Review Article ISSN 2639-9334

Gastroenterology, Hepatology & Digestive Disorders

Pediatric Obesity and Non-Hepatobiliary Gastrointestinal Disorders: A Comprehensive Review

Sandipan Sen[1] and Sudipta Misra[2]*

[1]*NRS Medical College, West Bengal, India.*

[2]*Summerville Medical Centre, Summerville, South Carolina, USA.*

***Correspondence:**
Sudipta Misra, Director, Pediatric Gastroenterology, Hepatology and Nutrition, Trident Health System, 295-A Midland Parkway, Suite 120, South Carolina, USA, Tel: 843 695 2700, Fax: 843 875 4046.

Received: 01 Nov 2024; **Accepted:** 09 Dec 2024; **Published:** 19 Dec 2024

Citation: Sandipan Sen, Sudipta Misra. Pediatric Obesity and Non-Hepatobiliary Gastrointestinal Disorders: A Comprehensive Review. Gastroint Hepatol Dig Dis. 2024; 7(4): 1-8.

ABSTRACT

Background and Aims: *Obesity is a pervasive health issue in children. It affects multiple systems in the body including the gastrointestinal tract. Research on obesity-related gastrointestinal diseases has focused mostly on hepatobiliary disorders. However, non-hepatic gastrointestinal diseases such as gastroesophageal reflux, constipation, and functional abdominal pain, though common and debilitating, have not been highlighted in the context of obesity. These entities can downgrade the already compromised lifestyle of obese children. Some of these disorders are more difficult to treat in these children compared to their peers with normal body mass index.*

Method: *We reviewed the available literature on the association of obesity and these three common gastrointestinal disorders.*

Results: *There appears to be a strong correlation between childhood obesity and constipation and gastroesophageal reflux, and a probable correlation with functional abdominal pain.*

Conclusion: *We suggest that in view of the available literature, weight management should be an integral part of the management of gastroesophageal reflux, constipation, and functional abdominal pain in obese children. This gains relevance especially because of the recent approval of medications for the treatment of obesity in children.*

Keywords

Children, Obesity, Constipation, Gastroesophageal Reflux, Recurrent Abdominal pain.

Abbreviations

ACTH: Adrenocorticotrophic Hormone, BMI: Body Mass Index, CCK: Cholecystokinin, CRF: Corticotrophin Releasing Factor, EM: Esophageal microbiome, FAPS: Functional Abdominal Pain Syndrome, FC: Functional Constipation, FODMAP: Fermentable Oligo-, Di-, and Monosaccharides and Polyols, GER: Gastroesophageal Reflux, GERD: Gastroesophageal Reflux Disease, GET: Gastric Emptying Time, GI: Gastrointestinal, GLP: Glucagon Like Peptide, IL: Interleukin, OR: Odds Ratio, PYY: Peptide YY, TLESR: Transient Lower Esophageal Sphincter Relaxation, TNF: Tumor Necrosis Factor.

Introduction

Childhood obesity has reached endemic proportions. Worldwide, the number of overweight children has nearly tripled over the last 4 decades. Currently, over 340 million children and adolescents aged 5-19 years are classified as either obese or overweight [1]. In the United States alone, about 14.7 million children and adolescents aged 2-19 years are overweight with a prevalence rate of 19.7% [2]. Obesity causes major morbidity in children such as type-2 diabetes mellitus, cardiovascular diseases, asthma, stroke, obstructive sleep apnea etc. [3]. It also affects the quality of life and is associated with social and psychological problems such as depression, lowered self-esteem, etc. Studies have shown that childhood obesity is an important determinant of adult obesity and obesity-related co-morbidities and complications in later life [4].

Studies of obesity-related gastrointestinal morbidities have mostly focused on Metabolic Disorders associated Steatotic liver disease (formerly known as NAFLD), Metabolic Disorders associated Steatohepatitis (formerly known as NASH), and cholelithiasis [5]. Emerging data indicate that pediatric obesity is also associated with other major gastrointestinal diseases such as constipation, gastroesophageal reflux, and functional abdominal pain [6,7]. Such associations have not been emphasized enough in the pediatric literature. Recognition of this association and including weight management in the treatment protocol may help improve the overall outcome in these children.

The objective of this review is to discuss the known literature on the association of pediatric obesity with constipation, gastroesophageal reflux, and functional abdominal pain along with the pathophysiology. We hope to help the clinician recognize this association and use it in their day-to-day practice. To highlight the recent developments and future direction of research, we have included a paragraph on microbiome in each section.

Method

Ovid® and Pub Med® databases were queried with keywords such as 'Reflux' and phrases such as 'Constipation AND Obesity' with filters such as 'Children', and 'Adolescents', etc. as necessary. The bibliography of the key papers was also scanned for appropriate references. The relevant papers were reviewed and findings were included in this article.

Obesity and Functional Constipation

Functional constipation (FC) is one of the most prevalent gastrointestinal disorders reported in adults and children worldwide [8]. The reported prevalence of FC ranges between 0.5% and 32.2% among the pediatric population, with a pooled prevalence of 9.5% (95% CI, 7.5-12.1%) [9]. Many have abdominal pain (as high as 47.5%) and fecal incontinence [10]. FC further degrades an already compromised lifestyle in obese children.

The available literature on obesity and FC is contradictory at first glance. FC has been reported to be the most common GI-related morbidity in obese children [11]. It was reported in 23% of obese children, compared to 8.9% in the general population [12]. When compared to the age and sex-matched healthy controls, there was a preponderance of constipation among the obese children (21% versus 1%) [13]. Such association was consistent with the findings (18.44% versus 7.82%) of another clinic-based Italian study [14]. A US-based study reported that obesity increased the risk of developing constipation in children by almost 2-fold (odds ratio 1.83, p-value 0.01) [15]. In a retrospective observational study on children referred to a sub-specialty clinic for functional constipation, we observed a significantly higher number of overweight children among the constipation group than the control group (p-value <0.05) [16]. Another study on children referred to a pediatric gastroenterology clinic reported a higher prevalence of obesity in constipated children (22.7% versus 11.7%) than the controls (p-value <0.001) [17]. A prospective clinic-based case-control study also observed a higher obesity rate (8%) in constipated children [11]. Similar results were reported from outside Europe and North America as well. A study from India on 186 children reported obesity in 23.66% of cases with functional constipation. Encopresis with constipation was significantly higher among obese children (88.64%, p<0.001) [18].

On the other hand, two school-based studies from Columbia (N=2820) and Brazil (N=1077), did not document the increased incidence of constipation in obese children (Obese/control; Columbia 14.9%/12.9%, p=0.73; Brazil 19.4%, 18%, p=0.76) [19,20]. Another study from the Netherlands (N=2420) found no significant increase in the incidence of obesity among children with constipation (OR 1.01; 95% CI: 0.69-1.46) compared to those with normal weight [21].

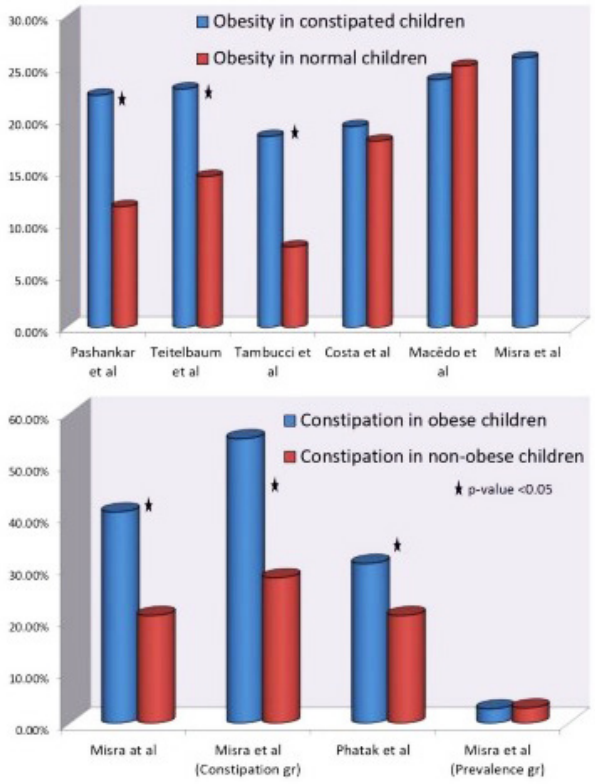

Figure 1: Constipation and Obesity in Children.

On close analysis, it appears that while most of the clinic-based studies reported an association between obesity and constipation, community-based studies refuted such claims (Figure 1). We reviewed the charts of 955 children in the primary care clinic [22]. We concluded that there was no association between constipation and obesity in the community setting. But obese children with constipation were 3 times more likely to be referred to the subspecialty clinic, for apparent treatment failure. This may explain the preponderance of obesity among constipated children in clinic-based studies. A prospective study is warranted to test this hypothesis as weight management may be another non-pharmacological tool for the treatment of constipation.

A number of mechanisms have been proposed as the causes of both constipation and obesity. High carbohydrate, low-fiber diet, and a sedentary lifestyle are associated with both obesity and constipation [21]. A study on middle-aged post-menopausal women found significant improvement in constipation symptoms and quality of life after 12 weeks of increased physical activity and low-calorie diet intake [23]. The "ileal break" concept, where a high-fat diet slows down intestinal motility and causes constipation in obese adults, has been proposed [24]. However, a study involving morbidly obese children didn't find any difference between the diet of children with or without constipation, including fiber and fat intake [13]. Daily exercise enhances colonic motility and accelerates gut peristalsis by stimulating the vagus nerve, increasing gut blood flow, and augmenting the release of GI hormones. Gut hormones like ghrelin and motilin take a pivotal role in the pathogenesis of constipation in overweight persons. Ghrelin, a "hunger hormone", augments initiation of the migrating motor complex in the stomach, and stimulates gastrointestinal motility [25]. In obese children, lower serum concentrations of ghrelin may contribute to decreased gut motility, which, in turn, causes constipation. Fat intake potentiates increased release of Glucagon like peptide-1, 2 (GLP-1, GLP-2), cholecystokinin (CCK), and inhibition of peptide YY (PYY), which leads to constipation by colonic smooth muscle relaxation. Obesity mediates tumor necrosis factor-alpha (TNF-a), IL-1, IL-6, and toll-like receptor (TLR) signaling, which are responsible for immunoinflammation [26]. It causes morphological changes in the interstitial cells of Cajal of the enteric nervous system and impairs the contractile function of intestinal smooth muscles.

Finally, psychosocial and behavioral abnormalities are postulated to play important roles in the co-occurrence of obesity and FC. Children with obesity have a 43% higher risk of anxiety and depression than the general population ($p<0.001$). Moreover, obesity makes children and adolescents more vulnerable to having low self-esteem (risk estimate 1.53; 95% CI: 1.16-2.02; $p=0.003$) and body dissatisfaction (risk estimate 4.05; 95% CI: 2.34-7.023; $p=0.001$) [27]. On the other hand, studies have identified childhood constipation as a potential risk factor for depression, attention difficulties, and poor school performance. Though there is little direct evidence identifying depression as a connecting bridge between constipation and obesity, we reported an increased incidence of psychological and behavioral problems in the group of overweight children with treatment-resistant chronic constipation [22]. Studies found a correlation between increased body weight and psychological stress [28]. Chronic stressful condition increases catecholamine production, especially epinephrine (E) and norepinephrine (NE). Both of these catecholamines affect GI blood flow, cause beta-receptor mediated GI smooth muscle relaxation, and ultimately, alter GI motility and increase GI transit time [24]. Additionally, stress releases cortisol by increasing corticotrophin releasing factor (CRF) and adrenocorticotropic hormone (ACTH). Cortisol increases plasma zinc concentration, which augments the secretion of CCK, an inhibitor of colonic contraction. Weight reduction interventions might help in the reduction of emotional stress, anxiety, and poor self-esteem and thus augment overall emotional and psychological well-being.

Gut microbiota is believed to hold the secrets of many human ailments. Disruption of gut microbiota, or dysbiosis, deranges the homeostasis between the 'good' and 'bad' bacteria of the colon and results in disease states. The role of the microbiome in obesity was dramatically revealed when a lean person became overweight after receiving a fecal transplant from an obese donor [29]. At this point, research mostly focuses on changes in the composition of gut microbiota that can alter energy metabolism and develop obesity [30]. In both mono and dizygotic twins studies, there were fewer Bacteroides ($p=0.003$), and abundant Actinobacteria($p=0.002$) in the obese sibling [30]. It has been further suggested in mice studies, that alteration in gut microbiota affects the efficiency of energy harvest from diet, along with utilization and storage of the calories, causing differences in weight gain. Similarly, studies have suggested the involvement of gut microbiota in the development of constipation in obese children. A cross-sectional study examined the stool samples of children using rRNA gene pyrosequencing and found that the fecal microbiota of constipated obese children had decreased representation of Prevotella and abundance of genera of Firmicutes spp. compared with the non-constipated obese controls [31]. Those with early insults to the gut microbiome due to necrotizing enterocolitis, sepsis, delayed enteral feeding, and other perinatal events were at greater risk of developing FC in later life [32]. These studies suggest that gut microbial population of constipated children contains less amount of Prevonella compared to healthy children. Increased levels Proteobacteria sp, Bacteroides sp., Parabacteroides sp., and Bifidobacterium longum, and decreased Alistipesfinegoldii and Ruminococcusspas were found in stool samples of children with intractable constipation.

Over-the-counter probiotic combinations have gained popularity for the treatment of FC without any scientific proof of efficacy. From the scanty evidence available from the literature, probiotic supplements containing Prevotella and L.rhamnosus strains are more likely to be effective than the random mix of probiotics available over the counter.

Summary

It appears that obese children are more likely to have treatment-resistant constipation. Incorporating weight management strategies in the treatment protocol may be helpful in resolving constipation in these children. This strategy can improve quality of life of these children as well. Large randomized studies are warranted to study the practical implications of weight management measures in treating childhood constipation.

Obesity and Gastroesophageal Reflux

Gastroesophageal reflux (GER) is common. About 60% of the population have reflux symptoms at least once a year, 20-30% once a week [33]. Almost all premature babies and most newborns have 2-3 reflux episodes per hour. It is a clinical diagnosis, and symptoms, such as heartburn, upper abdominal pain, food regurgitation, and retching are common in pediatric primary care settings. Montreal Definition and Classification provides the

clinical framework for diagnosing gastroesophageal reflux disease (GERD).

The association between obesity and GER is well-established in adults. A higher body mass index (BMI) is considered a risk factor for GER in the adult population. A meta-analysis of 30 adult studies published over 60 years found a significant association between high BMI and GER symptoms. The risk of GER was significantly higher (odds ratio1.89, 95% CI: 1.70-2.09) among the obese adults compared to their non-obese peers [34]. Obesity is a well-known risk factor for complications of GERD, like reflux esophagitis and Barrett's esophagus. An association between abdominal obesity and esophageal adenocarcinoma has been reported [35].

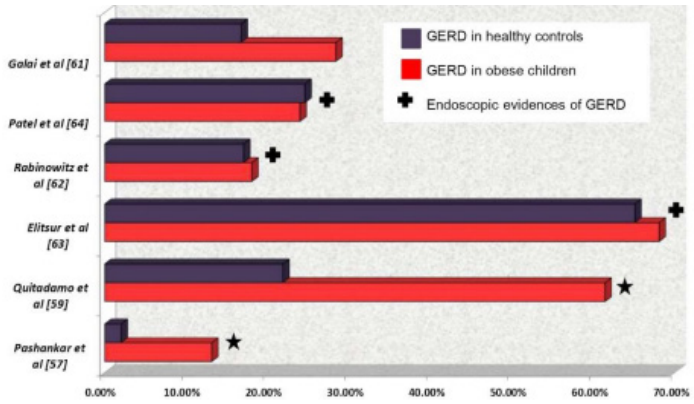

Figure 2: Gastroesophageal Reflux and Obesity in Children.

Pediatric studies, though sparser, support the association [Figure 2]. In a questionnaire-based study on children, obesity was significantly higher in boys with GERD (24.7% versus 16.7%, p=0.03) [36]. Another hospital-based study reported that obesity was more prevalent in children with GERD compared to controls (p<0.01) [11]. A higher prevalence of GER symptoms in obese children has been reported in questionnaire-based studies from the USA [37], Norway and Italy [38,39]. One of these studies found abdominal obesity as a risk factor for developing GER symptoms (62% versus 24%, p<0.005) and higher reflux symptoms score (average scores 3.1 versus 0.84, p-value <0.005) [39]. The only population-based large-scale cross-sectional study showed moderate to extremely obese children between the age group 6-19 years were more likely to have GERD (odds ratio 1.16, 95% CI: 1.07-1.25), than children with normal BMI [40]. Overall 20.9-38% of children with obesity had at least one symptom of GI reflux across various studies [41]. Epigastric pain and regurgitation were the most frequent symptoms reported [37,39]. Some studies report that the risk and severity of reflux are directly proportional to BMI-Z score, irrespective of the child being obese [37,39].

However, when biopsy-proven reflux esophagitis was the diagnostic criteria for GERD, the association with obesity disappeared. In a chart review of 738 children, obesity or overweight wasn't found to be an independent risk factor (p= 0.098) [42]. Similarly, two other studies failed to establish a relationship between obesity and microscopic features of reflux esophagitis [43,44]. This may be due to selection bias as only severe or long-lasting cases are usually selected for endoscopy. Even then, only 20% of children with GERD symptoms had reflux esophagitis by endoscopic evaluation [36]. Histological changes of esophageal mucosa occur over some time; therefore, erosive esophagitis becomes more prevalent with advancing age. Only 12% of children suffering from symptomatic GER develop esophagitis by 21 years of age [45].

These findings lead to the next logical question of whether weight management can be a primary or ancillary non-pharmacological treatment of childhood reflux disease. Unfortunately, this issue has not been addressed in the pediatric literature. In adults, 65% of obese patients had complete resolution of GER symptoms after a structured weight loss program in an interventional trial [46]. Dietary and lifestyle modifications led to symptomatic relief in another group of patients with GERD [47]. A significant correlation between the degree of weight loss and reduction of GER symptom scores was also seen in other adult studies [46] [Figure 3]. Such studies are highly desirable in the pediatric population to evaluate weight management as another facet of the management of GERD in children.

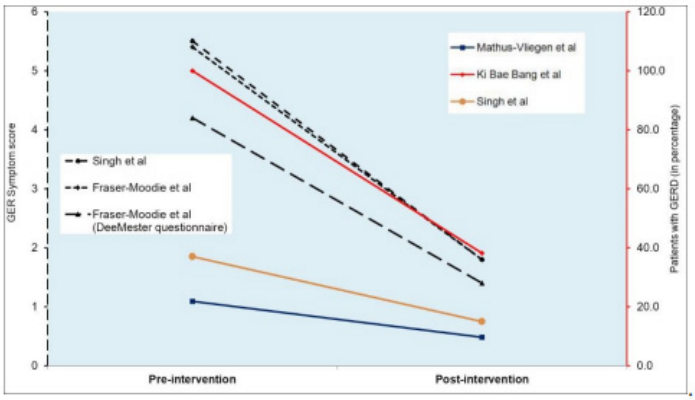

Figure 3: Effect of weight management on GERD based on changes in GER symptom score and percentage (%) of adults with GERD.

GER is caused by the inappropriate transient relaxation of the lower esophageal sphincters (TLESRs). Factors contributing to obesity, such as increased dietary fat intake, smoking, and alcohol use are found to be potential causes of both GERD symptoms and esophageal erosion in adults [47]. Decreased gastric emptying time (GET) is another cause of GERD as it increases gastric acid secretion, increases gastric volume, and thus increases the gastroesophageal pressure gradient, increasing the odds of GER [48]. Among children, increased fatty acid consumption causes delayed emptying causing reflux symptoms [14]. A study showed a direct relationship between waist circumferences, a surrogate for visceral adiposity, with GET. Symptomatic obese GER patients had a longer GET than their asymptomatic peers [49]. Feeding habits may also contribute to GER in obese children. A large amount of food intake in a short span of time may overwhelm the gastric accommodation capacity and increase intraluminal pressure leading to reflux symptoms [14,49]. Increased abdominal fat may increase intragastric pressure, interrupting the anti-reflux

mechanisms of the lower esophagus [50]. Recent studies have also focused on the roles of pro-inflammatory cytokines such as TNF alpha, IL-1 beta, IL-6 produced by M1 macrophages and mature adipocytes. Interaction between adipokines like leptin and adiponectin is also being investigated as a causal factor for the disrupted esophageal mucosal barrier in adults. Recently, studies based on genomic sequencing have focused on the role of esophageal microbiome (EM) in GERD. Some investigators have put more emphasis on microbial dysbiosis than gastric acid secretion in the development of esophageal mucosal diseases in adults. Various factors like age, diet, antibiotics and other medications, oral hygiene, smoking, etc. can disrupt the esophageal microbiome (EM). It results in persistent esophageal dysbiosis which generates a host of immunogenic responses, which ultimately propagates the inflammatory cascade. Researchers have evidence that non-erosive reflux disease is associated with a shift of EM away from Fusobacteria, Actinobacter spp. towards Proteobacteria and bacteroidetes. This novel insight into EM opens further research options to study the etiological role of esophageal microbiome in obesity and GERD.

In Summary

Unlike adults, the association between high BMI and GER symptoms has not been firmly established in children. However, sufficient evidence exists to suggest that such an association exists and that older obese children are more likely to have GER symptoms. More prospective pediatric studies are needed to establish the cause-and-effect relationship between the two. However, clinically, it may be wise to include weight management in the treatment regimen for GERD in obese children.

Obesity and Functional Abdominal Pain (FAP)

Functional abdominal pain syndrome (FAPS), may account for as much as 50% of all pediatric gastrointestinal clinic visits. Globally the prevalence of childhood functional abdominal pain is estimated to be around 15% [51]. It is defined by the latest Rome criteria, as a disorder of gut-brain interaction (DGBI) in children. FAP is more common in children older than 12 years (12.9% versus 13.8%). Its impact on the child and the family is highlighted by the fact that 80.5% of children with RAP reported missing school with a significant decline in quality of life [52].

There are few studies on FAP and obesity in children. In a cross-sectional school survey study with a validated questionnaire and Wong-Bakes FACES scale for FAP. FAP was significantly more frequent in obese children than in the control group (odds ratio 1.8, p-value 0.01) [53]. Every third of obese children reported abdominal pain. Similarly, obese children had a more than 2-fold increased risk of developing FAPS (odds ratio 2.1; p-value 0.007) [15].

A pediatric gastrointestinal clinic-based study showed that obesity was more prevalent (39.5% versus 30%, p-value 0.04) in adolescents with FAPS compared to healthy controls [41]. Obese children with FAP were older and were more likely to be hospitalized for FAP. Another pediatric study revealed a predominance of obesity among those diagnosed with FAP (16.2%, p-value 0.02) [11]. A small number of studies have refuted such findings. An analysis of 114 obese children showed no difference in the incidence of FAP, compared to the normal-weight children (2.60% versus 1.94%, p=1.00) [14,54]. Overall, the preponderance of evidence favors an association between FAP and obesity.

Various hypotheses have been postulated to explain how obesity can cause FAP. Dietary habit is considered the most likely connection between obesity and abdominal pain. Evidence suggests that a diet containing fermentable oligo-, di-, and monosaccharides and polyols (FODMAP) may precipitate gastrointestinal symptoms in patients with FAP [55]. These types of diet can cause weight gain as well. There are a few reports showing restriction of short-chain carbohydrates and a low FODMAP diet offers significant symptom relief in adult patients, but no conclusive data is available in the pediatric population [56]. One pediatric study found an inverse relationship between fruit consumption and FAP prevalence [53]. Both obesity and low fruit consumption were found to be independent risk factors for FAP.

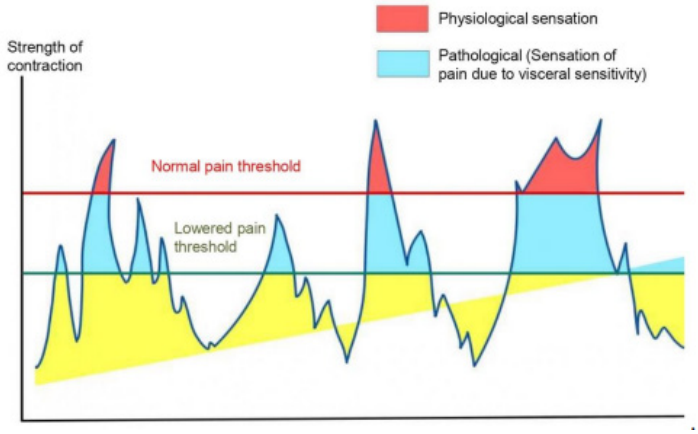

Figure 4: Schematic Diagram of intestinal motility and visceral hyperalgesia.

Visceral hypersensitivity, where the threshold of perception of pain is reduced, has been proposed to be the cause of co-existence of FAP and obesity [Figure 4] [57]. Hyperalgesia leads to the perception of pain even with physiological contractions of the gut. It is thought that obesity-induced inflammatory factors enhance pain perception of intestinal signals at the CNS level. This hyperexcitability ultimately leads to abnormal bowel movement and chronic abdominal pain. Obesity, with associated low-grade chronic inflammation, causes dysregulation of the gut-brain axis [58]. This non-infective, chronic persistent inflammation is caused by the low-grade synthesis of inflammatory mediators in the adipose tissues. These inflammatory mediators (adiponectin, TNF, IL-1, IL-6, leptin, resistin, etc.) induce neuroinflammation by activating free nerve endings and inducing pain-causing biological substances. Intestinal hyperpermeability and vitamin D deficiencies are other contributing factors that can enhance central pain perception via the gut-brain axis and increase the risk of chronic recurrent abdominal pain in the obese population [57].

The microbiome-gut-brain axis is the emerging concept explaining the shared biological mechanism between abdominal pain and obesity [59]. As discussed earlier, alteration of gut microbial diversity is evident in both children and adults with obesity compared to healthy ones [57]. Similarly, alteration of colonic bacterial flora, especially reduction in levels of beneficial bacteria like the actinobacteria, bifidobacteria in stool samples has been documented in patients with FAPS [60]. Both Lactobacillus and Bifidobacterium infantis are reported to downregulate T-helper cell response to provide an anti-inflammatory effect to the gut mucosa and cause symptomatic relief from abdominal pain. A randomized controlled trial with Bifidobacterium infantis, B. breve, and B. Longum reported resolution of abdominal pain in a significantly higher proportion of children (p=0.006) [61]. Conversely, microbial metabolites of pathogenic bacteria, such as protease and serotonin, activate sub-mucosal nerve endings and induce pain in adults. Despite having significant roles in both obesity and FAP, till now no study or trial has been conducted to assert a direct causal association between obesity and FAP about gut microbial dysbiosis. Moreover, almost all the studies studying the probable shared pathophysiology were among adults and irritable bowel syndrome. There is a gap in knowledge connecting obesity and FAP in children.

In Summary

The available studies don't establish a definite causal relation between FAP and obesity in children. No study investigating the direct role of weight loss in relieving functional abdominal pain is available in the literature. Non-pharmacological measures like dietary modification and exercise had been shown to improve symptoms of FAP, which indirectly causes weight loss. Therefore, a common-sense approach of including weight-reducing interventions for treating childhood FAP with obesity may be indicated.

References

1. World Health Organization. Obesity and overweight. 2021. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
2. Bryan S, Afful J, Carroll M, et al. NHSR 158. National Health and Nutrition Examination Survey 2017–March 2020 Pre-pandemic Data File. National Center for Health Statistics (U.S.); 2021. https://stacks.cdc.gov/view/cdc/106273
3. Smith JD, Fu E, Kobayashi MA. Prevention and Management of Childhood Obesity and Its Psychological and Health Comorbidities. Annu Rev Clin Psychol. 2020; 16: 351-378.
4. Murray. The GBD 2015 Obesity Collaborators. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. N Engl J Med. 2017; 377: 13-27.
5. Huang JS, Barlow SE, Quiros-Tejeira RE, et al. Childhood obesity for pediatric gastroenterologists. J Pediatr Gastroenterol Nutr. 2013; 56: 99-109.
6. Ho W, Spiegel BMR. The relationship between obesity and functional gastrointestinal disorders: causation, association, or neither? Gastroenterol Hepatol. 2008; 4: 572-578.
7. Phatak UP, Pashankar DS. Obesity and Gastrointestinal Disorders in Children. J Pediatr Gastroenterol Nutr. 2015; 60: 441-445.
8. Silveira EA, Santos AS e A de C, Ribeiro JN, et al. Prevalence of constipation in adults with obesity class II and III and associated factors. BMC Gastroenterol. 2021; 21: 217.
9. Koppen IJN, Vriesman MH, Saps M, et al. Prevalence of Functional Defecation Disorders in Children: A Systematic Review and Meta-Analysis. J Pediatr. 2018; 198: 121-130.
10. Kumar K, Gupta N, Malhotra S, et al. Functional constipation: A common and often overlooked cause for abdominal pain in children. Indian J Gastroenterol. 2023; 42: 274-278.
11. Teitelbaum JE, Sinha P, Micale M, et al. Obesity is Related to Multiple Functional Abdominal Diseases. J Pediatr. 2009; 154: 444-446.
12. Fishman L, Lenders C, Fortunato C, et al. Increased prevalence of constipation and fecal soiling in a population of obese children. J Pediatr. 2004; 145: 253-254.
13. Baan-Slootweg OH, Liem O, Bekkali N, et al. Constipation and Colonic Transit Times in Children with Morbid Obesity. J Pediatr Gastroenterol Nutr. 2011; 52: 442-445.
14. Tambucci R, Quitadamo P, Ambrosi M, et al. Association between Obesity/Overweight and Functional Gastrointestinal Disorders in Children. J Pediatr Gastroenterol Nutr. 2019; 68: 517-520.
15. Phatak UP, Pashankar DS. Prevalence of functional gastrointestinal disorders in obese and overweight children. Int J Obes. 2014; 38: 1324-1327.
16. Misra S, Lee A, Gensel K. Chronic Constipation in Overweight Children. J Parenter Enter Nutr. 2006; 30: 81-84.
17. Pashankar DS, Loening-Baucke V. Increased Prevalence of Obesity in Children With Functional Constipation Evaluated in an Academic Medical Center. Pediatrics. 2005; 116: e377-80.
18. Kumar SS, Kumar SS, Shirley SA. Prevalence of overweight and obesity in children with functional constipation aged 6 to 12 years attending outpatient department in a tertiary care hospital at Tamil Nadu, India. Int J Contemp Pediatr. 2020; 7: 2359.
19. Koppen IJN, Velasco-Benítez CA, Benninga MA, et al. Is There an Association between Functional Constipation and Excessive Bodyweight in Children? J Pediatr. 2016; 171: 178-182.
20. Costa ML, Oliveira JN, Tahan S, et al. Overweight and constipation in adolescents. BMC Gastroenterol. 2011; 11: 40.
21. Kiefte-de Jong JC, De Vries JH, Escher JC, et al. Role of dietary patterns, sedentary behaviour and overweight on the longitudinal development of childhood constipation: the Generation R study: Dietary patterns and constipation. Matern Child Nutr. 2013; 9: 511-523.
22. Misra S, Liaw A. Controversies on the relationship between increased body mass index and treatment-resistant chronic constipation in children. J Parenter Enter Nutr. 2022; 46: 1031-1035.

23. Tantawy S, Kamel D, Abdel-Basset W, et al. Effects of a proposed physical activity and diet control to manage constipation in middle-aged obese women. Diabetes Metab Syndr Obes Targets Ther. 2017; 10: 513-519.
24. Miron I. Gastrointestinal Motility Disorders in Obesity. Acta Endocrinol Buchar. 2019; 15: 497-504.
25. Chen CY, Tsai CY. Ghrelin and Motilin in the Gastrointestinal System. Curr Pharm Des. 2012; 18: 4755-4765.
26. Ding S, Lund PK. Role of intestinal inflammation as an early event in obesity and insulin resistance: Curr Opin Clin Nutr Metab Care. 2011; 14: 328-333.
27. Moradi M, Mozaffari H, Askari M, et al. Association between overweight/obesity with depression, anxiety, low self-esteem, and body dissatisfaction in children and adolescents: a systematic review and meta-analysis of observational studies. Crit Rev Food Sci Nutr. 2022; 62: 555-570.
28. Moore CJ, Cunningham SA. Social Position, Psychological Stress, and Obesity: A Systematic Review. J Acad Nutr Diet. 2012; 112: 518-526.
29. Alang N, Kelly CR. Weight gain after Fecal Microbiota Transplantation. Open Forum Infect Dis. 2015; 2: ofv004.
30. Turnbaugh PJ, Hamady M, Yatsunenko T, et al. A core gut microbiome in obese and lean twins. Nature. 2009; 457: 480-484.
31. Zhu L, Liu W, Alkhouri R, et al. Structural changes in the gut microbiome of constipated patients. Physiol Genomics. 2014; 46: 679-686.
32. Vandenplas Y, Carnielli VP, Ksiazyk J, et al. Factors affecting early-life intestinal microbiota development. Nutrition. 2020; 78: 110812.
33. Zhao Y, Encinosa W. Gastroesophageal Reflux Disease (GERD) Hospitalizations in 1998 and 2005. In: Healthcare Cost and Utilization Project (HCUP) Statistical Briefs [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2006.
34. Eslick GD. Gastrointestinal symptoms and obesity: a meta-analysis: GI symptoms and obesity. Obes Rev. 2012; 13: 469-479.
35. Cho JH, Shin CM, Han KD, et al. Abdominal obesity increases risk for esophageal cancer: a nationwide population-based cohort study of South Korea. J Gastroenterol. 2020; 55: 307-316.
36. Malaty H, Jkennard Fraley, Suhaib Abudayyeh, et al. Obesity and gastroesophageal reflux disease and gastroesophageal reflux symptoms in children. Clin Exp Gastroenterol. 2009;2: 31-36.
37. Pashankar DS, Corbin Z, Shah SK, et al. Increased Prevalence of Gastroesophageal Reflux Symptoms in Obese Children Evaluated in an Academic Medical Center. J Clin Gastroenterol. 2009; 43: 410-413.
38. Størdal K, Johannesdottir GB, Bentsen BS, et al. Asthma and overweight are associated with symptoms of gastro-oesophageal reflux. Acta Paediatr. 2006; 95: 1197-1201.
39. Quitadamo P, Buonavolontà R, Miele E, et al. Total and Abdominal Obesity Are Risk Factors for Gastroesophageal Reflux Symptoms in Children. J Pediatr Gastroenterol Nutr. 2012; 55: 72-75.
40. Koebnick C, Getahun D, Smith N, et al. Extreme childhood obesity is associated with increased risk for gastroesophageal reflux disease in a large population-based study. Int J Pediatr Obes. 2011; 6: e257-263.
41. Galai T, Moran-Lev H, Cohen S, et al. Higher prevalence of obesity among children with functional abdominal pain disorders. BMC Pediatr. 2020; 20: 193.
42. Elitsur Y, Dementieva Y, Elitsur R, et al. Obesity Is Not a Risk Factor in Children With Reflux Esophagitis: A Retrospective Analysis of 738 Children. Metab Syndr Relat Disord. 2009; 7: 211-214.
43. Patel NR, Ward MJ, Beneck D, et al. The Association between Childhood Overweight and Reflux Esophagitis. J Obes. 2010; 2010: 1-5.
44. Rabinowitz SS, Goli S, Xu J, et al. Lack of correlation between obesity and gastroesophageal reflux disease (GERD) in a pediatric cohort. Open J Pediatr. 2013; 3: 317-323.
45. Yamasaki T, Hemond C, Eisa M, et al. The Changing Epidemiology of Gastroesophageal Reflux Disease: Are Patients Getting Younger? J Neurogastroenterol Motil. 2018; 24: 559-569.
46. Singh M, Lee J, Gupta N, et al. Weight loss can lead to resolution of gastroesophageal reflux disease symptoms: A prospective intervention trial. Obesity. 2013; 21: 284-290.
47. De Groot NL, Burgerhart JS, Van De Meeberg PC, et al. Systematic review: the effects of conservative and surgical treatment for obesity on gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2009; 30: 1091-1102.
48. Buckles DC, Sarosiek I, McCallum RW, et al. Delayed Gastric Emptying in Gastroesophageal Reflux Disease: Reassessment with New Methods and Symptomatic Correlations. Am J Med Sci. 2004; 327: 1-4.
49. Quitadamo P, Zenzeri L, Mozzillo E, et al. Gastric Emptying Time, Esophageal pH-Impedance Parameters, Quality of Life, and Gastrointestinal Comorbidity in Obese Children and Adolescents. J Pediatr. 2018; 194: 94-99.
50. Barak N, Ehrenpreis ED, Harrison JR, et al. Gastro-oesophageal reflux disease in obesity: pathophysiological and therapeutic considerations. Obes Rev. 2002; 3: 9-15.
51. Herzlinger M, Cerezo C. Functional Abdominal Pain and Related Syndromes. Child Adolesc Psychiatr Clin N Am. 2018; 27: 15-26.
52. Korterink JJ, Diederen K, Benninga MA, et al. Epidemiology of Pediatric Functional Abdominal Pain Disorders: A Meta-Analysis. Zhang L, editor. PLOS ONE. 2015; 10: e0126982.
53. Malaty HM, Abudayyeh S, Fraley K, et al. Recurrent abdominal pain in school children: effect of obesity and diet. Acta Paediatr. 2007; 96: 572-576.

54. Fifi AC, Velasco-Benitez C, Saps M. Functional Abdominal Pain and Nutritional Status of Children. A School-Based Study. Nutrients. 2020; 12: 2559.

55. Shepherd SJ, Lomer MCE, Gibson PR. Short-Chain Carbohydrates and Functional Gastrointestinal Disorders. Am J Gastroenterol. 2013; 108: 707-717.

56. Thomassen RA, Luque V, Assa A, et al. An ESPGHAN Position Paper on the Use of Low-FODMAP Diet in Pediatric Gastroenterology. J Pediatr Gastroenterol Nutr. 2022; 75: 356-368.

57. Yanping W, Gao X, Cheng Y, et al. The interaction between obesity and visceral hypersensitivity. J Gastroenterol Hepatol. 2023; 38: 370-377.

58. Lee SH, Kim KN, Kim KM, et al. Irritable Bowel Syndrome May Be Associated with Elevated Alanine Aminotransferase and Metabolic Syndrome. Yonsei Med J. 2016; 57: 146.

59. Mayer EA, Savidge T, Shulman RJ. Brain–Gut Microbiome Interactions and Functional Bowel Disorders. Gastroenterology. 2014; 146: 1500-1512.

60. Mars RAT, Yang Y, Ward T, et al. Longitudinal Multi-omics Reveals Subset-Specific Mechanisms Underlying Irritable Bowel Syndrome. Cell. 2020; 183: 1137-1140.

61. Giannetti E, Maglione M, Alessandrella A, et al. A Mixture of 3 Bifidobacteria Decreases Abdominal Pain and Improves the Quality of Life in Children With Irritable Bowel Syndrome: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Crossover Trial. J Clin Gastroenterol. 2017; 51: e5-10.