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Narrative Review

Systematic review: Sarcopenia in paediatric inflammatory bowel disease

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SUMMARY

Background: Low skeletal muscle mass (MM) and deteriorated function (sarcopenia) can be a frequent complication in paediatric inflammatory bowel disease (IBD).
Aim: To conduct a systematic review of the paediatric IBD literature on skeletal muscle function and mass and identify interventions that could affect them.
Methods: Systematic searches (EMBASE, Medline, Cochrane library central for registered control trials and Web of Science) were conducted using the terms 'lean body mass' (LM), 'fat free mass' (FFM) or 'MM' and 'IBD'.
Results: Fourteenth studies were included, presenting data from 439 Crohn's disease (CD), 139 ulcerative colitis (UC) and 2 IBD-unclassified participants compared with healthy matched or unmatched groups or reference populations. Six out of 14 studies reported lower LM, whilst 7 studies observed lower MM and FFM in CD patients compared to healthy controls. Research in UC patients reported lower LM in 3 studies, lower MM in 3 studies and lower FFM in 4 studies. Three prospective studies measured the impact of enteral feeding and showed improvement on disease activity and LM or FFM, while one retrospective study did not show any impact on LM.
Conclusion: Despite the variety of experimental approaches and methods used to assess sarcopenia, most studies showed reduction in MM, LM and FFM in IBD. Nutritional intervention may have a positive effect on LM and FFM. Future research should focus on standardizing the terminology and methodologies used in assessing body composition and investigating sarcopenia in diseased and matched healthy control cohorts in adequately powered studies with a longitudinal design.

1. Introduction

Weight loss and growth failure are prevalent problems in paediatric inflammatory bowel disease (IBD) [1–3]. Weight loss has been described in 70% of children with Crohn's disease (CD) and in 34% with ulcerative colitis (UC) [4] with growth failure described in 40% of children with CD and in 10% with UC [5]. As a result, changes in body composition are commonly reported in both in paediatric IBD and are often accompanied by alterations in muscle mass (MM) related compartments (lean mass; LM and fat free mass; FFM) when compared with healthy control populations [6]. Specifically, loss of LM in paediatric cohorts has been reported to be as high as 93.6% in CD and 48% in UC [7]. Aetiologies for the alterations in body composition may be diverse but can include low-calorie intake, nutrient malabsorption, elevated levels of

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inflammatory cytokines, surgeries and concomitant pharmacotherapies [6].

Maintaining skeletal muscle mass is a tightly controlled proteostasis between muscle protein synthesis and muscle protein breakdown [8]. Muscle tissue from patients with active CD shows a significant decrease in expression of muscle hypertrophy signalling proteins with no apparent change in the expression of atrophy signalling [9]. These molecular changes may, at least partly, underpin the reduction in LM previously observed in patients with CD [2]. Failure to maintain LM can result in sarcopenia, first described in 1989 by Rosenberg as the loss of skeletal muscle mass and strength associated with physical disability and poor quality of life [10]. The prevalence of sarcopenia among adults with IBD is higher in CD (59%) than in UC (27%) when compared to a control healthy population (8.3%) [11] based on criteria of the International Consensus on Sarcopenia, which defined sarcopenia as a skeletal muscle index two standard deviations below the norm for young, healthy adults [12]. However, several methodologies and diverse definitions have been used to define sarcopenia; thus, contributing to a lack of high-quality data and appropriate definitions [13]. Furthermore, research in paediatric sarcopenia is hindered by lack of longitudinal data, limited number of outcomes-based research and low study quality [14]. In addition, studies investigating skeletal muscle composition and function in paediatric IBD are sparse [8,14] and interventional studies are lacking. Furthermore, one aspect of the published literature that is frequently overlooked, is the variety of experimental techniques employed to assess body composition and the inconsistent use of related terminology. For example, the terms LM and FFM (and often MM) are frequently used interchangeably in the literature due to the lack of understanding that they refer to separate body composition compartments, which makes it difficult to align specific research outcome measures with differences in body composition between paediatric IBD patients and healthy control populations.

Exploring the presence and aetiology of sarcopenia in paediatric IBD is important in informing the design of interventions and treatments aiming to reverse MM loss and fatigue and their associated long-term adverse outcomes. The aim of this review of literature is to systematically describe changes in skeletal muscle function and mass and related body compartments in paediatric IBD, and in doing so appraise relevant interventions aiming to reverse those changes, identify gaps in the literature and improve the design of future interventional studies.

2. Methodology

2.1. Criteria for inclusion and exclusion

The study designs included in this review were randomised controlled trials, prospective, or concurrent cohort and cross-sectional studies pertaining to children aged ≤18 years who have IBD confirmed through histology irrespective of their sex and race. Editorials, opinion papers, literature reviews and any studies not in the English language were excluded.

2.2. Search strategy

A database search was undertaken on Medline, Embase, Cochrane library central for registered control trials and Web of Science on the 20th January 2023. Details of the search strategy are provided in Supplementary Table 1. A manual reference search of selected manuscripts was undertaken to enhance our strategy.

This review was registered on PROSPERO (reference number CRD42020196776) on 25/08/2020.

2.3. Data extraction and quality assessment

The selected studies were initially screened for eligibility by two authors (BAJ and SJR). The abstracts were reviewed and those eligible were included for full text review. The full manuscripts were independently assessed (BAJ and SJR) as per the inclusion criteria. Any disagreements were resolved by discussion and consensus with the other authors (KT and GWM).

The data extracted includes specific details about population demographics, context, culture, geographical location, study methods and muscle compartments. Data pertaining to disease phenotype as classified by the Paris classification [15] were included. All papers were read in full, but only data reflecting the aims of the review were extracted.

2.4. Risk of bias

Bias we assessed through the Joanna Briggs Institute (JBI) critical appraisal tool [16] (Supplementary Tables 2, 3, 4, 5 and 6). This was assessed independently by two authors (BAJ and SJR) while any disagreements were resolved by consensus with co-authors (KT and GWM).

3. Results

The literature search produced 422 manuscripts. After removing duplicates, 282 manuscripts were chosen for screening. After abstract and full manuscript screening, 12 manuscripts were selected to be included in this review and 2 further manuscripts were added from reference lists from published literature. The selection process of the chosen studies is demonstrated in the CONSORT diagram in Fig. 1 and the main characteristics of the studies included in this review are summarised in Supplementary Table 7.

3.1. Sample characteristics

The 14 studies involved in the review were published between 1982 and 2021. Ten studies were observational in design, while of the four interventional studies included, three studies were non-randomised and one had a randomised design. Studies were undertaken in the UK [17–19], Canada [20–23], the United States of America [24], Germany [25,26], Poland [27], Australia [28], Croatia [29] and Israel [30]. The total number of patients in those studies was 580 with IBD.

The participants' age range was 5–18 years, with a predominant male gender (58%) and only a single study [22] did not report the gender split. The majority (n = 439) of the participants studied had CD (76%), 139 had UC (24%), 2 had unclassified IBD (0.3%) and 160 were healthy volunteers (22%). The concomitant medication reported were anti-tumour necrosis alpha therapies (n = 39), corticosteroids (n = 133), 5-amino salicylic acid (n = 110), sulfasalazine (n = 7), immunosuppressant agents (n = 69), antibiotic therapies (n = 3), anti-diarrhoeal agents (n = 3) and proton pump inhibitors (n = 2). Nutritional therapy was prescribed for 4 weeks in 12 participants and ≥4 weeks in 2 participants. Vitamin D and calcium supplementation were used in 3 participants. Only one study [30] assessed the relationship between drug therapy and muscle mass by using MRI to evaluate the psoas area index (PAI). An intestinal resection was performed in 11 participants, with the indication described as stricturing disease in 3 participants, penetrating disease in 2 participants and a colectomy and ileostomy formation in 1 participant.

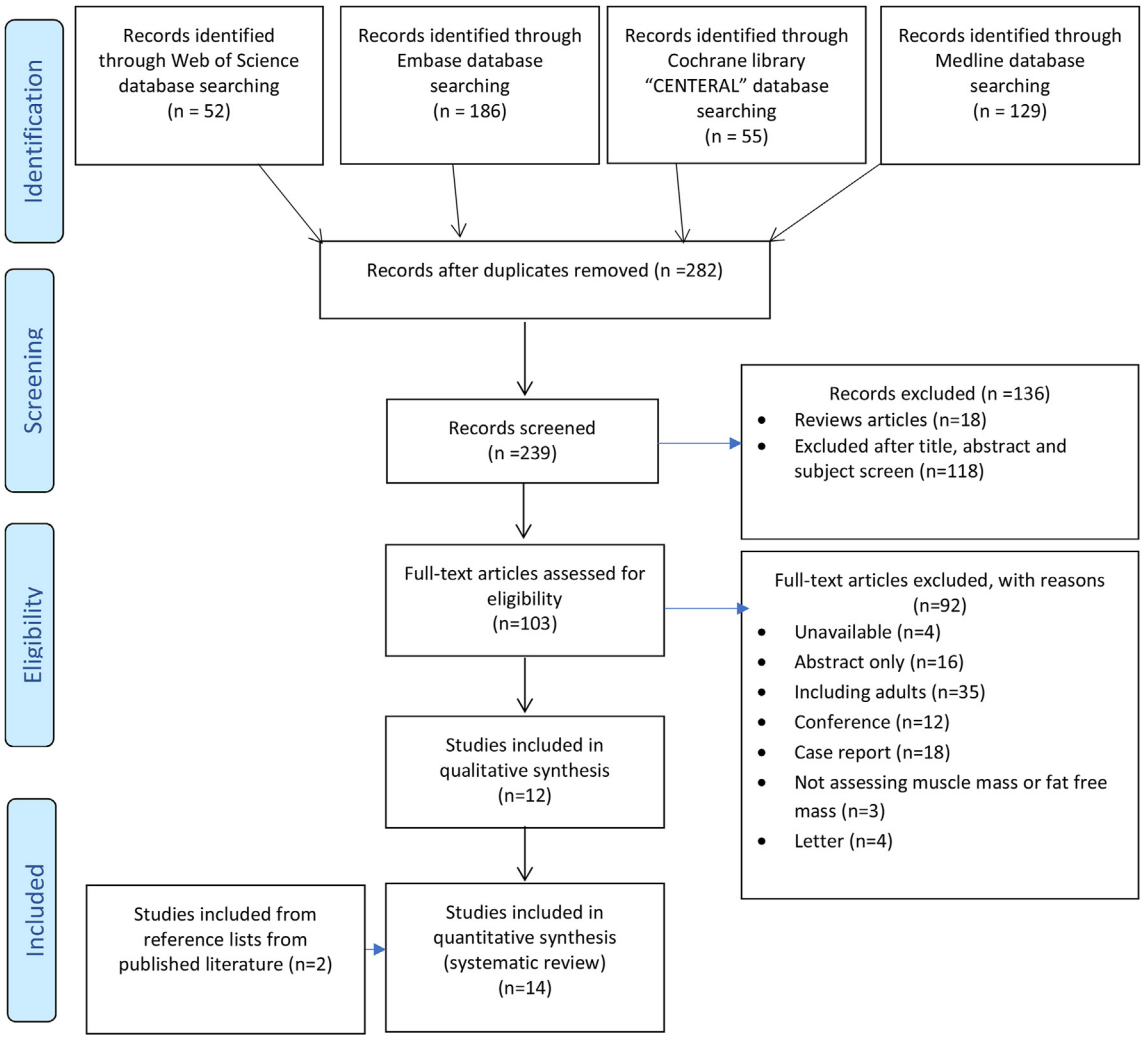

Fig. 1. Flow chart of studies selection process.

3.2. Study quality and risk of bias

According to JBI critical appraisal tools, 9 studies [19–22,25,26,28–30] were considered as of good quality with their total score being ≥75% with the other 5 studies [17,18,23,24,27] having a total score of <75% with study subjects, setting and confounding factors not identified or described in detail. The grades and total scores are demonstrated in Supplementary Tables 6, 7, 8, 9 and **10**. In terms of comparability between diseased cohorts and healthy controls, one study used an unmatched unhealthy group [30], 6 studies [17,19,20,26,28,30] used historical reference data unmatched to their own with 7 studies [17,19,22,24,26,28,29] recruited a healthy volunteer cohort adjusted for confounding factors such as age, gender, height and puberty status. Findings were matched for age and sex based on control populations and presented as z-score in 6 studies [18,21,22,24,25,27].

3.3. Disease duration and activity

Disease duration was only reported in four studies [24,26,27,29]. Motil et al. [24] recruited CD patients with disease duration of 2–5 years, whereas Werkstetter et al. [26], recruited newly diagnosed patients with CD and UC with a disease duration of 2 months or less (CD = 23, UC = 7). Wiech et al. [27], recruited newly diagnosed patients with CD and UC (CD = 10, UCC = 10), with less than one-year (CD = 3, UC = 4) and more than one-year (CD = 12, UC = 14) disease duration, whereas Trivic et al. [29] recruited CD patients with mean disease duration 48.2 ± 8.1 months and UC patients with mean disease duration 50.6 ± 11.6 months. Only two studies reported exact disease duration of their participants [24,29].

Disease activity status was assessed in 11 studies with different measures such as Paediatric Crohn's Disease Activity Index (PCDAI), Paediatric Ulcerative Colitis Activity Index (PUCAI) and C-reactive protein (CRP) [17,18,20–23,25–28,30]. Most studies recruited patients with a wide variety of disease activity states ranging from deep remission to severely active disease (see Table 1 for details) with only a single study objectively reporting disease activity through biomarker assessment [18]. One study [30] assessed the relationship between muscle mass and disease activity and indicated that IBD patients in remission had significant higher median psoas area index (PAI; calculated as the average psoas area divided by body surface area) measured by MRI [PAI (mm^2/m^2) = 411 (312–519)] when compared with those in mild [PAI (cm^2/m^2) = 312 (223–330), P = 0.001], moderate [PAI (mm^2/m^2) = 292 (234–365), P < 0.001] and severe [PAI (mm^2/m^2) = 278 (185–332), P = 0.003] disease activity.

3.4. Assessment of muscle composition and function

The most common methodology used to assess body composition was dual energy x-ray absorptiometry (DEXA) (n = 222)

Table 1
Muscle composition findings from the studies included in this review.

Authors	Parameter measured	Methods	Median (min; max) or mean ± S.D in CD and UC vs. controls			
			IBD	CD	UC	Controls
Motil et al. [24]	FFM (kg)	whole body potassium	-	29.9 ± 1.7*↓	-	42.7 ± 4.3
	MM (kg)	urinary creatinine excretion	-	21.8 ± 0.6*↓	-	33.8 ± 4.3
	Upper arm muscle circumference (mm)	skinfold thickness	-	18.5 ± 1.2**↓	-	22.9 ± 3.3
Khoshoo et al. [23]	FFM (kg)	BIA	-	30.5 ± 7.7	-	-
Ward et al. [21]	LM for age and gender (z-score)	DEXA	−2.0 ± 0.9**↓	-	-	AMRF
	LM for height (z-score)		−1.0 ± 0.9**↓	-	-	AMRF
Wiskin et al. [17]	upper arm muscle area (z-score)	Triceps skinfold and mid-upper arm circumference	-	−1.3**↓ (−1.8; −0.5)	-	RF
			-	-	−0.6 (−1.4; −0.2	RF
Werkstetter et al. [26]	Muscle CSA at baseline (z-score)	p-QCT	−1.7 (−3.3; −0.3)]	-	-	RF
	Muscle CSA for height at baseline (z-score)		−1.5 (−4.9; 0.2)	-	-	RF
	Δ of the M-CSA between baseline and final measurements (z-score)		+0.8**↑ (−0.8; 2.9)	-	-	RF
	Δ of the Muscle CSA for height between baseline and final measurements (z-score)		+1.2**↑ (−0.3; 3.9)	-	-	RF
Werkstetter et al. [25]	Muscle CSA ^{height} at baseline (z-score)	p-QCT	-	−2.5**↓ (−3.5; −1.0)	-	AMRF
Brookes et al. [28]	LM for height (z-score)	DEXA	-	−1.1 ± 1.1**↓		AMRF
	LM for height, adjusted for bone age (z-score)		-	−1±1.1**↓	-	AMRF
Ward et al. [20]	LM (z-score)	DEXA	-	−2.5 ± 1.1**↓	-	RF
	LM for height (z-score)		-	−2.3 ± 1.0**↓	-	RF
	Muscle CSA (z-score)	Tibia p-QCT	-	−1.5 ± 1.1**↓	-	RF
Mager et al. [22]	FFM (%)	DEXA	73.4 ± 6.1	74.1 ± 5.9	72.3 ± 6.8	-
	LM/height^2 (kg/m^2)		14.7 ± 16.3	12.6 ± 2.2	19.3 ± 28.6	-
	LM-height^2 (z-score)		−0.7 ± 1.6	−1.0 ± 1.2**↓	0.0 ± 2.2	AMRF
	Appendicular LM/height^2 (kg/m^2)		13.5 ± 5.6	12.8 ± 5.5	8.3 ± 12.9	-
	Appendicular, LM-height^2 (z-score)		−0.9 ± 1.8	−1.3 ± 1.2*↓	−0.3 ± 2.5	AMRF
Wiech et al. [27]	FFM (kg)	BIA	-	-	38.1 ± 12.9	39.2 ± 13.4
			-	35.0 ± 12.0*↓	-	42.9 ± 13.5
Davis et al. [18]	FFM (z-score)	DEXA	-	−0.8 ± 0.2*↓	-	0.1 ± 0.4
	LM (kg)		-	39.3 ± 1.5	-	46.0 ± 4.5
	Appendicular LM (kg)		-	18.7 ± 0.8	-	22.9 ± 2.6
	ASMI (kg/m^2)		-	6.8 ± 0.2	-	7.6 ± 0.4
Ashton et al. [19]	combined psoas CSA (cm^2)	MRI	-	15.1 (6.8; 24.3)	-	-
	psoas area (z-score)		-	−2.1 (−0.4; −3.4)	-	RF
Atlan et al. [30]	PAI (mm^2/m^2)	MRI	326 (259; 418)**↓	-	-	528 (439; 615)
			-	326 (267; 418)	326 (201; 437)	-
Trivic et al. [29]	FFM (%)	DEXA	-	65.8 ± 2.3	71.6 ± 2.6	-
	LM (%)		-	64.8 ± 4.3**↓	68.2 ± 2.5	-
	LM (z-score)		-	−1.6 ± 0.3	−2.0 ± 0.4	AMRF

IBD= Inflammatory bowel diseases (CD + UC), CD group = Crohn's disease group, UC group = Ulcerative colitis group, HC group = Healthy control group, LM = Lean mass, MM = muscle mass, FFM= Fat free mass, SMM=Skeletal muscle mass, ASMI = Appendicular skeletal muscle index PAI= Psoas area index, Muscle CSA^{height} = Muscle cross sectional area per height, DEXA = Dual energy x-ray absorptiometry, p-QCT = Peripheral quantitative computerized tomography, BIA= Bioelectrical impedance analysis, MRI = Magnetic resonance imaging, RF = reference group, AMRF = age-matched reference group, Δ = difference,* = $P < 0.05$ statistically significant, ** = $P \leq 0.01$, ↑/↓ = increment or reduction between study groups.

[18,21,22,28,29]. Other methodologies used were peripheral quantitative computerized tomography (p-QCT) (n = 113) [20,25,26], bioelectrical impedance analysis (BIA) (n = 73) [23,27], magnetic resonance imaging (MRI) (n = 111) [19,30] and skinfold thickness (n = 55) [17]. Motil et al. [24], used whole-body potassium and urinary creatinine excretion. The main muscle composition findings from those studies are summarised in Table 1 and the main muscle function findings are summarised in Table 2.

3.5. Lean mass (LM)

LM measured by DEXA was reported as an outcome variable in 7 studies (total n = 380, CD = 303, UC = 75) [18,20–22,28,29]. Half of these studies indicated that children with IBD had lower LM than healthy groups [18,20,21,28]. These changes were mainly predominant in CD, with only 4 studies including UC patients [20–22,29]. Ward et al. [21] observed significantly lower mean z-score LM for age and gender (−2.0 ± 0.9; $P < 0.001$) and mean z-score of LM for height [−1.0 ± 0.9; $P < 0.001$] in IBD groups when compared to controls. In accordance, Ward et al. [20] reported significantly lower mean z-scores of LM for age and gender [−2.5 ± 1.1; $P < 0.0001$] and mean z-scores LM for height [−2.3 ± 1.0; $P < 0.0001$] in CD group than a healthy reference population. Similarly, Brookes et al. [28] reported a significant reduction in the mean z score of LM for height (−1.1 ± 1.1, $P < 0.001$), even after adjusting for bone age (−1.0 ± 1.1, $P < 0.001$) in CD group than a healthy reference population.

Davies et al. [18] showed a trend towards a difference between CD and a healthy control group in LM (39.3 ± 1.5 kg vs. 46.0 ± 4.5 kg; $P = 0.08$), appendicular LM (18.7 ± 0.8 kg vs. 22.9 ± 2.6 kg; $P = 0.06$) and appendicular skeletal muscle index (ASMI) (6.8 ± 0.2 kg/m^2 vs. 7.6 ± 0.4 kg/m^2; $P = 0.05$), respectively. Trivic et al. [29] showed a significant difference in percentage LM relative to whole body

Table 2
Muscle function findings from the studies included in this review.

Study	Muscle function measures	CD	Controls
Werkstetter et al. [25]	Handgrip strength z-score	[-1.7↓* (−2.8, 0.8)]	AMRF
Ward et al. [20]	Peak Jump power of muscle CSA z-score	[0.8 (0.5–1.1)]	RF
Davis et al. [18]	Handgrip dynamometer (kg/kg forearm LM)	Dom (25.6 ± 1.5) Non-dom (24.3 ± 1.4)	Dom (23.8 ± 1.3) Non-dom (23.9 ± 1.1)

CD group = Crohn's disease group, Muscle CSA = Muscle cross sectional area, Dom = dominant arm.
Non-dom = non dominant arm, RF = reference group, AMRF = age-matched reference group.

weight in CD group when compared to UC (65 ± 4% vs. 68 ± 3%, respectively; P = 0.001) but they did not include a comparator control group in their study. However, there was no difference in LM z-scores between groups (−1.6 ± 0.3 vs. −2.0 ± 0.4, respectively; P = 0.5). In contrast, Mager et al. [22] demonstrated a significant difference between CD and UC patients in the mean z-score of LM for height (CD = −1.0 ± 1.2 vs. 0.0 ± 2.2; P = 0.01) and the mean z-score of appendicular LM for height (CD = −1.3 ± 1.2 vs. UC = − 0.3 ± 2.5; P = 0.03), but not in the LM/height^2 (12.6 ± 2.2 kg/m^2 vs. 19.3 ± 29.0 kg/m^2; P = 0.9) nor in the appendicular LM/height^2 (12.8 ± 5.5 kg/m^2 vs. 8.3 ± 13.0 kg/m^2; P = 0.2).

3.6. Muscle mass (MM)

One study (n = 6, CD = 6, UC = 0) estimated whole body MM by urinary creatinine excretion [24]. This study used a small sample size of CD, (n = 6) and reported a lower mean MM in the CD group when compared with a healthy control group (21.8 ± 0.6 kg vs. 33.8 ± 4.3 kg; P < 0.05, respectively).

Muscle cross sectional area (M-CSA) was assessed by p-QCT (which uses forearm or tibia as regions of interest in computed tomography [7]) in 3 studies [20,25,26] and by MRI in 2 studies [19] (n = 123, CD = 116, UC = 7). In a prospective longitudinal study [26] in a newly diagnosed IBD cohort, the z-score M-CSA was lower at baseline (−1.7 (−3.3 to −0.3) than a healthy reference group, even after correction for height (−1.5 (−4.9 to 0.2). At the end of follow-up (median interval 2.4 years), the IBD M-CSA z-score M-CSA was significantly improved (+0.8 (−0.8 to 2.9) P < 0.01), even after correction for height (+1.2 (−0.3 to 3.9). In this mixed IBD cohort, nutritional therapy was only prescribed to CD patients for <4 weeks and this was complimented with standard licenced pharmacological therapies. The design of the study precluded further evaluation of the effectiveness of the intervention and whether MM may normalize independently of disease activity. Similarly, mean z-score M-CSA measured at the tibia by pQCT in the study by Ward et al. [20] was significantly lower in CD when compared to a healthy reference population [−1.5 ± 1.1 range (−3.9, 1.2); P < 0.01]. This was also true even after adjusting for confounders [25].

MRI was used in two recent studies [19,30]. Ashton et al. [19] assessed combined (left and right) psoas CSA [median = 15 cm^2, range (7; 24 cm^2)] in a CD group with these measures shown to be significantly lower than the comparative healthy norm assessed using computer tomography scans [median z-score = -2.1, range (−0.4 to −3.4)]. Atlan et al. [30] found the median PAI in IBD group to be significantly lower than the control group [IBD = 326 mm^2/m^2, range (259–418) vs. Controls = 528 mm^2/m^2, range (439–615), P < 0.001], while it was comparable between CD and UC groups [CD = 326 mm^2/m^2 (267–418) vs. UC = 326 mm^2/m^2 (201–437), P = 0.8].

3.7. Fat free mass (FFM)

FFM was measured as a direct outcome in 6 studies (n = 197, CD = 143, UC = 79) [18,22–24,27,29] and indirect outcome in 2 studies (n = 61, CD = 43, UC = 18) [17,24]. CD patients have been shown to have significantly less FFM (kg) when compared to healthy control groups when either whole body potassium (29.9 ± 1.7 kg vs. 42.7 ± 4.3 kg; respectively; P < 0.05) [24] and BIA (35.0 ± 12.0 kg vs. 42.9 ± 14.0 kg, respectively; P = 0.03) [27] measures were used. In contrast, no difference in FFM was observed between UC and healthy control groups though it is noted that the UC patients were in remission [27]. In two studies [22,29], no significant difference was observed in the mean %FFM between CD and UC patients (CD = 66 ± 2% vs. UC = 72 ± 3%; P = 0.1 and CD = 74 ± 6% vs. UC = 72 ± 7; P = 0.2, respectively). A single study (n = 55; CD = 37, UC = 18) estimated FFM using upper-arm muscle area (UMA) z-score as measured by combining triceps skinfold and mid-upper arm circumference. Both IBD types showed negative UMA z-scores [CD = −1.3 (−1.8 to −0.5) and UC = −0.59 (−1.36 to −0.15)] when compared to a healthy reference range [17]. Similarly, Motil et al. [24], (n = 6, CD = 6, UC = 0) estimated muscle size using skinfold thickness for upper arm muscle and reported significant decrease in CD when compared to healthy controls (CD = 19 ± 1 mm vs. healthy controls = 23 ± 3 mm, respectively; P < 0.01).

3.8. Muscle function

When compared to a reference population (Table 2), a significant attenuation in hand-grip strength was described in a single CD study [25] (n = 10, CD = 10, UC = 0) [median score −1.7 kg (−2.8 to 0.8); P = 0.02]. However, such a difference was not replicated by Davies et al. [18] who observed comparable handgrip strength between CD and healthy control groups in both dominant arm (25.6 ± 1.5 vs. 23.8 ± 1.3 kg/kg forearm LM, respectively) and non-dominant arm (24.3 ± 1.4 vs. 23.9 ± 1.1 kg/kg forearm LM, respectively). Similarly, peak jump power was similar between CD and a healthy reference group [20].

3.9. Nutrition and muscle composition

Two prospective studies [23,25] and one retrospective study [30] have investigated the effect of a nutritional intervention on body composition in patients with CD (n = 67, CD = 67, UC = 0) presented in Table 3. Investigators either used exclusive enteral nutrition (EEN) or oral nutritional supplementation [23–25,30]. Motil et al. provided 1500 ml of Osmolite or Ensure via nasogastric tube (NGT) to their CD patients overnight for 8–10 h for 7 months, which increased daily dietary protein and energy intakes by 40% and showed comparable height gains in the CD and control groups post supplementation, whereas weight gain was significantly higher in the CD group (1.2 ± 0.3 kg vs. 0.4 ± 0.2 kg; P < 0.01).

Werkstetter et al. [25] administered exclusive Modulen formula (Modulen®; Nestlé, Frankfurt, Germany) via oral consumption or NGT to CD patients based on the energy requirements for ideal body weight for height over 8 weeks with the volume decreasing gradually over the last 2–4 weeks until transition to a normal diet. The PCDAI, median z-score of forearm M-CSA^{height} [baseline z-score vs. week 12: [1.0 (0.6–1.8); P = 0.002] and handgrip strength [baseline z-score vs. week 12: 0.7 (−1.0 to 2.8); P = 0.07] improved after

Table 3
Effects of nutritional and physical activity interventions on muscle composition and function.

	Study design	Nutritional intervention	Physical activity	Muscle measurement		IBD	CD
Khoshoo et al. [23]	3 weeks randomized crossover intervention	Peptamen and vital HN The target energy intake was 170% of REE	-	FFM (kg)	BIA		pretreatment = 30.5 ± 7.7*↓ vs, after 3 weeks = 34.7 ± 7.7 vs. after 6 weeks = 37.5 ± 6.4
Werkstetter et al. [25]	52 weeks non-randomised intervention	Exclusive Modulen formula via oral or NGT for 12 weeks	-	Muscle CSA ^{height} z-score	p-QCT		Δ Baseline vs. week 12 = [1.0**↑ (0.6–1.8)] Δ week 12 vs. week 52 = [-0.1 (−0.7 to 0.8)]
				Handgrip strength z-score			Δ Baseline vs. week 12 = [+0.7 (−1.0 to 2.8)] Δ week 12 vs. week 52 = [+0.4 (−1.6 to 2.7)]
Atlan et al. [30]	Retrospective cohort study of 11 years	-	62.3% of CD treated with EEN for induction	PAI	MRI	-	No correlation between EEN and PAI
Trivic et al. [29]	Cross sectional cohort	-	PA measured by fitbit charge 2 with average time spent in moderate to vigorous PA 45.7 ± 8.2 min/day	Correlation between the time spent in moderate to vigorous PA (min/day) and LM z-score	DEXA	Unstandardized coefficient 114.9 vs. standardized coefficient 0.4; P = 0.03	-

IBD= Inflammatory bowel diseases (CD + UC), CD group = Crohn's disease group, UC group = Ulcerative colitis group, ♂ = Male, ♀ = Female, LM = Lean mass, MM = muscle mass, FFM= Fat free mass, SMM=Skeletal muscle mass, Muscle CSA = Muscle cross sectional area, Muscle CSA^{height} = Muscle cross sectional area per height, PAI= Psoas area index, DEXA = Dual energy x-ray absorptiometry, p-QCT = Peripheral quantitative computerized tomography, BIA= Bioelectrical impedance analysis, MRI = Magnetic resonance imaging, EEN = exclusive enteral nutrition, NGT= Nasogastric tube, EEN = exclusive enteral nutrition, NGT= Nasogastric tube, Δ = the difference,* = P ≤ 0.05 statistically significant, ** = P ≤ 0.01 statistically significant.

supplementation compared to baseline data. Only 10 patients were on immunosuppressants and 9 patients were on 5-ASA but no patients were exposed to corticosteroids or biological therapies during follow-up. Similarly, Khoshoo et al. [23] used Peptamen and Vital HN formulae with target energy intake 170% of resting energy expenditure (REE) for 3 weeks in a crossover design in CD patients and found both FFM (measured using BIA) [after 3 weeks = 34.7 ± 7.7 kg and after 6 weeks = 37.5 ± 6.4 kg vs. pretreatment = 30.5 ± 7.7 kg; P < 0.05] and triceps skinfold thickness [after 3 weeks = 10 ± 3 mm and after 6 weeks = 13 ± 3 mm vs. pretreatment = 8 ± 3 mm; P < 0.05] significantly improved after the feeding treatment compared with pretreatment. Atlan et al. [30] reported that in CD patients treated with EEN as induction therapy there was no correlation between EEN and PAI.

3.10. Physical activity and muscle mass

Trivic et al. [29] (n = 40, CD = 20, UC = 18, IBD-U = 2) was the only cross-sectional study that measured physical activity (PA) in IBD patients using fitbit charge 2 (Fitbit Inc., USA) as presented in Table 3 and showed average time spent in moderate to vigorous PA was 45.7 ± 8.2 min/day in this cohort. A significant positive correlation was observed between time spent in moderate to vigorous PA and LM z-score measured by DEXA (P = 0.03).

4. Discussion

This systematic review describes sarcopenia by studying the alterations in MM-related compartments and their function and evaluates interventions aimed at normalising MM in paediatric IBD. In addition, it appraises relevant interventions that impact on muscle aiming to reverse those changes to identify the gaps in the literature and improve the design of future interventional studies.

Most [17–22,24,25,27,28,30] but not all [23,26,29] studies show a considerable reduction in MM-related compartments in IBD paediatric cohorts but of the 3 studies that have assessed muscle function only one showed a reduction in muscle strength when compared to healthy volunteer groups. Our results are similar to previous systematic reviews on body composition in paediatric [7] and adults [13] patients with IBD. However, Thangarajah et al. [7] included adult patients making their findings less representative of a paediatric population. Moreover in that review, the diverse measures used to quantify MM and possible interventions used to normalize it were not covered. When compared to healthy volunteer data sets, a significant decrease in MM-related compartments persists even with normalization of disease activity in CD [31] and UC [32], and across IBD populations [18,21,22,25–28].

Worse disease activity is associated with a lower muscle mass [17,18,20,22,28] and normalization of disease activity is associated with an improved muscle mass, albeit possibly as a result of nutritional therapy [23,25]. One study [30] assessed the relationship between muscle mass and disease activity and indicated that IBD patients in remission had significant higher median PAI measured by MRI when compared with those in mild, moderate or severe disease state. Moreover, they also found that patients treated with biological therapy tended to have higher PAI than patients treated with immunosuppressant agents. This may be related to the fact that biological agents are associated with higher induction rates [33] and probably a higher rate of normalisation in MM [34]. Corticosteroids are commonly used as induction therapy in IBD. Indeed, 23% of patients in the studies included in this review were treated with glucocorticoids to induce clinical remission. Corticosteroids promote muscle degradation and alter fat-related body composition [35]. Indeed, decreased LM and increased FM were documented in patients with cachectic diseases treated by long-term corticosteroid therapy [36], which promotes sarcopenic obesity characterised by low MM and physical weakness and increased bodyweight [37]. However, none of the studies included in this review had systematically examined the effect of drug management on disease activity and MM-related compartments in IBD patients, and this should be an important topic for future investigations. Interestingly, FFM in CD [24] was reduced when compared to a healthy reference population [17] or healthy control group [27]. These observations were not replicated in UC cohorts

that were in remission, once again underlining the strong symbiosis between muscle compartments and disease activity, a relationship that is possibly independent of disease type. In addition, it is essential to consider confounding factors that could affect body composition especially in paediatric populations, such as ethnicity, gender, age, pubertal status, and height as these factors can be responsible for variations in body compartments [38–40], with height being directly linked to bone age and puberty [41,42].

There is a limited number of published studies investigating the effect of long-term nutritional therapies on body composition and muscle function in IBD paediatric populations, which makes it difficult to draw appropriate conclusions about their efficacy. Indeed, only three prospective studies [23–25] have measured the impact of nutrition on body composition in CD patients and showed improvement on disease activity, LM and FFM. Exclusive nutritional intake of the specific IBD polymeric formula Modulen® showed a significant improvement in muscle function using handgrip strength along with an improvement in muscle cross-sectional area [25]. Similarly, semi-elemental formula used for 3 weeks in a crossover design in CD patients found that FFM significantly improved after the feeding compared with baseline measures when assessed using BIA [23]. Modulen® is 100% casein-based and contains essential (e.g. leucine and lysine) and non-essential (e.g. glutamic acid) amino acids which have anti-inflammatory properties leading to an improvement in disease activity and intestinal mucosal integrity [43] and thereby improving LM [44,45].

A recent study indicates that newly diagnosed IBD patients have high prevalence of malnutrition and micronutrient deficiencies which can impact upon disease progression. Hence, it is crucial routine screening for malnutrition using high sensitivity screening tools such as the Malnutrition Universal Screening Tool (MUST) and Saskatchewan IBD Nutrition Risk Tool (SaskIBD-NR) is used to identify those who are at risk of malnutrition [46]. In addition, there are no specific dietary requirements to be followed during the remission phase; all IBD patients in remission should receive consultation by a specialist dietician as part of the multidisciplinary approach required to improve their nutritional status and prevent malnutrition and nutrition-related disorders [47].

This review identified several limitations and heterogenous measures within the studies covered making it difficult to draw appropriate conclusions. We have included some studies that involved paediatric populations with participants aged up to 18 years old [18,22,27], but the age of 18 is typically considered as an adult not a paediatric patient [48]. Studies to date had relatively small sample sizes populated by patients with diverse disease characteristics. Some studies did not recruit a healthy volunteer cohort, so all comparisons relied on historic data sets obtained from different healthy populations [17,19,20,26,28] or unmatched controls [30]. By far, the biggest limitation relates to the methodologies used to measure body compartments. In some studies, the measured outcomes did not always align with the terminology used and/or the correct outcomes of the methods applied. For example, the terms LM and FFM (and often MM) are frequently used interchangeably in the literature due to the lack of understanding that they refer to separate body composition compartments. Indeed, LM and MM (typically assessed by imaging techniques including DEXA, MRI, CT or ultrasound) have been reported through measures of whole body potassium and creatinine excretion [24]. However, whole body potassium is typically used to estimate FFM and not LM or MM [49]. MM itself has been reported as an outcome of BIA measurements [27]. However, BIA is used to estimate FFM and indirectly FM but not MM [50,51]. In addition, some studies have used anthropometric measurements (such as BMI, skinfold thickness and mid-upper arm circumference) to estimate FFM or (incorrectly) MM [17,24] but these measurements lack sufficient accuracy and sensitivity [50,52]. DEXA can assess LM directly and could also estimate FFM if bone mineral density (BMD) is measured concurrently [53], but this has not always been the case [18]. These observations unfortunately may limit the impact of these studies and the frequent interchangeable use of LM, FFM and MM make it difficult to comprehend and compare data from different studies. Furthermore, bias assessment identified that some studies did not adjust for potential confounders such as age, gender, pubertal status, ethnicity and height [19,20,23,26,28,30]. Collectively, these heterogeneities restrict the direct comparison of key findings between outcomes of different studies, which is further compounded by the fact that no studies attempted to use predefined criteria for the definition of sarcopenia (possibly due to a lack of consensus on relevant cut-off points among IBD paediatrics) precluding the assessment of its prevalence in these populations. Therefore, it is important that future studies are designed to reduce risk of bias by identifying and describing in detail subject characteristics, methodologies and confounding factors.

In conclusion, standardization of body composition and sarcopenia terminology along with valid use of assessment tools in adequately powered populations with appropriately matched comparators are key essentials in future studies. Despite current limitations in the published literature, it appears that LM, FFM and MM were significantly reduced in children with IBD. Readouts for body compartments and muscle function should be available with follow up longitudinal data urgently needed to assess the effect of muscle growth, IBD therapies, surgical intervention, nutritional therapies and disease phenotype on these outcomes. Adequate dietary protein supplementation over an adequate period combined with concomitant physical activity may improve MM and its function. However, studies using interventions designed to have minimal attrition are needed before such therapies can be used as standard care across worldwide health care systems.

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Author contribution

GWM is the guarantor of the article. GWM and KT designed the research. BA and SR conducted the study and acquired the data. KT and GWM provided study supervision. BA, KT and GWM analysed and interpreted the data. BA, KT, MJ and GWM draughted the article. All authors critically revised the article for important intellectual content and approved the final version of the article, including the authorship list.

Declaration of competing interest

Dr Moran has receives research funding from Astra Zeneca and Janssen. Dr Moran works as a consultant with Alimentiv and Endoread. All the other authors declare no conflict of interest or financial disclosure to report.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2023.08.009.

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