance, short-chain soluble and highly fermentable dietary fiber can cause abdominal discomfort and distension [35,36]. Murray., *et al.* showed that gluten exclusion results in rapid improvements in diarrhea, bloating, abdominal pain, nausea or vomiting and lactose intolerance which was in contrary with our results only in terms of bloating [37]. Also Mustalagti., *et al.* indicated that GFD was associated with GI symptoms reduction and quality of life improvements [38]. Midhagen., *et al*. evaluated GI Symptom Rating Scale including diarrhea, indigestion, abdominal pain, constipation, and reflux in adults in remission phase after 8-12 years of gluten restriction. Contrary to our results, their findings showed that adult CD patients on a GFD for several years experienced more GI symptoms such as indigestion, constipation, and abdominal pain compared to general population [39]. As Pulidoa., *et al.* indicated, in adult patients with more than 5 years adherence to GFD, GI symptoms especially diarrhea and nausea/vomiting continued to appear. This could stem from poor nutrition education and lack of knowledge about the gluten content of foods specially in products without label [40].

This research was limited in several ways. The first limitation of study was the design of the research which was retrospective and the second one was lack of control group due to ethical considerations. Lack of measuring body composition parameters is another limitation. In addition, short duration of follow up might be considered as a limiting factor for assessing nutritional indices in children especially height. Also we had no exact evaluation of the dietary amounts of micro and macro nutrients.

Conclusion

In conclusion GFD might improve growth retardation in terms of body weight and BMI among underweight children. Adherence to GFD also have beneficial effects on reduction of CD related complications. To reach more conclusive results, further prospective trials are warranted. Further clinical trials are needed to assess effects of adherence to GFD on serological tests such as TGA-IgA, GI biopsy, anemia, growth hormone, bone markers, depression, and quality of life in future.

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