RESEARCH ARTICLE

The impact of a gluten-free diet on the growth pattern of Saudi children with coeliac disease

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Abstract

Objective: To assess the growth pattern of children with coeliac disease after the introduction of a gluten-free diet.

Methods: The retrospective study was conducted at King Abdulaziz University Hospital, Jeddah, Saudi Arabia, and comprised data from January 2015 to December 2018 of children aged 2-16 years with biopsy-proven coeliac disease. Serial measurements of height-for-age and weight-for-age z-scores were recorded at 0, 4, 8, 12 and 16 months. Data on insulin-like growth factor-1 and insulin-like growth factor binding protein-3 obtained at diagnosis and during follow-up was retrieved. Clinical, demographic, and laboratory data was extracted from the patients' medical files. Data was analysed using SPSS 22.

Results: Of the 47 patients, 25(53.2%) were boys and 22(46.8%) were girls. The overall mean age was 8.7±3.4 years. There was a significant time effect for weight-for-age and height-for-age z-scores ($p<0.001$). There was significant increase in the secretion of insulin-like growth factor-1 and insulin-like growth factor binding protein-3 ($p<0.05$) during the first 8 months of a gluten-free diet.

Conclusion: The administration of gluten-free diet for Saudi children with coeliac disease normalized growth parameters and improved the endogenous secretion of growth factors.

Keywords: Celiac disease, Growth, Child, Saudi Arabia. (JPMA 71: 1388; 2021)

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Introduction

Coeliac disease (CD) is an immune-related enteropathy elicited by dietary gluten and related prolamins in genetically-susceptible individuals carrying human leukocyte antigen (HLA) DQ2 or DQ8 alleles and is characterised by a range of non-specific symptoms and signs, including faltering linear growth, stunting and poor weight-gain.[1] CD prevalence 1.5-2.2% has been reported in children in Saudi Arabia.[2,3] Growth impairment can be a significant manifestation of the disease in Saudi children; it is often an indication to look for CD.[4] Indeed, a significant proportion of Saudi Arabian children with CD present with isolated short stature.[5,6] The linear growth of children tends to improve solely with gluten-elimination from the diet, but a lack of response after one year of strict gluten-elimination should be investigated for the possibility of combined CD and growth hormone deficiency.[7] Many guidelines recommend screening for CD using serological tests in children with symptoms suggestive of CD, such as growth failure.[1,8,9]

Regardless of the mode of presentation, growth impairment in children with CD remains an important concern for most patients and their families.[10] Malnutrition resulting from malabsorption is the main determinant of growth failure, but impaired growth hormone (GH) secretion because of suppressed hypothalamic pituitary axis may also play a role in the mechanism of growth failure.[11] Anti-pituitary antibodies have been reported to contribute to linear growth impairment in children with newly-diagnosed CD, likely mediated via insulin-like growth factor-1 (IGF-1).[12] The secretion of IGF-1 and insulin-like growth factor-binding protein-3 (IGFBP-3) is significantly affected in patients with active CD following long-term gluten exposure.[13,14] A gluten-free diet (GFD) is reported to stimulate the secretion of IGF-1 and IGFBP-3 that may play a role in the catch-up growth process following the institution of a strict GFD.[15]

Life-long provision of GFD often reverses CD manifestation and stimulates linear growth through improvement of nutritional status and through recovery of the GH pituitary axis.[16-18]

To the best of our knowledge, there are currently no studies on the trend of growth pattern following the introduction of a GFD in Saudi children with CD. The current study was planned to fill the gap by assessing the pattern of linear growth of CD children following GFD, and by evaluating the association with GH and GH-related factors that can be utilised for monitoring linear growth response.

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Patients and Methods

The retrospective study was conducted at King Abdulaziz University Hospital, Jeddah, Saudi Arabia after approval from the institutional ethics review committee, and comprised data from January 2015 to December 2018. Data collection was commenced and completed between 1st and 31st of August 2019. Data was related to children with documented regular attendance at the paediatric gastroenterology clinic for the first 16 months post-diagnosis. Data of patients with associated co-morbidities affecting growth, such as chronic illnesses, endocrine disorders, and genetic and chromosomal abnormalities was excluded. Growth data comprising serial measurements of weight and height was extracted from the hospital's health information system. Clinical, demographic and laboratory data was collected from patients' medical charts.

CD diagnosis was based on the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) criteria[1]: having positive antibody testing to tissue transglutaminase-Immunoglobulin-A (tTG-IgA), followed by small intestinal biopsy obtained through upper gastrointestinal endoscopy for confirmation. The assessment of the adherence to GFD was based on dietary history and the normalisation of the initial tTG-IgA level following GFD commencement. Histopathology was graded using the Marsh-Oberhuber classification.[19]

Anthropometric measures, including serial measurements of height and weight, were collected at 0, 4, 8, 12, 16 months and converted to standard deviation (z) scores. Weight-for-age z-score (WAZ) and height-for-age z-score (HAZ) were calculated using Epi-Info 7.2.

Available results of investigations of GH or growth-related factors by the paediatric endocrinologist for patients with severe short stature were also recorded. The GH provocation test at the institution is usually performed using two pharmacological tests. Clonidine (150 micrograms/m^2 body surface area orally) and glucagon (15 micrograms/kg intramuscular [IM]) stimulation tests were performed on two different occasions, followed by a timely collection of blood samples at 0, 30, 60, 90, 120, 150, 180 and 210 minutes post-stimulation. The diagnosis of GH deficiency (GHD) was based on low GH response (peak GH level <10ng/mL) after the results of two different pharmacological tests. IGF-1 was measured in plasma by radioimmunoassay (RIA) after acid-alcohol extraction. IGFBP-3 was measured by RIA in diluted serum. Data was analysed using SPSS 22. A one-way repeated-measure analysis of variance (ANOVA) with post-hoc analysis was used to compare changes of repeated anthropometric and growth factor measures over time, and a mixed-design ANOVA was used when testing the repeated growth measures between categories, such as gender and level of adherence. Data were checked for normality prior to application of ANOVA. $P<0.05$ was taken as statistically significant.

Results

Of the 47 patients, 25(53.2%) were boys and 22(46.8%) were girls. The overall mean age was 8.7±3.4 years (range: 2.4-16 years). The most commonly presented symptoms were abdominal pain 17(36%), abdominal distention

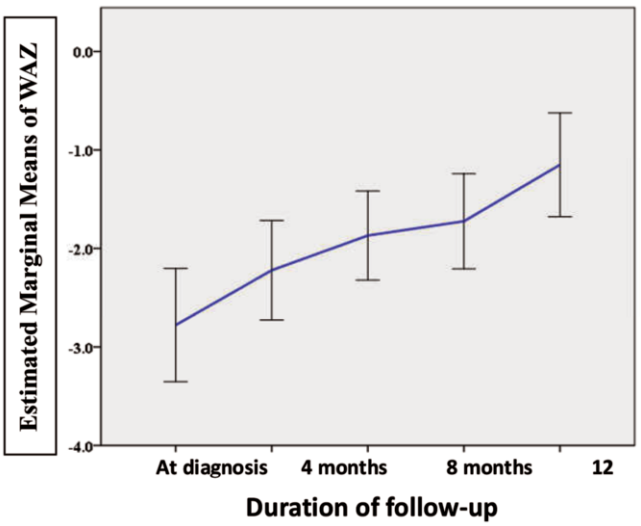

Figure-1: Changes in the marginal means of weight for age z-score (WAZ) (95% confidence intervals [CI]) in children with coeliac disease (CD) after gluten-free diet (GFD).

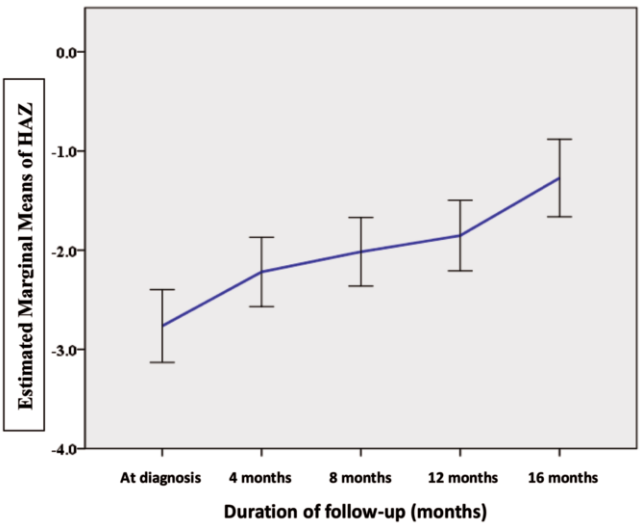

Figure-2: Changes in the marginal means of height for age z-score (HAZ) (95% confidence intervals [CI]) in children with coeliac disease (CD) after gluten-free diet (GFD).

Table-1: Demographic, clinical and laboratory characteristics of the study cohort (n=47).

	Males Mean ± SD or n (%)	Females Mean ± SD or n (%)	Total Mean ± SD or n (%)
Number of patients	25 (53.2)	22 (46.8)	47 (100)
Age (Years)	8.5±3.5	8.9±3.4	8.7±3.4
Parents' consanguinity	1 (4)	3 (13.6)	4 (8.5)
First degree relative with CD	2 (8)	4 (18.2)	6 (12.8)
Presenting symptoms			
Abdominal pain	10 (4)	7 (31.8)	17 (36.2)
Abdominal distention	11 (44)	6 (27.3)	17 (36.2)
Loss of appetite	10 (40)	6 (27.3)	16 (34)
Loss of weight	8 (32)	6 (27.3)	14 (29.8)
Diarrhoea	10 (40)	2 (9)	12 (25.5)
Vomiting	7 (28)	2 (9)	9 (19)
Mouth ulcers	6 (24)	3 (13.6)	9 (19)
Arthralgia	4 (16)	4 (18.2)	8 (17)
WAZ	-2.4±1.9	-3.2±1.9	-2.8±1.9
HAZ	-2.3±1.2	-3.3±1.1	-2.8±1.2
tTG-IgA level (iu/ml)	127.7±72.7	145.4±76	134.6±74.3
Histopathology (Marsh scoring)			
Marsh 3 a	10 (40)	4 (18.2)	14 (29.8)
Marsh 3 b	7 (28)	9 (40.9)	16 (34)
Marsh 3 c	8 (32)	9 (40.9)	17 (36.2)
Haemoglobin (g/dL)	11.5±1.9	12±1.3	11.7±1.7
Albumin (g/L)	37.4±2.1	37.4±4.4	37.4±3.4
GH Peak (ng/ml)	10.6±4.9	15.2±9.1	12.7±7.4
IGF-1 (ng/ml)	117.6±99.5	153.1±93.7	133.4±96.8
IGFBP-3 (ng/ml)	3036±972	3346±1226	3174±1081

SD: Standard deviation, CD: Coeliac disease, WAZ: Weight for age z-score, HAZ: Height for age z-score, tTG-IgA: Tissue transglutaminase, GH: Growth hormone, ALP: Alkaline phosphatase, IGF-1: Insulin-like growth factor-1, IGFBP-3: Insulin-like growth factor-binding protein-3.

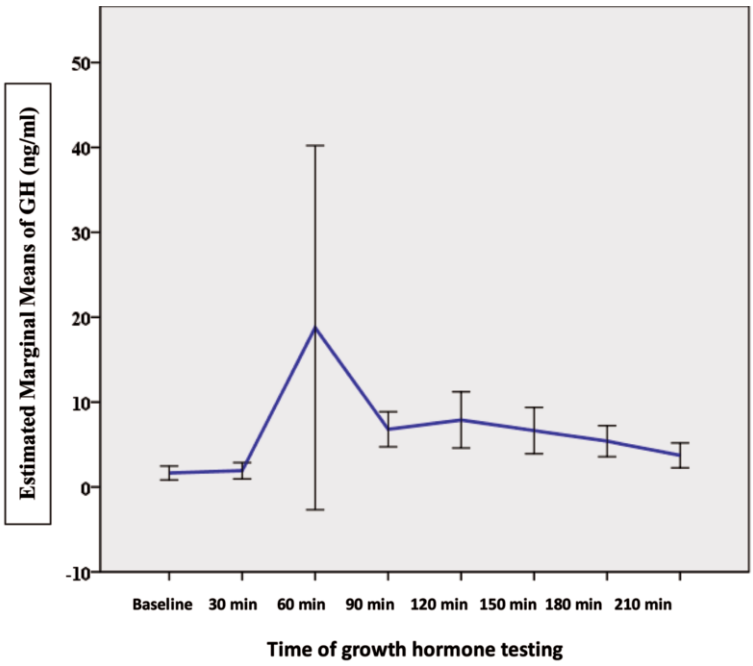

Figure-3: Growth hormone secretion pattern during provocation test in children with coeliac disease (CD).

17(36%), sever stunting 17(36%), loss of appetite 16(34%), weight-loss 14(30%), diarrhoea 12(25.5%), and vomiting 9(19%) (Table-1).

Overall mean WAZ at diagnosis was -2.8±1.9; for boys -2.4±1.9, and for girls -3.2±1.9. Significant time-based effects were noted (Figure-1).

HAZ <-2 indicating stunting was found in 40(85%) patients. The mean HAZ at diagnosis was -3±0.99. Significant changes with time were noted (Figure-2).

Pairwise comparison showed significant differences between each time period ($p<0.001$).

Apart from the gender difference in the estimated means of HAZ linear trend ($p=0.002$), there was no difference between males and females ($p>0.05$). The degree of adherence to GFD did not differ in either WAZ or HAZ trends between patients in any of the corresponding groups (Table-2).

GH assessment using two pharmacological agents was performed on 30(63.8%) patients at

Table-2: Effect of Adherence to GFD and gender on the growth of children with CD.

	Adherence to GFD				Gender			
	Good N=40 Mean±SD	Poor N=7 Mean±SD	F	P*	Males N=25 Mean±SD	Females N=22 Mean±SD	F	P*
Weight for age Z-score (WAZ)								
WAZ 0	-2.97±1.9	-3.4±2.5	0.08	0.78	-2.4±1.9	-3.2±1.9	1.4	0.24
WAZ 4	-2.2±1.7	-2.5±1.9			-1.9±1.8	-2.6±1.6		
WAZ 8	-1.9±1.6	-1.9±1.5			-1.6±1.6	-2.2±1.5		
WAZ 12	-1.8±1.5	-1.5±2.3			-1.5±1.6	-1.9±1.7		
WAZ 16	-1.2±1.7	-1.1±2.2			-0.9±1.8	-1.3±1.9		
Height-for-age Z-score (HAZ)								
HAZ 0	-2.7±1.3	-2.9±1.3	2.1	0.16	-2.3±1.2	-3.3±1.1	10.4	0.002**
HAZ 4	-2.1±1.1	-2.8±1.4			-1.7±1.0	-2.8±1.1		
HAZ 8	-1.9±1.1	-2.7±1.4			-1.5±0.9	-2.6±1.1		
HAZ 12	-1.7±1.2	-2.5±1.4			-1.3±1.1	-2.4±1.1		
HAZ 16	-1.1±1.2	-2.0±1.8			-0.9±1.0	-1.3±1.3		

*Mixed-design ANOVA test, **p<0.01
GFD: gluten-free diet, CD: Coeliac disease, SD: Standard deviation.

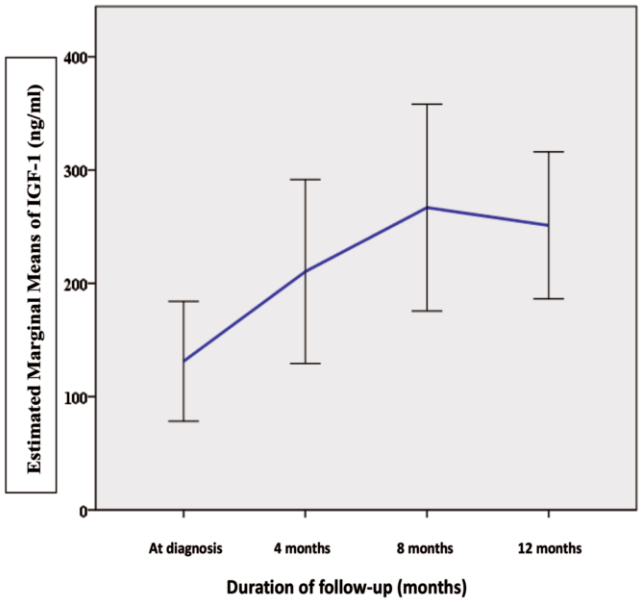

Figure-4: Changes in the estimated marginal means (95% confidence intervals [CI]) of insulin-like growth factor-1 (IGF-1) levels following gluten-free diet (GFD) administration in children with coeliac disease (CD).

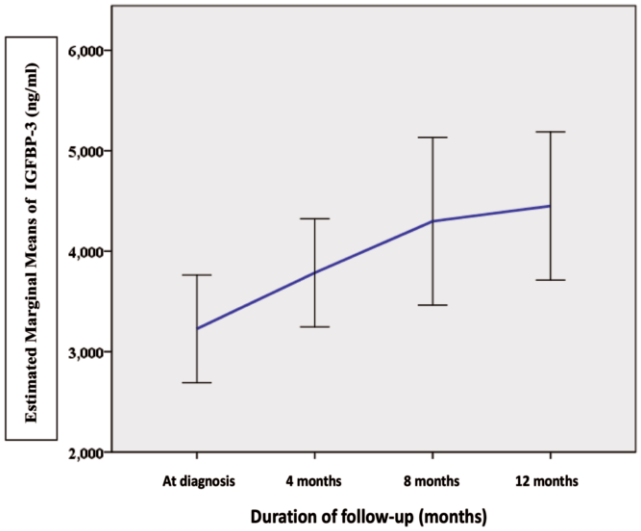

Figure-5: Changes in the estimated marginal means (95% confidence intervals [CI]) of insulin-like growth factor-binding protein-3 (IGFBP-3) levels following gluten-free diet (GFD) administration in children with coeliac disease (CD).

the time of diagnosis. GHD was found in 11(23%) patients. The peak GH secretion occurred at 60 minutes for most children with normal GH secretion (Figure-3).

There was statistically significant difference in either mean weight change (p=0.45) or mean height change (p=0.15). None of the patients required GH treatment.

Mean IGF-1 was 133.4±96.8ng/ml (range: 25-382ng/ml) and mean IGFBP-3 was 3174±1081ng/ml (range: 913-5280ng/ml).

IGF-1 changes after the introduction of GFD during follow-up was performed for 17(36%) patients and showed significant increase from the baseline (p=0.01). The difference was mainly between baseline and 8 months (p=0.01), and between baseline and 12 months (p=0.02) (Figure-4). Mean IGFBP-3 showed a significant trend over time following the introduction of GFD (p=0.004). The difference was significant between baseline and 8 months (p=0.02), and between baseline and 12 months (p=0.006) (Figure-5).

There was no significant differences in the mean weight (p=0.766) or height (p=0.916) changes in relation to low

haemoglobin (Hb). Similarly, no significant differences were found between high CD serology and mean weight (p=0.07) or mean height (p=0.190).

Discussion

Growth impairment is one of the most significant manifestations that occur commonly in CD patients. The growth impairment may reflect various nutritional deficiencies resulting from nutrient malabsorption, which occurs following villous atrophy of the small intestinal mucosa after prolonged exposure to gluten.[20] Impairment of GH production from the pituitary glands and lack of response to GH have been implicated as possible contributing mechanisms of growth failure.[13,14]

Growth failure may precede CD diagnosis in the absence of gastrointestinal symptoms in many patients.[20] This provokes researchers to advocate universal auxological screening for CD in all children to identify children with possible CD,[21] especially in the context of frequent recommendations against mass screening of children using serological testing in Europe and the United States.[1,22,23]

Catch-up growth is defined by the WHO as rapid, compensatory growth during rehabilitation from prior nutritional deficit or illness.[24] Nutritional rehabilitation of children with CD leads to acceleration of growth,[17,18,24-27]. The current study demonstrated exponential increase in WAZ and HAZ growth parameters following the introduction of GFD over a period of 16 months. This increase did not differ between GH-deficient children and children with normal GH levels. Children normalised their growth parameters by 8-10 months of nutritional rehabilitation with overshot after 12 months of GFD (Figures-1, 2). This pattern has been consistent with earlier studies.[25,28] Different studies reported variable growth patterns in CD patients, finding both complete[17,25,27-29] and incomplete catch-up growth.[18,30,31] This variation may be attributed to differences in the studied population, degree of adherence to GFD, and the growth status at the time of diagnosis.[32] The current study found no significant differences according to the degree of GFD adherence on catch-up growth parameters probably because of the small number of patients in the non-adherent group. The finding, however, is consistent with literature[17] and may be explained by a lack of a clear relationship between GFD adherence and recovery of the small intestinal mucosa, which may lag behind in some patients despite good adherence.

The improvement in growth parameters shown in the current study is in line with earlier studies.[13,14]

The current study has limitations, including retrospective design, relatively small sample size, lack of formal sample size power calculation, and a lack of long-term follow-up data.

Conclusion

CD children had normalised growth parameters and improved endogenous secretion of growth factors with the administration of GFD.

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Conflict of Interest: None.

Source of Funding: None.

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