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Conceptual Model of Lean Body Mass in Pediatric Inflammatory Bowel Disease

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Abstract

Youth with inflammatory bowel disease (IBD) demonstrate deficits in lean mass (LM) placing them at increased risk for future health problems, including reduction of bone mass and impaired bone architecture. Research suggests that deficits in LM are multifactorial, including influences from the disease and its treatment, and health behaviors such as diet and physical activity. Based on a systematic literature review examining factors related to LM deficits in IBD, this article presents a conceptual model to explain the development of LM in youth with IBD. The model considers predictors of LM across 4 domains: demographic; medical; diet; and physical activity. Much existing research is cross-sectional, but suggests multiple factors work together to promote or inhibit LM accrual in youth with IBD. The conceptual model, developed based on empirical findings to date, can be used to understand and further elucidate the process through which LM is developed and maintained, to inform the development of empirically supported clinical interventions, and to guide future research objectives and priorities.

Keywords

conceptual model; health behaviors; lean mass; pediatric inflammatory bowel disease

LEAN BODY MASS IN PEDIATRIC INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD), including Crohn disease (CD) and ulcerative colitis (UC), is defined by chronic, relapsing, and remitting inflammation of the gastrointestinal tract resulting from genetic, environmental, and microbial influences. Pediatric IBD accounts for approximately 25% of all diagnoses with peak age of diagnosis occurring in adolescence (1). Although rates are rising, the current incidence is approximately 10 per

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100,000 youth in North America with an overall estimated total of 70,000 youth with IBD in the United States (1,2).

With treatment advances, therapy goals have moved from symptom reduction and control to achievement of mucosal healing, restoration of growth, and elimination of complications (2,3). In line with these goals, attention must be paid to deficits in body composition associated with pediatric IBD. Linear growth failure and body composition deficits are common and persist beyond achievement of remission (4,5). In a report of 21 studies with a total of 1479 children with IBD, 93.6% of patients with CD and 47.7% of patients with UC showed deficits in lean mass (LM) compared to healthy controls (6). For the purposes of this review the term LM includes both lean body mass and fat-free mass with the difference being that lean body mass includes essential lipids in addition to total body mineral, protein, and water. As a result of this, lean body mass may be slightly higher than fat-free mass. It is important to note that LM is not synonymous with muscle mass, which looks specifically at contractile muscle tissue. Because of the measurement techniques, LM (both lean body mass and fat-free mass) is routinely used as a proxy despite including nonmuscle components.

In IBD, initial hypotheses associated LM deficits with active disease and low body mass index (BMI); however, following weight restoration, youth with IBD continue to show chronic deficits compared to healthy peers (7–9). Despite proportional deficits in fat and LM at baseline, weight restoration is explained by gains in fat mass (FM) without similar gains in LM (7,10). Although LM deficits are affected significantly by disease status and malnutrition, these factors do not explain the phenomenon in whole.

Persistent LM deficits (myopenia) can have deleterious effects including decreased physical function, metabolic dysregulation, increased risk of infection, reduction of bone mass and disordered bone geometry and architecture (11–13). In addition to known effects in the general population, LM deficits may negatively affect specific disease-related outcomes in individuals with IBD, including postoperative complications and efficacy of biologics. Recent research indicates that an increased rate of major postoperative complications is correlated with IBD-induced myopenia, including mortality and morbidity (14,15). In addition, low LM at the initiation of anti-TNF treatment is also indicative of higher nonresponse rates (16). Although these relations may be heightened due to the severity of disease at time of surgery or initiation of biologics, the impact of LM on both current and future disease outcomes is critical. As such, understanding factors associated with LM accrual is vital to developing therapeutic interventions designed to promote LM. LM deficits seen in patients with IBD are multifactorial and may be explained by interactions between disease processes, dietary intake, and malnutrition, as well as activity levels, occurring during key developmental periods of childhood and adolescence (5,17).

Previous reviews (4,6) have addressed LM deficits in patients with IBD. Although these reviews provide valuable information on LM deficits in these patients, they do not focus on the unique factors influencing LM accrual during childhood and adolescence outside of the medical comorbidities of IBD. Examining these influences is critical, given that chronic LM deficits lead to negative health outcomes in adulthood (11,12). This systematic review presents a conceptual model integrating demographic, medical, diet, and physical activity

(PA) influences on LM in youth with IBD. We consider the predictors of LM in pediatric patients with IBD with a specific emphasis on modifiable factors that may mitigate long-term health risks. Below, we describe the model and then present specific predictors within each conceptual domain based on existing evidence. Because published data in pediatric IBD is limited, we reference relevant data from healthy youth and adult patients with IBD when appropriate. Implications of the model for future research and clinical interventions are discussed.

It is important to note that the techniques used to measure LM in the studies included in this review differ based on technological advances over time and the inclusion of additional primary variables of interest (ie, bone density). Although beyond the scope of this review, LM evaluation techniques may be categorized by the number of body compartments being assessed based on the 5-level model of human body composition, with methods measuring more compartments being relatively more accurate. For example, 2-compartment models divide the body into FM and fat-free mass and include anthropometry, densitometry, bioelectric impedance, or isotope dilution for total body water. Three compartment models, measured by dual-energy x-ray absorptiometry, divide the body into FM, lean body mass, and bone mass. Although there is no criterion standard of measurement in the assessment of body composition in youth, dual-energy x-ray absorptiometry may be the most appropriate for pediatric IBD given that it can provide estimates of both FM and LM that may serve as indicators of nutritional status, and bone density, which is known to be suboptimal in youth with IBD.

METHODS

Three online databases were searched for relevant articles: PubMed, Medline, and CINAHL. Search terms were (“lean body mass” OR “muscle mass” OR “body composition” AND (“pediatric Inflammatory Bowel Disease” OR “pediatric Crohn’s Disease” OR “pediatric Ulcerative Colitis”). Searches were limited to articles published in English between January 1997 and July 2017. Studies reporting on predictors or correlates of lean body mass in pediatric IBD were selected for inclusion, as were intervention or review articles whose primary outcome was body composition in the context of pediatric IBD. Where applicable, studies reporting on predictors or correlates of lean body mass in healthy youth were also included. References of included articles were searched to identify studies not found in the initial database search.

The literature search yielded 798 articles. Following a review of titles and abstracts, the search was narrowed to 12 articles that appeared to meet the inclusion criteria described above. Careful readings of the full manuscripts along with review of these manuscripts’ reference sections yielded a total of 53 empirical or review articles related to body composition in pediatric IBD.

CONCEPTUAL MODEL

LM is a multidimensional health outcome, resulting from a number of interacting influences (7,10,12,18). IBD further complicates LM through the impact of disease-related factors that

may compound variables already known to alter LM (eg, age, race, and health behavior factors). Our literature review, as outlined below, yielded 4 domains of influence, conceptualized as demographic, medical, diet, and PA that we propose as predictors of LM in youth with IBD. Within each domain, individual constructs that emerged as potential unique predictors are listed with examples of causal mechanisms that may explain how the constructs predict LM.

Conceptualizing LM through a model (Fig. 1) provides a useful framework to demonstrate pathways between the proposed domains and LM. The model is unique in that it explains LM from a comprehensive vantage point. This approach is consistent with the biopsychosocial model of health and illness (19) and emphasizes the role of multiple interactive influences on LM accrual. Uncovering ways in which pediatric IBD patients' demographic and medical characteristics interact with health behaviors to influence LM will allow for greater accuracy in our ability to explain and promote this important health outcome. In addition, by targeting modifiable factors under the control of the individual with IBD, we open avenues for clinical intervention development that may influence health outcomes across the lifespan.

CORRELATES AND PREDICTORS OF LEAN MASS

Demographic

Demographic predictors of LM in youth with IBD encompass characteristics of the patient that influence LM but are not readily modifiable. Similar to healthy youth, both age and sex play a role in LM levels in pediatric IBD. Both boys and girls have reduced LM compared to controls, although adolescents tend to show greater deficits compared to younger children (6,20). Girls demonstrate significantly higher FM and lower LM compared with boys who tend to present with lower LM only (20–23). In one study, after adjusting for race, Tanner stage, age, and FM for height z scores, deficits in LM remained for both sexes, although were still more pronounced in girls compared with boys (23). Among girls, LM deficits were most pronounced in those diagnosed during adolescence suggesting that age and sex differences may be influenced by timing of diagnosis and achievement of peak height velocity (4).

Medical

Medical predictors of LM deficits include type of diagnosis (CD vs UC), disease status (ie, active disease vs remission), and treatment modality (eg, use of corticosteroids, anti-TNF agents). In a recent review reporting on patients with active disease (5 studies; n = 160), LM deficits were documented across all studies, although in 2 studies, 50% of patients were receiving systemic steroids that may have influenced LM. In support of the persistence of LM deficits despite disease activity and use of steroids; however, in patients with inactive disease (5 studies; n = 214), LM deficits were noted in 58% of the patients (6) suggesting that in a significant subset of patients, deficits persist despite achievement of remission. As previously documented, LM deficits are more pronounced in patients with CD compared with patients with UC, a finding that is likely related to differences in the underlying disease processes, because patients with CD tend to experience greater malnutrition and growth-

related complications compared to youth with UC. Given the location of disease involvement, youth with CD often present with malnutrition and growth stunting that may lead to linear growth delay and chronic LM deficits.

Despite medical treatment and restoration of BMI, patients with CD continue to demonstrate features of cachexia, evidenced by normal fat stores but diminished LM (4,24). Use of steroids, a common frontline treatment used during acute episodes of IBD, is also known to reduce LM through changes in protein synthesis and degradation of skeletal muscle (25). Contrastingly, treatment with anti-TNF agents is associated with improvements in LM in youth with IBD (26–32). In addition to mounting the immune response, TNF- α affects metabolism through inhibiting insulin-like growth factor (notably IGF-1)-induced anabolism by increasing lipolysis, coupled with stimulating proteolysis and muscle catabolism using a nuclear factor- κ B pathway (27,28). These mechanisms are associated with a reduction in weight and LM (27,29). The therapeutic use of anti-TNF agents has been widely regarded to ameliorate malnutrition and encourage regular growth and muscle mass development in pediatric patients with IBD (27–30). The observed increase in weight and BMI during anti-TNF treatment can perhaps be attributed to the decreased severity of the proinflammatory cytokine response and improved nutritional status (26,32). Previous findings have supported a significant muscle improvement in male patients with less significance in female peers (23,26,33). The anti-TNF agent-associated LM increase has been demonstrated in both the presence and absence of steroid therapy but should be further studied to determine specific mechanisms of action (2).

It is likely that medical factors, including underlying disease processes (ie, chronic inflammation, malnutrition, and stunting), treatment side effects (ie, chronic steroid use), and disease duration, interact leading to LM deficits in this population. Given the relatively recent changes in medical treatment, including the use of steroid-sparing effective biologics, more research should be done to assess LM deficits in current cohorts of patients compared with patients treated before the introduction of biologics.

Dietary

Inadequate dietary intake, often due to decreased appetite and food aversion, is believed to be the leading cause of malnutrition in pediatric IBD (12). Additional related factors that contribute to malnutrition include upregulation of the immune system response during active disease states resulting in altered energy and nutrient requirements and malabsorption secondary to inflammation. Although data are limited, one study was conducted in a sample of 17 pediatric patients with CD treated with exclusive enteral nutrition (EEN) therapy (34). Participants showed increases in LM but not FM after 30 days of EEN, although LM plateaued during the second half of the EEN course. Follow-up analyses indicated that gains in LM were shown only for patients who achieved remission suggesting that the effects of EEN on LM are likely a combination of increased energy intake and decreased gastrointestinal inflammation leading to better absorption and normalization of energy and nutrient requirements (34). No studies have assessed the role of specific macronutrients in the development of LM in pediatric patients with IBD; however, research has shown that high-fat, lower-carbohydrate diets have been shown to protect LM and improve muscle

composition in other populations (35–38). Specifically, interventions evaluating these diets, under both weight loss and weight maintaining conditions, have been associated with a reduction in FM and a preservation of LM across both healthy and chronically ill adult populations (35–38). A crossover diet intervention was conducted in 30 women with polycystic ovary syndrome who consumed a eucaloric low-carbohydrate diet (41%:19%:40% energy from carbohydrates:protein:fat) for 8 weeks and a standard diet (55:18:27) for 8 weeks. Results indicated that, without calorie restriction, the low-carbohydrate diet resulted in a preferential loss of FM while preserving LM (35). The shift in body composition to proportionally less FM relative to LM suggests that a high-fat, low-carbohydrate diet improves fat oxidation while preserving LM (35). These data have direct implication for youth with IBD who demonstrate a proportionally higher FM relative to LM regardless of BMI.

Physical Activity

Youth with IBD show significantly impaired aerobic and anaerobic exercise capacity compared to reference values, in addition to documented deficits in muscle and bone strength, although this is not related to disease duration or current disease activity (39,40). Only one study has concurrently evaluated LM with PA finding that youth with CD demonstrate significantly lower LM, grip strength, and PA compared to healthy controls (9). Of interest, these findings were noted in patients with quiescent and mild disease suggesting that PA and LM deficits occur beyond achievement of remission. In adult patients with CD, research has documented deficits in PA compared to healthy peers (41). In addition, a large proportion of adults with CD do not meet national PA guidelines with estimates ranging from between 49% and 83% of patients reporting inadequate PA levels (42,43). Despite high levels of inactivity, PA has been shown to be safe and beneficial in both adult and pediatric patients with IBD and is associated with increased quality of life and decreased disease activity and IBD-related symptoms (44–47). Although the specific protective effects of PA in IBD are unknown, it is likely partly due to the known anti-inflammatory actions of regular moderate exercise (44,48).

No studies to our knowledge have assessed LM following exercise in pediatric or adult IBD; however, a large body of literature exists demonstrating the role of resistance training (RT) in LM accrual across other populations (47,49,50). Cunha et al (51) compared changes in strength and body composition in prepubertal males following 12 weeks of RT 3 times per week or a nonexercise control group (CTR). They found increases in strength and LM in both groups; however, there were greater gains in strength in the RT group and RT protected against gains in FM that were observed in the CTR group (51). In addition, Alberga et al (52) assessed the effects of 12 weeks of RT performed 2 times a week in obese prepubertal children and found increases in weight, height, and LM in the RT and CTR group; however, only the RT increased measures of strength and there was greater increase in leg LM compared to CTR. Initiating an RT regimen at diagnosis as tolerated by the patient may mitigate the disproportionate gains in FM compared with LM documented after weight restoration in addition to promoting LM accrual through remission initiation.

IMPLICATIONS

The proposed conceptual model and accompanying review may be used for a wide range of purposes, but we see 3 as primary: understanding the processes through which LM is developed and maintained in the target population, informing development of empirically supported diet and PA intervention programs, and guiding further research objectives.

Development of effective interventions to increase LM among youth with IBD requires an understanding of the modifiable processes that determine LM. Examination of specific relations between the current model's domains and their corresponding factors will illuminate the process leading to LM accrual and maintenance. The model conceptualizes dietary intake and PA as mediators of the relations between the other domains and LM. Because IBD is a chronic illness with no known cure, addressing these behaviors as early on in the disease process as possible is vital to successful outcomes.

In addition to guiding the development of interventions, the conceptual model informs future research objectives related to LM in pediatric IBD. Areas of future research may include validation of the model across subsets of youth with IBD (eg, CD vs UC, male vs female, child vs adolescent) or between youth with IBD and other pediatric populations (eg, youth with other chronic illnesses, healthy children). In addition, assessment of diet and PA patterns across disease groups and disease severity levels will allow for the refinement of potential interventions and ultimately will promote intervention efficacy.

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What Is Known

- Lean body mass deficits are common in youth with inflammatory bowel disease.
- These deficits persist despite normalization of body mass index and may contribute to both current and long-term disease outcomes including osteoporosis.

What Is New

- Factors contributing to lean body mass deficits include both modifiable and nonmodifiable variables.
- In addition to the achievement and maintenance of remission through medical therapy, interventions should focus on modifiable variables, including health behaviors, to improve lean body mass deficits in youth with inflammatory bowel disease.

FIGURE 1.

Conceptual model of lean body mass development in pediatric patients with inflammatory bowel disease to be evaluated in the proposed study. MVPA = moderate-to-vigorous physical activity.