DR DARCY QUINN HOLT (Orcid ID : 0000-0001-7752-6279)

Received Date : 04-Nov-2016

Revised Date : 07-Feb-2017

Accepted Date : 07-Feb-2017

Article type : Original Scientific Paper

First decision date: 16-Nov-2016

Running head: Visceral adiposity predicts post-op CD recurrence

Visceral Adiposity Predicts Post-Operative Crohn's Disease Recurrence

Darcy Quinn Holt MBBS^{1,2}, Gregory Thomas Moore MBBS PhD^{1,2}, Boyd Josef Gimnicher Strauss MBBS PhD², Amy L Hamilton^{3,4}, Peter De Cruz MBBS PhD⁴, Michael A Kamm MD PhD^{3,4}

¹Department of Gastroenterology & Hepatology, Monash Health, Melbourne, Australia; ²Monash University, Melbourne, Australia; ³Department of Gastroenterology, St Vincent's Hospital, Melbourne, Australia; ⁴University of Melbourne, Melbourne, Australia

Address for correspondence:

Dr Darcy Holt

Department of Gastroenterology & Hepatology, Monash Health

246 Clayton Road, Clayton Victoria 3168, Australia

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/apt.14018](https://doi.org/10.1111/apt.14018)

This article is protected by copyright. All rights reserved

Visceral adiposity predicts post-op CD recurrence

darcy.holt@monashhealth.org

Telephone +61 3 95943177 Fax +61 3 95946250

Running title

Visceral adiposity predicts post-op CD recurrence

MeSH Key words

Crohn Disease, intra-abdominal fat, abdominal obesity, sarcopenia

Summary

Background

Excessive visceral adipose tissue has been associated with poorer outcomes in patients with inflammatory bowel disease.

Aim

We sought to determine whether body composition was associated with outcome in a prospective study of post-operative Crohn's disease patients.

Methods

The POCER study evaluated management strategies for prevention of post-operative Crohn's disease recurrence; subjects were enrolled after resection of all macroscopic Crohn's disease and were randomised to early endoscopy and possible treatment escalation, or standard care. The primary endpoint was endoscopic recurrence at 18 months. 44 subjects with cross-sectional abdominal imaging were studied, and body composition analysis performed using established techniques to measure visceral adipose tissue area, subcutaneous adipose tissue area, and skeletal muscle area.

Results

The body composition parameter with the greatest variance was **visceral adipose tissue**. Regardless of treatment, all subjects **with visceral adipose tissue**/height² > 1.5 times the gender-specific mean experienced endoscopic recurrence at 18 months, (compared to 47%) [relative risk 2.1, 95% CI 1.5-3.0, P = 0.012]. Waist circumference correlated strongly with **visceral adipose tissue area** ($\rho = 0.840$, P < 0.001). Low **skeletal muscle** was prevalent (41% of patients), but did not predict endoscopic recurrence; however appendicular **skeletal muscle** indices correlated inversely with faecal calprotectin ($\rho = 0.560$, P = 0.046).

Conclusions

Visceral adiposity was an independent risk factor for endoscopic recurrence of Crohn's disease after surgery. Sarcopenia correlated with inflammatory biomarkers. Measures of visceral adipose tissue may help to stratify risk in post-operative management strategies.

The POCER study was registered with ClinicalTrials.gov number NCT00989560.

Introduction

Visceral adipose tissue has distinct metabolic activity, cellular composition, inflammatory infiltrate and cytokine production¹. In Crohn's disease, **visceral adipose tissue** has a different profile of adipocytokine expression than in healthy controls, and is the main source of serum TNF- α ², which is a specific target of **Crohn's disease** treatment. Mesenteric "fat wrapping" of the intestine in **Crohn's disease** was recognised by Crohn as a feature of the condition³, and is disease-specific, correlating with transmural inflammation⁴. Inflammatory activity in the submucosal and stromal tissues has been

Visceral adiposity predicts post-op CD recurrence

implicated in post-operative **Crohn's disease** recurrence, with myenteric plexitis a described risk factor for recurrence⁵⁻⁸.

There is considerable variation in the anatomical deposition of fat among individuals of the same body mass index and same total fat mass^{9,10}, with cross-sectional abdominal imaging providing accurate measurement of fat area and volume¹⁰⁻¹³. Patients with **Crohn's disease** are known to have a higher ratio of intra-abdominal to total abdominal fat, and higher **visceral adipose tissue** area, than controls^{14,15}. Pro-inflammatory genes are up-regulated with increasing **visceral adipose tissue** volume¹⁶. In the obese state, **visceral adipose tissue** is infiltrated by inflammatory cells; adipose tissue macrophages can account for as much as 40 per cent of the cellular mass¹⁷. The pro-inflammatory milieu of an enlarged **visceral adipose tissue** compartment may predispose to recurrent **Crohn's disease** after surgery.

The majority of patients with Crohn's Disease will require surgery for the condition¹⁸, and recurrence after surgery is common, with 48-93% of patients having endoscopic lesions at 1 year post operation¹⁹. Optimal post-operative management to prevent recurrence has been the focus of much research. Identification of risk factors for relapse and appropriate escalation of therapy appear to improve outcomes and resource utilisation²⁰⁻²³.

Few patient-related factors have been identified as increasing risk of post-operative **Crohn's disease** recurrence; smoking status is the most recognised, conferring more than double the risk^{19,20,22}. In this study, we sought to determine whether body composition is a predictor of, and relates to, post-operative **Crohn's disease** recurrence in a cohort of patients who had resection of all macroscopic **Crohn's disease**.

Materials and Methods

The POCER study was a prospective, randomised controlled trial in post-operative **Crohn's disease** patients, examining the role of early endoscopic surveillance and treatment escalation for mucosal recurrence. **This study has**

been the source of a number of publications^{20,21,23-28}. Patients were enrolled after surgery for Crohn's disease with resection of all macroscopic disease. All patients received 3 months of metronidazole (400mg orally twice-daily; dose reduced or discontinued if not tolerated). Patients with prior resections, smokers or those with perforating disease also received azathioprine (2mg/kg/day) or 6-mercaptopurine (1.5mg/kg/day) unless intolerant – in which case, adalimumab at standard induction and maintenance doses was used. Patients were randomised 2:1 to colonoscopy 6 months post-operatively (active care) or no colonoscopy (standard care). If patients were on corticosteroids at study enrolment, they were tapered and ceased by week 12. Patients with endoscopic recurrence (Rutgeerts score²⁹ ≥ 2) at 6 months received treatment escalation: to thiopurine, thiopurine with fortnightly adalimumab, or weekly adalimumab as appropriate. The primary endpoint of the study was endoscopic recurrence at 18 months. Stool samples were collected at baseline (pre-operatively) and at 6, 12 and 18 months after surgery; markers of inflammation, including calprotectin, lactoferrin and S100A12 were assayed. Other clinical and biochemical data were collected at 6, 12 and 18-month time points. The study included 174 patients at 17 hospitals in Australia and New Zealand.

Subjects who had an abdominal CT or MRI within 12 months prior to enrolment at the primary POCER study site were identified by cross-reference with that site's radiology database. Scans had been performed as clinically appropriate and were not part of the study protocol, therefore only a subset of the POCER subjects were included in this analysis. Digital Imaging and Communications in Medicine images at L3 and L4-5 levels were imported and analysed for body composition using SliceOmatic 4.3 (TomoVision, Montreal, Canada) by a single experienced operator, who was blinded to study categories and treatments. An intra-observer coefficient of variation of 1.5% was recorded, consistent with ranges of 0.2%-3.4% cited in a validation study³⁰, which also found inter-investigator coefficient of variation 0.9%-4.8%. The data obtained were de-identified prior to further analysis. For CT images, Hounsfield unit (HU) ranges were used to differentiate between components of body composition; tissue from -30 to +150 HU was segmented as muscle.

Further correction and manual segmentation was performed according to tissue planes. For MRI scans, visual identification of tissue planes by the same operator was used to segment images. Analysis of this nature has been shown to provide similar results as CT analysis in the same subjects³¹, using software providing results interchangeable with SliceOmatic³². Visceral adipose tissue area, subcutaneous adipose tissue area and skeletal muscle area were calculated for the relevant segments. Ratios between these variables and patient height were calculated. Using previously described formulae³³, estimations were made of appendicular skeletal muscle indices (ASMI), total body fat mass and fat-free mass. Waist circumference was measured from images using a recognised technique³⁴.

Statistical considerations

Values for body composition parameters were expressed as a proportion of the gender-specific mean value for the cohort. Endoscopic outcomes were assessed at 18 months. Modified intention-to-treat analysis included patients who withdrew prior to 18 months with exit colonoscopy findings carried forward; patients without colonoscopy were assigned a Rutgeerts score of i2 (endoscopic recurrence).

Data were analysed with Prism 6 (GraphPad Software, La Jolla, CA) and SPSS statistics 24 (IBM Corp, Armonk, NY). A P value <0.05 was considered significant. Spearman correlation coefficients were calculated for nonparametric correlations. Mann-Whitney tests were used to analyse differences between means for categorical data. Contingency analysis was performed with Fisher's exact test. Receiver operator characteristic (ROC) curves were used to identify cut-off values between outcome categories.

Ethical considerations

This analysis of the POCER study dataset and acquisition and analysis of previously performed imaging studies was approved by the Human Research Ethics Committee of St Vincent's Hospital Melbourne (approval LRR: 054/15),

as was the original POCER study (approval HREC-A 077/09). The POCER study was registered with ClinicalTrials.gov number NCT00989560.

Results

Of the 66 subjects enrolled at the primary study site, 44 patients (67%) had imaging performed at that site, with available electronic images, prior to study entry. Of these, 33 had been assigned to active care, and 11 to standard care, with 10 patients withdrawing before 18 months (figure 1). Characteristics of the subjects are described in table 1. The median time between abdominal imaging and surgery was 56 days (IQR 22-127 days prior to surgery); 25 studies were CT scans and 19 were MRI. There was no difference in rates of endoscopic recurrence in groups divided according to indication for scan ($P = 0.928$). There were no differences in any anthropometric or body composition parameter between the high risk and low risk groups, nor between those randomised to endoscopy or standard care. In the endoscopy group, there was no statistically significant difference in body composition parameters between 8 patients who stepped up therapy and those who did not. Steroid use in the preoperative period was not associated with a difference in mean values of any body composition measurement or derivative, but was associated with a significantly smaller change in faecal calprotectin from baseline to 18 month measurements (mean change $-173\mu\text{g/g} \pm 964$ vs. $-1958\mu\text{g/g} \pm 1202$, $P = 0.013$). Preoperative steroid use (within 2 weeks of surgery) was also associated with a “high risk” categorisation ($P = 0.003$) and initial treatment with adalimumab ($P = 0.008$). The use of steroids was not different between those who had endoscopic recurrence (11/25) and those who did not (8/19, $P = 1.000$).

Relationships with adipose tissue

Mean values of body composition measurements are shown in table 2. The parameters with the greatest variance were the visceral adipose tissue area at L3 [expressed as a proportion of gender mean, with SD 0.909] and this value divided by height squared (“visceral adipose tissue/height index” [VHI]

[expressed as a proportion of gender mean, with SD 0.937]). Both exhibited an asymmetric distribution: there was significant rightwards skew (VHI 2.14) and excessive kurtosis. Other body composition parameters, such as BMI, did not demonstrate such variability or departure from a normal distribution (figure 2). Of this cohort of IBD patients, 29.5% had a BMI in the overweight or obese range, compared with 63.4% in the general Australian population³⁵.

Area under the ROC curve analysis showed VHI/gender mean was more sensitive and specific than visceral adipose tissue area, or visceral adipose tissue area/height², for detecting endoscopic remission, although this only became a discriminant at higher than mean values. A cut-off value of 1.5 times the mean was identified. All patients with visceral adipose tissue area, or VHI, >1.5 times the gender-specific mean were assigned endoscopic recurrence at 18 months (figure 2), whereas 47% of those with VHI >1.5 × (gender mean) had recurrence (relative risk 2.1 [CI 1.5-3.0], P = 0.012). Three subjects with VHI >1.5 × (gender mean) did not undergo endoscopy at the 18-month endpoint – all experienced clinical recurrence prior (at 4.7 months, 15.1 months and 17.3 months respectively). High/low risk status, randomisation outcomes, and drug treatments including step-up therapy were not significantly different between these patients and the remainder of the cohort. Early withdrawal rate did not vary significantly between these groups (P = 0.322).

Contingency analysis found that VHI >1.5 × (gender mean) was highly specific for endoscopic recurrence (100% [82%-100%]) with sensitivity of 29% (12%-51%). Positive predictive value was 1.00 (0.59-1.00) and negative predictive value 0.53 (0.35-0.70). Above a cut-off visceral adipose tissue area/height² value of 51cm²/m², all 8 patients had endoscopic recurrence (figure 2).

There was no relationship between other body composition parameters and outcome measures, disease activity indices or biochemical markers such as C-reactive protein or faecal calprotectin. There was no significant difference in

the mean CDAI at 18 months between those with VHI greater than or less than 1.5 times the gender mean (117.6 vs. 85.0, $P = 0.341$). 43% of those with $VHI > 1.5 \times$ (gender mean) had taken steroids at the time of surgery, this was the same proportion as those with $VHI \leq 1.5 \times$ (gender mean) [$P = 0.938$]. The mean VHI was not different between those who had not taken steroids and those who had ($30.99 \text{ cm}^2/\text{m}^2$ vs 35.60 , $P = 0.884$).

From chi-square analysis, the relative risk of recurrence in patients with excessive visceral adiposity (2.1) was similar to that of smokers in the sample selected in this analysis (RR 2.1 [1.2-3.6], $P = 0.015$).

Waist circumference (WC) strongly correlated with fat area measurements, in particular visceral adipose tissue area ($\rho = 0.840$, $P < 0.001$); however, in patients with visceral adipose tissue area > 1.5 times the gender mean, this correlation between visceral adipose tissue area and waist circumference was not significant. The range of WC measurements was much smaller than the range of VHI, with a more symmetrical distribution (skewness 0.93 vs. 2.35) and less kurtosis. The range of WC values as a proportion of gender mean was 0.77-1.38 (IQR 0.89-1.10), whereas the VHI range was 0.12-4.81 (IQR 0.37-1.28). This smaller variation and symmetrical distribution from the mean diminished the discriminative value of waist circumference in comparison to VHI, although all 4 patients with a waist circumference > 1.3 times the gender mean had endoscopic recurrence. Gender-specific WC cut-off values for prediction of recurrence could not be identified, but all 5 (3 female, 2 male) patients with $WC > 105\text{cm}$ experienced recurrence ($P = 0.060$).

Relationships with skeletal muscle

Low muscle mass was prevalent: 41% of patients had a calculated ASMI consistent with sarcopenia as defined by an appendicular skeletal muscle index less than two standard deviations below a young adult mean measured by whole body dual-energy X-ray absorptiometry^{36,37}. No patient had the combination of low muscle mass and obesity ("sarcopenic obesity"). Skeletal muscle area did not predict endoscopic outcomes. There was a moderate

inverse correlation between skeletal muscle area and faecal inflammatory markers (calprotectin, lactoferrin and S100A12) at baseline. Calculated ASMI also showed inverse correlation with faecal markers ($\rho = -0.564$, $P = 0.005$ for calprotectin; correlation coefficients and P values similar for other faecal markers [figure 3]). This relationship was consistent across the study duration, with an inverse correlation between ASMI and the change in calprotectin from baseline to 18 months ($\rho = 0.560$, $P = 0.046$) suggesting that increased muscle mass was associated with reduced intestinal inflammation regardless of treatment effects (figure 3). The mean baseline faecal calprotectin was significantly higher in patients with sarcopenia ($2570\mu\text{g/g} \pm 879$ vs. $1095\mu\text{g/g} \pm 1074$, $P = 0.003$).

Discussion

Identifying excessive visceral adipose tissue as a risk factor for post-operative Crohn's disease recurrence, regardless of treatment, in the setting of a prospective randomised study is a novel finding. As a proof of concept study, we chose an arbitrary measure of visceral adiposity with internal reference to describe the poorer outcomes experienced by subjects with a corrected visceral adipose tissue significantly higher than the median. The large range of values of VHI compared with anthropometric measures such as waist circumference allowed identification of statistically significant predictors of outcome within a small dataset. In the POCER study, smoking was identified as a risk for endoscopic recurrence with a relative risk of 2.8^{20} . Excessive visceral adiposity conferred a similar increase in relative risk in our analysis.

Lifetime steroid exposure was not assessed in this study, and the effect of steroid use on body composition parameters in the short term is not well-defined in patients with inflammatory diseases, with visceral adipose tissue accumulation being described as a characteristic of Crohn's disease, independent of steroid use^{14,38-40}.

Visceral adiposity predicts post-op CD recurrence

The prevalence of sarcopenia in this cohort of patients requiring surgery for complicated Crohn's disease was an expected finding, however, the association between low skeletal muscle mass and faecal calprotectin has not previously been described.

Successful risk stratification and appropriate perioperative management are key to preventing postoperative recurrence of Crohn's disease⁴¹, with previous studies associating increased hazard with patient and surgical parameters such as smoking, disease behaviour, resection length and history of previous resection¹⁹, serology^{28,42} and microbial factors²⁶. Prior steroid use has been associated with a reduced risk of post-operative recurrence in a meta-analysis⁴³. Individualised post-operative medical care based on risk factors, with early monitoring for recurrence and escalation of therapy if necessary, allows cost-effective management^{20-22,44,45}.

This study is limited by the post-hoc analysis of a sample of the entire study, with sample size preventing more rigorous subgroup regression analysis, including the role of body composition in drug efficacy and therapeutic monitoring. Although randomisation to active treatment, smoking status and excessive visceral adiposity were identified as variables contributing to risk of Crohn's disease recurrence, larger patient numbers and more data regarding prior therapy and surgical findings may have allowed more robust analysis of the interaction between these and other possibly contributory factors such as corticosteroid use, disease duration and extent of resection. Abdominal imaging was not part of the study protocol, and there was variation in the time between scan and surgery. However, we have previously shown that a strong correlation existed between body composition analysis using abdominal imaging obtained as part of routine clinical care, compared with dedicated whole body dual energy X-ray absorptiometry (DXA) studies performed at a different time in Crohn's disease patients; with scans performed a median 21 days (IQR 0-135 days) apart. Notably, there was no correlation between time between scans and difference between the values³³ suggesting that despite active intestinal inflammation or symptoms, body composition parameters remained stable over this period. Nevertheless, the strengths of a prospective

trial support the data obtained, with all subjects having no macroscopic disease at induction, defined follow-up and predetermined end points.

Our paper adds to a small, but growing, body of literature regarding the role of body composition in inflammatory diseases. Crohn's disease patients in clinical remission have been found three times more likely than healthy controls to have sarcopenia⁴⁶, with a recent systematic review⁴⁷ finding that body composition parameters often varied from population norms, including lower bone mineral density⁴⁸, lower body mass index (BMI) and lower fat-free mass^{49,50}. Expansion of the visceral adipose tissue compartment in Crohn's disease is also described, with a four-fold increase in adipocyte number compared to controls⁵¹ and an increased volume of visceral adipose tissue^{15,38,52}.

Measures of visceral adipose tissue have been associated with the likelihood of Crohn's disease recurrence in a retrospective cohort analysis of post-surgical patients⁵³. The current study validates those findings in a prospective study and in another ethnic population, their subjects exclusively being Han Chinese. In that study, a higher ratio of visceral adipose tissue to subcutaneous adipose tissue (mesenteric fat index) correlated with recurrence, consistent with another small retrospective study which demonstrated a higher incidence of penetrating or stricturing disease in patients with a higher mesenteric fat index⁵⁴. Visceral adiposity - but not BMI - was a risk factor for longer operative times, more blood loss, longer intestinal resection, more post-operative ileus and more complications overall in another retrospective cohort study using pre-operative CT scan to perform body composition analysis³⁹. We do not have data regarding these surgical factors in our study. An observational cohort study found that penetrating or stricturing Crohn's disease was associated with an increased visceral adipose tissue/fat mass ratio, and that a high visceral adipose tissue/fat mass ratio was associated with increased disease activity at followup¹⁵. High mesenteric fat index, but not BMI nor abdominal circumference, was associated with 30-day morbidity in a retrospective cohort of 143 patients⁵⁵. Conversely, a lower mesenteric fat index has been associated with more post-operative infectious

Visceral adiposity predicts post-op CD recurrence

complications in Crohn's disease⁵⁶. The mesenteric fat index or visceral adipose tissue/fat mass ratio were not associated with any of the outcome measures in our study.

Increased visceral adipose tissue is associated with alterations in gut microbial population ratios⁵⁷, with similar alterations present in inflammatory bowel disease^{58,59}. This interplay between an altered microbiota and host immune system is another possible mechanism of visceral adiposity being associated with Crohn's disease recurrence.

We found that inflammatory biomarkers showed an inverse correlation with skeletal muscle mass; although this has not previously been described with faecal calprotectin, in patients undergoing colorectal surgery for malignancy, low muscle mass was associated with higher serum calprotectin⁶⁰. While this association may be explained by the fact that inflammation and cachexia are catabolic states, causing reduced muscle mass, there may be a bidirectional influence. Skeletal muscle has been shown to exert an anti-inflammatory effect in inflammatory diseases through the action of myokines such as IL-6, IL-7 and IL-15^{61,62}.

In this analysis of a set of patients from a prospective interventional study, excessive visceral adiposity was an independent risk factor for endoscopic recurrence of Crohn's disease after surgery. Sarcopenia also correlated with elevations in faecal calprotectin. Further research may lead to validation of these findings and the integration of measures of visceral adipose tissue into post-operative management strategies.

Acknowledgements

Thanks is given to Dr Melissa Moore (St Vincent's Hospital Melbourne) for assistance with access to imaging studies and to Dr Suong Le (Monash Health) for statistical advice.

Authorship statement

Darcy Holt is the guarantor of this article. All authors devised the study. DH, AH, MK and PDC collected the data. DH performed the analysis and drafted the manuscript. All authors contributed to the critical review and revision of the manuscript. All authors approved the final version of the article, including the authorship list.

Conflicts of interest and sources of funding

This work was supported by Crohn's and Colitis Australia (the Angela McAvoy AM Fellowship to Gregory Moore). Darcy Holt has received an emerging researcher fellowship from Monash Health, and honoraria from AbbVie and Janssen. Peter De Cruz has received educational support, consulted on advisory boards, and been a speaker at educational symposia sponsored by Shire, Ferring, Janssen, Takeda, AbbVie, and Baxter. Peter De Cruz is supported by a David Bickart Clinician Research award from the University of Melbourne and Bushell Postdoctoral award from the Gastroenterological Society of Australia (GESA). Amy Hamilton is supported by an NHMRC Dora Lush post-graduate award and an Australian Government Research Training Program Scholarship. For the remaining authors, no conflicts of interest or sources of funding are declared.

Tables

Table 1 Characteristics of study participants

Female, n	24	54.5%
Age, y $\pm$ SD	37.8 $\pm$ 14.2	
Disease duration (mean $\pm$ SD)	5.5 $\pm$ 4.0	
BMI, kg/m ² (mean $\pm$ SD)	23.5 $\pm$ 4.9	
Initial post-operative drug therapy		
Metronidazole only	8 (17.8%)	
Thiopurine	26 (57.8%)	
Adalimumab	10 (22.2%)	
Steroid use, n	20	45.5%
Days between scan and surgery	56 (22-127)	

(median $\pm$ IQR)

Indication for scan, n

Active disease/inflammation	14
Obstructive/stricture	14
Penetrating/fistulising	6
Perianal disease	1
Information unavailable	9

Table 2 Mean values of body composition parameters (BMI: body mass index, VAT: visceral adipose tissue area, SAT: subcutaneous tissue area, IMAT: intermuscular adipose tissue area, SM: skeletal muscle area)

	Gender			Endoscopic outcome		
	Male	Female	P	Remission	Recurrence	P
	n = 20	n = 24		n = 19	n = 25	
Weight, kg (mean $\pm$ SD)	76.9 $\pm$ 13.0	65.1 $\pm$ 18.6	0.019	72.8 $\pm$ 14.8	68.8 $\pm$ 18.9	0.451
Height, m (mean $\pm$ SD)	1.80 $\pm$ 0.07	1.66 $\pm$ 0.08	<0.001	1.77 $\pm$ 8.39	1.70 $\pm$ 0.11	0.019
BMI, kg/m ² (mean $\pm$ SD)	23.66 $\pm$ 3.54	23.39 $\pm$ 5.87	0.855	23.12 $\pm$ 3.29	23.84 $\pm$ 5.89	0.614
Waist circumference, cm (mean $\pm$ SD)	89.0 $\pm$ 12.7	87.1 $\pm$ 15.0	0.65	87.9 $\pm$ 9.8	87.9 $\pm$ 16.5	0.995
VAT, cm ² (mean $\pm$ SD)	126.7 $\pm$ 106.0	75.2 $\pm$ 73.9	0.076	88.7 $\pm$ 49.5	106.1 $\pm$ 115.6	0.504
SAT, cm ² (mean $\pm$ SD)	122.5 $\pm$ 76.7	170.2 $\pm$ 132.4	0.144	149.9 $\pm$ 79.4	147.5 $\pm$ 133.2	0.942
IMAT, cm ² (mean $\pm$ SD)	6.7 $\pm$ 4.2	4.5 $\pm$ 3.2	0.056	6.2 $\pm$ 3.9	5.0 $\pm$ 3.8	0.310
SM, cm ² (mean $\pm$ SD)	155.4 $\pm$ 28.2	104.9 $\pm$ 20.7	<0.001	138.1 $\pm$ 37.1	120.0 $\pm$ 31.9	0.096

Figure legends

Figure 1 Trial profile and patient disposition

Figure 2 (A) Values for BMI (body mass index) were clustered around the gender-specific mean. VHI (visceral adipose tissue area/height²) exhibited a

greater range, with all subjects with VHI >1.5 times the gender mean demonstrating endoscopic recurrence; (B) All subjects with visceral adipose tissue area/height² (VHI) >51cm²/m² had endoscopic recurrence

Figure 3 (A) A negative association between calculated appendicular skeletal muscle index (ASMI) and faecal calprotectin existed, and (B) was consistent across the study period

References

1. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. *Nat Rev Immunol*. 2011 Feb 1;11(2):85–97.
2. Desreumaux P. Specific targeting of IL-6 signalling pathway: a new way to treat IBD? *Gut*. 2000 Oct 1;47(4):465–6.
3. Crohn BB, Ginzburg L, Oppenheimer GD. Regional ileitis; a pathologic and clinical entity. *Am J Med*. 1952 Nov 1;13(5):583–90.
4. Sheehan AL, Warren BF, Gear MW, Shepherd NA. Fat-wrapping in Crohn's disease: pathological basis and relevance to surgical practice. *Br J Surg*. 1992 Sep 1;79(9):955–8.
5. Ng SC, Lied GA, Kamm MA, Sandhu F, Guenther T, Arebi N. Predictive value and clinical significance of myenteric plexitis in Crohn's disease. *Inflamm Bowel Dis*. 2009 Sep 30;15(10):1499–507.
6. Decousus S, Boucher A-L, Joubert J, Pereira B, Dubois A, Goutorbe F, et al. Myenteric plexitis is a risk factor for endoscopic and clinical postoperative recurrence after ileocolonic resection in Crohn's disease. *Dig Liver Dis*. 2016 Mar 3;48(7):753–8.
7. Sokol H, Polin V, Lavergne-Slove A, Panis Y, Treton X, Dray X, et al. Plexitis as a predictive factor of early postoperative clinical recurrence in Crohn's disease. *Gut*. 2009 Aug 1;58(9):1218–25.
8. Bressenot A, Peyrin-Biroulet L. Histologic features predicting postoperative Crohn's disease recurrence. *Inflamm Bowel Dis*. 2015

Jan 31;21(2):468–75.

9. Matsuzawa Y. Establishment of a concept of visceral fat syndrome and discovery of adiponectin. *Proc Jpn Acad, Ser B*. 2010;86(2):131–41.
10. Yoshizumi T, Nakamura T, Yamane M, Islam AH, Menju M, Yamasaki K, et al. Abdominal fat: standardized technique for measurement at CT. *Radiology*. 1999 Apr 1;211(1):283–6.
11. Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge M-P, Albu J, et al. Visceral adipose tissue: relations between single-slice areas and total volume. *Am J Clin Nutr*. 2004 Aug;80(2):271–8.
12. Shen W, Wang Z, Punyanita M, Lei J, Sinav A, Kral JG, et al. Adipose tissue quantification by imaging methods: a proposed classification. *Obes Res*. 2003 Jan;11(1):5–16.
13. Mourtzakis M, Prado CMM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab*. 2008 Oct;33(5):997–1006.
14. Desreumaux P, Ernst O, Geboes K, Gambiez L, Berrebi D, Müller-Alouf H, et al. Inflammatory alterations in mesenteric adipose tissue in Crohn's disease. *Gastroenterology*. 1999 Jul;117(1):73–81.
15. Büning C, Kraft von C, Hermsdorf M, Gentz E, Wirth EK, Valentini L, et al. Visceral Adipose Tissue in Patients with Crohn's Disease Correlates with Disease Activity, Inflammatory Markers, and Outcome. *Inflamm Bowel Dis*. 2015 Nov;21(11):2590–7.
16. Osborn O, Olefsky JM. The cellular and signaling networks linking the immune system and metabolism in disease. *Nat Med*. 2012 Mar 6;18(3):363–74.
17. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante

- AW. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest*. 2003 Dec 1;112(12):1796–808.
18. Cosnes J, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology*. 2011 May;140(6):1785–94.
 19. Buisson A, Chevaux J-B, Allen PB, Bommelaer G, Peyrin-Biroulet L. Review article: the natural history of postoperative Crohn's disease recurrence. *Aliment Pharmacol Ther*. 2012 Mar;35(6):625–33.
 20. De Cruz P, Kamm MA, Hamilton AL, Ritchie KJ, Krejany EO, Gorelik A, et al. Crohn's disease management after intestinal resection: a randomised trial. *Lancet*. 2015 Apr 11;385(9976):1406–17.
 21. Wright EK, Kamm MA, De Cruz P, Hamilton AL, Ritchie KJ, Bell SJ, et al. Cost-effectiveness of Crohn's disease post-operative care. *World J Gastroenterol*. 2016 Apr 14;22(14):3860–8.
 22. De Cruz P, Kamm MA, Prideaux L, Allen PB, Desmond PV. Postoperative recurrent luminal Crohn's disease: a systematic review. *Inflamm Bowel Dis*. 2012 Apr;18(4):758–77.
 23. De Cruz P, Kamm MA, Hamilton AL, Ritchie KJ, Krejany EO, Gorelik A, et al. Efficacy of thiopurines and adalimumab in preventing Crohn's disease recurrence in high-risk patients - a POCER study analysis. *Aliment Pharmacol Ther*. 2015 Oct;42(7):867–79.
 24. De Cruz P, Bernardi MP, Kamm MA, Allen PB, Prideaux L, Williams J, et al. Postoperative recurrence of Crohn's disease: impact of endoscopic monitoring and treatment step-up. *Colorectal Dis [Internet]*. 2013 Feb;15(2):187–97.
 25. Wright EK, Kamm MA, De Cruz P, Hamilton AL, Ritchie KJ, Krejany EO, et al. Measurement of fecal calprotectin improves monitoring and detection of recurrence of Crohn's disease after surgery. *Gastroenterology*. 2015 May;148(5):938–947.e1.

26. Wright EK, Kamm MA, Wagner J, Teo S-M, Cruz PD, Hamilton AL, et al. Microbial Factors Associated with Postoperative Crohn's Disease Recurrence. *J Crohns Colitis*. 2016 Jul 27;:jjw136.
27. Wright EK, Kamm MA, De Cruz P, Hamilton AL, Ritchie KJ, Krejany EO, et al. Effect of intestinal resection on quality of life in Crohn's disease. *J Crohns Colitis*. 2015 Jun;9(6):452–62.
28. Hamilton AL, Kamm MA, De Cruz P, Wright EK, Selvaraj F, Princen F, et al. Serologic Antibodies in Relation to Outcome in Post-Operative Crohn's Disease. *Journal of Gastroenterology and Hepatology*. 2016 Dec 15.
29. Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. *Gastroenterology*. 1990 Oct;99(4):956–63.
30. Irving BA, Weltman JY, Brock DW, Davis CK, Gaesser GA, Weltman A. NIH ImageJ and Slice-O-Matic Computed Tomography Imaging Software to Quantify Soft Tissue. *Obesity*. 2007 Feb;15(2):370–6.
31. Kullberg J, Brandberg J, Angelhed J-E, Frimmel H, Bergelin E, Strid L, et al. Whole-body adipose tissue analysis: comparison of MRI, CT and dual energy X-ray absorptiometry. *Br J Radiol*. 2009 Feb;82(974):123–30.
32. Bonekamp S, Ghosh P, Crawford S, Solga SF, Horska A, Brancati FL, et al. Quantitative comparison and evaluation of software packages for assessment of abdominal adipose tissue distribution by magnetic resonance imaging. *Int J Obes Relat Metab Disord*. 2008 Jan;32(1):100–11.
33. Holt DQ, Strauss BJG, Lau KK, Moore GT. Body composition analysis using abdominal scans from routine clinical care in patients with Crohn's Disease. *Scand J Gastroenterol*. 2016 Jun 30;51(7):842–7.
34. Ciudin A, Salvador R, Budoy A, Ciudin A, Spinu C, Diaconu MG, et al.

Measurement of waist circumference for retrospective studies - prospective validation of use of CT images to assess abdominal circumference. *Endocrinol Nutr.* 2014 Mar;61(3):147–52.

35. Australian Health Survey: First Results, 2011-12. ausstats.abs.gov.au. Australian Bureau of Statistics; 2012 Oct. Report No.: 4364.0.55.001.
36. Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, et al. Epidemiology of sarcopenia among the elderly in New Mexico. *American Journal of Epidemiology.* 1998 Apr 15;147(8):755–63.
37. Gallagher D, Visser M, De Meersman RE, Sepúlveda D, Baumgartner RN, Pierson RN, et al. Appendicular skeletal muscle mass: effects of age, gender, and ethnicity. *J Appl Physiol.* 1997 Jul;83(1):229–39.
38. Katznelson L, Fairfield WP, Zeizafoon N, Sands BE, Peppercorn MA, Rosenthal DI, et al. Effects of growth hormone secretion on body composition in patients with Crohn's disease. *J Clin Endocrinol Metab* [Internet]. 2003 Nov;88(11):5468–72.
39. Ding Z, Wu XR, Remer EM, Lian L, Stocchi L, Li Y, et al. Association between high visceral fat area and postoperative complications in patients with Crohn's disease following primary surgery. *Colorectal Dis.* 2016 Feb 2;18(2):163–72.
40. Funt SA, Krinsky G, Horowitz L. Clinical image. MR demonstration of submucosal fat in a patient with Crohn's disease. *J Comput Assist Tomogr.* 1996 Nov;20(6):940–1.
41. Jones GR, Kennedy NA, Lees CW, Arnott ID, Satsangi J. Systematic review: The use of thiopurines or anti-TNF in post-operative Crohn's disease maintenance--progress and prospects. *Aliment Pharmacol Ther.* 2014 May 31;39(11):1253–65.
42. Prideaux L, De Cruz P, Ng SC, Kamm MA. Serological antibodies in inflammatory bowel disease: A systematic review. *Inflamm Bowel Dis.*

2011 Nov 8.

43. Pascua M, Su C, Lewis JD, Brensinger C, Lichtenstein GR. Meta-analysis: factors predicting post-operative recurrence with placebo therapy in patients with Crohn's disease. *Aliment Pharmacol Ther.* 2008 Aug 31;28(5):545–56.
44. Regueiro M, Feagan BG, Zou B, Johanns J, Blank MA, Chevrier M, et al. Infliximab Reduces Endoscopic, but Not Clinical, Recurrence of Crohn's Disease After Ileocolonic Resection. *Gastroenterology.* 2016 Jun;150(7):1568–78.
45. Bodini G, De Cassan C, Savarino V, Savarino E. Letter: biological therapies are effective for prevention of post-operative Crohn's disease recurrence. *Aliment Pharmacol Ther.* 2014 Jul 31;40(3):322–2.
46. Schneider SM, Al-Jaouni R, Filippi J, Wiroth J-B, Zeanandin G, Arab K, et al. Sarcopenia is prevalent in patients with Crohn's disease in clinical remission. *Inflamm Bowel Dis.* 2008 Nov;14(11):1562–8.
47. Bryant RV, Trott MJ, Bartholomeusz FD, Andrews JM. Systematic review: body composition in adults with inflammatory bowel disease. *Aliment Pharmacol Ther.* 2013 Aug;38(3):213–25.
48. Bernstein CN, Leslie WD, Leboff MS. AGA technical review on osteoporosis in gastrointestinal diseases. *Gastroenterology.* 2003 Mar;124(3):795–841.
49. Bryant RV, Ooi S, Schultz CG, Goess C, Grafton R, Hughes J, et al. Low muscle mass and sarcopenia: common and predictive of osteopenia in inflammatory bowel disease. *Aliment Pharmacol Ther.* 2015 Mar 5;41(9):895–906.
50. Tjellesen L, Nielsen PK, Staun M. Body composition by dual-energy X-ray absorptiometry in patients with Crohn's disease. *Scand J Gastroenterol.* 1998 Sep;33(9):956–60.

51. Peyrin-Biroulet L, Chamaillard M, Gonzalez F, Beclin E, Decourcelle C, Antunes L, et al. Mesenteric fat in Crohn's disease: a pathogenetic hallmark or an innocent bystander? *Gut*. 2007 Apr 1;56(4):577–83.
52. Thangarajah D, Chappell KE, Gale C, Parkinson JR, Epstein J, Hyer W, et al. P415 MRI assessment of body composition in paediatric Crohn's disease; intra-abdominal adipose tissue association with disease severity. *J Crohns Colitis*. 2014;8:S239.
53. Li Y, Zhu W, Gong J, Zhang W, Gu L, Guo Z, et al. Visceral fat area is associated with a high risk for early postoperative recurrence in Crohn's disease. *Colorectal Dis*. 2015 Mar;17(3):225–34.
54. Erhayiem B, Dhingsa R, Hawkey CJ, Subramanian V. Ratio of visceral to subcutaneous fat area is a biomarker of complicated Crohn's disease. *Clin Gastroenterol Hepatol*. 2011 Aug;9(8):684–687.e1.
55. Connelly TM, Juza RM, Sangster W, Sehgal R, Tappouni RF, Messaris E. Volumetric fat ratio and not body mass index is predictive of ileocelectomy outcomes in Crohn's disease patients. *Dig Surg*. 2014;31(3):219–24.
56. Stidham RW, Waljee AK, Day NM, Bergmans CL, Zahn KM, Higgins PDR, et al. Body Fat Composition Assessment Using Analytic Morphomics Predicts Infectious Complications After Bowel Resection in Crohn's Disease. *Inflamm Bowel Dis*. 2015 Mar 27;:1.
57. Abdou RM, Zhu L, Baker RD, Baker SS. Gut Microbiota of Nonalcoholic Fatty Liver Disease. *Dig Dis Sci*. Springer US; 2016 Feb 22;61(5):1268–81.
58. Albenberg LG, Wu GD. Diet and the intestinal microbiome: associations, functions, and implications for health and disease. *Gastroenterology*. 2014 May;146(6):1564–72.
59. Wu GD, Bushman FD, Lewis JD. Diet, the human gut microbiota, and IBD. *Anaerobe*. 2013 Dec;24:117–20.

60. Reisinger KW, Derikx JPM, van Vugt JLA, Meyenfeldt von MF, Hulsewé KW, Olde Damink SWM, et al. Sarcopenia is associated with an increased inflammatory response to surgery in colorectal cancer. *Clin Nutr*. 2016 Aug;35(4):924–7.
61. Benatti FB, Pedersen BK. Exercise as an anti-inflammatory therapy for rheumatic diseases-myokine regulation. *Nat Rev Rheumatol*. 2014 Nov 25.
62. Pedersen BK. Exercise-induced myokines and their role in chronic diseases. *Brain Behavior and Immunity*. Elsevier Inc; 2011 Jul 1;25(5):811–6.

Author Manuscript

apt_14018_f3.eps

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Holt, DQ;Moore, GT;Strauss, BJG;Hamilton, AL;De Cruz, P;Kamm, MA

Title:

Visceral adiposity predicts post-operative Crohn's disease recurrence

Date:

2017-05-01

Citation:

Holt, D. Q., Moore, G. T., Strauss, B. J. G., Hamilton, A. L., De Cruz, P. & Kamm, M. A. (2017). Visceral adiposity predicts post-operative Crohn's disease recurrence. ALIMENTARY PHARMACOLOGY & THERAPEUTICS, 45 (9), pp.1255-1264. <https://doi.org/10.1111/apt.14018>.

Persistent Link:

<http://hdl.handle.net/11343/292494>