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REVIEW ARTICLE

Sarcopenia and frailty in inflammatory bowel disease: Emerging concepts and evidence

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Abstract

Sarcopenia is a condition marked by progressive loss of skeletal muscle mass and function while frailty is a multidimensional concept characterized by diminished physiological reserve and increased vulnerability to stressors. Both of these were previously considered as related to aging and shown to impact the quality of life and carry prognostic significance. Emerging data show that both sarcopenia and frailty carry similar relevance in chronic illness. Inflammatory bowel disease (IBD) is characterized by chronic inflammation of the gastrointestinal tract and malnourishment, both of which contribute to the development of sarcopenia by increasing protein breakdown and reducing protein synthesis. The coexistence of frailty further compounds the clinical complexity of IBD patients. Published evidence suggests a bidirectional association with IBD contributing to muscle wasting, while the resultant sarcopenia and frailty could further exacerbate the disease course. Sarcopenia and frailty are independently associated with adverse outcomes, including hospitalizations, increased surgical interventions, and surgical complications. As therapeutic strategies for IBD evolve, understanding the nuanced relationship between inflammatory bowel disease, sarcopenia, and frailty is crucial for devising holistic management. Comprehensive care should encompass not only disease-modifying therapies but also interventions targeting frailty and sarcopenia, as they have been shown to have a significant impact not only on the disease course but also on the quality of life. Future research could focus on further elucidating underlying mechanisms, simple screening strategies, and developing targeted interventions to improve the overall quality of life for individuals grappling with the complex interplay of IBD, sarcopenia, and frailty.

Introduction

Both sarcopenia and frailty emerged as important concepts in the elderly population because of their significant implications on health and quality of life. These concepts have led to the development of assessments, tools, and interventions aimed at preventing or managing age-related muscle loss and enhancing the overall health and resilience of frail elderly people. Healthcare professionals use this concept to identify individuals at high risk and to tailor care that addresses the specific needs and challenges faced by the elderly population.[1] Increasingly, the relevance of sarcopenia and frailty is being explored in the realm of chronic diseases as emerging data showed the impact of sarcopenia and frailty on the outcomes of the disease course and quality of life.[2–4] Lately in the field of gastroenterology, sarcopenia and frailty have been shown to impact the disease course, and outcomes of treatment including post-transplant outcomes in patients with cirrhosis.[5,6] In this article, we review the conceptual framework of sarcopenia and frailty, their prevalence in patients with inflammatory bowel disease (IBD), the relationship between these conditions and disease activity, and their impact on outcomes and response to IBD-related therapies.

Frailty

The frailty construct has several domains, including physical, cognitive, psychosocial, and emotional. Fried's group was the first to give an operational definition of frailty in 2001 based on the analysis of data from a large cohort, the Cardiovascular Health study group.[7] However, Fried's phenotype was mostly confined to the physical domain of frailty. Rockwood later proposed a cumulative deficit model and devised the frailty index that included an assessment of cognitive impairment and psychosocial factors. The frailty index classifies frailty into mild, moderate, and severe phenotypes.[8]

Frailty, like sarcopenia, is a manifestation of cellular senescence. It is a result of age-related mitochondrial dysfunction and progressive accumulation of reactive oxygen species leading to a rise in inflammatory mediators in blood and tissues (inflammaging) and increased cellular apoptosis. However, unlike

sarcopenia, frailty is not singularly focused on myopenia and the resulting muscle dysfunction. Changes at the cellular level manifest across various organ systems (musculoskeletal, nervous, vascular, immune, and endocrine systems) leading to the frail phenotype.[9] The result is a state of decreased reserve and function across these systems, leading to increased vulnerability to stressors and adverse outcomes after exposure to stressors.[10]

Frailty, although associated with aging, is not sine qua non of aging. Long-standing inflammatory conditions are associated with or known to cause frailty, irrespective of age.[11–14] It is also important to recognize that frailty may be reversible with the correction of underlying stressors, nutrition support, and strength training.[15]

Defining frailty

There is no accepted standard definition for frailty. Theoretically, physical frailty is defined as "A clinical syndrome with a distinct phenotype associated with a decreased reserve and high vulnerability to stressors and with risk of adverse outcomes including mortality."[9] However, the operational definition of frailty as per Fried's group is dependent on satisfying at least three of the five characters mentioned in Table 1.[7] On the other hand, Rockwood et al. described an all-encompassing frailty index that measures 92 symptoms. The frailty index is calculated as the fraction of deficits present from the overall (if a person has 24 symptoms, then his FI would be 24/92, i.e., 0.26).[8] The overview of the concept of frailty and sarcopenia is shown in Figure 1.

Identifying frailty

There are broadly two methods to assess frailty: one is through questionnaires, and the other is through objective tests. Available tools to identify frailty use either of these approaches independently or a composite of these. Comprehensive geriatric assessment (CGA) is considered the gold standard of all available tools to detect frailty. It assesses frailty across seven domains, that is, functional, comorbidities, polypharmacy, nutritional, cognitive, psychosocial, and geriatric syndromes in the elderly, and is a sensitive tool to detect various degrees of frailty in the elderly.[17] CGA, however, is very elaborate and difficult to administer in a routine clinical setting. Hence, several screening tools are available, like PRISMA-7, the Clinical Frailty Scale, and the FRAIL scale, which identify patients at risk and select them for detailed evaluation with CGA. CGA has a role not only in detailed assessment but also in making a comprehensive

Table 1 Criteria for Pre-frail and Frail individuals as per Fried group

S.NO	Parameter	Criteria	
1	Weight loss	Unintentional weight loss of 4.5 kg over the last 12 months	
2	Weakness	Reduced grip strength (adjusted for gender and BMI)[†]	
		Men	Cutoff for grip strength (Kg)
		BMI ≤24	≤29
		BMI 24.1–26	≤30
		BMI 26.1–28	≤30
		BMI >28	≤32
		Women	
		BMI ≤23	≤17
		BMI 23.1–26	≤17.3
		BMI 26.1–29	≤18
		BMI >29	≤21
3	Slowness	Walk time for 4 m or 15 feet at usual pace (adjusted for gender and standing height)[‡]	
		Men	Cutoff for Time to Walk 15 feet
		Height ≤ 173 cm	≥7 s
		Height > 173 cm	≥6 s
		Women	
		Height ≤ 159 cm	≥7 s
		Height > 159 cm	≥6 s
4	Exhaustion	Self-reported	
5	Physical activity	Assessed by the WHO-Global physical activity questionnaire or a short version of the Minnesota leisure time physical activity questionnaire (adjusted for sex)[†]	
		Sex	Physical activity per week (Kcal)
		Men	<383
		Women	<270
Score 0: Robust			
Score 1–2: Pre-Frail			
Score ≥ 3: Frail			

[†]Values derived from the lowest 20% of the Cardiovascular Health study cohort.[16]
[‡]Values derived from the slowest 20% of the Cardiovascular Health study cohort.[16]
BMI, body mass index.

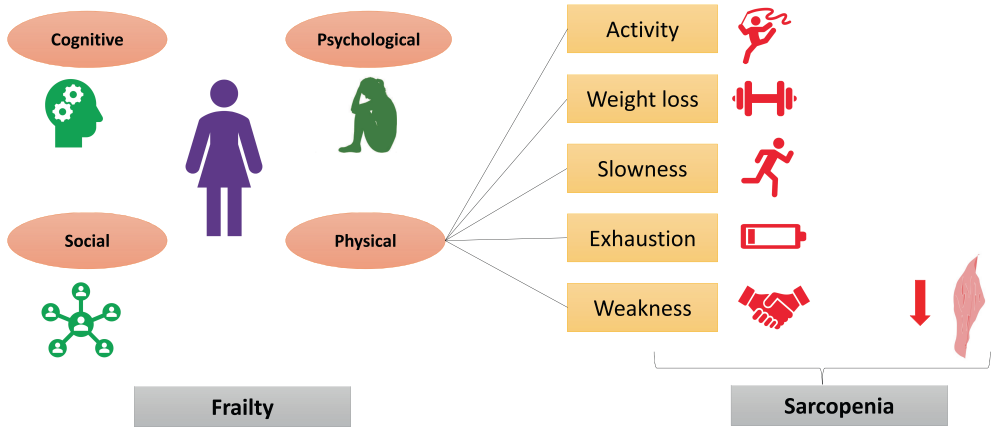

Figure 1 Overview of the concept of frailty and sarcopenia. Frailty is multifaceted and is measured predominantly across four domains, i.e., cognitive, psychological, social, and physical. The physical frailty domain is calculated across several variables like activity (assessed through physical activity scale), unintentional weight loss (>4.5 kg loss in 1 year), slowness (>7 s to travel 15 feet), exhaustion (self-reported; at least 3 days a week), and weakness (reduced grip strength). Sarcopenia on the other hand is a measure of reduced grip strength along with reduced muscle mass, which is a part of one of the frailty domains.

Table 2 Summary of commonly employed tools used for the screening and assessment of frailty

S.No	Setting	Tools	Comments
1	Whole population screening	e-Frailty Index	Time taking. Requires population data. Requires expertise in data analysis.
2	Community based screening	Timed Up and Go test (TUG test)	Can be done by non-clinicians. Easy to use. Can be used in both community and acute care setting
		Indicator of relative need (IoRN)	Clinician administered. Easy to use. Can be used in both community, primary and acute care setting.
3	Self-assessment tools	Frail non-Disabled questionnaire (FiND) Prisma 7	Self-administered questionnaire Can be done at both community level and primary care centers
4	Predictors of individual risk of decline	Acutely presenting older patient (APOP) Identification of seniors at risk (ISAR)	Questionnaire Used in acute clinical setting. Easy to use
5	Severity of frailty	Clinical frailty scale	Acute care setting Administered by Geriatrician
		Frailty phenotype	Both primary care and acute care setting Administered by clinician. Easy to use

interventional plan and for follow-up. There are no specific recommendations for timing and methods of screening frailty in IBD patients. Present studies have employed different tools to measure frailty in IBD patients. From the available tools, Timed Up and Go test (TUG test) and Indicator of Relative Need (IoRN) can be employed easily in a clinical setting for screening of frailty. Several different tools used for the measurement and the setting for the usage of these tools are summarized in Table 2.

Frailty in IBD

Prevalence of frailty in IBD. A meta-analysis of 1 495 695 patients with IBD showed the pooled prevalence of frailty at 18% (95% CI: 12%–24%). However, there was considerable heterogeneity in the studies (I^2: 99.9%) and the scales that were used to measure frailty were different in the studies.[18] In a prospective study by Salvatori et al., reporting on a cohort of 386 IBD patients, the prevalence of pre-frailty and frailty in

IBD patients was 17% and 28%, respectively, as assessed by Fried's phenotype. However, in the age group of ≥60 years, the prevalence of frailty rose to 24.2% and there was no significant difference in the prevalence of frailty between UC and CD. They also have shown that disease activity, steroid usage, and extraintestinal manifestations were significantly higher in frail individuals and multivariate analysis showed that disease activity was an independent predictor of frailty.[19]

Impact of frailty on IBD

Disease activity. Among UC and CD, in the retrospective study by Kochar et al., CD patients had a higher prevalence of frailty (60%). They noted that there was no difference in the levels of inflammatory markers among the frail and non-frail IBD patients.[20] In a retrospective analysis of 2978 IBD patients, where frailty was defined based on frailty index (score > 0.27), patients with more than five flares were higher in the frail group (35.6% vs. 27.5%); however, this finding was not found to be significant on regression analysis.[21] In a prospective cohort study by Salvatori et al., in frail IBD individuals, defined as per Fried's criteria, active disease was higher in the individuals who maintained a frail phenotype (73%) as compared with those with pre-frail (34%) and fit phenotypes (17%, *P*:0.012). Multivariate analysis found that frailty was associated with clinically active disease (OR:0.1, 95% CI: 0.01–0.6), extraintestinal manifestations (OR:0.1, 95% CI: 0.02–0.8), and is inversely related to biological use (OR:21.7, 95% CI: 3.4–263). This suggests that therapy with biologics may have a role in the improvement of frailty status.[22] Another prospective cohort study in elderly IBD patients measured frailty by geriatric deficit assessment and found a direct relationship between the number of geriatric deficits with clinical (OR:2.192, 95% CI: 1.284–3.743), biochemical disease activity (OR:3.358, 95% CI: 1.936–5.825), and fecal calprotectin levels (OR: 2.721, 95% CI: 1.376–5.379). Interestingly, it was noted that the CD patients had higher geriatric deficits (OR: 1.799, 95% CI: 1.179–2.743).[23]

IBD therapy. Regarding the requirement of surgical intervention in frail IBD patients, there is heterogeneity in the literature. Kochar et al. noted that a history of IBD-related surgery was higher in frail (32%) than fit (11%) IBD patients ($P < 0.01$), a similar finding noted in the study by Singh et al., where frail patients had higher rates of abdominal surgery than non-frail patients (14.4% vs. 9.6%).[20,24] Contrary to these findings, another retrospective analysis by Kochar et al., using a different frailty scale to diagnose frailty, found that there was no significant difference in the prior IBD surgery among the frail and non-frail group (11% vs. 9%, *P*:0.41).[21] However, Qian et al. have noted that frailty was independently associated with a lower risk of surgery (HR: 0.8, 95% CI: 0.66–0.91) and frail patients had a lower incidence of disease flare as compared with fit IBD patients (14.8% vs. 30.9%, $P < 0.01$).[21]

Anti-TNF therapy was shown to improve frailty scores with a mean overall improvement from 19.83 to 11.8 (*P*:<0.001), with 45% of frail patients showing improvement in scores to >50% and a complete improvement seen in 12% of cases. Response to therapy was significantly associated with lower post-treatment frailty (OR:0.24, 95% CI: 0.16–0.34).[25] Surprisingly, Singh et al., from their retrospective analysis of 5987 IBD patients initiated on biologicals, found that the risk of serious infections was higher in frail patients who were on vedolizumab (OR:1.69, 95% CI: 1.03–2.79) but not on anti-TNF α therapy (OR:1.03, 95% CI: 0.83–1.27).[24] A similar finding was noted by Asscher et al. in IBD patients on biologicals, where the risk of infections was independently associated with comorbidities, as measured by the Charlson comorbidity index (CCI), in patients on vedolizumab (OR:1.387, 95% CI: 1.022–1.883) and ustekinumab (OR:1.621, 95% CI: 1.034–2.541).[26] However, Kochar et al. have noted that pretreatment frail individuals who were initiated on anti-TNF therapy and immunomodulators are at increased risk of infections compared with non-frail individuals even after adjusting for all the confounders like age and steroid use (OR:2.05, 95% CI: 1.07–3.93; OR:1.81, 95% CI: 1.22–2.70 respectively). Infection-related hospitalization between frail and non-frail groups was significantly higher in patients initiated on immunomodulators (OR:2.08, 95% CI: 1.33–3.26) but not on biologicals (OR:1.51, 95% CI: 0.62–3.66).[27] It is unclear whether the risk of infection is related to the frail status or the underlying disease activity and the therapies.

Post-operative outcomes. In a retrospective analysis of 9023 patients of Crohn's disease who underwent bowel resection, frailty (simplified frailty index ≥2) was a better predictor of postoperative (post-op) outcomes than age (OR-2.59, 95% CI: 1.84–3.63). They also noted that frailty was associated with the need for emergency surgery (sFI ≥2–13%, *P*:0.01) and malnutrition (sFI≥2–48.9%, *P*:0.01).[28] In a retrospective analysis of 943 UC cases who underwent colectomy, frailty was present in 19.5% of cases and was an independent predictor of overall morbidity (aOR:25.5, $P < 0.001$) and serious morbidity (aOR:66.8, $P < 0.001$). Frail patients also had a higher incidence of post-op complications including septic (aOR:31.26, *P*:0.006), cardiopulmonary (aOR:216.3, $P < 0.001$) and Clavien class IV complications (aOR:204.9, $P < 0.001$).[29] However, in another study by Cohan et al., in UC patients undergoing colectomy with IPAA, there was no difference between frail and non-frail patients in the mean number of complications (0.31 vs. 0.34, p: 0.36) and the length of hospital stay (7.4 vs. 7.7 days, *P*: 0.25).[30]

Mortality. In a retrospective study from a nationwide database of 1 405 529 IBD patients (36% UC, 63% CD), the overall prevalence of frailty was 10.9%, and it progressively increased from 10.2% to 11.5% over 5 years (2010–2014). In this report, ICD-9-CM from Johns Hopkins clinical groups frailty was the e-frailty (electronic) index employed to diagnose frailty. Frailty was an independent predictor of readmission risk (RR: 1.16 95% CI: 1.14–1.17) and mortality on readmission (RR: 1.12, 95% CI: 1.02–1.23).[31] Similar findings were noted in another retrospective analysis of 47 402 IBD admissions where frail IBD patients had higher readmission rates (HR: 1.21, 95% CI: 1.17–1.25), in-hospital mortality (HR: 1.57, 95% CI: 1.34–1.83), and IBD-related severe hospitalizations (HR: 1.22, 95% CI: 1.16–1.29).[32] In the analysis of 11 001 IBD cases, Kochar et al. noted that after adjusting for other confounders like age, duration of IBD, history of surgery, and immunosuppression use, the frail IBD cohort had significantly higher mortality compared with fit patients (OR: 2.90, 95% CI: 2.29–3.68).[20] Gondal et al., have also noted that

Table 3 Studies on frailty in patients with inflammatory bowel disease

Author and year	Study population	Number	Frailty measures	Prevalence of frailty	Outcome	OR/RR/HR and *P* value
Wolf et al., 2021[28]	CD with bowel resections	9023	Simplified frailty index (sFI)	sFI ≥1 in 1610 (17.8%)	Higher sFI (≥2) is associated with	
					morbidity (OR)	2.59 ($P < 0.001$)
					malnutrition	$P < 0.01$
					emergency surgery	$P < 0.01$
Telemi BS et al., 2018[29]	UC with colectomy, frailty as a predictor (OR)	943	Modified frailty index (mFI)	mFI of 0.09: 184 (19.5%)	Complications (OR)	
					Septic	31.26 (*P*:0.006)
				mFI ≥0.18: 121 (12.8%)	Cardiopulmonary	216.3 ($P < 0.001$)
					Clavien class IV	204.9 ($P < 0.001$)
					Morbidity (OR)	
					Overall	25.5 ($P < 0.001$)
					serious	66.8 ($P < 0.001$)
Cohan J et al., 2015[30]	UC with colectomy and IPAA	2493	Frailty trait count	NA	Mean number of complications	0.31 vs. 0.34, *P*: 0.36
					Length of hospital stay	7.4 vs. 7.7 days, *P*: 0.25
Faye S et al.[31]	Admitted IBD	UC—510 199 (36%) CD—888 981 (63%)	ICD-9-CM codes from Johns Hopkins clinical groups frailty	152 974 (10.9%)	Increased risk of readmission (RR)	1.16 (1.14–1.17)
					Increased risk of readmission (RR) mortality in CD	1.32 (1.13–1.55)
Qian S et al., 2021[32]	Admitted IBD	47,402	Hospital frailty risk score	15 507 (32.7%) Medium frailty—14 207 High frailty—1480	IBD-related severe hospitalizations (HR)	1.22 (1.16–1.29)
					Higher readmission rates (HR)	1.21 (1.17–1.25)
					Higher inpatient mortality (HR)	1.57 (1.34–1.83)
Kochar B et al., 2020[20]	Admitted IBD on predictors of frailty	11 001	Based on ICD-10 codes	675 (6%)	≥1 comorbidities (CCI)	17.31 (8.14–36.79)
					Hospitalization	7.67 (4.62–12.73)
					All cause	2.29 (1.85–2.83)
					IBD related	
Kochar B et al., 2022[25]	On response of frailty to anti-TNF, predictors of post treatment frailty	1210 CD: 71% UC: 29%	Claims-based frailty index (CFI)	189 (15.6%)	Pretreatment frailty (OR)	2.10 (1.35–3)
					IBD-related hospitalization (OR)	1.63 (1.15–2.3)
Singh S et al., 2020[24]	Risk of infections in patients on biologicals	5987 IBD	Hospital frailty risk score	2350 (39.3%)	Risk of serious infections (HR)	
					Anti TNF α	1.03 (0.83–1.27)
					Vedolizumab	1.69 (1.03–2.79)
Gondal et al., 2020[21]	Mortality and disease activity in IBD	2978 IBD UC: 53.5% CD: 46% Indeterminate: 0.5%	Frailty index (score > 0.27)	953 (32%)	Mortality (OR)	1.52 (1.07–2.16)
					>5 IBD flares (OR)	1.2 (0.99–1.45)

(*Continues*)

Table 3 (Continued)

Author and year	Study population	Number	Frailty measures	Prevalence of frailty	Outcome	OR/RR/HR and *P* value
Salvatori S et al., 2023[22]	Prospective cohort	64 with IBD and frailty	Fried frailty score	Median 8-month follow-up	Extraintestinal manifestations (OR)	0.1 (0.02–0.8)
					Clinically active disease (OR)	0.1 (0.01–0.6)
					Biological use (OR)	21.7 (3.4–263)
Asscher et al., 2022[23]	Prospective multicenter study on IBD factors associated with geriatric deficits	405 IBD CD: 191 UC: 202 IBD-UC: 12	Geriatric assessment	Moderate deficits: 160 (39.5%) Severe deficits: 32 (7.9%)	Crohn's disease (OR)	1.799 (1.179–2.743)
					Clinical disease activity (OR)	2.192 (1.284–3.743)
					Fecal calprotectin (OR)	2.721 (1.376–5.379)
					Previous all-cause hospitalization (OR)	1.994 (1.267–3.137)
Kochar et al., 2020[27]	Retrospective study on patients being initiated on biologicals and immunomodulators	1299 on anti-TNF and 2676 on immunomodulator	Frailty risk score (ICD-10)	Anti-TNF: 68 (5.2%) Immunomodulator: 212 (7.9%)	Risk of infection on anti-TNF (OR)	2.05 (1.07–3.93)
					Risk of infection on Immunomodulator (OR)	1.81 (1.22–2.70)

Anti-TNF, anti-tumor necrosis factor; CD, Crohn's disease; CFI, Claims-based frailty index; HR, hazard ratio; IBD, inflammatory bowel disease; IBD-UC, inflammatory bowel disease-unclassified; ICD, international classification of diseases; IPAA, ileal pouch-anal anastomosis; mFI, modified frailty index; OR, odds ratio; RR, risk ratio; sFI, simplified frailty index, UC, ulcerative colitis.

the mortality rate was higher in IBD patients who were frail (defined as per FI) compared with non-frail (OR:1.52, 95% CI: 1.07–2.16).[21] Studies relating to IBD and frailty are summarized in Table 3.

IBD and aging. Back in 2010, epidemiological estimates showed that people of ≥65 years with IBD constituted 20% of the total IBD population.[33] Given the chronic nature of the condition and lack of curative therapies, it is estimated that the cohort of IBD with ≥65 years of age will increase to a third of the IBD cohort.[34] Aging is associated with multiple comorbidities, and people with IBD are no exception, resulting in polypharmacy adding to the pill burden in the elderly. This potentially leads to nonadherence to IBD treatment.[19,35] IBD also brings up a new spectrum of complications, especially in the elderly, associated with steroid use like cataracts and osteoporosis. The risk of infections and malignancies due to the use of immune suppressants, biologics, and small molecules may be higher in the elderly.[36,37] Elderly with IBD have a significantly increased risk of postoperative complications (OR in CD: 1.4 and UC: 1.74), mortality (OR in CD:11.6 and UC:4.39), infections (OR in CD: 1.11 and UC: 1.52), and embolic events (OR in CD: 1.68 and UC: 1.35).[38] Long-term follow-up after ileal pouch-anal anastomosis in patients with UC showed that elderly patients have significantly higher incontinence rates (young: 25.25%, elderly: 44.91, *P*:<0.001), stool frequency (mean bowel movements per day in young: 5.55, elderly: 6.79, *P*:<0.001), and are at increased risk of dehydration and electrolyte loss (young: 23.6%, elderly: 60%, *P*:<0.001).[39] Kochar et al., in their retrospective study, have noted that the prevalence of frailty increased as age progressed in IBD patients. Overall, 4% of IBD patients were frail who were in their 20s and almost one fourth of IBD patients were frail in their 90s.[20] Reduction in the ratio of T3/T4 has been identified as an independent marker of frailty in the elderly.[40] An extrapolation of this, Bertani et al., in their prospective study, included patients of elderly IBD, who were initiated on biologicals and the ratio of T3/T4 was used as a response predictor. They found that the baseline T3/T4 ratio was proportionate to the mucosal healing rates regardless of disease type and biological use.[41]

Sarcopenia

Sarcopenia deals with only the physical component of frailty but has been very well studied. Sarcopenia results from manifestations of a progressive (age-related) decline in muscle mass. The term sarcopenia, first used by Rosenberg in 1989, was not recognized as a separate disease entity until ICD-9.[42,43] It had no specific definition, evaluation, or diagnostic criteria and management aspects were uncertain. In the years 2010 and 2011, three consensus papers were released defining sarcopenia and diagnosing sarcopenia. Later ICD-10 recognized sarcopenia as a separate pathological entity (M62.84)[44–46].[47] Sarcopenia can be defined as a "progressive and generalized skeletal muscle disorder with significant reduction in skeletal muscle mass associated with low muscle strength and low physical performance.".[48]

Mechanism of sarcopenia

Muscle mass is maintained by a tightly regulated balance between protein synthesis and breakdown. Stimulation of muscle protein synthesis is by activation of the mTOR pathway. When insulin-like growth factor 1 (IGF-1) or insulin binds to IGF-1 receptors (a tyrosine kinase receptor) on the myocytes, it results in a chain of reactions leading to the phosphorylation of Akt, a cellular kinase.[49] Phosphorylated Akt, in turn, phosphorylates and activates mTOR complex 1 (mTORC1), activated mTORC1 stimulates protein synthesis by activating ribosomal protein kinase, which is p70-S6 kinase 1, and it also inhibits proteolysis by inhibiting autophagy-activating kinases ULK1/2.[50] The FoxO (Forkhead box O) family of transcription factors that have a role in promoting autophagy and maintenance of the ubiquitin-proteasome system causing cellular apoptosis, Akt phosphorylates members of the FoxO family, which leads to their inhibition.[51] Akt also enhances mitochondrial respiration by activating ATP citrate lyase (ACL) leading to increased ATP production, which is essential for protein synthesis in muscle. In addition, fibroblast growth factor 19 (FGF-19), secreted by enterocytes in response to bile acids, directly stimulates cytoplasmic protein synthesis via activation of the extracellular signal-regulated kinases (ERK).[52]

Protein breakdown is predominantly mediated by two pathways, that is, the ubiquitin-proteasome system and the autophagy-lysosomal system. Aging is associated with 'Somatopause', a phenomenon seen due to reduced GH secretion and thereby reduced circulating IGF-1 levels. IGF-1 is a major hormone required for maintaining muscle protein synthesis.[53–56] Thus, the interplay of all these factors is associated with a physiological reduction in muscle mass as age progresses. In patients with IBD, it was shown that the total levels of Akt were similar in both CD patients and matched healthy controls in the muscle biopsy specimens; however, the phosphorylated Akt (activated) levels were significantly lower in those with CD compared with matched healthy controls.[57] The mechanism of muscle protein synthesis and breakdown operating in patients with IBD is shown in Figure 2.

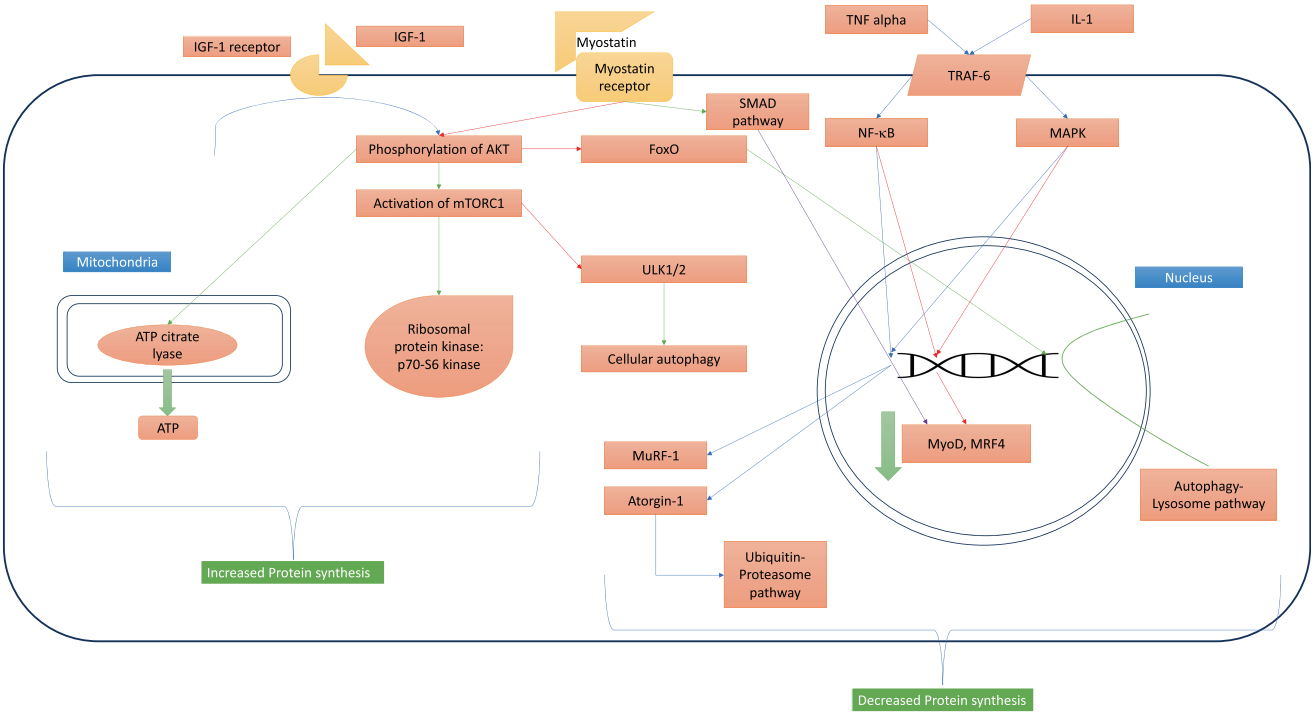

Figure 2 Mechanism of muscle protein synthesis and breakdown operating in patients with IBD. Muscle protein synthesis is stimulated by binding IGF-1 to its receptor leading to phosphorylation of Akt. Activated Akt activates mTORC-1 and inhibits FoxO and ULK1/2, both of which are involved in protein degradation. Activated mTORC-1 stimulates ribosomal protein kinases resulting in synthesis of proteins, and this is supported by an increase in ATP production in mitochondria by activated ATP citrate lyase, providing the energy required for protein synthesis. Protein breakdown is predominantly mediated by two pathways, that is, the ubiquitin-proteasome system and the autophagy-lysosomal system. Absence of IGF-1 stimulation releases FoxO from its cytoplasmic captivity, which translocate into nucleus and stimulate the autophagy-lysosome pathway. Inflammatory mediators (IL-1 and TNF alpha) activate the ubiquitin-proteasome pathway via the Nf-κB and MAPK pathways, which reduce the expression of myogenic genes and stimulate the production of MuRF-1 and Atorgin-1 proteins, both are ubiquitin ligases that are involved in the third step (E3) of ubiquitination. Myostatin receptor via Smad pathway directly reduce the expression of myogenic genes and indirectly by inhibiting the phosphorylation of Akt. In the absence of Akt activity, mTORC-1 complex is dormant, thus ULK1/2 remains uninhibited, leading to increased cellular autophagy. ATP: Adenosine triphosphate, FoxO: Forkhead box O, IGF-1: insulin-like growth factor 1. IGF-1R: insulin-like growth factor 1 receptor, IL-1: Interleukin 1, MAPK: mitogen-activated protein kinase, MRF4: myogenic regulatory factor 4, mTORC-1: mTOR complex 1, MuRF-1: muscle ring finger protein-1, MyoD: myoblast determination protein 1, NF-κB: nuclear factor-κB, TNF alpha: Tumor necrosis factor alpha, TRAF-6: TNF receptor-associated factor 6, ULK1/2: Unc-51-like autophagy-activating kinases 1 and 2.

Mechanisms of sarcopenia in IBD

Reduced IGF-1 levels. Circulating IGF-1 and IGF-1 binding protein-3 (IGFBP-3) are significantly lower in patients with IBD.[58,59] Therapy with infliximab and corticosteroids normalizes the circulating total IGF-1 and IGFBP-3 levels.[60,61] Thus, the reduction of IGF-1 levels in patients with active IBD reduces muscle mass by favoring protein catabolism.

Chronic inflammation. Patients with active IBD have increased circulating levels of proinflammatory cytokines like TNF-α and IL-6.[62] These act via mitogen-activated protein kinase (MAPK) and nuclear factor-κB (NF-κB) pathways involved in the transcription of muscle ring finger protein-1 (MuRF-1) and Atrogin-1 leading to proteasome-mediated degradation of ubiquitinated proteins.[63–65] IL-6 via the JAK–STAT pathway stimulates the expression of MuRF-1, Atorgin-1, and myostatin and increases the expression of proteasomal subunits cathepsin B and L, leading to protein degradation.[66,67] Myostatin (TGF-β family), produced from the skeletal muscle in response to IL-6, reduces the expression of myogenic genes via the Smad pathway and inhibits the phosphorylation and activation of Akt. Myostatin also activates the MAPK pathway, leading to increased expression of MuRF-1 and Atorgin-1.[68] Through these mechanisms, inflammation reduces myogenesis and increases protein breakdown.

Malnutrition. Malnutrition in IBD is multifactorial, encompassing factors such as inflammation-related anorexia, pain from strictures, reduced intestinal absorptive surface due to multiple intestinal resections and inflamed mucosa, dietary restrictions, bacterial overgrowth. It has similar incidence in both UC and CD.[69,70] Studies from the elderly cohort have shown that malnutrition is associated with severe sarcopenia and nutrition intervention and physical activity improve sarcopenia in the elderly.[71,72] Vitamin D plays an important role in the maintenance of musculoskeletal health, involved in the upregulation of IGF-2 and follistatin genes and the downregulation of the myostatin gene.[73] The prevalence of vitamin D deficiency is high in patients with UC and CD, with the latest study showing a prevalence rate of 65% in CD and 55% in UC.[74] Improvement in bone and muscle parameters with vitamin D supplementation was noted in pediatric IBD patients.[75]

Defining sarcopenia

The European Working Group on Sarcopenia in Older People (EWGSOP) has defined sarcopenia as the reduction in muscle mass along with a reduction in muscle strength or performance. Pre-sarcopenia refers to a reduction in muscle mass alone while severe sarcopenia was defined if all three are present.[44] Later in 2018, the working group noted that muscle strength rather than mass had a greater correlation with all-cause morbidity and mortality. In the 2018 operational definition by EWGSOP, sarcopenia was defined as a reduction in muscle strength and mass or quality. Probable sarcopenia was defined as a reduction in muscle strength and severe sarcopenia was defined as the presence of sarcopenia along with reduced physical performance.[76] The Asian working group on sarcopenia (AWGS) definition of sarcopenia is more on the lines of the older EWGSOP definition. They have defined possible sarcopenia as either a reduction in muscle strength or physical performance; sarcopenia was defined as the presence of reduced muscle mass along with either reduced muscle strength or physical performance and severe sarcopenia as the presence of all three parameters.[77] Different consensus definitions of sarcopenia are summarized in Table 4.[45,46,78–81]

Assessment of sarcopenia

Sarcopenia is assessed at three levels. First, screening was conducted on susceptible individuals to detect the presence of sarcopenia by assessing muscle strength, and then individuals with reduced muscle strength are assessed for reduced muscle mass and physical performance. Reduced muscle mass with optimal physical performance is categorized as sarcopenia. The presence of both reduced mass and physical performance is categorized as severe sarcopenia. Normal cutoff for grip strength and muscle mass varies between races and sexes and respective societies have given their cutoffs based on local studies, as mentioned in Table 5.

1. Assessing muscle strength: It is typically assessed by performing grip strength. It is performed with a handheld dynamometer, and the recommended device is the Jamar dynamometer. Hand grip correlates moderately with other body compartments strength and is relatively easy to perform, such as in those with hand deformities, knee flexor and extensor isometric torque can be measured.[79] Another easy way to assess muscle strength is through a chair stand test, where a patient is asked to stand up from a standard chair without support and arms flexed; the time taken for the subject to perform it five times is then recorded.[82]
2. Assessing muscle mass: Muscle mass of appendicular skeletal muscle or a total body skeletal mass can be assessed directly through DEXA scan, computed tomography (CT), and magnetic resonance imaging (MRI), and indirectly through bioelectrical impedance analysis. Both CT and MRI are considered as gold standard in noninvasive assessment of muscle quantity. Taller individuals would have larger mass when compared with shorter individuals, hence muscle mass is adjusted according to either height, weight, or BMI. Cross-sectional area at the L3 level correlates well with total skeletal mass and provides a window for assessing myopenia in IBD patients especially undergoing CT or MRI scans for other reasons.[83] Ultrasound is now emerging as a cheaper, alternative, and an accurate modality for assessing muscle mass of quadriceps femoris.[84]
3. Assessing physical performance: Gait speed is an accurate and easy measure of physical performance and has been shown to predict the adverse outcomes related to sarcopenia.[85] The time taken to walk for 4 meters is measured and gait speed is calculated; a speed of ≤0.8 m/s is considered as a marker of poor physical performance; this assessment can be done in a clinical setting and is recommended by EWGSOP2. A composite score of gait speed, chair stand test, and balance test forms a short physical performance battery (SPPB); a score of ≤8 out of 12 is suggestive of poor performance; however, it takes more than 10 min to administer SBBP. Other

Table 4 Various definitions of sarcopenia

S. no	Consensus Group	Year	Sarcopenia definition	
1	Special interest group[45]	2010	Low muscle mass and low gait speed	
2	European working group on sarcopenia in older people (EWGSOP)[44]	2010	Pre-sarcopenia	Reduced muscle mass
			Sarcopenia	Reduced muscle mass along with either reduction in muscle strength or performance
			Severe sarcopenia	Reduction in muscle mass, muscle strength and performance
3	International working group on sarcopenia[46]	2011	Low muscle mass and muscle function	
4	Society on sarcopenia, cachexia and wasting disorders[78]	2011	Low muscle mass with limited mobility (walking speed ≤1 m/s or <400 m distance covered during a 6-min walk)	
5	Asian working group on sarcopenia (AWGS)[79]	2014	Low Muscle mass along with either low handgrip strength or low gait speed	
6	Foundation for the national institutes of health sarcopenia project[80]	2014	Low muscle mass and low grip strength	
7	European working group on sarcopenia in older people (EWGSOP)[76]	2019	Probable sarcopenia	Low muscle strength
			Sarcopenia	Low muscle strength with reduced muscle quality or quantity
			Severe sarcopenia	Sarcopenia with reduced physical performance
8	Sarcopenia definitions and outcomes consortium[81]	2020	Presence of both Weakness (reduced grip strength) and slowness (reduced physical performance)	
9	Asian working group on sarcopenia (AWGS)[77]	2020	Possible sarcopenia	Reduced muscle strength or physical performance
			Sarcopenia	Low muscle mass along with either reduced muscle strength or physical performance
			Severe sarcopenia	Low muscle mass along with either reduced muscle strength and reduced physical performance

Table 5 Cutoffs for the diagnosis of sarcopenia

S.NO	Working Group	Parameter	Cutoff in Male	Cutoff in Female
1	European working group on sarcopenia in older people (EWGSOP)	Grip strength	<27 kg	<16 kg
		Muscle mass	<7 kg/m^2	<5.5 kg/m^2
2	Asian working group on sarcopenia (AWGS)	Grip strength	<28 kg	<18 kg
		Muscle mass		
		DEXA	<7 kg/m^2	<5.4 kg/m^2
		Bioelectrical impedance analysis	<7 kg/m^2	<5.7 kg/m^2
3	South Asian Working Action Group on Sarcopenia (SAWG-SARCO)	Grip strength	<27.5 kg	18 kg
		Muscle mass	<7 kg/m^2	<5.7 kg/m^2

tests like Timed Up and Go (TUG) and 400-meter walk tests can also be performed to assess physical performance.[76]

Prevalence of sarcopenia in IBD

Bryant et al. studied the prevalence of sarcopenia in IBD, diagnosed based on a reduction in muscle mass and grip strength. They noted that myopia was present in 21% and sarcopenia in 12% of cases, with no significant difference among patients with CD and UC (12% and 14%, respectively).[86] Another study by the same group in 2018 showed that the prevalence of sarcopenia in patients with IBD progressed over time from 9% to 15% over 2 years.[87] Another group from Italy studied the prevalence of sarcopenia in which muscle strength was assessed as a degree of asthenia measured through a visual analogue scale and found a higher rate of sarcopenia prevalence at 28%.[88] In 2021, ünal et al. studied the prevalence of sarcopenia, diagnosed based on the 2019 operational definition of EWGSOP, and found that 31.3% had myopenia while only 7.6% had sarcopenia, and severe sarcopenia was found in 2.6% of patients.[89] In another study in China where sarcopenia was diagnosed based on the AWGS definition, 56.3% had pre-sarcopenia, 30% had sarcopenia, and 8.1% had severe sarcopenia.[90] In a study from India on 114 patients with UC, the prevalence of sarcopenia and severe sarcopenia was 21.9% and 12.2%.[91] Data from the systematic review of sarcopenia in IBD showed that the overall prevalence

of pre-sarcopenia was 34%, myopenia was 42%, and sarcopenia was 17%, with no significant difference between UC and CD and similar occurrences in both the genders.[92] Studies on the prevalence of sarcopenia in IBD are summarized in Table 6 while those reporting myopenia are depicted in Table 7.

Nutrition status and sarcopenia in IBD

Sarcopenia is often thought to be associated with malnourishment, which is true in the elderly cohort, but studies in IBD show varying results.[71] A study on nutritional status and body composition of a cohort of 88 CD patients revealed that malnourishment is prevalent (21.6%), but a greater number of patients were overweight and obese (32.8%). Among these, most of the patients with myopenia either had a normal BMI (49%) or were overweight and obese (15.7%).[104] A similar finding was noted in a cohort of IBD patients who were initiated on anti-TNF therapy: 41.5% of patients with myopenia had normal BMI and 19.5% were considered to be overweight or obese.[105] A study of body composition in patients with CD suggests that BMI has only an intermediate correlation with skeletal muscle index (SMI) (r was between 0.5 and 0.7).[106] In a cross-sectional study where sarcopenia was measured as reduced muscle mass and muscle strength, the prevalence of normal BMI among patients with sarcopenia was as high as 76%.[86]

Relation to disease activity. A longitudinal analysis of 44 patients with UC showed that myopenia had a positive correlation with the Mayo score and myopenia was an independent risk factor for a higher Mayo score in patients with UC (OR-8.49, 95% CI: 1.80–40.1, $P = 0.007$). Patients with UC and myopenia also had higher colectomy rates ($P = 0.003$) and the myopenia improved significantly after colectomy ($P = 0.033$).[107] A retrospective study measured adverse outcomes, a composite of death or need for surgery, in patients with CD who underwent CT and found out that although nonsignificant the adverse event rate was higher numerically in patients with myopenia than those without (52% vs. 37.4%).[106] Further analysis showed that malnutrition had no significant effect on adverse outcomes (composite of surgery, hospitalization, abscess formation) but patients with myopenia had a significantly higher rate of adverse outcomes compared with those without myopenia (surgery: 63.3% vs. 27.8%, $P = 0.001$; hospitalizations: 61.2% vs. 36.1%, $P = 0.022$; abscesses: 51.0% vs. 16.7%, $P = 0.001$); myopenia and visceral obesity but not BMI were independent predictors for the need of surgery.[104] In contrast to the above findings, a study of myopenia (measured on CT at L3 level) in relation to disease activity (CDAI score) in patients with CD showed no significant difference in the prevalence of sarcopenia across varied disease activity (47.4%—moderately active, 42.1%—mildly active, and 10.5%—remission, $P = 0.228$). However, they have noted that the disease course was more aggressive in those with myopenia (31.6% vs. 16%, $P = 0.06$) and a higher requirement of surgery in patients with myopenia (31.6% vs. 4%, $P = 0.01$). A combination of myopenia and visceral fat to subcutaneous fat ratio of <0.88 was a better predictor of the need for surgery than sarcopenia alone.[93] In a cross-sectional study of CD patients, body composition was measured on CT, and although subcutaneous and visceral adiposity along with skeletal muscle index (SMI) were associated with moderate to severely active endoscopic disease, SMI performs the best in diagnosing disease activity with an AUC value of 0.865.[101] Similar findings were noted in a follow-up study of CD patients where authors noted that SMI had a negative correlation with disease activity and lower SMI was associated with severe disease ($P = 0.001$) and the SMI at the last follow-up was the only significant predictor of remission in patients with CD (OR-1.21, 95% CI: 1.03–1.42, $P = 0.021$).[108] Sarcopenia as a risk factor for poor outcomes was first shown in a prospective study of 110 IBD patients; after a 90-day follow-up period, sarcopenia was found to be associated with higher rates of surgery (OR = 6.651, 95% CI: 2.333–18.959, $P < 0.001$), re-hospitalization (OR-6.344, 95% CI:

Table 6 Studies reporting on prevalence of sarcopenia in inflammatory bowel disease as per revised definition (myopenia and grip strength)

S.no	Author	Year	Country	Number	Parameters measured	Prevalence
1	Bryant et al.[82]	2015	Australia	137	Muscle strength: Grip strength Muscle mass: DEXA (ASMI)	12%
2	Bryant et al.[83]	2018	Australia	110 CD-79 UC-28	Muscle strength: Grip strength Muscle mass: DEXA (ASMI)	15%
3	Pizzoferrato et al.[84]	2019	Italy	127 CD-69 UC-58	Muscle strength: Degree of asthenia based on VAS of 1–100 Muscle mass: DEXA and Bioelectrical impedance analysis	28%
4	Ünal et al.[85]	2021	Turkey	344 CD-122 UC-222	Muscle strength: Grip strength Muscle mass: Bioelectrical impedance analysis	7.6%
5	Liu et al.[86]	2022	China	110 CD-25 UC-85	Muscle strength: Grip strength Muscle mass: Bioelectrical impedance analysis	30%
6	Bharath et al.[91]	2023	India	114 (UC)	Muscle strength: Grip strength Muscle mass: DEXA (ASMI)	21.9%

ASMI, appendicular skeletal muscle index; CD, Crohn's disease; DEXA, dual energy X-ray absorptiometry; UC, ulcerative colitis: VAS, visual analogue scale.

Table 7 Studies reporting on myopenia in IBD from Asia

S. No	Author	Year	Country	Number	Parameter used to measure muscle mass	Prevalence	Outcome
1	Zhang T et al.[93]	2017	China	204 CD-105 UC-99	L3 skeletal muscle index on CT scan†	25.5%	Myopenia is associated with higher disease activity and poor clinical outcomes
2	Bamba S et al.[94]	2017	Japan	72 CD-43 UC-29	L3 skeletal muscle index on CT scan†	42%	Myopenia predicts intestinal resection
3	Zhang T et al.[95]	2017	China	114 (CD)	L3 skeletal muscle index on CT scan†	61.4%	Patients undergoing bowel resection with myopenia had higher post-operative complications
4	Bamba S et al.[96]	2020	Japan	187 CD-99 UC-88	L3 skeletal muscle index on CT scan†	34.7%	Myopenia is associated with prolonged hospital stay
5	Kang MK et al.[97]	2020	South Korea	443 (UC and CD)	Psoas muscle index on CT‡	34.9%	Sarcopenia was an independent risk factor for NAFLD in patients with IBD
6	Kurban M et al.[98]	2020	China	47 (CD)	Bioelectrical impedance analysis	66%	Body composition analysis is more accurate for muscle mass assessment than nutrition assessment scales
7	Lee CH et al.[99]	2020	South Korea	79 (CD)	L3 skeletal muscle index on CT scan†	51%	Myopenia correlated with CRP levels
8	Ge Xi et al.[100]	2021	China	233 (ASUC)	L3 skeletal muscle index on CT scan†	50.2%	Myopenia associated with failure of response to IV steroid, higher colectomy rates and postoperative complications
9	Boparai et al.[101]	2021	India	44 (CD)	L3 skeletal muscle index on CT scan†	43%	Combination of myopenia and high visceral fat was associated with poor outcomes in CD
10	Ge Xi et al.[102]	2022	China	254 (ASUC)	L3 skeletal muscle index on CT scan†	50%	Sarcopenia is an independent predictor for rescue therapy and colectomy
11	Nam K et al.[103]	2023	South Korea	1027 CD-854 UC-173	L3 skeletal muscle index on CT scan†	56.8%	Myopenia is associated with perianal CD

†L3 skeletal muscle index: Total cross-sectional area of the skeletal muscles at L3 level divided by height (in meters) squared.
‡Psoas muscle index: Total psoas cross-sectional area at L3 level divided by height (in meters) squared.
ASUC, acute severe ulcerative colitis; CD, Crohn's disease; NAFLD, non-alcoholic fatty liver disease; UC, ulcerative colitis.

2.874–14.003, $P < 0.001$) and death ($P = 0.003$); similar trend was seen in those with pre-sarcopenia when compared with controls.[90] Among patients with ulcerative colitis, disease severity was measured with the Mayo score. The prevalence of sarcopenia (13%) and severe sarcopenia (47.2%) was significantly higher in those with mild to moderately active and severe disease than in those who were in remission (6.3%) ($P < 0.001$).[91]

Impact on management

Acute severe colitis. In a retrospective analysis of the outcomes in patients with acute severe colitis (ASUC) sarcopenia (defined as a reduction in muscle mass at the level of L3 vertebrae) (OR: 3.130, 95% CI: 1.609–6.087, $P = 0.001$) along with disease extent, Mayo score and hemoglobin were risk factors for IV steroid failure. Sarcopenia remained to be an independent predictor of second-line therapy failure (OR: 3.401, 95% CI: 1.104–10.479, $P = 0.033$). In patients who underwent colectomy, the rate of post-op complications was significantly higher in those with sarcopenia compared with those without sarcopenia (58.6% vs. 33.3% respectively, $P = 0.037$); sarcopenia alone was an independent risk factor for post-op complications (OR: 4.157, 95% CI: 1.364–12.667, $P = 0.012$) in ASUC patients who underwent colectomy.[109] Another larger retrospective study of 254 patients with ASUC similarly assessed muscle mass on CT. It showed that patients with myopenia had a significantly higher need for rescue therapy (40.9% vs. 23.6%, $P = 0.003$) and a need for surgery (22.0% vs. 7.1%, $P = 0.001$). Still, the same did not stand true for those who were malnourished and well nourished; myopenia rather than BMI was an important determinant of the above outcomes and myopenia remained an independent risk factor for rescue therapy (OR: 4.079, 95% CI: 2.245–7.412, $P < 0.001$) and colectomy (OR: 1.985, 95% CI: 1.028–3.834, $P = 0.041$).[100]

Response to therapy. In a retrospective analysis of IBD patients, patients on Anti TNF therapy were analyzed after a median period of 24 months; those with skeletal muscle area less than the median value of the study group had greater rates of therapy failure than those with muscle area greater than the

median value (61.7% vs. 27.6%, $P = 0.014$).[102] Another 5-year follow-up study of IBD patients initiated on Anti TNF noted that skeletal muscle index (measured on CT) noted that SMI was an independent risk factor for secondary failure (HR: 2.15, 95% CI: 1.04–4.44, $P = 0.039$) and bowel resection (HR: 4.19, 95% CI: 1.01–17.3, $P = 0.048$).[110]

Surgery. In a retrospective study in patients with CD, myopenia (assessed on CT at L3) was found to be a risk factor for bowel resection on multivariate analysis in patients with CD, and in the post-op follow-up period, myopenia improved.[111] Another multicenter retrospective study of 187 IBD patients (CD-99, UC-89) showed that low psoas index (cross-sectional area of psoas at L3/height in m^2) on CT was a significant risk factor for both intestinal resection (OR: 0.754, 95% CI: 0.578–0.972, $P = 0.033$) and prolonged hospital stay (OR: 0.662, 95% CI: 0.480–0.883, $P = 0.004$) in both UC and CD cases.[94] Data from a single-center retrospective study in patients undergoing either elective or emergent surgery revealed that myosteatosis (muscle quality) rather than myopenia was associated with longer hospital stays (median duration: 13 vs. 10.5 days). On multivariate analysis, myosteatosis was an independent risk factor for readmission (OR: 4.803, 95% CI: 1.053–21.889, $P = 0.043$).[96] Another 5-year follow-up study on muscle quality, assessed on MRI, in patients with CD, showed that patients with lower muscle quality (lower intensity on MRI) had a significantly shorter resection-free period than those with higher muscle intensity on MRI ($P = 0.037$).[112] This suggests that muscle quality is an important parameter that needs to be taken into consideration and not muscle mass alone. This was addressed in the latest EWGSOP statement where they suggested a reduction in either muscle mass or quality for the diagnosis of sarcopenia.[76]

Role of IBD therapy on sarcopenia. In a retrospective study of patients admitted with ASUC, biological use was higher in patients without myopenia than in those with myopenia (7.9% vs. 0.8%, $P = 0.006$).[100] In another retrospective study of patients with CD, the median SMI values were significantly higher in those who were on Anti TNF therapy than those who were not ($P = 0.01$).[113] In a longitudinal cohort study on patients initiated on anti-TNF therapy, after a median follow-up of 5 years, there was a significant improvement in all the muscle parameters (skeletal muscle index; $P < 0.001$, skeletal muscle area; $P < 0.001$, psoas muscle area, $P = 0.03$) measured on CT.[114] In another retrospective study where the prevalence of myopenia was studied in patients who underwent surgery for IBD (surgical cohort) and who were initiated on biologics (medical cohort), after a follow-up period of 1 year, the prevalence of myopenia was higher in the surgical cohort when compared with the medical cohort (32% vs. 16%, $P < 0.02$).[115] The impact of biological use in IBD was also prospectively studied in patients with CD, where the assessment of muscle strength and mass was done at baseline and 25 weeks later and found that there was a significant improvement in both muscle strength ($P = 0.002$) and muscle mass ($P = 0.01$), and this gain was independent of steroid usage.[116]

Pediatric IBD. A study on the impact of Anti TNF therapy in pediatric IBD found that the skeletal muscle mass (as measured on Bioimpedance) at the end of induction and at the end of 6 months of therapy, the difference in skeletal muscle mass scores between the groups with and without sarcopenia had significantly reduced. However, there was no significant gain in muscle mass in the group who had no sarcopenia at the baseline.[117] Even in the pediatric group, there was a poor correlation between BMI and muscle mass, as shown in a cross-sectional study of 101 pediatric IBD cases; the psoas area index (average psoas area divided by body surface area) was significantly lower in children with IBD than those of controls ($P < 0.001$) and had a poor correlation with the BMI ($r = 0.019$). In the same study, they found out that PAI is associated with radiologically severe disease ($P = 0.03$) and is an important risk factor for the initiation of biological therapy (HR: 12.1, 95% CI: 1.4–104, $P = 0.023$) and disease exacerbation (HR: 8.9, 95% CI:1.5–53.1, $P = 0.016$).[118]

Interventions in IBD for sarcopenia

Nutrient supplementation. The recommended daily protein intake in IBD patients is 1 mg/kg/day for those who are in remission and 1.2–1.5 gm/kg/day for those with active disease.[119] These recommendations are not specific for those with sarcopenia but for IBD in general. There is still a lack of data on the effect of protein supplementation on muscle health in IBD patients. However, evidence from the meta-analysis of studies in the elderly had shown that protein supplementation along with physical activity had been shown to improve sarcopenia and frailty in the elderly.[72] Hence adequate protein consumption is of paramount importance for IBD patients, especially with sarcopenia. Additionally, data from pediatric IBD patients showed that daily supplementation of 2000 IU of cholecalciferol for a median period of 13.8 months showed improvement of both BMD and muscle power as compared with baseline.[75]

Exercise. In a pilot study in patients with Crohn's disease with quiescent or mild disease activity endurance and muscle training for 3 months had been shown to improve muscle strength and quality of life without improvement in disease activity.[120] In patients with childhood-onset IBD, physical exercise for 12 months showed that there was improvement in bone mineral density (BMD) and body composition as compared with the sedentary controls.[121] Similar outcomes were seen in pediatric IBD patients in remission, where moderate to vigorous physical activity had a significant positive correlation with BMD and lean body mass.[122] In an RCT of Crohn's disease patients who were randomized to either a resistance and impact training program or a sedentary life for 6 months, at the end of the study period patients who were in the exercise program had significantly higher BMD and muscle function than control.[123]

In addition to these measures, as discussed above, controlling the underlying disease activity would lead to an improvement in muscle mass.

Summary and recommendations

Frailty and sarcopenia are important measures for adverse outcomes in the elderly. Growing evidence in the field of IBD has shown that irrespective of age, frailty and sarcopenia have poor

outcomes on several aspects of the disease including activity, response to therapy, post-op outcomes, and overall mortality. Also, measuring overall well-being is an important outcome in several interventions related to IBD, of which sarcopenia and frailty are important contributors. However, the relationship between frailty, sarcopenia, and IBD remains poorly studied. The available data suggest that both frailty and sarcopenia are prevalent in those with active disease. From the existing evidence, we can logically conclude that the existence of frailty and sarcopenia in individuals with IBD is associated with poorer outcomes. Hence this should trigger us to identify at-risk individuals with IBD and screen them with appropriate tools. However, there are no specific recommendations on how to screen, when to screen, how frequently to screen, and how to intervene. Emerging data suggest that in individuals with IBD who were found to have sarcopenia or frailty, an inverted pyramid approach may be considered. The use of the most effective therapies (biologicals) being offered upfront could positively impact sarcopenia. There are still several lacunae in the available evidence as to the role of steroids in frail or sarcopenia with IBD, as steroids are known to positively modify the disease activity and yet negatively affect the musculoskeletal system as a result worsening both frailty and sarcopenia. There is no good grade of evidence to back up interventions targeting sarcopenia and frailty resulting in improvement of the disease outcomes, hence it cannot be recommended. But in total, the approach is to be wholesome, clinicians should be aware of the negative influences of sarcopenia and frailty on disease activity and outcomes and have an active lookout for it. It can be done opportunistically in patients who have undergone abdominal CT scans for the assessment of IBD or identifying the at-risk individuals with simple parameters or tests like handgrip strength or timed up-and-go tests. The role of aggressive management of active disease and interventions aimed at improving the muscle strength in such individuals should be actively studied as prospective data backing such approach are lacking.

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