Review Article

Link between Pediatric Inflammatory Bowel Disease and Growth Retardation: A Systematic Review

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ABSTRACT

The main objective of this study was to underlie the growth impairment mechanisms in pediatric inflammatory bowel disease (IBD) patients. A total of 584 pertinent publications were found after a comprehensive search across four databases. Full-text publications (293) were examined after duplicates were eliminated using Rayyan QCRI and relevance was checked; seven studies finally satisfied the requirements for inclusion. A total of 1927 children diagnosed with IBD were included in this research; 1467 with Crohn's disease (CD) and 460 with ulcerative colitis (UC). Males were 1153 (59.5%). Growth abnormalities, especially in CD patients, are commonly observed in children with IBD, often appearing strongly before age fifteen. These growth issues, including height and weight retardation, are worsened by chronic inflammation and are particularly severe in children with low weight at diagnosis. Younger children, particularly those under ten, are more affected than older children, especially in cases of UC. Adolescents with IBD may also experience disruptions in the pubertal growth spurt, possibly due to hormonal imbalances, such as reduced insulin-like growth factor-1 (IGF-1) availability. Pediatric IBD is closely linked to growth issues, especially in children with CD and those diagnosed at a young age. Early diagnosis and proper management are essential to support normal growth and prevent long-term effects. Clinicians should monitor growth as a key indicator of disease impact and provide nutritional and medical support. Further researches are needed to identify the best strategies to address growth problems and help these children reach their full potential.

Keyword: Inflammatory Bowel disease; Growth impairment; Ulcerative colitis; Crohn's disease; Systematic review.

Introduction

About 25% of inflammatory bowel disease (IBD) patients receive their diagnosis in childhood or adolescence [1], most often during the pubertal growth spurt. With one significant exception—growth failure and delayed puberty, which are prevalent in a large percentage of pediatric patients

And call for special attention—pediatric IBD patients have the same clinical characteristics and course of treatment as adults [2]. Therefore, optimizing growth to achieve target height is one of the most important goals of managing pediatric IBD [3].

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Although the exact causes of growth retardation are unknown, malnutrition and the severe inflammatory response that occurs during an active illness may be the main contributing factors. In fact, growth and the beginning and course of puberty may be impacted by the high pro-inflammatory cytokine levels brought on by the active disease [3, 4]. Height velocity, conveyed as a percentile or a standard deviations (SD) score according to gender and age, seems to be a more sensitive and accurate metric to detect growth retardation, even though growth failure can be characterized by a static height below the third percentile or a z-score below –2 SD [5]. Around the pubertal development spurt, the majority of children with IBD receive a diagnosis [6]. Up to 85% and 65% of juvenile patients with CD and UC, respectively, frequently experienced growth and pubertal progression consequences in addition to the anticipated weight loss [7, 8]. Up to 88% of IBD patients have subnormal linear growth prior to diagnosis and for 46% of patients, a decline in height velocity is the initial clinical indication of CD before weight loss or gastrointestinal symptoms manifest [9]. Pediatric IBD is the chronic disease that encompasses both CD and UC and significantly affects the well-being of children and adolescents. In contrast to adults, the onset in the pediatric age group often coincides with critical periods of physical and pubertal growth; thus, growth retardation represents a hallmark complication of the disease. These pathways are manifold and include chronic inflammation, malnutrition, and disturbances in hormonal pathways such as the growth hormone insulin-like growth factor-1 (IGF-1) axis. Growth failure remains a resistant challenge to clinicians and a source of immense psychological and developmental burdens for the affected children despite advances in therapeutic options. Developing an understanding of the relationship between pediatric IBD and growth retardation is important in working toward improved patient outcomes [9]; however, the literature is currently fragmented, often has variable findings, and limited synthesis. A systematic review is needed to synthesize existing evidence comprehensively, identifying gaps in knowledge and informing clinical practice and future research. The aim of this systematic review is to present available evidence on the prevalence of growth impairment and underlying mechanisms in pediatric IBD patients in order to provide an overview on the interrelationship between the two entities.

Methods

Search strategy: The PRISMA and GATHER criteria were adhered to in the systematic review. To locate pertinent research on growth impairment in pediatric IBD patients, a comprehensive search was carried out. Four electronic databases were searched by the reviewers: SCOPUS, Web of Science, Cochrane, and PubMed. The included studies were between 2015 and 2024. We eliminated any duplicates and uploaded all of the abstracts and titles that we could find using electronic searches into Rayyan QCRI. After that, all of the studied texts that met the requirements for inclusion based on the abstract or title were gathered for a thorough examination. Two reviewers independently assessed the extracted papers' suitability and discussed any discrepancies.

Study population—selection: The PEO (Population, Exposure, and Outcome) factors were implemented as inclusion criteria for our review: (i) Population: Pediatric patients, (ii) Exposure: IBD disease, and (iii) Outcome: Growth impairment.

Data extraction: Data from studies that satisfied the inclusion requirements were extracted by two objective reviewers using a predetermined and uniform methodology. The following information were retrieved and recorded: (i) First author (ii) Year of publication, (iii) Study design, (iv) Country, (v) Sample size, (vi) Age, (vii) Gender, (viii) Disease duration, and (ix) Main outcomes.

Quality review: Since bias resulting from omitted factors is frequent in studies in this field, we used the ROBINS-I technique to assess the likelihood of bias since it enables a thorough examination of confounding. The ROBINS-I tool was used for cohort designs where individuals exposed to different staffing levels were tracked over time and was designed to assess non-randomized studies. Each paper's risk of bias was evaluated independently by two reviewers, and any differences were settled by group discussion [10].

Results

The specified search strategy yielded 584 publications (Figure 1). After removing duplicates (n =291), 293 trials were evaluated based on title and abstract. Of these, 255 study failed to satisfy eligibility criteria, leaving just 38 full-text articles for comprehensive review. A total of 7 studies satisfied the requirements for eligibility with evidence synthesis for analysis were included. Sociodemographic and clinical outcomes: As illustrated in (Table 1), a total of 1927 children diagnosed with IBD (1467 with CD and 460 with UC) were included; 1153 (59.5%) were males.

Regarding study designs, five studies were retrospective cohorts [12, 15-18], one was a cross-sectional [13], and one was a prospective cohort [14]. Two studies were implemented in Saudi Arabia [15, 18], one in The UK [16, 17], one in Germany [12], one in Bahrain [13], and one in Canada [14]. Growth abnormalities, particularly in patients with CD, are frequently observed and seem to manifest strongly before the age of fifteen. These abnormalities include both height and weight retardation, which are likely exacerbated by the chronic inflammatory state of IBD [12]. Children with IBD often experience a substantial risk of linear growth impairment, particularly those who had low weight at the onset of their illness [13]. Delayed diagnosis and initiation of treatment in pediatric IBD patients correlate with worse growth outcomes, especially in those with CD. These delays result in a higher risk of linear growth impairment, emphasizing the need for early intervention as a modifiable factor that could improve patient outcomes [14]. Another significant finding is the age-dependent impact of IBD on growth, with children under ten years showing a more pronounced effect on linear growth compared to older children, particularly those with UC [15]. Furthermore, the potential disruption of the pubertal growth spurt in adolescents with IBD, especially those with CD, reflects how the disease affects not only childhood growth but also critical developmental stages [16]. This growth delay during puberty may be linked to systemic hormonal disruptions, such as impaired bioavailability of insulin-like growth factor-1 (IGF-1), which plays a vital role in normal growth. Additionally, findings suggest that height velocity in children with CD is notably impacted by both the severity of the disease and the age at diagnosis, further illustrating the importance of timely and effective disease management [17]. (Table 2) shows that, in evaluating the studies listed, a spectrum of biases can be observed regarding participant selection, intervention classification, and outcome measurement. Zhou et al. [12] displays moderate biases in confounding and selection, whereas Isa et al. [13] shows low bias across several categories. Ricciuto et al. [14] achieves low bias overall, while El Mouzan et al. [15], and Mason et al. [16] both report moderate biases in specific areas. Kherati et al. [17] presents a mixed profile with moderate biases in intervention classification. Ishige [18] reveals critical biases, indicating significant concerns that may affect the study's reliability.

Discussion

This review highlights a strong link between pediatric IBD and growth issues, especially in CD. Children with IBD are at a higher risk of growth problems due to the chronic inflammation that affects their ability to grow normally. Early-onset IBD, particularly in children under ten, seems to have a more severe impact on growth, which may lead to long-term consequences on their physical development. This is especially concerning because growth is not only about height; it also involves other aspects like bone health and overall well-being. The findings indicate that delays in diagnosing and treating IBD can worsen growth outcomes, suggesting that early and aggressive management might be necessary to help these children grow properly. Furthermore, adolescence is a critical period for growth, and IBD can interfere with the pubertal growth spurt, which might lead to short stature in adulthood [12-17]. A review by Amaro et al. [19] also stated that it is crucial to regularly measure height, weight, and pubertal stage in children and adolescents with chronic illnesses, such as IBD. Many pediatric IBD patients, particularly those with CD, present with growth retardation and delayed puberty because slowdown in height velocity might be the earliest indication of IBD onset, even months before weight loss and digestive symptoms appear. Ishige [18] found that growth impairment, particularly in CD, remains a significant consequence of IBD with a childhood onset. Maintaining good growth in young IBD patients appears to depend on avoiding corticosteroids and obtaining profound remission with enteral feeding or anti-TNF medications. Regarding CD, the growth deficit that frequently exacerbates childhood-onset CD is caused by a combination of proinflammatory cytokines generated from the inflamed colon and chronic undernutrition. The growth hormone (GH)–IGF-I axis is interfered with by both factors. Chronic, careless corticosteroid usage can exacerbate growth limitation brought on by illness. The degree of inflammation-related growth retardation may also be influenced by genetic variables. Growth delay can be prevented or treated by early disease detection, appropriate intestinal inflammation management, and provision of sufficient nutrients. A sign of therapeutic success is normal growth [20]. According to Ballinger et al. [21], rats with experimental colitis had higher hypothalamic release of serotonin (hydroxytryptamine, 5-HT), and this was linked to anorexia. Lung cancer patients have also been found to have decreased hypothalamus activity, which is linked to impaired appetite [22].

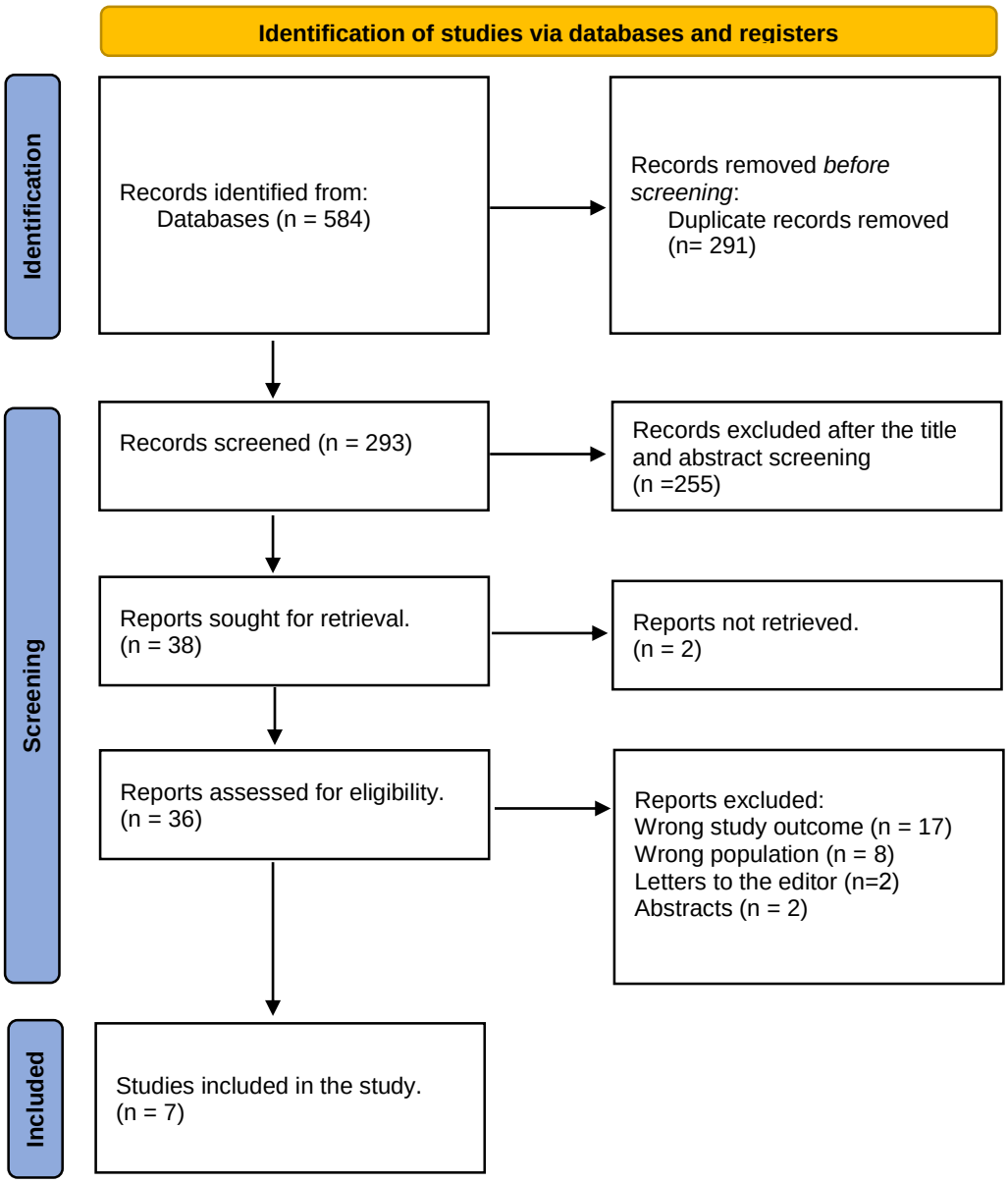

Figure 1: PRISMA flowchart [11].

Table 1: Outcome measures of the included studies.

Study ID	Study design	Country	Socio-demographic	CD*	UC**	Disease duration	Main outcomes
Zhou et al., 2024 [12]	Retrospect-ive cohort	Germany	N= 421 Age range: 0.6-15 Males: 250 (59.4%)	291	130	0.4-15	Growth abnormalities, particularly in CD patients, are a consequence of childhood IBD#. Growth abnormalities, including weight retardation, are likely to occur in IBD patients under the age of fifteen.
Isa et al., 2022 [13]	Cross-sectional	Bahrain	N= 88 Age range: 0-18 Males: 55 (62.5%)	47	41	0.4-10.9	Comparing pediatric IBD patients to the general population, this study revealed a high rate of linear growth impairment. The sole substantial risk factor for LGI was low weight at the onset of the illness.
Ricciuto et al., 2021 [14]	Prospective cohort	Canada	N= 898 Age range: 10.8-14.8 Males: 540 (60%)	898	NA	NM	Since delayed diagnosis is linked to worse patient outcomes, including as delayed treatment beginning and a higher risk of linear growth impairment in pediatric CD, it is a significant modifiable factor in the management of IBD.
El Mouzan et al., 2016 [15]	Retrospect-ive cohort	Saudi Arabia	N= 374 Age range: 0.3-0.16 Males: 219 (58.6%)	119	255	NM	The significance of age stratification in determining the impact of IBD on linear development is highlighted by the larger impact of IBD on linear growth in CD youngsters who have early-onset (<10 years) and in older children with UC, a trend that is rarely reported in the literature.
Mason et al., 2015 [16]	Retrospect-ive cohort	UK	N= 63 Age range: 10-16.6 Males: 35 (55.6%)	45	18	2.9-4.4	Despite making normal progress during puberty, adolescents with IBD frequently experience a reduction of the pubertal growth spurt. This is especially noticeable in CD and could be connected to how the illness affects IGF-1's## systemic bioavailability.
Kherati et al., 2024 [17]	Retrospect-ive cohort	UK	N= 47 Age range: 4-16 Males: 33 (68.8%)	47	NA	1 to 4	The severity of CD and the age of diagnosis have a major influence on bone growth and health. Our results specifically show that height velocity is significantly impacted by the age of diagnosis.
Ishige, 2019 [18]	Retrospect-ive cohort	Saudi Arabia	N= 36 Mean age: 8 ± 4 Males: 21 (58.3%)	20	16	NM	According to these statistics, growth failure in IBD patients is rare, but it was decreased by 50% over a 26-month period. The improvement in nutritional status during the management period may be the cause of this.

*CD: Crohn's disease, **: Ulcerative colitis, #: Inflammatory bowel disease, ##: Insulin-like growth factor-1

Table 2: Risk of bias assessment using ROBINS-I.

Study ID	Bias due to confounding	Bias in the selection of participants into	Bias in the classification of interventions	Bias due to deviations from the intended interval	Bias due to missing data	Bias in the measurement of outcomes	Bias in the selection of reported result	Overall bias
Zhou et al., 2024 [12]	Mod	Mod	Low	Low	Low	Low	Low	Low
Isa et al., 2022 [13]	Low	Mod	Low	Low	Low	Low	Low	Low
Ricciuto et al., 2021 [14]	Low	Low	Low	Low	Low	Mod	Low	Low
El Mouzan et al., 2016 [15]	Mod	Low	Mod	Mod	Low	Low	Low	Moderate
Mason et al., 2015 [16]	Mod	Mod	Low	Low	Low	Mod	Low	Moderate
Kherati et al., 2024 [17]	Low	Mod	Mod	Mod	Low	Mod	Low	Moderate
Ishige, 2019 [18]	Crit	Crit	Low	Low	Mod	Low	Low	Critical

Children with CD have delayed stomach emptying, but children with UC have normal emptying, according to Gryboski et al. [23]. Five of the 15 CD patients in this study experienced growth retardation, and 12 of them had upper gastrointestinal symptoms such nausea and anorexia. Regarding malabsorption, patients with active CD were often observed to have protein-losing enteropathy [24]. According to reports, GH resistance is a major factor in the growth failure that IBD patients experience [25]. Linear growth is regulated by the GH-insulin like growth factor (IGF)-1 axis, and individuals with active CD have lower levels of IGF-1 in their blood [26]. Growth failure in IBD patients may also be related to genetic background. In their study of 951 IBD subjects, including 317 CD patients, Lee et al. [27] found a substantial correlation between growth impairment and a variation in the DYM gene (dymeclin). It has been reported that healthcare providers should target the early diagnosis and treatment of IBD in children to prevent the occurrence of growth issues. It is crucial to conduct regular growth monitoring in pediatric IBD patients as stunted growth may be one of the first indicators of the disease affecting a child's development. Nutritional support is also one option that clinicians should take into account, and treatments that can improve the situation such as growth hormone therapy should also be a consideration in severe cases. For children with CD, however, preventing the long-term use of steroids is pivotal since they might aggravate the already existing growth delays. All things considered, comprehensive care including gastroenterologists, endocrinologists, dietitians, and psychologists may prove valuable in addressing both the physical and psychological aspects of growth impairment in pediatric IBD patients [12].

Strengths and limitations: This review has the merit of its extremely wide examination of a number of studies from several parts of the world, which gives it a global perspective on pediatric IBD and growth. The authors of this review use a diversity of research methodologies to offer an accurate and complete analysis of the matter, such as age, disease type (CD to UC), and the types of treatment. The conclusions derived from this method are, therefore, a lot stronger, and the information supplied can be well utilized by healthcare professionals treating different populations. This review is restricted by certain factors. Most of the studies that were reviewed tended to be retrospective in nature, meaning that they analyzed studies conducted some time back, thus in some instances details may lacking or distorted. Additionally, studies had different sample sizes and came from different nations, which may cause variations due to differences in the culture or health care system. Also, another limitation is that treatment types were not clearly stated in all the studies e.g., what medications used, what nutrition offered, hence it is challenging to evaluate the effect of growth other factors such as medications used.

Conclusion

In conclusion, pediatric IBD is inextricably linked to problems of stunted growth, that being especially true in children with CD, particularly those diagnosed at a young age. The early diagnosis and, more importantly, the proper management of IBD are crucial to achieving normal growth and preventing long-term effects in this group of children. Growth should be monitored as a key measure of disease impact by the clinician concerned, and nutritional and medical support should be given to help further development. More studies need to be carried to establish the best possible ways to tackle problems with growth in pediatric IBD, in addition to strategies to help this group of children reach their potential.

Conflict of Interest

None

Funding

None

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