Title: Patients with inflammatory bowel disease have higher abdominal adiposity and less skeletal mass than healthy controls.

Running title: Abdominal body composition in IBD

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What is already known about this subject?

- Patients with inflammatory bowel disease often have altered body composition.
- The type and distribution of abdominal fat has been associated with complicated disease and poor postoperative outcomes in patients with inflammatory bowel disease.

What are the new findings?

- In patients with treatment refractory inflammatory bowel disease, abdominal body composition is characterised by excessive fat deposition and skeletal muscle deficits.
- Physiological relationships between skeletal muscle mass with subcutaneous and visceral abdominal fat do not apply in inflammatory bowel disease or are reversed in such patients.
- A larger body size is anticipated for the same anthropometry in patients with inflammatory bowel disease than healthy controls.
- Pre-operative abdominal body composition is not predictive of post-operative outcomes.

Abstract

Background: Abdominal fat type and distribution have been associated with complicated Crohn's disease and adverse post-operative outcomes. There is a scarcity of studies which have assessed the abdominal distribution of fat and lean stores in patients with inflammatory bowel disease (IBD) and compared this with healthy controls.

Objective: This retrospective study aimed to compare the abdominal body composition in IBD patients who failed medical treatment and who had Computed tomography (CT) imaging prior to gastrointestinal surgery with healthy controls. Associations between pre-operative abdominal body composition and post-operative outcomes within a year of surgery were explored.

Participants/setting: Abdominal body composition was performed in 22, pre-surgical patients with medically refractory IBD (18 with Crohn's disease) and 22 healthy controls, using routinely acquired CT. Total fat, subcutaneous fat, visceral fat, and skeletal muscle cross-sectional area were measured.

Results: An independent disease effect was also observed explaining a fat deposition excess of 38 cm^2 and a skeletal muscle deficit of 15 cm^2 in IBD. Abdominal skeletal muscle correlated with visceral fat, for the control (rho=0.51, p=0.015), but not for the IBD group (rho=-0.13, p=0.553). A positive correlation observed between subcutaneous fat with skeletal muscle in the controls (rho=0.47, p=0.026), was reversed in the IBD group (rho=-0.43, p=0.045). Pre-operative abdominal body composition was not predictive of post-operative outcomes.

Conclusions: A higher degree of abdominal adiposity, less skeletal mass and a larger body size is anticipated for the same anthropometry in IBD patients. Pre-operative abdominal body composition is not associated with surgical outcomes.

Keywords: Inflammatory bowel disease, computed tomography, body composition

Introduction

Alterations in the body composition of patients with IBD have been previously described from studies using bioelectrical impedance analysis and dual x-ray absorptiometry [1]. However, as conventional body composition constants, such as hydration level of lean mass, have been developed in health, but differ in IBD [2], methods (e.g. DXA, impedance, double labelled water) which consider these constants in the calculation of body composition might produce erroneous results.

There are limited studies which have explored the segmental distribution of fat and lean stores in people with IBD using more sophisticated techniques. This is of particular importance as abdominal fat type and distribution has associated with aggressive disease [3] and infectious complications following bowel resection in Crohn's disease [4]. In a recent retrospective study, abdominal myopenia was associated with primary nonresponse to biologics [5].

Computed tomography (CT) and magnetic resonance imaging are routinely undertaken in clinical practice in IBD patients. A CT scan obtained at the third lumbar vertebrae offers the possibility to measure directly body compartments such as abdominal skeletal muscle mass, subcutaneous and visceral adipose tissue [6,7].

The primary aim of this study was to assess the abdominal body composition characteristics in a group of IBD patients who have failed medical treatment and have had a CT scan prior to gastrointestinal surgery. A secondary aim was to explore associations between pre-operative abdominal body composition and post-operative outcomes, within a year of IBD surgery.

Subjects and methods

Participants

The electronic pathology database from the NHS of Greater Glasgow & Clyde was searched for all IBD patients who had undergone a gastrointestinal surgery for medically refractory IBD between the periods 2012 to 2013. The medical records were then searched to identify patients who underwent a pre-operative CT scan of abdomen and 22 (18 with Crohn's disease and four with ulcerative colitis) were identified with anthropometry measurements available (Table 1). Disease characteristics, disease phenotype, prescribed medication and information on post-operative complications and incidence of clinical relapse within 12 months of operation were collected from the medical notes of the IBD participants (Table 1). Data on the postoperative complications were collected via review of the original surgical notes and notes of any surgical readmissions over the ensuing 12 months. The IBD patients had raised median concentration of CRP and low median serum albumin, indicating active systemic inflammatory response (Table 1). Two (9%) IBD patients had a BMI below 18.5 kg/m^2 (underweight) and two (9%) were obese (BMI>30 kg/m2).

A cohort of 22, patients who had CT studies due to acute abdominal pain and in whom no chronic or inflammatory pathology was found, was used as a control group. This group was selected from the same pathology database as the IBD group. None in the control group was underweight and 8 (36%) were obese (Table 1).

As this is a retrospective analysis of existing clinical data, no ethical committee review was required according to National Research Ethics Service guidance [8].

Assessment of body composition

Abdominal body composition was performed using CT images at the third lumbar vertebrae level. The images were analysed by two raters independently, as described previously [7]. In brief, the two raters defined the margins of the cross-sectional area (cm^2) of each abdominal body composition compartment using the freeware program NIH ImageJ (version 1.48). Total fat (excluding intramuscular fat), subcutaneous fat, visceral fat, visceral-to-subcutaneous fat ratio and skeletal muscle cross-sectional area [3] were identified using the Hounsfield unit (HU) thresholds (adipose tissue: -190 to -30; muscle: -29 to +150) [7]. An example is presented in Figure 1.

Statistical analysis

Differences in body composition compartments between the two groups were assessed with forward stepwise multivariate regression analysis. Univariate regression analysis was performed separately for each of the body composition compartments using *a priori* selected predictors (height, BMI, age and gender). Participant's condition (i.e. control or IBD) was a fixed term. Predictors with a p-value<0.1 were entered one-by-one in the multivariate model, starting with the one which was the most significant in univariate analysis. A final model was produced which included only significant predictors and the participant's condition (i.e. control or IBD); thus the independent effect of IBD on body composition could be explored controlling at the same time for the effect of other confounders such as age, height, gender and BMI. Correlations among composition characteristics were explored with Spearman rho correlation. Associations between body composition with short-term post-operative complications and a clinical relapse event within 12 months of IBD surgery were explored with logistic regression analysis.

Results

Predictors of abdominal body composition characteristics and the effect of IBD

In multivariate analysis, BMI was the strongest positive predictor of visceral and subcutaneous fat and so was height for skeletal mass (Table 2). Each unit of BMI increase was associated with 9.4 of visceral and 10.7 cm^2 increase of subcutaneous fat respectively. No such effect was found for skeletal muscle. Age was positively associated with visceral and subcutaneous fat (Table 2) and gender with skeletal muscle (Table 2). Females had on average 45 cm^2 less muscle than males (Table 2).

An independent effect of the participant's condition (i.e. IBD or control) was observed for subcutaneous fat and skeletal muscle but not for visceral fat (Table 2). After accounting for the effect of other confounders, an excess of 38 cm^2 for subcutaneous fat and a deficit of 15 cm^2 for skeletal muscle mass was observed in IBD people compared with controls (Table 2). There were no significant correlations between the abdominal body composition characteristics of the IBD patients with measurements of plasma CRP or serum albumin (all $p>0.05$).

Relationships among abdominal body composition characteristics

Relationships between abdominal body composition characteristics are displayed in Figure 2. Visceral fat was positively correlated with subcutaneous fat for both groups (IBD: rho=0.62, p=0.002) vs Controls: rho=0.61, p=0.002). Abdominal skeletal muscle was positively associated with visceral fat for the control group only (IBD: rho=-0.13, p=0.553) vs Controls: rho=0.51, p=0.015). While a positive correlation was observed

between subcutaneous fat with skeletal muscle in the controls (rho=0.47, p=0.026), this relationship was reversed in IBD patients (rho=-0.43, p=0.045) (Figure 2).

Pre-operative abdominal body composition characteristics and risk of post-operative complications and subsequent clinical relapse

Eight participants (38%) presented a post-operative complications with the majority of them being wound infections (n=5), followed by anastomosis leak (n=2) and pelvic abscess (Table 1). Four patients relapsed within 12 months of operation. None of the abdominal body composition characteristics was predictive of an increased risk of post-operative complications or a subsequent clinical relapse within 12 months of surgery (Table 3).

Discussion

Patients with medically refractory IBD were characterised by deficits in abdominal skeletal muscle mass and an accrual of subcutaneous fat. No alterations were observed with regard to visceral fat. Together, these abdominal body composition characteristics are suggestive of features of nutritional cachexia similar to those seen in other inflammatory conditions, like cancer [9] and can be attributed to undernutrition, the effect of pro-inflammatory cytokines and steroid treatment [10].

The relationship between skeletal muscle and the two adipose tissue compartments, seen in controls, was absent or reversed in IBD. The exact mechanism of this association is unknown but it is likely to be multifactorial and to involve diminished physical activity in patients with active IBD, the effect of inflammatory cytokines on muscle mass[11] and protein metabolism[12], the excessive use of steroids or a primary role of visceral fat in the initiation of colonic inflammation [13,14]. A previous study showed that normalisation of BMI at 2 years follow-up was not been associated with an increment in fat free mass CD [15] and collectively this evidence suggests that BMI change might not be good proxy for body alterations in IBD.

The clinical significance of these results should also be evaluated in the context of their ability to predict clinical outcomes. Previous research suggested an association between the visceral-to-subcutaneous fat ratio with post-operative complications [4] and disease severity [3] but this was not replicated in this small retrospective study of patients with medically refractory disease, prior to gastrointestinal surgery. Patients with IBD are at a higher risk of adverse cardiovascular events [16] than the general population and based on the current findings, a higher degree of abdominal adiposity for a given BMI than healthy individuals should be expected. Thus clinical attention should

be given to the avoidance of overnutrition, particularly now that the epidemic of obesity is becoming common in IBD [17]. It might be that the focus on the dietetic support of IBD patients should be extended from the management of undernutrition to the prevention and correction of obesity and interventions with physical activity and exercise to improve muscle mass.

The strength of this study is the inclusion of an essentially healthy control group for first time [3,4], as well as the direct and independent assessment of each of the abdominal compartments. This is a major advantage compared to previous studies in IBD where measurement error in one body compartment might have propagated to the estimation of the others [1]. The main limitations are the small sample size, the heterogeneous patient population in terms of disease characteristics and the retrospective design of the study. Use of concomitant treatment following surgery may have also influenced the risk of post-operative complications and subsequent clinical relapse. Also, our control group was younger and had higher BMI than our IBD patients, which may have confounded the results of this study. However, instead of stratifying our analysis by these confounders, which would have compromised further statistical power and increase bias due to multiple testing, we chose to apply multivariate regression modelling to control for their effect. A lack of a biological association between adipose tissue with gender was not observed, but not unexpectedly, as our analysis was performed in a cross-section of the abdomen, and expressed in units of area, rather than as a percentage of the total area.

Conclusions

Abdominal body composition characteristics in this study highlight the incidence of sarcopenia in medically refractory IBD patients. The significance of these findings in terms of clinical disease course and long-term outcomes of IBD should be explored in future prospective studies, particularly now that radiation-free MRI assessment is becoming more accessible and affordable. This study has clear implications for the nutritional assessment and management of people with IBD.

253 **Figure Legends**

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255 **Figure 1:** Abdominal body composition analysis using NIH ImageJ

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257 *Panels: (a) The original CT image (b) the scale is set at a known distance (10 cm) from*
258 *the original image, (c) definition of the total body fat area, applying the thresholds (-*
259 *190 to -30 HU) (d) definition of skeletal muscle area, after cropping the abdominal*
260 *contents and L3 vertebrae and applying the thresholds (-29 to + 150 HU).*

261

262 **Figure 2:** Correlations among abdominal body characteristics in people with IBD and
263 controls (blue circles: controls, brown squares: IBD)

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265 *Panels: (a) Subcutaneous fat vs skeletal muscle: IBD: (rho: -0.43, p=0.045) vs*
266 *Controls: (rho: 0.47, p=0.026); (b) Visceral fat vs skeletal muscle: (rho: -0.13,*
267 *p=0.553) vs Controls (rho: 0.51, p=0.015); (c) Subcutaneous fat vs visceral fat; IBD:*
268 *(rho: 0.61, p=0.002) vs Controls: (rho: 0.62, p=0.002)*

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325 **Table 1:** Participants characteristics

	IBD (n=22)	**Healthy Controls (n=22)**	**p-value**
*Disease location, n			
L1	6		
L2	8		
L3	4		
E1	1		
E2	1		
E3	2		
*Disease behaviour, n			
B1	6		
B2 + B2p	10		
B3 + B3p	6		
Treatment, n			
Aminosalicylates	13		
Steroids	16		
Thiopurines	7		
Biologics	7		
Type of surgery, n			
CD; colectomy	6		
CD; right hemicolectomy	9		
CD; left hemicolectomy	2		
CD; limited small bowel	1		
UC; subtotal colectomy	4		
Sex, males:females, n	12:10	12:10	1.000
[a]Age, years	47.5 (33:63)	39.5 (30.8:45.5)	0.045

[a]BMI, kg/m^2	23.6 (20.2:26.8)	27.3 (22.8:34.0)	0.037
[a]Height, m^2	166.0 (156:175)	171 (165:180)	0.078
[a]Albumin, g/L	25 (23.0:30.5)		
[a]Haemoglobin, g/L	104.5 (98.5:121.2)		
[a]C-reactive protein, mg/L	66 (20:142)		
Post-operative complications	8		
Wound infection	5		
Anastomotic leak	2		
Pelvic abscess	1		
Number relapsed at 12 months	4		

[a] Median (inter-quartile range); CD: Crohn's disease; UC: Ulcerative colitis; * disease phenotype based on the Montreal classification.

Table 2: Multivariate regression analysis of predictors of CT based abdominal body composition characteristics

	Visceral fat (cm^2)	**Subcutaneous fat (cm^2)**	**Skeletal muscle (cm^2)**	**Visc-to-subc ratio**	**Total fat (cm^2)**
			β coefficient; p-value		
Gender, males	NS	NS	30; p<0.001	0.3; 18%; p=0.004	NS
Age, years	1.6; p=0.004	1,1; p=0.038	NS	NS	2.7; p=0.001
BMI, kg/m^2	9.4; p=<0.001	10.7; p<0.001	NS	NS	20.1; p<0.001
Height, cm^2	NS	NS	153; p<0.001	NS	NS
Condition, IBD[a]	NS	38; p=0.035	-14.7; p=0.012	NS	62.7; p=0.019
R^2 of final model[b]	64%	65%	79%	18%	77%

NS: non-significant; [a] participant condition (IBD or controls) was a fixed term in both univariate and multivariate regression analysis; visc-to-subc fat ratio: ratio between visceral and subcutaneous fat area; [b] R^2 coefficient of determination

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336 **Table 3:** Pre-operative abdominal body composition characteristics and risk of post-
337 operative complications and subsequent clinical relapse at 12 months follow up

	Post-operative complications *Odd ratio, 95 CI*	**p-value**	**Relapse within 12 months** *Odd ratio, 95% CI*	**p-value**
Visceral fat	1.00 (0.99 : 1.01)	0.433	1.00 (0.99 : 1.02)	0.386
Subcutaneous fat	1.00 (0.99 : 1.01)	0.557	1.00 (0.99 : 1.02)	0.401
Skeletal muscle	1.00 (0.98 : 1.02)	0.949	0.99 (0.96 : 1.03)	0.785
Visc-to-subc ratio	0.69 (0.06 : 8.6)	0.773	1.12 (0.06 : 21.7)	0.942
Total fat	1.00 (1.00 : 1.01)	0.472	1.00 (1.00 : 1.01)	0.372

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341 Figure 1
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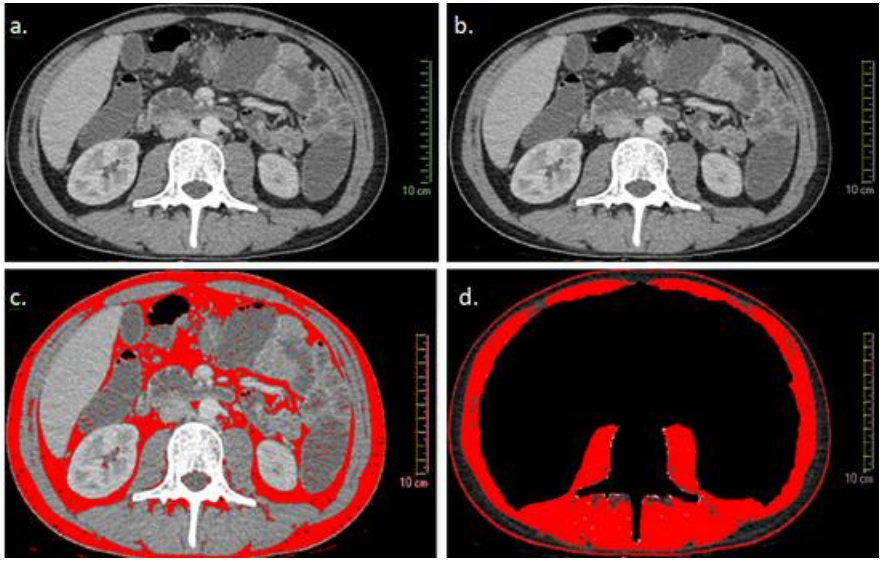

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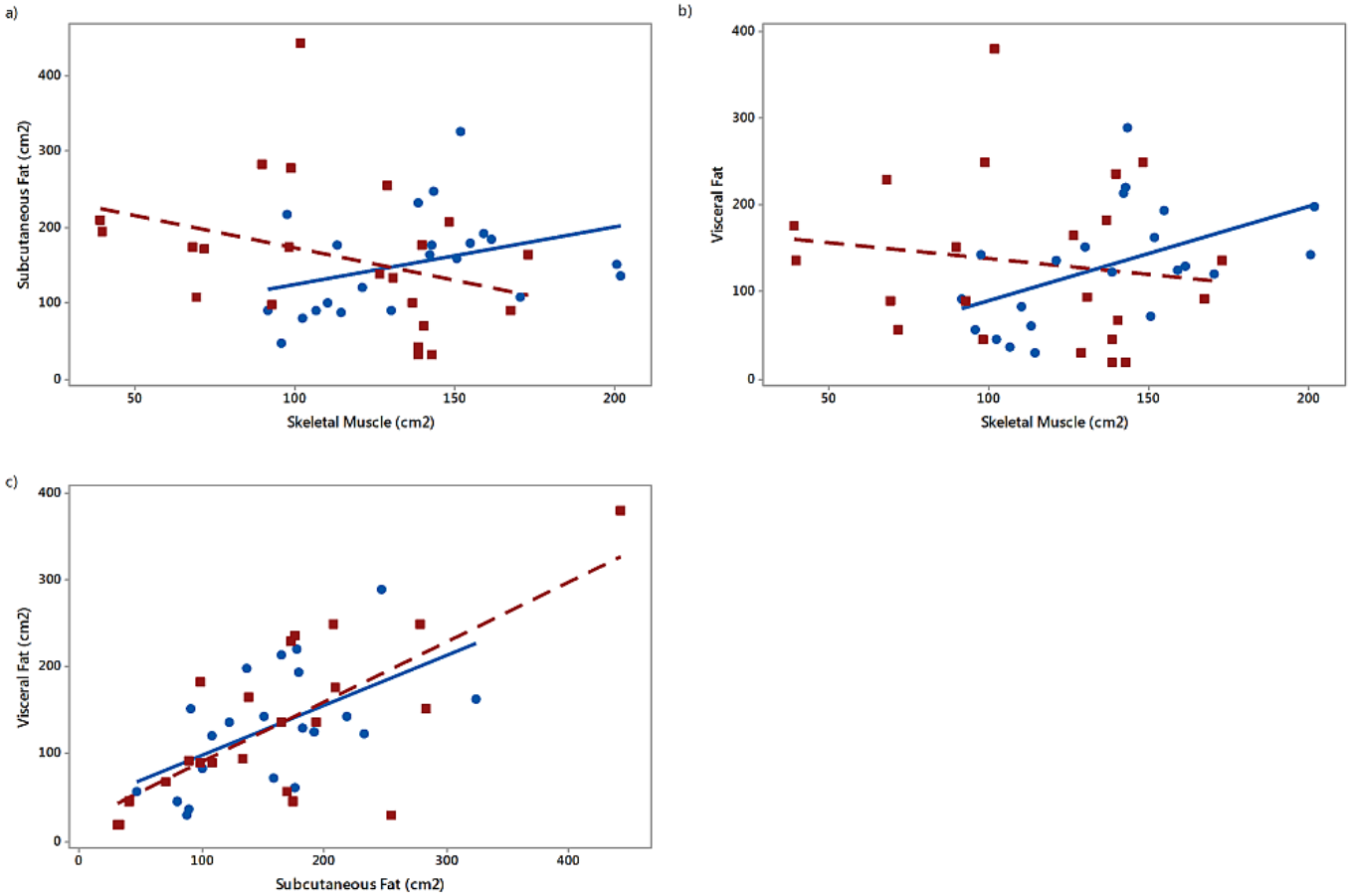
344 Figure 2



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