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Research Article

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Effect of Infliximab Therapy on Weight Gain in Pediatric Inflammatory Bowel Disease

Zahra Hejji[1*], Mamoun Elawad[1], Hatem Abdulrahman[1], Fatma Almudhka[1], Nazira Ibrahim[1], Belavendra Antonisamy[2], Anthony Akobeng[1]

[1]*Pediatric Medicine, Division of Gastroenterology, Sidra Medicine, Doha, Qatar*

[2]*Pediatric Medicine, Division of Pulmonology, Sidra Medicine, Doha, Qatar*

[*]**Corresponding author**

Zahra Hejji, Pediatric Medicine, Division of Gastroenterology, Sidra Medicine, Doha, Qatar.

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ABSTRACT

Objectives: Inflammatory Bowel Disease (IBD), comprising Crohn's disease and ulcerative colitis, presents a significant challenge in pediatric populations. The advent of biologics, notably infliximab, has revolutionized treatment by targeting tumor necrosis factor alpha (TNF-alpha) and reducing reliance on corticosteroids. Despite its efficacy, concerns have arisen regarding potential excessive weight gain among pediatric patients receiving infliximab.

Methods: We conducted a retrospective cohort study at our institution in Doha, Qatar, spanning 2015-2022, involving 60 IBD patients (<18 years). We assessed BMI z-score changes at 3, 6, 12, and 24-months post-infliximab initiation, and correlated clinical markers with patient demographics. Statistical analyses included t-test and repeated measures analysis of variance.

Results: Over a 24-month period, a significant increase in BMI z-score was observed across all age groups ($p< 0.001$), with peak gains noted at 6 months. Excessive weight gain was noted among all IBD types and subtypes of Crohn's ($p < 0.001$); however, no difference was noted between UC and Crohn's disease patients ($p = 0.135$).

Conclusion: Our findings show that children with IBD can gain excessive weight following infliximab therapy in pediatric IBD patients. It suggests a metabolic effect beyond mere nutritional improvement. As a result, further research is needed to elucidate underlying mechanisms and optimize clinical management strategies.

Keywords: Inflammatory Bowel Disease, Crohn's Disease, Ulcerative Colitis, Children, Obesity, Infliximab.

What is Known

- The advent of biologics, notably infliximab, has revolutionized treatment by targeting TNF-alpha and reducing reliance on corticosteroids.
- Weight gain is expected as a result of healing and improved gut absorption after biologics in Pediatric IBD.

What is New

- Excessive weight gain and shift of BMI z-score classification following infliximab therapy in pediatric IBD patients, especially after 6 months of treatment.
- It suggests a metabolic effect beyond mere nutritional improvement.

Introduction

Inflammatory Bowel Disease (IBD), is a chronic inflammatory disorder of the gastrointestinal tract. Subtypes of IBD include Crohn's disease, ulcerative colitis and IBD unclassified1. Treatment and management of IBD have evolved significantly over the past 25 years following the introduction of biologics. After understanding the disease pathophysiology, more targeted therapies have been introduced in the market to limit the usage of corticosteroids [1]. The mainstay treatment for IBD is anti-TNF alpha medication, such as infliximab [2]. Infliximab has revolutionized IBD treatment by being effective for inducing and

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maintaining remission without the need for steroids or surgical interventions [3]. Known side effects include allergic reactions, infections, or psoriasis [4]. Recent studies have suggested that infliximab use may be associated with excessive weight gain in IBD patients [5]. In this paper we explored the association of weight gain with infliximab among children with IBD.

Methods

This is a retrospective cohort study on the pediatric IBD population in Sidra Medicine, Doha, Qatar from 2015-2022. BMI z-score was reviewed at time of diagnosis, then compared against four intervals, at 3 months, 6 months, 12 months, and 24 months after starting infliximab. We analyzed weight gain and compared to the variations by age, gender, and disease types.

IBD was diagnosed based on ESPGHAN revised Porto criteria [6]. Demographic and clinical data including age, gender, BMI z-score, IBD type, and infliximab level were collected during the first 2 years of treatment. Close follow up for infliximab trough level, status of the disease (with histological changes and imaging), as well as inflammatory markers in blood and stool was carried out for all patients.

A total of 125 patients who received Infliximab were reviewed in our institution's pediatric IBD database. The data were filtered out to 60 patients (Figure 1). The following exclusion criteria were applied:

- Patient with Insufficient information,
- Patients with age below 6 years, considered very early onset IBD,
- Patients who were on steroids or had steroids in the last 6 months
- Patients who required combined biologic
- Patients with lost follow up due to change of country of residence.

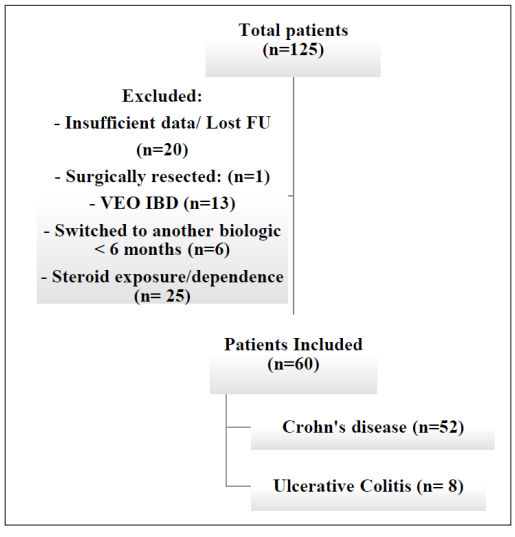

Figure 1: Method of Data Collection for this study

Statistical methods

For descriptive analyses, mean and standard deviation were used to summarize quantitative variables. Frequencies and percentages were used for categorical variables. For inferential analyses, the outcome variable, BMI z-score at the four intervals were compared between the basic characteristics, and precisely the 6 months periods where excessive weight was mostly observed. The mean BMI z-score was plotted over visits in months according to age groups, gender, nationality, disease subtypes using line plot. The mean BMI z-score response over time was assessed using repeated measures analysis of variance (RANOVA) according to gender, nationality, and disease subtypes. Statistical analyses were performed using the STATA software 18/SE (StataCorp LLC. 2023, College Station, Texas, USA).

Results

BMI z-score changes for a total of 60 pediatric patients (<18 years) with inflammatory bowel disease (IBD), (52 CD and 8 UC) were tracked over a duration of 24-months following infliximab treatment initiation. A significant increase in BMI z-score was noted in the two years, with a peak at 6 months of treatment (Figure 2). This was also evident among the three age groups ($p < 0.001$) (Figure 2). The data reveal a notable increase in BMI z-score over the 24- month treatment period, particularly among younger patients (< 12 years) compared to older adolescents (≥ 12 years), highlighting age-dependent variations in response to infliximab therapy.

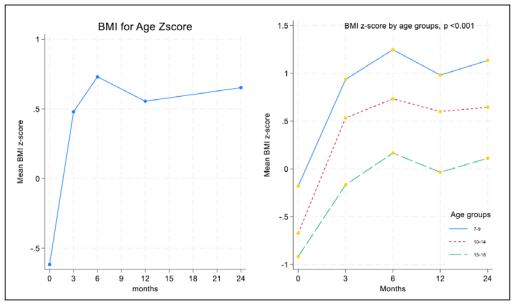

Figure 2: Profile of BMI z-score for all individual subjects and the mean BMI z-score by age groups. It illustrates the profile of BMI z-score for individual subjects and the mean BMI z-score across different age groups

There were variations in BMI z-score trends among different disease categories. Statistical analysis (Figure 3) highlighted a significant overall increase in BMI z-score across all diagnosis types over the 24-months period. The graph (Figure 3) highlights the proportion of patients whose BMI z-score exceeded 2 standard deviations (SD) from the mean (notated in red), indicating a substantial increase in BMI. The results showed a notable shift starting at 3 months post treatment initiation among a large subset of patients($p<0.001$). However, there was no statistically significant difference depicted among CD and UC patients ($p=0.135$).

In addition, BMI z-score was stratified by gender. Female slightly showed predominance on weight gain according to z-score over males, however it was not statistically significant ($p=0.265$).

Discussion

Infliximab is a revolutionary anti-inflammatory drug in the management of pediatric IBD [7].

It is a monoclonal antibody targeting TNF-alpha, and is effective for inducing and maintaining remission [5,6]. Although the focus of IBD management is to improve the general well-being

and improvement of nutritional status, limited studies discussed the effect of infliximab therapy on weight gain [3]. Thus, understanding the effect of the drug on body weight is essential in IBD management.

In this study, sixty pediatric IBD patients (52 CD and 8 UC) were enrolled. These patients had been on single biologic therapy with infliximab. The findings, following infliximab therapy, revealed excessive weight gain in children with IBD. The weight gain persisted over an extended period beyond the initial treatment phase. Rapid weight gain was observed as early as 3 months of infliximab treatment initiation. A report from a systemic review and meta-analysis that included twenty-six longitudinal studies for more than 1000 participants of both pediatric and adults IBD, found significant weight gain and BMI shift with infliximab [8]. Other published studies showed that among 851 adults with CD and UC, the average weight gain was up to 7.5 kg after induction therapy in 90 days [9]. Another retrospective study of 110 adult patients with IBD, confirmed rapid weight gain (60% of Crohn's cases) specially in the first 6 months, and was sustained to 1 year [10]. Pediatric study findings were found to be consistent with those of adults. A study carried out at Mayo Clinic on 268 IBD children, who had received infliximab, observed excessive weight gain with shift of classification from normal to obese among pediatric IBD patients [11].

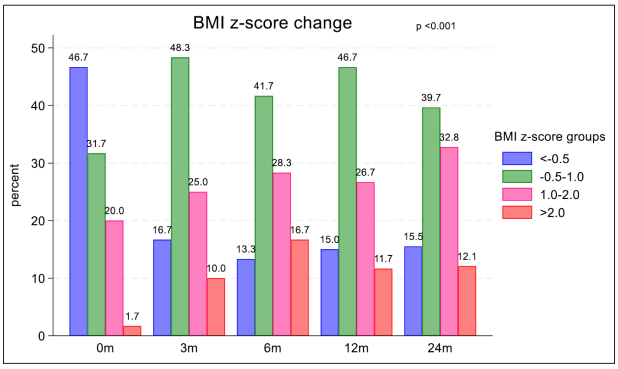

Figure 3: BMI z-score change after Infliximab from 0 to 24 months

Weight gain in IBD patients is a challenging topic as majority of the cases present with malnutrition. Therefore, weight gain is expected as a result of healing and improved gut absorption. Given the rapid nature of growth in pediatric population, Z-score for weight is a better assessment tool for weight gain compared to BMI or weight measurement. Current papers on this topic, described weight gain in percentage or BMI which were not accurate enough to compare among pediatric population in different age groups. However, some studies took detailed measurement to describe weight gain as body fat or muscle gain [9]. Six patients were evaluated for weight gain in a pilot study done in Cleveland Clinic which showed significant weight gain after six months of treatment (+2.21 kg/m2, p= 0.03) [7]. Body composition was assessed by two ways, bioelectric impedance analysis (BIA) & DXA scan. Results showed increase in overall fat percentage estimated per BIA (+3.15%, P=0.08) and lean mass [7].

Previous studies performed on weight gain were focused on Crohn's disease only and were mainly on adults [11]. The weight gain noted was explained by the reduced inflammatory burden and improved metabolism [9]. Theories for weight gain mainly goes with improvement of overall health, and with improvement of appetite [9]. However, the theory of nutrition improvement does not explain the weight gain observed in UC while on infliximab therapy [12]. This was also depicted by our study, which shows no statistical difference among the disease subtypes (p=0.135). This refutes the theory of improved nutrition being the sole cause of weight gain in pediatric IBD.

Table 1: Mean BMI Zscore at 6 months by age groups, gender,nationality and disease type

Charactesistics	BMI Zscore at 6 months	
	Mean(SD)	P value‡
Age (years)		
7-9	1.25(1.2)	0.056
10-14	0.73(1.1)	
15-18	0.17(1.1)	
Gender		
Male	0.61(1.3)	0.428
Female	0.84(0.9)	
Diagnosis		
Crohns	0.70(1.2)	0.609
Ulcerative colitis	0.92(1.0)	
Crohns- subtype		
Ileocolonic crohns	0.78(1.2)	0.696
PD crohns	0.32(1.1)	
SB crohns	0.75(0.9)	

There is strong evidence of infliximab, playing a role in alteration of metabolic pathways raising the risk of metabolic disease [13]. On average, most of the cases shifted from underweight to obesity in 2 years. This was evident as the z- score shifted from negative SD to > 2SD as demonstrated in Figure 3. This prolonged effect suggests a sustained metabolic influence of infliximab in pediatric patients, potentially altering their long-term weight trajectory. A meta-analysis in Kings College London also illustrated the risk of increase adipose tissue and hence increased insulin resistance and development of diabetes13. Infliximab was found to regulate lipolysis in IBD patients, and leading to increased weight by reducing inflammation and improving gut absorption as well [14].

In this study, there was also a slight variation among males to females, showing females gaining more weight compared to males (p= 0.267,). This attributes to our population variations, which were predominately males. A meta-analysis done on adults concluded the opposite findings of gender effect on weight gain compared to our study, as males were found to gain significantly more weight than women (4.3% increase in weight gain in men compared to 3.9% in women) [15,12]. In addition, a Kings College meta-analysis on the impact of TNF alpha on IBD population, showed excessive weight gain and evidence of increased risk in males and younger population [13].

It is important to acknowledge several limitations in our study. These include the retrospective nature of data collection, small sample size, and potential confounding variables such as dietary habits, unknown herbal medications use or other practices, and the variability in individual patient responses to infliximab therapy including genetic predisposition.

Future research could explore the underlying mechanisms driving BMI changes following infliximab treatment, including genetic, dietary, and lifestyle factors that may influence treatment outcomes. This could be achieved by larger longitudinal studies with extended follow- up periods. Thus, this approach can explore the mechanistic pathways underlying weight changes in response to infliximab therapy. Although this has been a retrospective study, a prolonged follow up period of over 2 years is an advantage. We have been able to observe sustained weight gain for 2 years. Also, we only included population who are naïve to biologics, and were receiving same induction protocols with infliximab follow up levels. As a result, it minimizes divergent treatments guidelines and strategies.

In conclusion, our study investigated the impact of infliximab treatment on pediatric patients diagnosed with IBD. There is significant shift in BMI z-scores from 3 months post-infliximab treatment, with a peak at 6 months. This underscores the early onset and rapid progression of metabolic changes associated with this therapy. This finding suggests a critical period during which clinicians should closely monitor BMI changes to mitigate potential metabolic risks. Future studies can be done with control groups, physical activity profile and diet for comparison.

Conflict of interest statement: All authors declare no conflict of interest.

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