Title:

Visceral adipose tissue is associated with stricturing Crohn's disease behaviour, faecal calprotectin and quality of life.

Running title: VAT in Crohn's disease

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ABSTRACT (248 words)**Background and Aims**

Visceral adipose tissue (VAT) has been proposed to play a pathogenic role in Crohn's disease (CD), however prospective data are lacking. The aim was to evaluate whether VAT is associated with CD behaviour, disease activity, quality of life (QoL) or outcomes.

Methods

Body composition data, clinical, anthropometric, disease activity (C-reactive protein (CRP) and faecal calprotectin (FC)) and QoL scores were gathered prospectively on adults with CD at 0, 12 and 24 months. VAT metrics including VAT: subcutaneous adipose tissue (SAT) ratio were calculated. IBD-related surgery and hospitalisation were recorded over extended follow-up (median 51 months). Multivariable linear mixed effects and logistic regression analyses were performed.

Results

Ninety-seven participants were assessed at baseline (55% male, median age 31 years), 84 at 12 and 72 at 24 months. Serial VAT:SAT measurements over 24 months were higher in those with stricturing CD behaviour at enrolment ($\beta=0.83$, 95%CI=[0.04,0.71], $p=0.03$). Higher serial VAT:SAT was also associated with elevated FC in patients with ileocolonic disease ($\beta=0.83$, 95%CI=[0.27,1.4], $p=0.004$) and lower QoL in those with ileal disease ($\beta=-4.5$, 95%CI=[-9.1, 0.09], $p=0.05$). However, no prospective associations were observed between serial VAT measurements and time to surgery or hospitalisation. No correlations were found between body mass index and disease behaviour, activity, or QoL.

Conclusions

VAT, rather than total body fat, is associated with stricturing CD behaviour, as well as elevated FC and reduced QoL in a disease distribution-dependent manner. The findings support the hypothesis that VAT plays a pathogenic role in CD.

Key words

Visceral adipose tissue, obesity, fat, body composition, Crohn's disease, inflammatory bowel disease

INTRODUCTION

Intestinal mesenteric fat wrapping or ‘creeping fat’ was first described by Burrill Crohn and colleagues as an important and disease-specific feature of ‘regional ileitis’.⁽¹⁾ Mesenteric fat accumulation occurs early in the course of CD and is evident in most small bowel resection specimens.^(2, 3) More than an innocent bystander, mesenteric adipocytes are a source of pro-inflammatory cytokines in CD, including tumour-necrosis factor-alpha (TNF- α), peroxisome proliferator-activating receptor-gamma, and interleukin-6.⁽²⁻⁵⁾ However, despite the plausible role of mesenteric fat in the pathogenesis of CD, debate persists as to whether creeping fat is a primary or secondary phenomenon, and whether there is any measurable contribution of VAT *per se* to the inflammatory process.⁽⁴⁾

Adipose tissue is anatomically distributed in two main compartments in the human body with distinct biochemical and metabolic characteristics; visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT).^(6, 7) In patients with CD, increased VAT compared to healthy controls is well described, yet is not able to be reliably detected by crude, non-specific anthropometric measures such as body mass index (BMI).^(3, 8, 9) Rather, cross-sectional imaging techniques such as computed tomography (CT) scanning and magnetic resonance imaging (MRI), have been used to quantify VAT in patients with CD.⁽¹⁰⁻¹³⁾ Although accurate in measuring VAT, cross-sectional imaging techniques are limited by radiation, expense and availability.^(6, 14) Dual energy X-ray absorptiometry (DXA) is performed routinely in patients with CD to assess bone mineral density (BMD).⁽¹⁵⁾ Whole body DXA is an accurate means of assessing VAT, which adds minimal radiation or time to standard lumbar spine and femur BMD DXA assessment. Despite this, VAT measurement by DXA has not previously been studied in patients with CD.⁽¹⁶⁻¹⁹⁾

The clinical significance of VAT as a biomarker for disease severity or outcomes has been evaluated in a number of studies, albeit with conflicting results.^(2, 3, 9-12, 20, 21) An increase in VAT has been associated with a complex CD phenotype (stricturing and/or fistulising disease), an increased likelihood of post-operative CD recurrence, increased post-operative morbidity and adverse pouch outcomes.^(9-12, 20, 21) However, these studies are limited by small sample sizes and retrospective study design. Moreover, heterogeneity in the techniques used to evaluate VAT, as well as the VAT metric reported, limit meaningful interpretation of results. Studies have variably reported VAT area, VAT: subcutaneous adipose tissue (SAT) ratio (labelled the Mesenteric Fat Index or MFI), VAT area/height squared (labelled the Visceral adipose Tissue / Height Index or VHI), and VAT: total fat mass ratio, and unsurprisingly findings differ depending on which metric of VAT measurement is used.^{(3, 9-12,}

20, 21)

Therefore to clarify the possible role of VAT in CD and make sense of the conflicting data published to date we gathered prospective data using an affordable technique (DXA) during routine care. In addition we examined the degree of correlation between various VAT metrics and their relationship to other established anthropometric measures. Thus, the aims of this study were to:

1. Evaluate whether VAT measured by DXA is associated with stricturing and/or fistulising disease, hospitalisation or surgery in CD
2. To prospectively examine whether VAT is associated with disease activity and/or quality of life (QoL) in CD
3. Explore the correlation between various VAT measures and other anthropometric assessments.

METHODS

Subjects

Consecutive patients with CD (aged 18-50 years and pre-menopausal if female) managed by a tertiary IBD Service were invited to participate in a prospective study between April 2012 and September 2013 (**Figure 1**). Those with medical or surgical comorbidities other than IBD, current pregnancy, or steroid use other than for IBD were excluded. Patients were reviewed at 12 and 24 months after their baseline assessment.

Subject data collection

Prospective data were captured by interview and questionnaire at 0, 12 and 24 months. A comprehensive case note, IBD database, endoscopy, histopathology and prescription review was undertaken by co-authors (RB, SO, CG, AL). Data capture included demographics, Montreal classification (baseline only), current IBD therapy, current and cumulative lifetime duration of corticosteroid use (equivalent to prednisolone $\geq 10\text{mg/day}$) and IBD-related surgery.⁽²²⁾

C-reactive protein (CRP) was used as a marker of systemic inflammation at each study time-point (CRP $< 5\text{mg/L}$ considered consistent with inactive disease). Faecal calprotectin (FC) was assessed as a marker of luminal inflammation using the CALPRO® ELISA (FC $< 100\mu\text{g/g}$ considered consistent with inactive disease).

Lifestyle factors were also assessed at 0, 12 and 24 months. Alcohol consumption was dichotomised into $< 20\text{g/day}$ vs. $\geq 20\text{g/day}$.⁽²³⁾ Habitual physical activity was assessed using the validated, self-administered Short International Physical Activity Questionnaire (IPAQ),

which estimates metabolic equivalent (MET)-minutes per week.⁽²⁴⁾ QoL was assessed by the validated Short Inflammatory Bowel Disease Questionnaire.⁽²⁵⁾

Extended prospective follow-up of specific IBD-related outcomes (corticosteroid use, hospitalisation, and surgery) was undertaken until July 2017, a median of 51 months from enrolment (IQR 48 – 54 months).

VAT and anthropometric assessment

At 0, 12 and 24 months, whole body dual energy X-ray absorptiometry (DXA, General Electric Lunar Prodigy Vision bone densitometer, system DF+13727; Encore 14.20, Madison WI, USA) was performed to evaluate body composition, using standard manufacturer protocols conforming to international guidelines.⁽²⁶⁾

Visceral adipose tissue (VAT) was measured using CoreScan® analysis software, which is documented to correlate well with CT scan measurements.^(16, 18, 19, 27, 28) The software estimates VAT in the android region by determining the abdominal wall margin and subtracting the subcutaneous adipose tissue (SAT) from android fat (VAT) (**Figure 2**). Multiple VAT metrics were then calculated including: VAT area (centimetres³), mass (grams), visceral adipose tissue/height index (VHI, VAT area (cm³)/height in metres, squared), and VAT:SAT ratio.

Participants' height (m) and weight (kg) were measured with standard Seca stadiometer and scale equipment at the time of DXA assessment. World Health Organisation (WHO) standard categories for BMI were used; <18.5kg/m² (underweight), 18.5-24.9 kg/m² (normal weight), 25-29.9 kg/m² (overweight), ≥30 kg/m² (obesity).^(29, 30) Waist and hip circumference (cm) were also measured at the time of DXA to enable calculation of a waist:hip circumference ratio (WHR).⁽¹⁸⁾

Ethical considerations

The study was approved by the Royal Adelaide Hospital Human Research Ethics Committee (#120304). Whole-body DXA does not confer significant additional radiation to standard BMD assessment. Radiation safety reported the radiation dose per DXA as 2.56µSv.

Statistical methods

Continuous outcomes were presented as means, standard deviations, medians and interquartile ranges (IQR), with categorical outcomes as counts and percentages, unless otherwise stated. Measures of VAT and anthropometrics were compared using Pearson

correlations. Comparisons in adiposity measures between CD phenotypes were performed using unpaired non-parametric Mann-Whitney-U tests. The lack of existing prospective data on VAT and disease outcomes in CD did not allow a formal power calculation to be performed. However, enrolment of 100 patients at baseline was assumed to provide adequate power for clinically relevant effect sizes and multivariable analysis, allowing for dropout over the study period. The line of enquiry within the study and associated statistical associations are described below.

Is VAT correlated with CD behaviour at baseline? Measures of adiposity (BMI, VHI, VAT:SAT) were initially compared between Montreal CD classification disease behaviour groups as assessed at study enrolment (inflammatory (B1) vs. stricturing or fistulising (B2 or B3)) using non-parametric unpaired Mann Whitney tests. Subsequently, logistic binomial regressions were constructed to assess factors associated with CD behaviour classifications (B1 vs. B2 or B3) as assessed at study enrolment. Cross-sectional factors included age, gender, VHI, VAT:SAT, BMI, IBD disease duration, prior surgery, faecal calprotectin and CRP.

What factors associated with serial VAT measurements over time? Linear mixed-effects models were constructed for serial VHI and VAT:SAT ratio measurements performed at 0, 12 and 24 months. Log-transformations were applied to the outcome variables, and random intercepts included per individual. Fixed effects covariates included Montreal phenotype as assessed at study enrolment, age, gender, IBD therapy (immunomodulator therapy, biologic therapy, cumulative duration of oral corticosteroid therapy), habitual physical activity (IPAQ), FC, CRP, alcohol intake, and prior CD-related resection .

Does VAT influence disease activity and/or QoL over time? Linear mixed-effects models were constructed to assess prospective associations between serial QoL, FC, and CRP levels performed at 0, 12 and 24 months. The latter two measures were log-transformed. Random intercepts were included per individual; the primary predictors of interest were VHI and VAT:SAT ratio (both log transformed) and their pairwise interactions with the Montreal disease behaviour classification as assessed at study enrolment (both L and B criteria). Analyses were adjusted for covariates listed for the prior analysis as well as BMI, with these factors being included as fixed-effects.

In all models residuals and, where appropriate random effect estimates, were examined to ensure that model distributional assumptions were not violated. Log-likelihood ratio (LLR) tests of nested models assessed differences across factors with multiple levels. A limited list

of factors believed associated with each outcome was determined *a priori*. These factors, along with associated factors identified in the full models were included in a final, reduced model for each outcome. As reported in regression analyses, β coefficient describes the change in the dependent variable for each unit change in the fixed effect covariate.

Does VAT predict time to surgery and/or hospitalisation over extended follow-up?

Possible predictors for time to hospitalisation and time to IBD-related surgery over the extended prospective follow-up period were evaluated with Cox regression analyses. Follow-up was calculated as time-to-last contact or death using Kaplan-Meier methodology with deaths censored. The primary predictors of interest were VAT metrics (included in the model as the average of repeated measures over time) and Montreal CD behaviour as assessed at study enrolment. Adjustment for other covariates was not performed due to a limited number of events. Survival curves were constructed using the Kaplan-Meier method.

All tests were two-tailed and assessed at the 5% alpha level. Analyses were performed on R software (v3.4.3).

RESULTS

Baseline subject characteristics

One hundred and thirty-five patients with CD were assessed for eligibility during the enrolment period (April 2012- September 2013), 38 of who were excluded (**Figure 1**). 97 patients were enrolled at baseline, of who 84 (87%) completed 12 and 72 (74%) completed 24 month follow up. Median duration of extended follow-up for surgical and hospitalisation events was 51 months (95% CI 48-54).

Median age was 31 years (range 18-49), median age of diagnosis 21 years (range 9-48) and disease duration 8.1 years (IQR 4.7- 12.5 years) (**Table 1**). CD distribution was ileal (L1) in 28 (29%) patients, colonic (L2) in 32 (33%) and ileocolonic (L3) in 37 (38%). At baseline, disease behaviour was classified as inflammatory (non-stricturing, non-penetrating, B1) in 43 (44%) patients, stricturing (B2) in 38 (39%) and penetrating (B3) in 16 (16%). 40 (41%) patients had undergone abdominal surgery for CD prior to enrolment: 36 (37%) ileal/ileocolic resection, 4 (4%) colectomy and 6 (6%) multiple operations. 27 (28%) patients were on oral corticosteroid therapy at baseline and 47 (48%) on biologic therapy.

The cohort was predominantly Caucasian (98%). 25 (26%) patients were current smokers and 4 (4%) self-reported consumption of >20g alcohol per day. Habitual physical activity measured in MET minutes/week was low in 44 (45%), medium in 22 (23%) and high in 19

(20%) patients.⁽²⁴⁾ Mean SIBDQ score was 50/70 (SD=12.6). QoL was severely reduced (SIBDQ <45/70) in 23 patients (24%), moderately reduced (SIBDQ 45-60/70) in 38 (39%), and normal (SIBDQ >60/70) in only 21 (22%).⁽²⁵⁾ Mean BMI was 26.5 kg/m² (SD= 5.4), with 5 (5%) classified as underweight, 24 (25%) overweight and 25 (26%) obese.^(29, 30)

Baseline VAT and CD behaviour

There were no significant differences in VAT between B1 and B2/B3 patients, as VHI or VAT:SAT (VHI mean 222.3 ± 216 vs. 286 ± 250; VAT:SAT 0.55 ± 0.53 vs. 0.64 ± 0.56; respectively, all comparisons non-significant) (**Supplementary Figure 1**). There was also no significant difference in the BMI between the groups (BMI mean 26.1 ± 5.4 vs. 26.6 ± 5.7, respectively, p = 0.58) at baseline.

However, VAT:SAT was positively associated with stricturing or fistulising (B2/3) CD behaviour at baseline in multivariable logistic regression analysis (log(OR)=1.4, 95%CI=[0.2, 2.6], p = 0.02). This was in contrast to BMI, which did not significantly associate with behaviour. Female gender was also associated with B2/3 disease at baseline (female vs. male log(OR) = 1.6, 95%CI=[0.3, 2.9], p = 0.01) (**Table 2**).

Associations with serial VAT measurements over study period

Serial VAT:SAT measurements at 0, 12, and 24-months were higher in patients with B2 disease in linear mixed effects analyses (β =0.38, 95%CI = [0.04,0.71], p = 0.03) (**Table 3**). VAT:SAT was positively associated with age (β =0.037, 95%CI=[0.022, 0.052], p<0.001) and male gender (β =1.0, 95%CI=[0.7, 1.3], p<0.001). VAT:SAT was negatively correlated with CD-related abdominal surgery prior to enrolment (β =-0.41 95%CI=[-0.73,-0.09], p = 0.01). Similar results were observed for VHI (**Supplementary Table 1**).

VAT associations with disease activity over study period

A positive association between serial VAT:SAT and FC measurements at 0, 12, and 24-months was observed in patients with ileocolonic (L3) disease distribution in linear mixed effects analyses (β =0.83, 95%CI=[0.27,1.4], p = 0.004, **Table 4, Figure 3**). In contrast, a negative association was observed between VHI and FC levels (β =-0.38, 95%CI=[-0.68,-0.09], p = 0.01). No associations between VAT:SAT or VHI and CRP levels over the study period were observed (**Supplementary Table 2**). BMI was not associated with either FC or CRP.

Predictors of IBD-related hospitalisation or surgery over extended follow-up

Over the extended follow-up period (median 51 months), 45 patients (46%) were hospitalised and 18 (18%) underwent IBD-related surgery. The event rates were higher in those patients with classified as B2/3 as compared to B1 at enrolment (**Supplementary Figure 2**).

No associations with VAT metrics were detected with either time to hospitalisation or surgery after adjusting for baseline disease phenotype (distribution and behaviour) (**Table 5**). Only B2 CD behaviour was associated with time to surgery ($\beta=1.4$, 95%CI=[0.05, 2.7], $p = 0.04$), whilst there was a trend for fistulising phenotype to increase risk of surgery ($\beta=1.3$, 95%CI=[-0.2, 2.9], $p = 0.08$).

VAT associations with QoL over study period

A negative association between serial VAT:SAT and QoL measurements at 0, 12, and 24-months was observed in patients with ileal CD (L1) and to a lesser extent in those with ileo-colonic disease compared to patients with colonic disease in linear mixed effects analyses (interaction $p=0.03$, 2 degrees of freedom) (**Supplementary Table 3 & Supplementary Figure 3**). QoL was also positively associated with male gender ($\beta=5.8$, 95%CI=[0.7, 11], $p=0.03$).

Correlations between VAT, overall adiposity and anthropometric assessments

Because VAT is reported variably in previous studies, correlations amongst different VAT metrics were analysed (**Figure 4**). VHI (visceral adipose tissue/height² index) correlated almost perfectly with VAT mass (g) and strongly with both overall fat mass (g) and VAT:SAT. On the other hand, VAT:SAT correlated strongly VAT mass (g) but poorly with overall fat mass (g).

Further correlation analyses explored the relationship between visceral adiposity and other clinical anthropometric assessments (**Supplementary Figure 4**). Waist circumference and BMI both strongly correlated with VHI, whereas WHR only moderately correlated with VHI. Correlations with VAT:SAT ratio were much lower. A very weak correlation was observed between VAT:SAT and BMI and only weak correlations between VAT:SAT and waist circumference and WHR .

DISCUSSION

In a prospective well-characterised cohort of patients with CD, visceral adipose tissue (VAT) was associated with stricturing disease behaviour at baseline and independently associated with both faecal calprotectin and QoL in a disease distribution-dependent manner when measured serially over 24 months. In contrast, there was no association between overall adiposity, as measured using BMI, and CD phenotype, disease activity or QoL, suggesting a specific role for VAT as previously proposed.

That VAT is associated with CD behaviour is supported by early surgical descriptions and retrospective or cross-sectional studies.^(2, 11, 13, 20) Several studies have reported that VAT is associated with higher rates of surgery, raised inflammatory markers, increased surgical morbidity, or higher rates of post-operative CD recurrence.^(9, 10, 12, 13, 21, 31) An association between VAT and disease behaviour in CD is plausible given that visceral adipocytes are a source of cytokine production in CD (including TNF-alpha and IL-6) and are likely to play a role in innate immunity.^(3-5, 32) Bacterial translocation may lead to immune infiltration of mesenteric fat, perpetuating the inflammatory response with resultant mesenteric fat hypertrophy.^(33, 34) In contrast, overall adiposity as measured using BMI is not associated with CD behaviour or activity in this or other studies.⁽³⁵⁻³⁸⁾ This highlights the different metabolic profiles between VAT and SAT compartments.^(39, 40)

We report a positive association between VAT and FC measurements in patients with ileocolonic disease over 24-months. This is first study to examine serial measures of both inflammation and VAT concurrently. Some small studies have reported conflicting findings on the relationship between VAT and clinical disease activity.^(3, 20, 31) It is notable that fat-wrapping in CD is more often a feature of ileal than colonic disease, although elevated FC associates with colonic inflammation, and may be normal even in the presence of large ileal ulcers.^(2, 3, 41) To account for the association between VAT:SAT and FC in ileocolonic disease, it is possible that this reflects ileal fat wrapping and colonic inflammation is detected by FC. However, given that VHI, an alternative measure of VAT, was inversely associated with FC, the association needs substantiation. The lack of observed association between VAT and CRP may reflect the known modest correlation between CRP and luminal inflammation in CD,^(31, 42-44) although VAT is potent source of IL-6. Higher serial VAT, but not BMI measurements, were also associated with reduced QoL in patients with ileal CD. This is the first reported association between VAT and QoL in CD. Impaired QoL in IBD has been previously associated with active disease (for which VAT may be a surrogate marker), psychological comorbidity, disability, or nutritional deficiency⁽⁴⁵⁻⁴⁷⁾

There are limitations to this study before VAT measurements can be considered clinically useful in CD. Firstly, VAT was independently associated with previous surgery, gender and advanced age, meaning that any predictive index needs to account for these variables. The influence of gender was confounding since female gender was associated with complicated CD behaviour, yet male gender correlated with higher VAT, in keeping with the non-IBD population.⁽¹⁹⁾ Prior abdominal surgery was associated with a classification of complicated disease behaviour at enrolment, yet independently associated with lower serial VAT measurements during follow-up, as well as a trend toward lower FC over time. It is conceivable that mesocolic excision of visceral fat reduced the risk of post-operative recurrence and improved disease control.⁽⁴⁸⁾ Secondly, without published IBD-specific VAT risk ‘cut-offs’, clinical interpretation of VAT measurements is limited. Thirdly, there was no observed association between VAT and hospitalisation or surgery over more than 4 years of follow-up. Although other studies have reported an association between VAT and outcomes in CD, they have been limited by retrospective or post-hoc design and lacked analysis of confounding variables.^(9-12, 20) Although prospective, the number of events at time of analysis in this study suggests that the multivariable analysis for surgery and hospitalisation was underpowered for small-moderate effect sizes. Classification of CD behaviour at study enrolment without adjustment over time was another potential limitation although hospitalisation and surgery acted as surrogate makers of disease behaviour. Furthermore, this patient cohort was predominantly Caucasian, which may limit generalizability.

This study illustrates that VAT metrics differ from one another from one another and associated with unique risk profiles in CD. VHI was shown to correlate only moderately with VAT:SAT ratio. Similar disparity between VAT metrics has been reported in other studies; VHI but not VAT:SAT ratio was shown to be a significant predictor of postoperative CD recurrence.⁽¹²⁾ The distinction between VAT metrics in imparting cardio-metabolic risk has been well reported, yet most existing IBD studies only report a single VAT metric.⁽³⁹⁾ DXA is an accurate measure of VAT compared to CT scanning, relatively inexpensive and associated with minimal associated ionising radiation.^(16, 18) Our data emphasise the importance of incorporating multiple VAT metrics into future studies in CD, which may readily achieved using DXA which is in routine use for measuring bone density in IBD.

In summary, VAT is associated with stricturing CD behaviour, as well as prospective disease activity and QoL. The challenge remains to determine the influence of VAT on CD outcomes from diagnosis and whether interventions to reduce VAT can modify disease course in CD. Until such data are available, VAT as a biomarker in CD holds promise, but is not yet ready for prime time.

Authorship statement

The manuscript, including related data, figures, and tables has not been previously published and the manuscript is not under consideration elsewhere.

Guarantor of article: Robert Bryant

Author contributions: RB, CS, FDB, SPLT and JMA were involved in the conception and design of the project. RB, CS, SO, CG, SS, AV, AL, FDB, and JMA were involved in data acquisition and management. All authors were involved in analysis and interpretation of research data, and drafting and revision of the article.

All authors approved the final version of the manuscript.

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Statement of Interests

There are no conflicts of interest to declare for any of the authors.

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REFERENCES

1. Crohn BB, Ginzburg L, Oppenheimer GD. Landmark article Oct 15, 1932. Regional ileitis. A pathological and clinical entity. By Burril B. Crohn, Leon Ginzburg, and Gordon D. Oppenheimer. *Jama*. 1984 Jan 06;251(1):73-9.
2. Sheehan AL, Warren BF, Gear MW, Shepherd NA. Fat-wrapping in Crohn's disease: pathological basis and relevance to surgical practice. *The British journal of surgery*. 1992 Sep;79(9):955-8.
3. Desreumaux P, Ernst O, Geboes K, Gambiez L, Berrebi D, Muller-Alouf H, Hafraoui S, Emilie D, Ectors N, Peuchmaur M, Cortot A, Capron M, Auwerx J, Colombel JF. Inflammatory alterations in mesenteric adipose tissue in Crohn's disease. *Gastroenterology*. 1999 Jul;117(1):73-81.
4. Schaffler A, Herfarth H. Creeping fat in Crohn's disease: travelling in a creeper lane of research? *Gut*. 2005 Jun;54(6):742-4.
5. Fink C, Karagiannides I, Bakirtzi K, Pothoulakis C. Adipose tissue and inflammatory bowel disease pathogenesis. *Inflammatory bowel diseases*. 2012 Aug;18(8):1550-7.
6. Shuster A, Patlas M, Pinthus JH, Mourtzakis M. The clinical importance of visceral adiposity: a critical review of methods for visceral adipose tissue analysis. *The British journal of radiology*. 2012 Jan;85(1009):1-10.
7. Dusserre E, Moulin P, Vidal H. Differences in mRNA expression of the proteins secreted by the adipocytes in human subcutaneous and visceral adipose tissues. *Biochimica et biophysica acta*. 2000 Jan 03;1500(1):88-96.
8. Bruining DH, Loftus EV, Jr., Ehman EC, Siddiki HA, Nguyen DL, Fidler JL, Huprich JE, Mandrekar JN, Harmsen WS, Sandborn WJ, Fletcher JG. Computed tomography enterography detects intestinal wall changes and effects of treatment in patients with Crohn's disease. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*. 2011 Aug;9(8):679-83.e1.
9. Ding Z, Wu XR, Remer EM, Lian L, Stocchi L, Li Y, McCullough A, Remzi FH, Shen B. Association between high visceral fat area and postoperative complications in patients with Crohn's disease following primary surgery. *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland*. 2016 Feb;18(2):163-72.
10. Connelly TM, Juza RM, Sangster W, Sehgal R, Tappouni RF, Messaris E. Volumetric fat ratio and not body mass index is predictive of ileocollectomy outcomes in Crohn's disease patients. *Digestive surgery*. 2014;31(3):219-24.
11. Erhayiem B, Dhingsa R, Hawkey CJ, Subramanian V. Ratio of visceral to subcutaneous fat area is a biomarker of complicated Crohn's disease. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*. 2011 Aug;9(8):684-7.e1.
12. Holt DQ, Moore GT, Strauss BJ, Hamilton AL, De Cruz P, Kamm MA. Visceral adiposity predicts post-operative Crohn's disease recurrence. *Alimentary pharmacology & therapeutics*. 2017 May;45(9):1255-64.

13. Van Der Sloot KW, Joshi AD, Bellavance DR, Gilpin KK, Stewart KO, Lochhead P, Garber JJ, Giallourakis C, Yajnik V, Ananthakrishnan AN, Alizadeh BZ, Xavier RJ, Khalili H. Visceral Adiposity, Genetic Susceptibility, and Risk of Complications Among Individuals with Crohn's Disease. *Inflammatory bowel diseases*. 2017 Jan;23(1):82-8.
14. Shen W, Wang Z, Punyanita M, Lei J, Sinav A, Kral JG, Imielinska C, Ross R, Heymsfield SB. Adipose tissue quantification by imaging methods: a proposed classification. *Obesity research*. 2003 Jan;11(1):5-16.
15. Harbord M, Annese V, Vavricka SR, Allez M, Barreiro-de Acosta M, Boberg KM, Burisch J, De Vos M, De Vries AM, Dick AD, Juillerat P, Karlsen TH, Koutroubakis I, Lakatos PL, Orchard T, Papay P, Raine T, Reinshagen M, Thaci D, Tilg H, Carbonnel F. The First European Evidence-based Consensus on Extra-intestinal Manifestations in Inflammatory Bowel Disease. *Journal of Crohn's & colitis*. 2016 Mar;10(3):239-54.
16. Kaul S, Rothney MP, Peters DM, Wacker WK, Davis CE, Shapiro MD, Ergun DL. Dual-energy X-ray absorptiometry for quantification of visceral fat. *Obesity (Silver Spring, Md)*. 2012 Jun;20(6):1313-8.
17. Miazgowski T, Krzyzanowska-Swiniarska B, Dziwura-Ogonowska J, Widecka K. The associations between cardiometabolic risk factors and visceral fat measured by a new dual-energy X-ray absorptiometry-derived method in lean healthy Caucasian women. *Endocrine*. 2014 Nov;47(2):500-5.
18. Direk K, Cecelja M, Astle W, Chowieńczyk P, Spector TD, Falchi M, Andrew T. The relationship between DXA-based and anthropometric measures of visceral fat and morbidity in women. *BMC cardiovascular disorders*. 2013 Apr 03;13:25.
19. Rothney MP, Catapano AL, Xia J, Wacker WK, Tidone C, Grigore L, Xia Y, Ergun DL. Abdominal visceral fat measurement using dual-energy X-ray: association with cardiometabolic risk factors. *Obesity (Silver Spring, Md)*. 2013 Sep;21(9):1798-802.
20. Buning C, von Kraft C, Hermsdorf M, Gentz E, Wirth EK, Valentini L, Haas V. Visceral Adipose Tissue in Patients with Crohn's Disease Correlates with Disease Activity, Inflammatory Markers, and Outcome. *Inflammatory bowel diseases*. 2015 Nov;21(11):2590-7.
21. Liu G, Wu X, Li Y, Rui Y, Stocchi L, Remzi FH, Shen B. Postoperative excessive gain in visceral adipose tissue as well as body mass index are associated with adverse outcomes of an ileal pouch. *Gastroenterology report*. 2016 Sep 25.
22. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut*. 2006 Jun;55(6):749-53.
23. McGuire S. U.S. Department of Agriculture and U.S. Department of Health and Human Services, Dietary Guidelines for Americans, 2010. 7th Edition, Washington, DC: U.S. Government Printing Office, January 2011. *Advances in nutrition (Bethesda, Md)*. 2011 May;2(3):293-4.

24. Ainsworth BE, Macera CA, Jones DA, Reis JP, Addy CL, Bowles HR, Kohl HW, 3rd. Comparison of the 2001 BRFSS and the IPAQ Physical Activity Questionnaires. *Medicine and science in sports and exercise*. 2006 Sep;38(9):1584-92.
25. Irvine EJ, Zhou Q, Thompson AK. The Short Inflammatory Bowel Disease Questionnaire: a quality of life instrument for community physicians managing inflammatory bowel disease. CCRPT Investigators. Canadian Crohn's Relapse Prevention Trial. *The American journal of gastroenterology*. 1996 Aug;91(8):1571-8.
26. Hans DB, Shepherd JA, Schwartz EN, Reid DM, Blake GM, Fordham JN, Fuerst T, Hadji P, Itabashi A, Krieg MA, Lewiecki EM. Peripheral dual-energy X-ray absorptiometry in the management of osteoporosis: the 2007 ISCD Official Positions. *Journal of clinical densitometry : the official journal of the International Society for Clinical Densitometry*. 2008 Jan-Mar;11(1):188-206.
27. Kvist H, Chowdhury B, Grangard U, Tylen U, Sjostrom L. Total and visceral adipose-tissue volumes derived from measurements with computed tomography in adult men and women: predictive equations. *The American journal of clinical nutrition*. 1988 Dec;48(6):1351-61.
28. Mellis MG, Oldroyd B, Hind K. In vivo precision of the GE Lunar iDXA for the measurement of visceral adipose tissue in adults: the influence of body mass index. *European journal of clinical nutrition*. 2014 Dec;68(12):1365-7.
29. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organization technical report series. 2000;894:i-xii, 1-253.
30. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary. Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults. *The American journal of clinical nutrition*. 1998 Oct;68(4):899-917.
31. Colombel JF, Solem CA, Sandborn WJ, Booya F, Loftus EV, Jr., Harmsen WS, Zinsmeister AR, Bodily KD, Fletcher JG. Quantitative measurement and visual assessment of ileal Crohn's disease activity by computed tomography enterography: correlation with endoscopic severity and C reactive protein. *Gut*. 2006 Nov;55(11):1561-7.
32. Schaffler A, Scholmerich J. Innate immunity and adipose tissue biology. *Trends in immunology*. 2010 Jun;31(6):228-35.
33. Peyrin-Biroulet L, Chamaillard M, Gonzalez F, Beclin E, Decourcelle C, Antunes L, Gay J, Neut C, Colombel JF, Desreumaux P. Mesenteric fat in Crohn's disease: a pathogenetic hallmark or an innocent bystander? *Gut*. 2007 Apr;56(4):577-83.
34. Peyrin-Biroulet L, Gonzalez F, Dubuquoy L, Rousseaux C, Dubuquoy C, Decourcelle C, Saudemont A, Tachon M, Beclin E, Odou MF, Neut C, Colombel JF, Desreumaux P. Mesenteric fat as a source of C reactive protein and as a target for bacterial translocation in Crohn's disease. *Gut*. 2012 Jan;61(1):78-85.
35. Flores A, Burstein E, CIPHER DJ, Feagins LA. Obesity in Inflammatory Bowel Disease: A Marker of Less Severe Disease. *Digestive diseases and sciences*. 2015 Aug;60(8):2436-45.
36. Hass DJ, Brensinger CM, Lewis JD, Lichtenstein GR. The impact of increased body mass index on the clinical course of Crohn's disease. *Clinical gastroenterology and hepatology : the*

- official clinical practice journal of the American Gastroenterological Association. 2006 Apr;4(4):482-8.
37. Pringle PL, Stewart KO, Peloquin JM, Sturgeon HC, Nguyen D, Sauk J, Garber JJ, Yajnik V, Ananthakrishnan AN, Chan AT, Xavier RJ, Khalili H. Body Mass Index, Genetic Susceptibility, and Risk of Complications Among Individuals with Crohn's Disease. *Inflammatory bowel diseases*. 2015 Oct;21(10):2304-10.
 38. Seminerio JL, Koutroubakis IE, Ramos-Rivers C, Hashash JG, Dudekula A, Regueiro M, Baidoo L, Barrie A, Swoger J, Schwartz M, Weyant K, Dunn MA, Binion DG. Impact of Obesity on the Management and Clinical Course of Patients with Inflammatory Bowel Disease. *Inflammatory bowel diseases*. 2015 Dec;21(12):2857-63.
 39. Kaess BM, Pedley A, Massaro JM, Murabito J, Hoffmann U, Fox CS. The ratio of visceral to subcutaneous fat, a metric of body fat distribution, is a unique correlate of cardiometabolic risk. *Diabetologia*. 2012 Oct;55(10):2622-30.
 40. Fontana L, Eagon JC, Trujillo ME, Scherer PE, Klein S. Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. *Diabetes*. 2007 Apr;56(4):1010-3.
 41. Gecse KB, Brandse JF, van Wilpe S, Lowenberg M, Ponsioen C, van den Brink G, D'Haens G. Impact of disease location on fecal calprotectin levels in Crohn's disease. *Scandinavian journal of gastroenterology*. 2015 Jul;50(7):841-7.
 42. Falvey JD, Hoskin T, Meijer B, Ashcroft A, Walmsley R, Day AS, Garry RB. Disease activity assessment in IBD: clinical indices and biomarkers fail to predict endoscopic remission. *Inflammatory bowel diseases*. 2015 Apr;21(4):824-31.
 43. Jones J, Loftus EV, Jr., Panaccione R, Chen LS, Peterson S, McConnell J, Baudhuin L, Hanson K, Feagan BG, Harmsen SW, Zinsmeister AR, Helou E, Sandborn WJ. Relationships between disease activity and serum and fecal biomarkers in patients with Crohn's disease. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*. 2008 Nov;6(11):1218-24.
 44. Mosli MH, Zou G, Garg SK, Feagan SG, MacDonald JK, Chande N, Sandborn WJ, Feagan BG. C-Reactive Protein, Fecal Calprotectin, and Stool Lactoferrin for Detection of Endoscopic Activity in Symptomatic Inflammatory Bowel Disease Patients: A Systematic Review and Meta-Analysis. *The American journal of gastroenterology*. 2015 Jun;110(6):802-19; quiz 20.
 45. Irvine EJ. Quality of life issues in patients with inflammatory bowel disease. *The American journal of gastroenterology*. 1997 Dec;92(12 Suppl):18s-24s.
 46. Fiest KM, Bernstein CN, Walker JR, Graff LA, Hitchon CA, Peschken CA, Zarychanski R, Abou-Setta A, Patten SB, Sareen J, Bolton J, Singer A, Marrie RA. Systematic review of interventions for depression and anxiety in persons with inflammatory bowel disease. *BMC research notes*. 2016 Aug 12;9(1):404.
 47. Burgell RE, Asthana AK, Gibson PR. Irritable bowel syndrome in quiescent inflammatory bowel disease: a review. *Minerva gastroenterologica e dietologica*. 2015 Dec;61(4):201-13.

48. Coffey JC, O'Leary DP, Kiernan MG, Faul P. The mesentery in Crohn's disease: friend or foe? *Current opinion in gastroenterology*. 2016 Jul;32(4):267-73.