Asian Journal of Pediatric Research

7(4): 107-116, 2021; Article no.AJPR.81646
ISSN: 2582-2950

Growth Failure in Pediatric Inflammatory Bowel Disease: A Preliminary Analysis

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJPR/2021/v7i430229
Editor(s):
(1) Dr. Nicolas Padilla-Raygoza, Institute of Public Health, Mexico.
Reviewers:
(1) Amaechi Dennis, Veritas University, Nigeria.
(2) Ramazan Karabulut, Gazi University, Turkey.
(3) Fatima Bello Nma Jiya, Usmanu Danfodiyo University, Nigeria.
Complete Peer review History, details of the editor(s), Reviewers and additional Reviewers are available here: https://www.sdiarticle5.com/review-history/81646

Original Research Article

Received 15 October 2021
Accepted 20 December 2021
Published 22 December 2021

ABSTRACT

Background: Inflammatory bowel disease (IBD) is a chronic relapsing disease, characterized by chronic inflammation of the gastrointestinal tract (GIT). The incidence of IBD has been increasing over the last two decades, for example, from 1999- 2008 incidence increased from 21.3 to 26.2 per 100,000. Inflammatory bowel disease is mainly classified into two types: Crohn's disease (CD), and ulcerative colitis (UC). Both types can be identified and distinguished through laboratory tests such as ESR, CRP, and fecal calprotectin, radiographic imaging, and direct visualization via colonoscopy. The etiology of growth failure in IBD, BMI z-score of less than -2.5, is poorly understood; however, chronic inflammation, low-calorie intake, and consequential steroid treatment are the most important factors. This study aims to determine the incidence of growth failure and associated factors in pediatric patients with IBD.

Methods: This was a retrospective cohort study of children aged 15 years and below, with the diagnosis of IBD. Data were obtained from the pediatric gastroenterology department pediatric inflammatory bowel disease database from 2007 to 2017. Our study identifies the prevalence of growth failure via a calculated BMI z-score of less than -2.5 among the pediatric inflammatory bowel disease (PIBD) population. The Chi-square test is used for categorical data and Wilcoxon rank-sum test for continuous data. A p-value <0.05 was considered statistically significant. All analyses were carried out with Stata IC/15.1 (StataCorp LP, College Station, TX, USA).

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Results: A total of 36 patients were included. The mean age of children with growth failure at the time of IBD diagnosis was 8 (±4), and more than half of them (58.3%) were boys. The incidence of growth failure at the time of diagnosis was 22.2% and declined to 11.1% over 26 months. Furthermore, the mean BMI z-score gradually improved from -0.741 to -0.1 over the same period of follow-up after proper management and multidisciplinary involvement.

Conclusion: Growth failure in IBD patients according to our data is uncommon, however, it was reduced by 50% over 26 months. This could be attributed to nutritional status improvement over the management period. We recommend following the stepwise approach according to the severity of the disease and managing IBD patients by a multidisciplinary team. However, due to the relatively small sample size and low growth failure incidence, a large-scale study is recommended to determine any causal relations.

Keywords: Inflammatory bowel disease; crohn's disease; ulcerative colitis; pediatric; growth failure.

1. INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic relapsing disease that is characterized by chronic inflammation of the gastrointestinal tract (GIT). Normally, the immune system only responds to invading pathogens. However, in IBD, the immune system reacts inappropriately and attacks healthy cells in the GIT [1]. The incidence and prevalence of IBD have increased worldwide from 1999- 2008 incidence increased from 21.3 to 26.2 per 100,000 [2]. Inflammatory bowel disease is mainly classified into two types: Crohn's disease (CD), and ulcerative colitis (UC). Both types can be identified and distinguished through laboratory tests such as ESR, CRP, and fecal calprotectin, radiographic imaging, and direct visualization via colonoscopy. Crohn's disease can affect any part of the GIT from mouth to anus and can also affect the skin, eyes, liver, and joints. While UC mainly affects the colon, rectum, and innermost layer of the intestinal wall, patients with UC may also present with extra-intestinal manifestations. In both types, children experience variable asymptomatic periods of remission and active inflammatory periods. Active periods are characterized by clinical features such as diarrhea, fever, fatigue, abdominal pain, cramping, blood in the stool, and reduced appetite, leading to unintended weight loss [1-4]. Approximately 20% of all IBD patients first present during childhood or adolescence, and around 10% of the estimated 1.4 million Americans with IBD are under the age of 17 [5]. The height velocity is reduced in about 46% of children before IBD diagnosis [6]. The etiology of growth failure in IBD is poorly understood, however, chronic inflammation, low-calorie intake, and consequential steroid treatment are the most important factors [7]. Moreover, IBD inhibits insulin-like growth factor-1 (IGF-1), insulin, thyroid hormones, and sex steroids, which are all essential for bone formation [8].

There are many risk factors, both modifiable and non-modifiable, that negatively affect the growth of children with IBD. An example of modifiable risk factors is medication intake. For instance, the prolonged use of steroids and lipopolysaccharide therapy is associated with growth failure [9]. Non-modifiable risk factors include IBD type, gender, genes, hormone levels, and disease activity. Growth retardation is seen more in children with CD, compared to children with UC [7]. Studies have revealed that boys with IBD are at increased risk for growth failure compared to girls [10]. Genetic variation in CARD15 and neutralizing GM-CSF antibodies are associated with growth failure in pediatric patients with IBD [11]. Furthermore, growth hormone (GH) stimulates the production of IGF-1, which is the key mediator at the growth plate of bones. However, children with IBD have impaired GH stimulation that consequently affects IGF-1 production, which affects growth negatively [12]. Finally, patients with active disease have a high metabolic rate that results in a decreased body mass index (BMI), small mid-arm muscle circumference (MAMC), and low serum protein level compared to patients in remission [13].

Many studies have investigated risk factors of growth failure in children with IBD, but extensive literature reviews have been done, however, studies that address transportation difficulties, missed follow-up, low family income, and low parental education level as risk factors for growth failure in children with IBD could not be found.

Our aim is to determine the incidence of growth failure and associated factors in pediatric patients with IBD by examining the growth

parameters at diagnosis and follow-up among children diagnosed with inflammatory bowel disease at King Abdulaziz Medical City (KAMC) Jeddah. This study will increase the public data available regarding the risk factors of growth failure in children with IBD in Saudi Arabia.

2. METHODS

This was a retrospective cohort study. Data were obtained from the pediatric gastroenterology department pediatric inflammatory bowel disease database at King Abdulaziz Medical City (KAMC) Jeddah from January 2007 to December 2017. The inclusion criteria included all patients aged 15 and younger. Patients with comorbid diseases (malignancy, endocrinological and rheumatological disease), patients who underwent major bowel resection or bypass surgery, and patients with incomplete data were excluded from the study. A total of 36 patients who met the inclusion and exclusion criteria were assessed.

The severity of the disease is usually estimated based on validated scores, Pediatric Crohn's Disease Activity Index and Pediatric Ulcerative Colitis Activity Index, classify the patient into remission, mild, moderate, or relapse [14, 15]. The pediatric age group at King Abdulaziz Medical City (KAMC) Jeddah is defined as a patient who is between 0-15 years of age. Data collection was performed by research team members through a standard data collection tool designed for this study includes demographic data, date of diagnosis, type of the disease, growth parameter for each visit, nutritional assessment, and educational level of the patients and their parents and other social assessment. The main source for obtaining data was patient medical records. The data collected included information to confirm the correct diagnosis, nutritional data upon the diagnosis and thereafter, and the medical treatment and nutritional plans. The completed data collection sheet was transferred to an excel sheet on a secured computer. The data was encrypted and stored in a locked file accessed only by the primary investigator.

Our study identifies the prevalence of growth failure via a calculated BMI z-score of less than -2.5 among the pediatric inflammatory bowel disease (PIBD) population.

2.1 Data Analysis

Descriptive statistics were used to describe the data. Demographic data and baseline characteristics between the groups were compared using the Chi-square test for categorical data and Wilcoxon rank-sum test for continuous data. Because each child in the sample had multiple visits and childhood BMI usually tracks with age, we examined the rate of change in BMI by calculating the z-score by plotting the BMI on WHO BMI for age chart [16]. A p-value <0.05 was considered statistically significant. All analyses were carried out with Stata IC/15.1 (StataCorp LP, College Station, TX, USA).

3. RESULTS

The cases included 36 PIBD patients whose ages ranged from 4 to 15 years old (mean age at diagnosis was 8 (±4)). Boys represented most of the sample 21(58.3%). Only 3(8.33%) of study participants were not attending school, while 6(16.7%) were in elementary school, 11(30.6%) were in intermediate school, and 16(44.4%) were in high school. There were 16 patients diagnosed with UC (44.4%), and 20 patients diagnosed with CD (55.5%). Most of the children attended their scheduled appointment and had regular follow-up (86,1%), and only (13.9%) missed their follow-up. Approximately half of the children had transportation difficulties (e.g., live far away, or do not have car) 16(44.4%). Regarding the parental educational level of fathers and mothers, 1(2.8%) and 2(5.6%) were illiterate, 11(30%) and 13(36.1%) had completed elementary to high school, and 24(66.7%) and 21(58.3%) had attained a higher education degree, respectively. In terms of financial status, 10(27%) had an income less than 1300$, 12(33.3%) had a monthly family income level from 1300 to 2600$, and 14(32.8%) had an income of 2601$ and more (Table 1). On the assessment of food intake, 22(61.1%) were on a regular diet (balanced family diet), 10(27.8%) were on a special diet (e.g., mashed food and formula), and 4(11.1%) were on a poor diet (e.g., unbalanced diet; inadequate intake of fibers, minerals, and vitamins).

It was found that 4(11.1%) of patients had moderate growth failure and 4(11.1%) of patients had severe growth failure. After six visits, the incidence of moderate growth failure decreased to 3(8.3%) and the incidence of severe growth failure decreased to 1(2.8%). The growth failure was reduced by 50%, from 8(22.2%) to 4(11.1%) because of the nutritional improvement (Table 2).

Additionally, gradual improvement in the BMI score of patients from the time of diagnosis until visit six over an average of 26 months of follow-up was seen as demonstrated in Fig. 1 and Fig. 2.

Table 1. Patient demographics (n=36)

Variables		N (%) or mean ± SD
Gender:	Boys	21 (58.3)
	Girls	15 (41.7)
Age, years:		13.9 ± 3.51
Grade:	Not studying	3 (8.3)
	Elementary	6 (16.7)
	Intermediate	11 (30.6)
	High school	16 (44.4)
Diagnosis:	Ulcerative colitis	16 (44.4)
	Crohn's disease	20 (55.5)
Nutritional assessment:	Regular diet	22 (61.1)
	Special diet (formula/mashed)	10 (27.8)
	Poor diet	4 (11.1)
Follow Up:	Yes	31 (86.1)
	No	5 (13.9)
Transportation difficulty:	Yes	16 (44.4)
	No	20 (55.6)
Income, Dollar:	<1300	10 (27.8)
	1300-2600	12 (33.3)
	2601 or more	14 (32.8)
Father education level:	Illiterate	1 (2.8)
	Elementary-High school	11 (30.6)
	Higher education	24 (66.7)
Mother education level:	Illiterate	2 (5.6)
	Elementary-High school	13 (36.1)
	Higher education	21 (58.3)

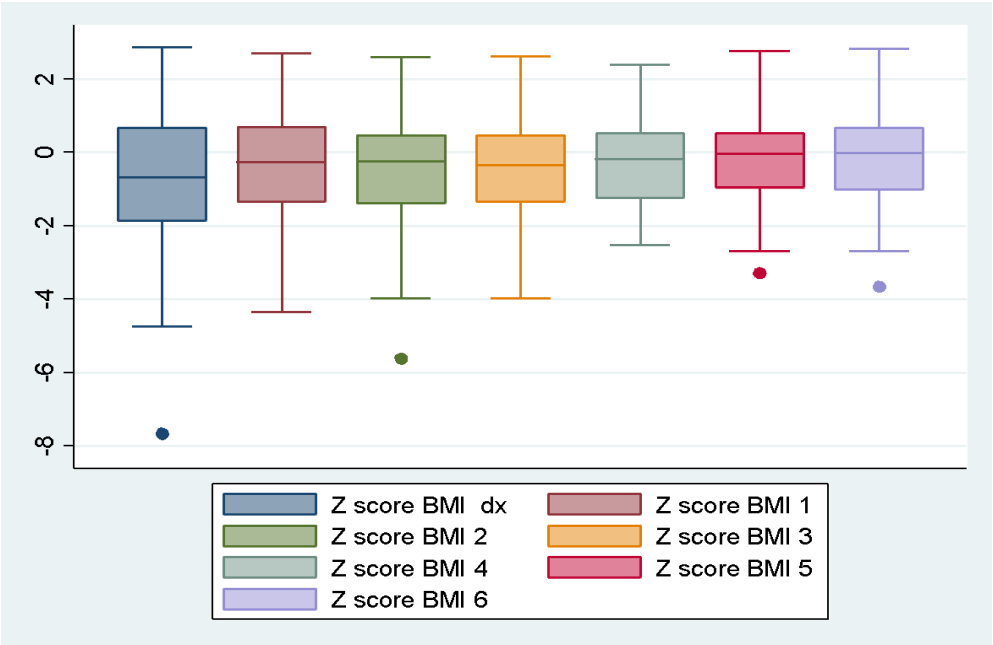

Fig. 1. Trend of BMI Z score over mean of 26 months follow up

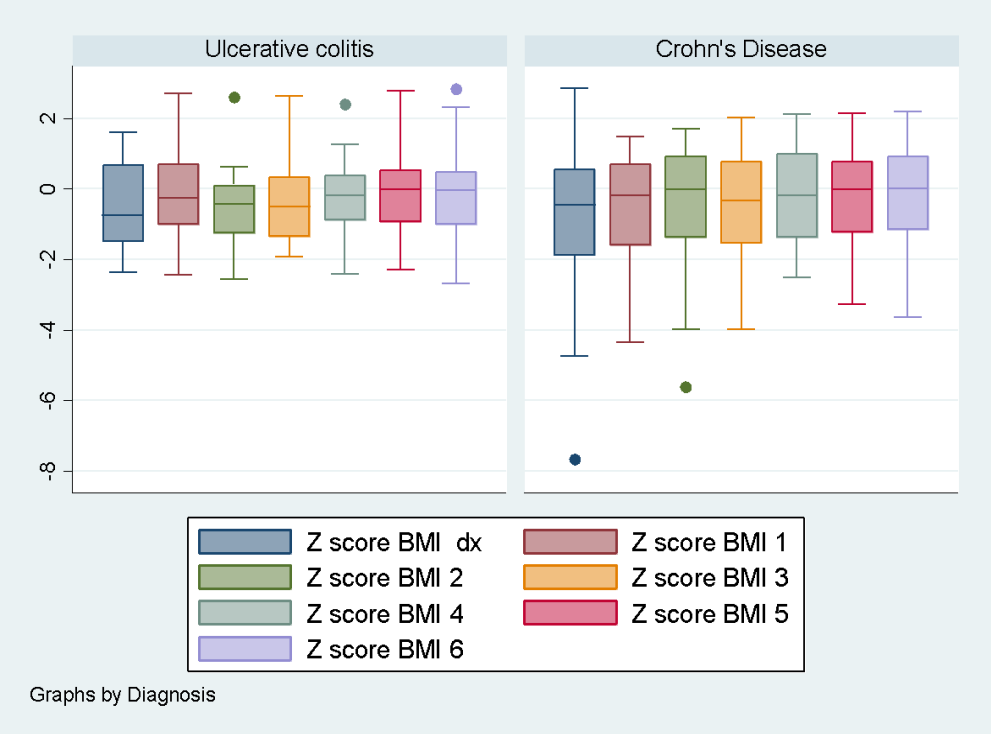

Fig. 2. Trend of BMI Z score over follow up period after diagnosis

Table 2. Incidence of growth failure at diagnosis and visit six

	At diagnosis N(%)	At visit six N (%)
Normal growth	28 (77.7)	32 (88.9)
Moderate growth failure	4 (11.1)	3 (8.3)
Severe growth failure	4 (11.1)	1 (2.8)
Mean BMI Z score*	-0.741	-0.1

** p<0.02*

There was a notable change in the activity index of the disease in IBD patients at the time of diagnosis compared to the activity during the follow-up visits. While (52.78%) of patients were in remission at the time of diagnosis, the incidence increased to (69.44%) at visit 6. Additionally, the activity index that indicates a mild state of disease at the time of diagnosis is 11(30.56%), whereas it is 5(13.89%) at visit 6. Also, the activity index that indicates a moderate state of disease at the time of diagnosis was 4(11.11%), whereas was 1(2.78%) at visit 6. Finally, while 2(5.56%) of patients were in relapse at the time of diagnosis, the incidence increased to 5(13.89%) at visit 6. (Table 3).

The difference in the mean BMI score of growth failure was insignificant at diagnosis and at visit six as shown in Table 2 (p=0.325). There was a statistically significant difference between activity index at diagnosis and visit six (p =0.011). (Table 4)

4. DISCUSSION

The findings of this study support results from previous studies that have shown that children with IBD have a low incidence of growth failure [17]. Animesh et al [17] retrospectively analyzed 898 children newly diagnosed with CD enrolled in the ImproveCareNow network from September 2006 to October 2014 to evaluate disease-related outcomes in overweight and obese children with CD compared to normal-weight children. Their study revealed that the incidence of growth failure in these patients was only 14% [17]. Another study performed to determine if pediatric patients with IBD experienced excessive weight gain when exposed to anti-TNF therapy included 69 pediatric patients with IBD [18]. Patients had at least one year of anti-TNF therapy and follow-up. At the initiation of anti-TNF therapy, the mean weight SDS was -0.65 (SD 1.4), while the mean BMI SDS was -0.59 (SD 1.3). At baseline, (21.7%) of patients were

Table 3. Activity index of six consecutive visits throughout two years

Activity index:	At Diagnosis N (%)	1st visit N (%)	2nd visit N (%)	3rd visit N (%)	4th visit N (%)	5th visit N (%)	6th visit N (%)
Remission	19 (52.8%)	25 (69.4%)	24 (66.7%)	25 (69.4%)	26 (72.2%)	27 (75%)	25 (69.4%)
Mild	11 (30.6%)	7 (19.4%)	8 (22.2%)	7 (19.4%)	6 (16.7%)	5 (13.9%)	5 (13.9%)
Moderate	4 (11.1%)	3 (8.3%)	1 (2.8%)	2 (5.6%)	3 (8.3%)	2 (5.6%)	1 (2.8%)
Relapse	2 (5.6%)	1 (2.8%)	3 (8.3%)	2 (5.6%)	1 (2.8%)	2 (5.6%)	5 (13.9%)

Table 4. Activity index at diagnosis and visit six

Activity index:	UC at diagnosis N (%)	CD at diagnosis N (%)	Total N (%)	P-value at diagnosis	UC at visit 6 N (%)	CD at visit 6 N (%)	Total N (%)	P-value at visit 6
Remission	9 (56.3%)	10 (50.0%)	19 (52.8%)	0.325	11 (68.8)	14 (70)	25 (69.4%)	0.011
Mild	4 (25%)	7 (35%)	11 (30.6%)		0	5 (25%)	5 (13.9%)	
Moderate	1 (6.3%)	3 (15%)	4 (11.1%)		0	1 (5%)	1 (2.8%)	
Relapse	2 (12.5%)	0	2 (5.6%)		5 (31.3%)	0	5 (13.9%)	

Abbreviation: UC: Ulcerative colitis, CD: Crohn disease

underweight (weight SDS -1.645). The rate of growth failure in children in previous studies was comparable to the growth failure rate we found at diagnosis (22.2%). In addition, a retrospective cohort of 253 pediatric IBD patients demonstrated patients' BMI before infliximab initiation and at last infliximab infusion. 217 (85.77%) children had a normal BMI throughout the study, while 26 (10.28%) who started with a normal BMI had an elevated BMI at last follow up, and 10 (3.95%) had elevated BMI at infliximab start and at last follow up [19]. No statistically significant association was seen between children with growth failure and the proposed factors which are: the type of diagnosis, patient age, level of parental education, nutritional assessment, compliance to follow up, and transportation difficulty. Because our patient number was small, further study will be required.

5. CONCLUSION AND RECOMMENDATION

In summary, growth failure in IBD patients according to these data is uncommon, however, it was reduced by 50% over 26 months. This could be attributed to nutritional status improvement over the management period. We recommend following the stepwise approach according to the severity of the disease and managing IBD patients by a multidisciplinary team. Due to the relatively small sample size with low growth failure prevalence, all proposed risk factors did not demonstrate a significant association, and a large-scale study is required. Nevertheless, this result was expected as a single-center study can only encompass a relatively small sample of children with IBD.

ETHICAL APPROVAL

The study was conducted after obtaining IRB approval from the ethics committee in King Abdulaziz International Medical Research Center (KAIMRC).

CONSENT

No consent form was needed since we used chart review for data collection. All personal information was kept anonymous and safe. Only the investigators of this study had access to the file.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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APPENDIX A

Data Collection form

Data collection form:		
Serial number:		
Gender:	Boys	
	Girls	
Age, years:		
Weight, KG:	At diagnosis	Date(DD/MM/YY)
	Visit 1	Date(DD/MM/YY)
	Visit 2	Date(DD/MM/YY)
	Visit 3	Date(DD/MM/YY)
	Visit 4	Date(DD/MM/YY)
Height, cm:	At diagnosis	Date(DD/MM/YY)
	Visit 1	Date(DD/MM/YY)
	Visit 2	Date(DD/MM/YY)
	Visit 3	Date(DD/MM/YY)
	Visit 4	Date(DD/MM/YY)
BMI:	At diagnosis	Date(DD/MM/YY)
	Visit 1	Date(DD/MM/YY)
	Visit 2	Date(DD/MM/YY)
	Visit 3	Date(DD/MM/YY)
	Visit 4	Date(DD/MM/YY)
Z-score:	At diagnosis	Date(DD/MM/YY)
	Visit 1	Date(DD/MM/YY)
	Visit 2	Date(DD/MM/YY)
	Visit 3	Date(DD/MM/YY)
	Visit 4	Date(DD/MM/YY)
Date of diagnosis:		
Diagnosis:	Ulcerative colitis	
	Crohn's disease	
The severity of diagnosis, use PCDAI or PUCAI:	At diagnosis	
	Score 1	
	Score 2	
	Score 3	
	Score 4	
	Score 5	
Medication at diagnosis:		
Medication change:	Date	
	Name of medication	
Grade:	Not studying	
	Elementary	
	Intermediate	
	High school	
Nutritional assessment:	Regular diet	
	Special diet (formula/mashed)	
	Poor diet	
Follow Up:	Yes	
	No	
Transportation difficulty:	Yes	
	No	
Income, Dollar:	<1300	
	1300-2600	
	2601 or more	
Father education level:	Illiterate	

	Elementary-High school Higher education
Mother education level:	Illiterate Elementary-High school Higher education
Separated family:	Yes No
Nutritional assessment and management by specialized dietician:	Yes No
Frequency of hospitalization since of diagnosis:	

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/81646