MONASH University

The Role of Body Composition in the Treatment of Crohn's Disease

Darcy Quinn Holt

MBBS (Melb)

A thesis submitted for the degree of Doctor of Philosophy at

Monash University in 2017

Faculty of Medicine, Nursing and Health Sciences

School of Clinical Sciences at Monash Health

Copyright notice

I certify that I have made all reasonable efforts to secure copyright permissions for third-party content included in this thesis and have not knowingly added copyright content to my work without the owner's permission.

Abstract

Background

Crohn's disease (CD) is a chronic inflammatory condition affecting the gastrointestinal tract, with severe implications for quality of life. Its incidence is increasing, its cause is unknown, and no cure is available. Treatments include nutrition, medications and surgery. Dynamic research underpins medical therapy for CD, but adverse effects and high treatment costs are common.

Patients with CD frequently suffer malnutrition and reduced muscle and bone mass. Body composition analysis identifies these changes. Body composition predicts toxicity and response to chemotherapy for cancer patients, predicts survival in elderly patients, and it holds promise of predicting the severity and behaviour of an individual patient's CD, as well as the likelihood of response to medications or probability of toxicity. This offers an opportunity to tailor better, safer and more cost-effective care.

Aims

The aims of this research were to explore interactions between body composition and treatments for CD through several linked studies.

Methods

A systematic review of the literature was performed. An anonymous survey was undertaken of members of Australian national groups for support of inflammatory bowel and clinician professional associations.

Imaging studies obtained as part of routine clinical care in patients with CD were analysed using dedicated software, with areas of skeletal muscle and adipose tissue employed to create a model of body composition that was validated by reference to contemporaneous dual-energy X-ray absorptiometry.

This model formed the basis of a study correlating drug dose, body composition and levels of thiopurine metabolites.

A cohort of inflammatory bowel disease patients prescribed anti-tumour necrosis factor alpha (TNF) therapy was subject to retrospective analysis of body composition and time to treatment failure.

Data from a prospective, randomised controlled trial of treatment to prevent post-operative recurrence of CD were analysed to determine whether body composition was a predictor of outcomes after surgery.

Results

Australian inflammatory bowel disease patients and their treating clinicians have different views regarding diet. The prevalence of self-reported overweight and obesity in a national cohort was less than in the general population; patients with high corticosteroid exposure were more likely to be overweight or obese.

A highly accurate model of body composition was derived from analysis of a single abdominal image.

Therapeutic levels of thiopurine drugs did not correlate with weight or with body composition, but higher doses of drug relative to fat-free mass or total body weight were associated with increased levels of potentially hepatotoxic metabolites.

Patients with low levels of skeletal muscle had significantly earlier loss of response to anti-TNF therapy.

Patients with high levels of visceral adipose tissue experienced endoscopic recurrence of CD after surgery.

Conclusion

Body composition is related to CD activity and severity. Variances in body composition affect drug metabolism and outcomes of treatment, with low muscle mass a risk factor for thiopurine toxicity and anti-TNF failure and high visceral adipose tissue area associated with recurrence of CD after surgery. Analysis of body composition adds prognostic value to an individualised model of CD, and may deliver improved patient outcomes.

Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

Signature: 

Print Name: Darcy Holt

Date: 02 February 2017

Publications and presentations during enrolment

Peer-reviewed journal publications relevant to thesis

1. Holt DQ, Strauss BJ, Moore GT. Weight and Body Composition Compartments do Not Predict Therapeutic Thiopurine Metabolite Levels in Inflammatory Bowel Disease. Clin Trans Gastroenterol. 2016 Oct 27;7(10):e199. (Journal impact factor 3.472)
2. 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. (Cited twice; journal impact factor 2.329)
3. Holt DQ, Strauss BJ, Moore GT. Patients with inflammatory bowel disease and their treating clinicians have different views regarding diet. J Hum Nutr Diet. 2016 Jul 14. (Journal impact factor 2.583)
4. Holt DQ, Varma P, Strauss BJG, Rajadurai AS, Moore GT Low muscle mass at initiation of anti-TNF therapy for inflammatory bowel disease is associated with early treatment failure: a retrospective analysis. Eur J Clin Nutr 2017;80:271. (Journal impact factor 2.709)
5. Holt DQ, Moore GT, Strauss BJG, Hamilton AL, De Cruz P, Kamm MA Visceral adiposity predicts post-operative Crohn's disease recurrence. Aliment Pharmacol Ther. 2017;45(9):1255–64. (Journal impact factor 5.727)

Conference proceedings and abstracts relevant to thesis

1. Holt D, Strauss B, Moore G. P537. Weight and body composition compartments do not predict thiopurine metabolite levels. J Crohns Colitis. 2016 Mar 1;10(suppl 1):S373–3.
2. Holt D, Varma P, Strauss B, Moore G. Low muscle mass at treatment initiation is associated with early loss of response to anti-TNF therapy for Inflammatory Bowel Disease. Journal of Gastroenterology and Hepatology 2015;30 (Suppl. 3):131.
3. Holt DQ, Moore G, Strauss BJG. Single Slice CT Measurement of Skeletal Muscle Area Correlates with Total Body Lean Tissue Mass by DXA in Patients with Crohn's Disease. Clin Nutr. 2013 Oct 12;32(5):S144.
4. Holt DQ, Strauss BJ, Moore GT. Thiopurine metabolite levels correlate with body composition in patients with inflammatory bowel disease. Journal of Gastroenterology and Hepatology. 2013;28:91.
5. Holt DQ, Moore GT, Strauss BJ. PP056-MON Single slice CT measurement of skeletal muscle area correlates with total body lean tissue mass by DXA in patients with Crohn's disease. Clin Nutr. Elsevier; 2013;32:S144

Peer-reviewed journal publications not relevant to thesis

1. Holt DQ, McDonald JF, Murray ML, Hair C, Devonshire DA, Strauss BJ, et al. Clinical selection criteria can predict futile intervention in patients referred for percutaneous endoscopic gastrostomy insertion. Intern Med J. 2015 Jun;45(6):648–52.

Conference proceedings and abstracts not relevant to thesis

1. Varma P, Rajadurai AS, Holt DQ, Devonshire DA, Desmond CP, Swan MP, et al. Outcomes from salvage therapy strategies for loss of response in inflammatory bowel disease patients on TNF-alpha mono-and combination therapy. Journal of Gastroenterology and Hepatology. 2016;31:153–3.
2. Varma P, Rajadurai AS, Holt DQ, Devonshire DA, Desmond CP, Swan MP, et al. Immunomodulator co-therapy is not superior to anti-TNF monotherapy at preventing first loss of response in inflammatory bowel disease patients: long term outcomes in a real world cohort. Journal of Gastroenterology and Hepatology. 2016;31:152–2.
3. Freckelton J, Holt DQ, Borsaru A, Moore GT. The role of body composition in diverticular disease. Journal of Gastroenterology and Hepatology. 2016;31:158–9.
4. Varma P, Yeaman F, Holt D, Moore G Immunomodulators provide no reduction in loss of response for inflammatory bowel disease patients starting anti-TNF-alpha therapy. Journal of Gastroenterology and Hepatology 2015;30:140–1.
5. Hodge A, Mack A, Tuck C, Tchongue J, Holt D, Sievert W, et al. Non-alcoholic fatty liver disease intermittent fasting time intervention (NIFTI): fasting without calorie restriction improves hepatic transient elastography, visceral adiposity and insulin resistance compared to standard care. Journal of Gastroenterology and Hepatology. 2014;29(Suppl. 2):68.
6. Ha P, He T, Lim J, Sahhar L, Le S, Rusli F, et al. Do Tenofovir and Entecavir affect renal function in patients with chronic hepatitis B (CHB)? A two-year observational study from a single Australian centre. Journal of Gastroenterology and Hepatology. 2012;27:77–8.
7. Tang JY, Holt D, Moore G. Use of endoscopy for management of acute non-variceal upper gastrointestinal bleeding: utility of pre-endoscopy scoring systems. Journal of Gastroenterology and Hepatology. Journal of Gastroenterology and Hepatology. 2011 Sep;26(41).
8. Holt D, Tang J, Moore G. Long term outcomes of single dose infliximab bridging therapy in severe ulcerative colitis. Journal of Gastroenterology and Hepatology. 2011 Aug 1;26(s4):56–67.
9. Holt D, Kong H, Strauss B. Maintenance of Bone Mineral Density, with Body Composition Changes, in Very Long-Term Parenteral Nutrition. Clin Nutr. 2011 Jan 1;6(1):63EP–PB–.

Thesis including published works declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis. This thesis includes five original papers published in, or accepted for publication, by peerreviewed journals. The core theme of the thesis is the role of body composition in the treatment ofCrohn's disease. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, Darcy Holt, working within the School of Clinical Sciences at Monash Health, Monash University under the supervision of Prof. Boyd Strauss and Dr. Gregory Moore. The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research. In the case of chapters 3- 7, my contribution to the work involved the following:

Thesis Chapter	Publication Title	Status	Nature and% of student contribution	Co-author names, Nature, and% of contribution
3	Patients with inflammatory bowel disease and their treating clinicians have different views regarding diet	Published	85% (study design, survey formulation & administration, analysis, manuscript preparation)	Prof BJ Strauss, Dr GT Moore (Jointly 15%: study design, critical appraisal and revision of manuscript)
4	Body composinon analysis using abdominal scans from routine clinical care in patients with Crohn's disease	Published	80% (study design, data acquisition and statistical analysis, manuscript preparation)	Prof BJ Strauss, Dr GT Moore (Jointly 15%: study design, critical appraisal and revision of manuscript) Dr Ken Lau (5%: access to scans, review of manuscript)
5	Weight and body composition compartments do not predict therapeutic thiopurine metabolite levels m inflammatory bowel disease Low muscle mass at initiation of anti TNF therapy for inflammatory bowel disease is associated with early treatment failure	Published	85% (study design, data acquisition and statistical analysis, manuscript preparation)	Prof BJ Strauss, Dr GT Moore (Jointly 15%: study design, critical appraisal and revision of manuscript)
6		Accepted *(Eur]* Clin Nutr.)	70% (study design, body composition scan acquisition and analysis, data analysis and manuscript preparation)	Dr Poornima Varma, Dr Anton Rajadurai (15%: Chart review and data collection) Prof BJ Strauss, Dr GT Moore (Jointly 15%: study design, critical appraisal and revision of manuscript)
7	Visceral adiposity predicts recurrence in post-operative Crohn's disease patients	Accepted: (Aliment Pharmacol Ther.)	70% (study design, body composition scan acquisition and analysis, data analysis and manuscript preparation)	Dr GT Moore, Prof BJG Strauss, A Hamilton, Dr P De Cruz, Prof MA Kamm (30%) All authors devised the study. DH, AH, MK and PDC collected the data. All authors contributed to the critical review and revision of the manuscript.

No co-author is a Monash University student.

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis, although the original numbering is also kept intact.

Student signature: [redacted] Date: 08 Feb 2017

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor signature: [redacted] Date: 09 February 2017

Acknowledgements and dedications

The shoulders of many giants were stood on to make this work. I realise it is a particularly fortunate, and indulgent, position to be able to write a PhD thesis. I hope that the research adds to knowledge on this topic, but for me the process of undertaking a PhD has been – like exposure to a growth factor – one of personal differentiation and maturation. The research itself is incremental, and owes everything to dedicated clinicians and scientists who make the world of academic medicine an inspiring place.
Having been given the necessary time and support from important people in my life has made this thesis possible. I owe a debt of gratitude to many.

I am especially grateful to my supervisors for their assistance, encouragement, and patience, over the elephantine gestation of this thesis.

To Professor Boyd Strauss – who has been a steadfast inspiration. Boyd is the epitome of an academic, with a pan-encyclopaedic knowledge that he administers with humour, generosity and kindness. I could not have done any of this without Boyd's help, and his example as a clinician-scientist is one I aspire to. Our regular scheduled discussions have sustained me through the writing of this thesis and I will miss them a great deal.

To Dr Greg Moore, who has been a mentor for nearly a decade – applying growth factors from a time when I was a little more pluripotent. Greg's enthusiasm, his theobromine-fuelled active intelligence and his ready supply of 'Dad jokes' have made the concept of research a pleasure. Despite being so busy and important, he has always had time to bandy about new ideas for research and has taught me everything I know about inflammatory bowel disease, allowing me to develop as a clinician in the field.

I am very appreciative of the allowances made by my employers, particularly Monash Health – for assistance with an Emerging Researcher Fellowship and Clinical Academic Fellowship at the start of my candidacy – and to Professor Bill Sievert and Dr Sharon Marks for allowing me to keep my toe in the clinical pond, and pay the bills, for the years it has taken me to be a student. I gratefully acknowledge the research opportunities that have been given to me by Monash University, Monash Health, and am thankful for generous collaborators such as Prof. Michael Kamm, Dr Peter de Cruz, Ms Amy Hamilton, Dr Suong Le and Dr Poornima Varma. I gratefully acknowledge the support of an Australian Government Research Training Program Scholarship to offset university fees.

My family makes me who I am, and are my life away from the glow of the computer screen. I would like to dedicate this thesis to them. My parents, Ross and Denise, have always given me unconditional encouragement. They provided me with the fundamentals: a happy home, and an education that began long before school with a sense of scientific enquiry and respect for literacy. My sister Courtney has produced three children in the time it has taken me to write this: she was always an over-achiever. She has been a valued source of cheeky good counsel.
Barry the dog has been nothing but a distraction: but he did help my mental health.

And of course: Andrew, my partner, has been patient, thoughtful and has prioritised my needs for time with the computer at the expense of other activities of daily living. I am very grateful for his unwavering support and these domestic sacrifices and allowances.

Table of contents

Chapter 1: Introduction

Context – background, current theory and current practice

Crohn's disease is a chronic, idiopathic, inflammatory disease of increasing incidence. It is characterised by ulceration and transmural inflammation of the gastrointestinal tract. Crohn's disease is a cause of significant disability, reduction of quality of life, and health care costs in the Australian setting. Current treatment guidelines recommend escalating immunosuppressive medication based on disease severity and behaviour. Adverse effects from therapy are frequent, and the majority of patients require surgery for the condition.

As drug treatment options for Crohn's disease expand, with different mechanisms of action, pharmacokinetics and potential toxicities, it is increasingly important to identify predictors of treatment response or harm. Most of the identified predictive factors are disease-specific: perianal fistulising disease, penetrating or stricturing complications and upper gastrointestinal location confer a worse prognosis. Patient-specific factors are less well-described, although young age at diagnosis and smoking status are associated with increased complications and a need for more intensive treatment. Current research has validated models of outcome prediction in Crohn's disease based on disease-specific, serological and genetic variables.

Body composition analysis is the use of various techniques to quantify functional, anatomic and tissue compartments. It is acknowledged that inflammatory diseases, particularly Crohn's disease, change body composition. Low skeletal muscle mass, frequently in conjunction with low body weight, is typical.

Conceptually, routine evaluation of body composition represents a valuable addition to clinical care: analysis is accessible, variations in body composition have significant pharmacokinetic effects, and body composition reflects the severity and duration of Crohn's disease, which are independent predictors of outcome. However, there is a lack of prospective trials that utilise body composition to select therapeutic drug, drug dose or perioperative management strategy and report clinical outcomes.

Tailoring treatment regimens to individual patients by appropriately dosing medications, and choosing therapies based on likelihood of response, provides better care and cost benefits. An individualised approach is the subject of growing research into aetiologic, metabolic and prognostic factors.

This thesis explores the extent to which body composition contributes to these factors.

Overview of the thesis

This thesis comprises published works which explore the relationship between body composition and treatment for Crohn's disease. Interactions between body composition and disease behaviour, drug metabolism, response to treatment and outcomes after surgery are topics covered in the publications and discussion.

A systematic review of the literature (chapter 2) has been performed with a view to publication, and recently updated. This places the research elements of the thesis in context. Occasional repetition of aims and methods, themes or findings may be expected in a thesis consisting of published and submitted papers. The systematic review contains references to three publications (two published articles and one abstract) that were generated during this candidature and identified by the search strategy. While this places the research in context, it does not serve to emphasise the gaps in the current literature that this body of work seeks to fill.

The systematic review is followed by five papers published, or accepted for publication, in separate chapters, accompanied by linking introductory and commentary text.

An examination of patient and clinician attitudes to diet and weight in inflammatory bowel disease (chapter 3) provides a qualitative basis for determining priorities for research in this area. Chapter 4 describes validation of a technique for measuring body composition – using computed tomography images obtained as part of routine clinical care in patients with Crohn's disease – which allows retrospective analysis of existing patient cohorts. The use of this technique to examine the relationship between body composition and levels of drug metabolites measured in blood samples is detailed in a published retrospective cohort study forming chapter 5. Low muscle mass was found to be associated with earlier failure of treatment in analysis of a different cohort (chapter 6). Post-surgical recurrence of Crohn's disease was assessed in a prospective randomised control trial; retrospective analysis of body composition in a sample of patients from this trial, described in chapter 7, demonstrated poorer outcomes were associated with excessive visceral adiposity.

A concluding chapter (chapter 8) synthesises the findings of the individual findings and proposes future research directions.

Hypotheses and aims

Chapter 3: Patients with inflammatory bowel disease and their treating clinicians have different views regarding diet

- *Hypothesis 1:*
    - That patients with inflammatory bowel disease believe diet is an important influence on their disease and restrict their dietary intake, but that clinicians provide a variety of advice
- *Aims:*
    - To determine patient and clinician attitudes to diet in inflammatory bowel disease
    - To seek data regarding weight, body habitus, medical treatment and past surgery in a large sample of patients
    - To elicit differences in beliefs and clinical practices between dietitians, surgeons and physicians treating inflammatory bowel disease patients
    - To determine whether there was an association between overweight or obesity and increased treatment intensity in a national cohort

Chapter 4: Body composition analysis using abdominal scans from routine clinical care in patients with Crohn's Disease

- *Hypothesis 2:*
    - That cross-sectional abdominal imaging obtained by computed tomography (CT) and magnetic resonance imaging (MRI) during routine clinical care for patients with Crohn's disease allows accurate estimation of body composition parameters
- *Aims:*
    - To correlate cross-sectional areas of skeletal muscle and adipose tissue obtained by analysis of CT or MRI images obtained during routine clinical care with body composition measurements by whole-body dual energy X-ray absorptiometry (DXA) in patients with Crohn's disease
    - To define and validate formulae to estimate whole body fat mass and fat-free mass from analysis of a single cross-sectional image
    - To identify a most predictive level for performing such analysis

- To describe the prevalence of significantly low muscle mass/sarcopenia in a cohort of Crohn's disease patients

Chapter 5: Weight and body composition compartments do not predict therapeutic thiopurine metabolite levels in inflammatory bowel disease

- *Hypothesis 3:*
  - That weight-based dosing is inferior to dosing by body composition parameters at achieving therapeutic thiopurine metabolite levels
- *Aims:*
  - To apply body composition analysis to a cohort of inflammatory bowel disease patients with available thiopurine metabolite level results
  - To determine associations between thiopurine metabolite levels and drug dose adjusted for weight, body mass index, body surface area and body composition compartments

Chapter 6: Low muscle mass at initiation of anti TNF therapy for inflammatory bowel disease is associated with early treatment failure

- *Hypotheses 4 & 5:*
  - That body composition parameters predict response to anti-TNF therapy
  - That patients with increased visceral adipose tissue mass have a lesser clinical response to anti-TNF therapy
- *Aims:*
  - To apply body composition analysis to a cohort of inflammatory bowel disease patients with available clinical outcome data after commencement of anti-TNF therapy
  - To determine associations between body composition parameters/phenotypes and time to loss-of-response after anti-TNF induction

Chapter 7: Visceral adiposity predicts recurrence in post-operative Crohn's disease patients

- *Hypotheses 6 & 7:*
  - That body composition parameters predict endoscopic recurrence after surgery for Crohn's disease

  - That increased visceral adipose tissue is associated with less response to treatment with adalimumab, and with lower serum adalimumab levels
- *Aims:*
  - To apply body composition analysis to a set of subjects from a randomised controlled trial examining the effect of routine early assessment and treatment escalation after surgery for Crohn's disease
  - To determine the importance of body composition parameters as predictors of endoscopic recurrence and treatment failure after surgery for Crohn's disease, compared to established risk factors such as smoking, prior surgery and penetrating Crohn's disease phenotype

List of abbreviations

ADA	Adalimumab
ASMI	Appendicular skeletal muscle index
ATI	Antibodies to infliximab
BFI	Body fat index
BFMI	Body fat muscle index
BIA	Bioelectrical impedance analysis
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
CD	Crohn's disease
CDAI	Crohn's disease activity index
CONSORT	Consolidated standards of reporting trials
CRP	C reactive protein
CT	Computed tomography (scan)
CTE	Computed tomography enterography
CZP	Certolizumab
DXA	Dual energy X-ray absorptiometry
EEN	Exclusive enteral nutrition
EN	Enteral nutrition
ESR	Erythrocyte sedimentation rate
FFM	Fat-free mass
FFMI	Fat-free mass index
FHNC	Functional hepatic nitrogen clearance
FM	Fat mass
FODMAP	Fermentable oligosaccharides, disaccharides, monosaccharides and polyols
FSH	Follicle stimulating hormone
FW	Free water
GC	Glucocorticoid
GV	Growth velocity
HDL	High-density lipoprotein
HV	Height velocity
HVSDS	Height velocity standard deviations
IAAT	Intraabdominal adipose tissue
IAF	Intraabdominal fat
IBD	Inflammatory bowel disease
IBDQ	Inflammatory bowel disease questionnaire
IFX	Infliximab
IGF	Insulin-like growth factor
IL	Interleukin
IMAFT	Intramuscular adipose-free tissue
IMAT	Intermuscular adipose tissue
IVNAA	In vivo neutron activation analysis
JAK	Janus kinase
LOR	Loss of response
LTM	Lean tissue mass
MFI	Mesenteric fat index
MIF	Macrophage migration inhibitory factor
MMPN	Methylmercaptopurine nucleotide
MRI	Magnetic resonance imaging (scan)
MUAC	Mid upper arm circumference
NA	Not applicable
NS	Not significant
OR	Odds ratio
PCDAI	Paediatric Crohn's disease activity index
PK	Pharmacokinetic(s)
PMI	Precision Medicine Initiative
PN	Parenteral nutrition
PNR	Primary non-response
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
RCT	Randomised controlled trial
SAT	Subcutaneous adipose tissue
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SF	Subcutaneous fat
SFA	Subcutaneous fat area
SM	Skeletal muscle
SMI	Skeletal muscle index
SMM	Skeletal muscle mass
SMP	Skeletal muscle percentage
TBK	Total body potassium
TBP	Total body protein
TBW	Total body water
TGN	Thioguanine nucleotides
TNF	Tumour necrosis factor alpha
TPMT	Thiopurine methyltransferase
UC	Ulcerative colitis
VAT	Visceral adipose tissue
VFA	Visceral fat area
WHO	World Health Organisation

Chapter 2: The role of body composition in the treatment of Crohn's Disease: A systematic review

Structure of review

Introduction

Crohn's Disease is a chronic inflammatory disease, characterised by transmural inflammation of the digestive tract. This inflammation, associated malnutrition, and immunosuppressive drug therapy may contribute to altered body composition in Crohn's disease patients[1].

The concept of metabolically distinct body compartments, and measurement of these compartments, has evolved from a two-compartment model (fat mass and fat-free mass) proposed in the 1950s, using underwater weighing techniques by Behnke and colleagues[2]. Three-, four- and six-compartment models are now in use depending on the technique applied, comprising combinations of measures of fat mass, total body water, total body protein, soft tissue minerals, bone minerals, and glycogen[3]. Body weight or body mass index may not accurately estimate lean and adipose tissue compartments[4], which may be better quantified in clinical practice by various techniques[5] including bioelectrical impedance analysis (BIA), cross-sectional or volumetric computed tomography (CT) or magnetic resonance imaging (MRI) analysis, dual-energy x-ray absorptiometry (DXA) and air displacement plethysmography.

In addition to these conceptual compartments, the understanding that the fat compartment exhibits different metabolic behaviour in different anatomical locations has led to the development of techniques for assessing visceral adipose tissue as a distinct entity. There is considerable variation in the anatomical deposition of fat among individuals of the same body mass index and same total fat mass[6,7]. The intra-abdominal fat compartment, or visceral adipose tissue, has distinct metabolic activity, cellular composition, inflammatory infiltrate and cytokine production[8]. In Crohn's disease, mesenteric "fat wrapping" of the intestine was recognised as disease-specific by Burril B Crohn[9], and correlates with transmural inflammation[10]. Hyperplasia, rather than hypertrophy, of visceral adipose tissue is a hallmark of Crohn's disease, with up to four times the cellular mass per unit area of adipocytes in Crohn's disease compared to controls[11]. Multi-slice CT and MRI scanning are generally accepted as the reference standard for determining visceral adipose tissue volume although single-slice imaging has shown a good correlation (r=0.95-0.99) with volume estimation from multi-slice analysis[12,13].

Whole body DXA is a widely-used body composition technique involving low-dose ionising radiation (approximately 3.6 μSv; background radiation exposure is 7 μSv per day[14]). It

provides a sensitive and specific measure of bone mineral density at selected skeletal sites[15], and is widely used for this application. In areas where the beam does not intersect bone, the ratio of the attenuation of the two X-ray energies can be used to estimate fat and lean tissue masses individually[16]. Extrapolation of these values applied to a whole body DXA scan can provide estimates of total body fat and lean mass as well as bone mineral density[15], and correlates well with alternatively obtained measures of these components of the four-compartment model of body composition[17].

There is good correlation between DXA and CT measurements of abdominal adiposity[18], but DXA is not able to distinguish fat contained within the abdominal cavity from subcutaneous fat. A combination of anthropometric measures and values from DXA may accurately estimate visceral adipose tissue volume[19], although a number of studies have shown that correlation with CT measures of intra-abdominal fat vary with gender with $r = 0.46$ to $r = 0.85$[20-22].

The assessment of skeletal muscle mass by DXA, is well described and validated[23] and the formulation of an appendicular skeletal muscle index (ASMI) has been incorporated into standard definitions of sarcopenia, the condition of reduced muscle mass in conjunction with impaired muscle strength or physical performance[5,24]. Appendicular skeletal muscle index, from DXA, is the appendicular skeletal muscle mass, in kg, divided by the square of the height in metres. Values more than two standard deviations below a young adult mean for gender are considered in the sarcopenic range[24].

Identification of sarcopenia by DXA offers important prognostic information in cohorts of elderly or obese patients, or those with malignancy[12,24-27]. Our own validation study confirmed that skeletal muscle area from single-slice imaging at a lumbar level correlates well with total body fat mass, fat-free mass and appendicular skeletal muscle mass obtained by DXA in patients with Crohn's disease[28].

Contemporary therapy options for Crohn's disease include a small role for 5-aminosalicylates, but standards of care comprise immunomodulators such as thiopurines and methotrexate, corticosteroids and monoclonal antibodies to tumour necrosis factor alpha (anti-TNF drugs)[29-31].

Some of these medications are dosed in adult patients according to weight – which has a variable correlation with body composition compartments. In particular, the anti-TNF drug infliximab has weight-based dosing, whereas its counterparts adalimumab and certolizumab

have fixed doses. Azathioprine and 6-mercaptopurine (6MP), the thiopurines, are purine antimetabolites and traditionally dosed by weight, although this practice varies. Methotrexate is generally given as a fixed dose[31].

Recent additions to the pharmacological armamentarium against Crohn's disease have been an anti-interleukin 12 and 23 antibody (ustekinumab; binary dosing with a weight cut-off), anti-integrin antibodies (particularly vedolizumab and etrolizumab; fixed doses), and emerging therapies such as new oral small molecules such as Janus kinase (JAK) inhibitors (for example, tofacitinib and peficitinib [JAK 1 & 3], and filgotinib [JAK 1]), anti-sense oligonucleotides to SMAD7 (mongersen), alpha-4 integrin antagonists and sphingosine-phosphate receptor agonists[32]. With these new medications, endpoints for defining treatment success have also changed. Whereas many early studies examined clinical remission or clinical response, often using the Crohn's Disease Activity Index (CDAI: a score based on the past week's stool frequency, abdominal pain, general well-being, extra-intestinal manifestations of Crohn's disease, use of anti-diarrhoeal medications, presence of an abdominal mass, low haematocrit, percentage deviation from standard body weight[33]), recent research incorporates endoscopic assessment of disease, quality of life indicators such as the Inflammatory Bowel Disease Questionnaire (IBDQ)[34], and biomarkers such as faecal calprotectin and serum C-reactive protein.

Determination of body composition may have important implications for prognosis and treatment of patients with Crohn's disease, with studies in other inflammatory conditions demonstrating associations between low muscle mass and poor clinical outcomes[35-38] and treatment toxicity[39-41].

We sought to perform a systematic review of the literature regarding the role of body composition in the treatment of Crohn's Disease.

Methods

A search was performed on 30 July 2016, of OVID MEDLINE® 1946 – present, Embase Classic+Embase 1947-present, Cochrane Central register of Controlled Trials and Cochrane Database of Systematic Reviews 2005-present, using the following search term:

1. exp Inflammatory Bowel Diseases/
2. crohn*.mp. [mp=tx, hw, sa, ti, ab, kw, ct, ot, sh, tn, dm, mf, dv, nm, kf, px, rx, ui]
3. ulcerative colitis.mp. [mp=tx, hw, sa, ti, ab, kw, ct, ot, sh, tn, dm, mf, dv, nm, kf, px, rx, ui]
4. exp Body Composition/
5. exp Body Constitution/
6. sarcopenia.mp. or exp Muscle, Skeletal/ or exp Sarcopenia/ or exp Muscular Atrophy/
7. myopenia.mp.
8. visceral adipose tissue.mp. or exp Intra-Abdominal Fat/
9. exp Adipose Tissue/ or fat mass.mp.
10. exp Thioguanine/ or exp 6-Mercaptopurine/ or exp Immunosuppressive Agents/ or exp Azathioprine/
11. methotrexate.mp. or exp Methotrexate/
12. exp Infliximab/
13. adalimumab.mp. or Adalimumab/
14. infliximab.mp. [mp=tx, hw, sa, ti, ab, kw, ct, ot, sh, tn, dm, mf, dv, nm, kf, px, rx, ui]
15. vedolizumab.mp.
16. exp steroids/ or prednisolone/
17. prednisolone.mp. [mp=tx, hw, sa, ti, ab, kw, ct, ot, sh, tn, dm, mf, dv, nm, kf, px, rx, ui]
18. hydrocortisone.mp. [mp=tx, hw, sa, ti, ab, kw, ct, ot, sh, tn, dm, mf, dv, nm, kf, px, rx, ui]
19. exp Mesalamine/
20. mesalazine.mp. [mp=tx, hw, sa, ti, ab, kw, ct, ot, sh, tn, dm, mf, dv, nm, kf, px, rx, ui]
21. exp Aminosalicylic Acids/ or olsalazine.mp.
22. exp Sulfasalazine/ or balsalazide.mp.
23. 1 or 2 or 3
24. 4 or 5 or 6 or 7 or 8 or 9
25. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
26. 23 and 24 and 25

Articles were limited to those published in English and involving human subjects. A total of 677 records were identified for screening by this search strategy and from recursive searching of the references of full-text articles reviewed (figure 2.1).

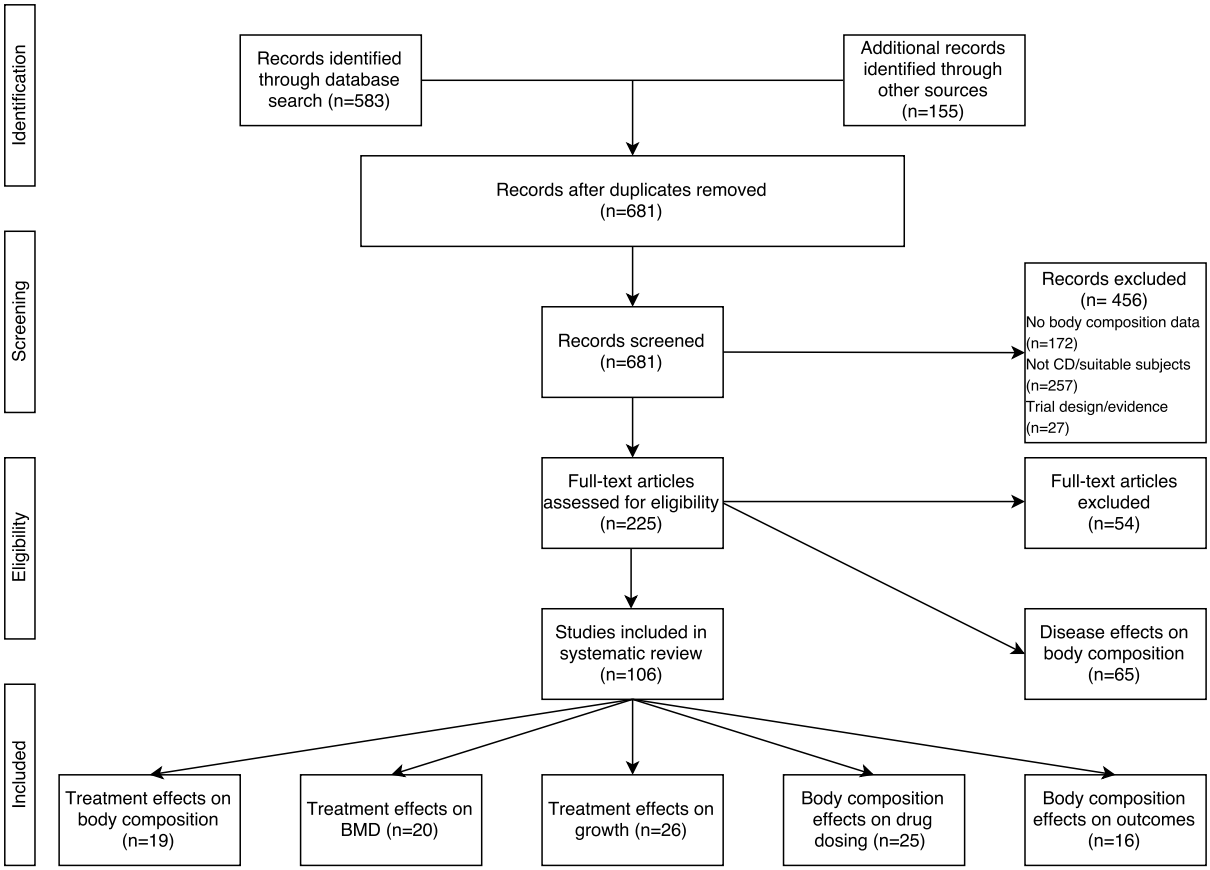


Figure 2.1 PRISMA study flow diagram

The search strategy was designed to combine body composition, Crohn's disease and treatments. EPPI-Reviewer 4 (EPPI-Centre, University of London, UK) was used to collate and categorise studies. The included studies were all subject to peer review – either by publication in peer-reviewed journals, or by selection for conference presentation. Adult and paediatric studies were included. Inclusion criteria comprised: primary study group were individuals with Crohn's disease, and experimental methods made use of body composition, weight or anthropometric measures. There was no restriction based on study type.

Thematic division was made according to the primary findings of the study, into the following subjects: a) treatment effects on body composition; b) treatment effects on bone mineral density (BMD); c) treatment effects on growth; d) body composition effects on drug dosing; and e) body composition effects on outcomes. Papers best-matched to a sixth category, disease effects on body composition, were identified and are listed in a selected bibliography (Table 6). This group was not analysed in further detail, as a recent systematic review of the literature has been published[1].

Results

Treatment effects on body composition

Nineteen studies (Table 1) reported the effect of Crohn's disease treatment on body composition parameters. Of these, 14 were prospective cohort studies (n=1851), one a retrospective cohort study (n=20), one was a meta-analysis (n=1442), one, a cross-sectional survey (n=558 Crohn's disease) and two were randomised control trials (n=34).

The meta-analysis examined the association between body mass index and inflammatory bowel disease[42], including 897 Crohn's disease patients, and found that BMI was lower than 1202 matched controls and that the mean BMI was lower in papers where no therapy was given for Crohn's disease, although this was not statistically significant.

Enteral nutrition

Exclusive enteral nutrition is recognised as appropriate first-line treatment for moderately active Crohn's disease in children[43]. A paediatric prospective cohort study[44] found that resting energy expenditure measured by indirect calorimetry was not reduced per unit mass in Crohn's disease patients compared to controls, despite reduced body weight and reduced lean tissue (body composition was measured by anthropometry, bioelectrical impedance analysis, total body potassium, $H_2{}^{18}O$, and bromide space studies). Enteral nutrition caused an increase in all body composition compartments and an increase in resting energy expenditure. There was greater height and lean body mass increase in enteral nutrition-treated patients compared to prednisolone treatment. Two other studies in this group reported outcomes in paediatric patients. One was a randomised control trial of two formulations of peptide-based exclusive enteral nutrition in 14 children with Crohn's disease[45]; weight, fat-free mass and skinfold thickness increased during enteral feeding, with Crohn's disease activity reducing.

Although considered adjunctive therapy in adults[46], an adult prospective cohort study involving 61 patients[47] reported increased skeletal muscle mass, protein mass and reduced resting energy expenditure in patients who achieved remission by the use of exclusive enteral nutrition. However, the body composition techniques were not specified in the methods section of this article, and the statistical conclusions have been criticised as invalid[48] in a letter to the editor, which highlighted inappropriate statistical tests and inconsistent results. No rebuttal or corrigendum appears to have been published.

Another study examining exclusive enteral nutrition in an adult cohort (n=30) of Crohn's disease patients[49] found that the patient group had a mean weight of 11.3kg below that of an age- and sex-matched control group. In vivo neutron activation analysis, DXA, bioelectrical impedance analysis and total body potassium were used to assess body composition compartments. After 3 weeks of exclusive enteral nutrition, weight increased by a mean of 1.9kg, with an equal increase in body protein and fat. A small (n=20) randomised control trial comparing two weeks of oral elemental nutrition to high-dose corticosteroids in adults with active Crohn's disease[50] found that diet improved disease activity and increased body weight. Corticosteroids were associated with an increase in fat-free mass (measured by bioelectrical impedance).

Corticosteroids

The other paediatric study to report treatment effects on body composition (n=31) examined changes in intravenous amino acid kinetics over a two-week period of corticosteroid use in newly-diagnosed Crohn's disease[51]. The rates of appearance of phenylalanine (32%) and leucine (26%) increased significantly, reflecting increased protein breakdown, and the rate of appearance of urea also increased significantly (273%), reflecting increased protein loss.

We conducted a survey targeted to members of a national inflammatory bowel disease patient support group. This found a self-reported prevalence of overweight or obesity of 39%[52], with patients who reported taking more than 10 courses of corticosteroids more likely to be overweight or obese. Conversely, a 2-year repeated-measures study of bisphosphonate use presented in abstract[53] found corticosteroid use was associated with lower body fat and lower BMI, using DXA to determine body composition and bone mineral density. Despite the prevalence of corticosteroid use in Crohn's disease, our search strategy did not identify any other studies where corticosteroid use was examined as a covariate of body composition.

Anti-TNF drugs

The first three months of anti-TNF therapy for refractory Crohn's disease was associated with an increase in BMI and muscle parameters measured by bioelectrical impedance analysis in a prospective cohort study of 33 Crohn's disease and 7 ulcerative colitis patients[54]. No changes

in measures of fat mass were noted, and no difference between the effect of infliximab or adalimumab was discernible. A repeated-measures cohort study[55] involving 20 Crohn's disease patients assessed visceral adipose tissue used CT enterography images prior to commencement of infliximab in comparison to images obtained a median of 447 days later. Disease activity was scored on the images and cross-sectional area of muscle and fat compartments was measured. Subjects were divided into responders (n=10), partial responders (n=4) and non-responders (n=6). Some of the smaller fat compartments showed a difference in change over time, but these findings must be interpreted with caution as sample size was small, confidence intervals were wide, and insufficient detail was given regarding the statistical methods in this poster abstract. Another poster abstract described bioelectrical impedance analysis in 8 patients receiving infliximab induction[56]; a primary response in disease activity was seen in seven of eight patients and there was a trend towards increased fat-free mass at week 6, with an increase in phase angle, which is generally considered a marker of cell mass and nutritional status[57].

A four-week trial of infliximab induction in 20 Crohn's disease patients was associated with weight gain without alteration in body composition by bioelectrical impedance[58]. An increase in serum leptin and serum cholesterol was independent of weight gain, and was felt to have been related to downregulated inflammatory mediators. In a larger (n=132) set of prospective cohort studies[59], total abdominal fat area (measured by MRI) increased by 18% in one set of 21 patients 8 weeks after infliximab induction, with a predominant increase in visceral adipose tissue (27% increase), which was independent of BMI or steroid use. Infliximab maintenance therapy was associated with reduced fasting glycaemia and HbA1c, in both patients treated with steroids at baseline and those who were not. Total cholesterol and HDL cholesterol increased in the first 3 months of treatment and remained stable thereafter.

Over a 60-week period, 50 patients with Crohn's disease commencing infliximab experienced an increase in body mass index[60], with a greater increase in patients who achieved a clinical remission. Being underweight and the presence of small bowel disease were factors predicting increased weight gain after infliximab. Similarly, a prospective cohort of 30 infliximab-treated Crohn's disease patients[61] found that nutritional risk index correlated with Crohn's disease severity. Clinical response to infliximab was associated with weight gain – undernutrition, and achieving clinical remission, were again identified as factors predicting greater weight gain.

Commencement of infliximab was found to reverse skeletal muscle wasting in 23 Crohn's disease patients in a prospective study[62] utilising quadriceps MRI and dynamometry to demonstrate increased muscle volume and strength after 25 weeks.

Functional hepatic nitrogen clearance was a technique used to demonstrate protein catabolism associated with prednisolone use for 1 week (functional hepatic nitrogen clearance increased by 50%, P = 0.03) in an observational study of 37 patients with active inflammatory bowel disease[63], with the opposite effect seen in patients treated with infliximab (reduced by 15%, P = 0.09).

Treatment effects on bone mineral density

Twenty-one trials (n=1077) were identified (Table 2) as examining the effect of medication or vitamin supplementation on bone mineral density (BMD) in Crohn's disease patients. Most studies were retrospective cohort analyses examining short-term changes in BMD associated with corticosteroid use, with heterogeneous results.

Three randomised control trials were identified. One of these examined fluoride supplementation in inflammatory bowel disease patients with low BMD (lumbar t-score below -2)[64]. The control arm of the study was placebo; all subjects received vitamin D and calcium supplements. Lumbar spine bone density increased significantly in both groups; the effect of fluoride was not significant. Another randomised control trial examined 12 weeks of different regimens of intravenous methylprednisolone in 19 inflammatory bowel disease patients[65]; the steroid dose was tapered each week and administered either each day, or in 1-3 doses each week to provide the equivalent weekly dose. Daily dosing was associated with a reduction in total body bone mineral density, with a trend towards increased fat mass compared to bolus dosing. The other randomised placebo-control trial examined the efficacy and safety of intranasal calcitonin in childhood inflammatory bowel disease (n=63)[66].In participants with Crohn's disease, the spinal BMD z-score improved between screening and 9 months compared to a negative change in the placebo group, however, this advantage did not persist to the conclusion of the study at 18 months.

Six studies reported bone density outcomes in patients receiving anti-TNF therapy. Peripheral quantitative computed tomography (pQCT) was used to measure BMD in a paediatric cohort of 19 subjects[67] at baseline and after 6 months of therapy. Despite improved disease activity,

pubertal progression and corticosteroid reduction, no change in muscle or BMD z-scores was seen. A cross-sectional study of 83 Crohn's disease patients[68] found that those on infliximab had lower BMD; this was ascribed to more severe disease. Higher cumulative corticosteroid exposure was also associated with lower BMD. In a paediatric study of 78 Crohn's disease patients[69], pQCT showed prevalent osteopenia and myopenia; bone and muscle volumes increased after diagnosis and commencement of treatment. Although a small number of patients received anti-TNF drugs, no analysis of this subgroup was undertaken. Corticosteroid use was associated with an increase in cortical volumetric bone mineral density; this was in conjunction with reduced disease activity. In 45 adult Crohn's disease patients commencing infliximab therapy[70], increased BMD was noted after approximately two years , independent of weight change. Two paediatric studies from the same institution monitored outcomes of anti-TNF therapy, with DXA one year prior to therapy and one year after commencement. Infliximab was associated with increased weight gain, a majority achieving catch-up growth and stable BMD[71]. Similar findings were noted in a group of 18 patients treated with adalimumab[72].

Medical management of Crohn's disease, including vitamin D and calcium supplementation, was associated with a slight increase in BMD over a median time of approximately 4 years in a cohort of 84 patients[73]. Risk factors for low BMD were age, male sex, increasing age at diagnosis and low BMI.

There were mixed results regarding the effect of corticosteroid use on BMD. An association with short stature but not low BMD was found, with a correlation between disease activity and height z-score approaching statistical significance in a cohort of 104 children and young adults with Crohn's disease[74]. A smaller paediatric cross-sectional study[75] (n=32) found that children with Crohn's disease who had received steroids had significantly reduced BMD compared with those who had not and compared to healthy controls. No correlation was found between magnitude of steroid usage and reduction of bone mineral content. A cross-sectional study of 75 Crohn's disease patients[76], using a definition of osteoporosis as being 2 standard deviations below an age- and sex-matched mean, found a prevalence of osteoporosis of 30.6%, with higher mean lifetime steroid exposure in that group. A similar proportion of patients meeting the WHO definition of osteoporosis[77] (30%) was found in a cross-sectional analysis of 91 Crohn's disease patients[78]; those with osteoporosis had higher corticosteroid use, lower BMI, longer duration of disease and more bowel resections. Linear regression analysis identified only BMI

and bowel resection history as significant risk factors. In a retrospective cohort study of 29 patients from the same centre[79], baseline BMD was low (z-scores spine -1.6, femur -1.4) but no significant change in BMD was noted over a mean time of 41 months, despite the use of corticosteroids in 93% of patients during the interval. BMI increased and ESR reduced during the study period, and 9 patients used bisphosphonates, 20 calcium supplementation and 11 vitamin D.

A prospective cohort study[80] found that mean BMD was lower in Crohn's disease patients than in ulcerative colitis or healthy control. A correlation was found between BMD and BMI, and an inverse correlation with lifetime steroid dose. 30 Crohn's disease patients had repeated measures of BMD at a mean interval of 21 months. There was no change in BMD, regardless of steroid use; in patients with ulcerative colitis, however, a reduction in BMD associated with steroid use was observed. In a paediatric prospective cohort study involving 17 Crohn's disease patients and 30 with ulcerative colitis[81], bone mineral density and bone mineral content did not improve in a majority over a 5-year interval, despite good disease control. Low lumbar spine BMD was associated with completed pubertal development, low body weight, and greater lifetime cumulative weight-adjusted prednisolone dose. Another paediatric prospective cohort study[82] found that mean BMD was lower in 58 Crohn's disease patients than those with ulcerative colitis or healthy controls, and osteopenia was associated with low BMI and higher serum interleukin-6. Prednisolone use did not correlate with low BMD. Clinical improvement was associated with bone mineral content gain, but this did not normalise.

A cross-sectional paediatric analysis of 90 inflammatory bowel disease patients[83] found a 20% rate of significantly low BMD more than 2 standard deviations below age- and sex-matched mean) in males and 8% in females. A similar proportion of osteoporosis was noted in steroid-naïve and steroid-treated patients. A prospective cohort of 24 paediatric Crohn's disease patients were followed for 12 months with regular measurements of bone density using quantitative ultrasound[84]: one-third of patients were in remission, one-third had active disease, and one-third were in remission and treated with oxandrolone. Most of those with active disease were treated with prednisolone. There was no significant change in measurement expressed as z-scores in patients in remission, but those with active disease experienced bone density loss and those on oxandrolone some gain.

In 15 adult patients receiving corticosteroids for active disease, significant bone mineral density loss was noted at the femoral neck after two months[85]. No change was noted over the same period in patients with inactive Crohn's disease recruited as controls; previous corticosteroid use was not associated with baseline BMD, although weight, site of disease and dietary calcium deficiency were associated with low BMD. It was unclear whether disease activity or corticosteroid use was a cause of BMD loss in the study period: paucity of evidence of a causal direction is reviewed in the discussion section.

Treatment effects on growth

Twenty-six studies (Table 3) were identified as investigating relationships between treatment interventions and growth parameters. As expected, most of these studies were in paediatric cohorts. One adult study[86] examining correlations between growth hormone, androgens and body composition, was included due to its prominent citation in the literature. This study, however, was cross-sectional rather than interventional.

Twelve studies examined the effect of monoclonal antibodies to tumour necrosis factor alpha (anti-TNF drugs) on growth; 4 were prospective, and 9 retrospective cohort studies. In these studies, height, weight and body mass index (BMI) were generally expressed as z-scores, relative to a population mean. The change in velocity of height and weight growth were analysed. Several papers discussed the concept of "catch-up growth"[87], whereby accelerated growth toward a genetically-determined target occurs after treatment of a growth-inhibiting condition. Eleven of the papers including data on anti-TNF effects reported significant catch-up growth after treatment initiation, with growth velocity highest in subjects who experienced clinical response or remission after treatment initiation[88-93] and in those for whom corticosteroid cessation was possible[90,94]. Corticosteroid use was also identified as a risk factor for impaired growth in the only study not to demonstrate a statistically significant change in growth velocity with anti TNF therapy[95]. In that study, a non-significant improvement in growth velocity was found in patients treated for more than 1 year with infliximab compared with those treated for less time. Increased growth velocity was reported as a secondary outcome in another paediatric study of adalimumab in refractory Crohn's disease[96].

One retrospective cohort study examined testosterone supplementation in 8 boys with Crohn's disease and delayed growth and puberty[97], finding that transdermal or parenteral administration of testosterone was associated with improved growth, pubertal progression and

virilisation at 6 months. Pubertal stage was found to be a determinant of growth velocity after treatment[93,94,97,98], with evidence of a bidirectional influence – Crohn's disease is associated with delayed puberty[99].

Five prospective studies (either randomised controlled trials [RCT] or prospective cohort studies) examined the use of recombinant human growth hormone (rhGH) in children with Crohn's disease[100-104]. Of these, one study reported negative findings[100]; in 8 older children (mean age 17.2 years), rhGH was not associated with changes in markers of protein synthesis. The other papers reported improvements in growth velocity, height and weight, with greater effects seen after 12 months of therapy than after 6 months.

Body composition effects on drug dosing

Seventeen papers (Table 4) were identified as reporting the effects of body composition parameters – either simple measures such as weight, height, BMI, or more technical analysis of body composition compartments – on dosing of drugs used to treat Crohn's disease. Of these, four papers (n=475) reported relationships with adalimumab, six (n=585) related to thiopurines, two (n=2237) to certolizumab, four studies (n=816) examined infliximab and one study (n=2554) concerned vedolizumab. Outcome measures included serum drug or metabolite levels and pharmacokinetics. The endpoints of clinical response and loss of response are discussed in more detail in the section "Body composition effects on outcomes".

Serum drug or metabolite levels

Thiopurine dosage in inflammatory bowel disease has conventionally been based on weight[105]. The measurement of erythrocyte concentrations of thiopurine metabolites has been shown to predict therapeutic efficacy and now provides a basis for dose individualisation[46,106]. A questionnaire study of US gastroenterologists[107] found a variety of practice regarding thiopurine prescription and monitoring, with 46% of respondents using metabolite level testing, and 76% reporting a maximal dose of 1.0-2.5 mg/kg azathioprine or (62%) 1.0-1.5 mg/kg 6MP.

In inflammatory bowel disease patients, leukopenia has been associated with erythrocyte 6-thioguanine nucleotide (6TGN) levels >400[108], whereas clinical response has been associated with 6TGN levels between 230 and 400. We analysed a single-centre cohort of adult patients[109],

and found no correlation between 6TGN levels and weight, BMI or any body composition parameter measured by DXA and CT. Potentially hepatotoxic 6 methylmercaptopurine (6MMP) levels did, however, correlate with azathioprine dose, thiopurine dose/kg body weight, thiopurine dose/kg of fat-free mass, thiopurine dose/body surface area and thiopurine dose/BMI. A larger cross-sectional study[110] also did not demonstrate any significant association between weight-based thiopurine dosing and 6TGN. Instead, a negative correlation was identified between BMI and 6TGN, as well as between calculated body fat index (using age, BMI and sex) and 6TGN. Similar data had been presented by the same authors as a conference abstract[111]. A higher degree of correlation was seen between dose of azathioprine/kg body weight and 6MMP levels than 6TGN levels in a paediatric cohort[112], although both metabolites showed a statistically significant relationship with drug dose/weight.

One study[113], presented in abstract, reported that the difference between serum adalimumab levels at weeks 6 and 12 was modest negatively correlated with body surface area (BSA), fat free mass index and skeletal muscle index measured by bioelectrical impedance analysis. This finding suggests muscle mass may play a role in adalimumab pharmacokinetics. No difference was seen with fat parameters nor fluid compartments. Adalimumab levels were found to be relatively stable on an individual basis, but exhibited substantial inter-patient differences in a retrospective cohort pharmacokinetic study[114], which found that baseline BMI inversely correlated with serum adalimumab concentrations at week 28 of standard induction and maintenance dosing. Similarly, in a phase 3 trial of certolizumab in Crohn's disease[115], an inverse correlation was observed between baseline body weight and certolizumab trough levels after a loading dose[116]; higher plasma concentrations correlated with endoscopic response. Lower body weight was associated with lower trough infliximab levels in a paediatric prospective cohort study which utilised standard weight-based dosing[117].

Pharmacokinetics

The first study to describe the pharmacokinetics of infliximab in inflammatory bowel disease with a compartment model[118] identified two factors, weight and sex, as contributing to a two-compartment model by altering central volume of distribution. The authors attributed these influences to variations in plasma volume. A larger pharmacokinetic study of infliximab in Crohn's disease[119] found that body weight had a non-linear effect on infliximab clearance, with decreased infliximab trough levels for low body weight patients; a 40 kg patient may be

expected to have 80% of the reference (70kg) patient exposure and a 90kg patient 110%. This finding implied that low body weight patients may be at risk of loss of response due to drug clearance at fixed weight-based doses, and corroborates the findings of Hämäläinen[117]. The largest pharmacokinetics study of infliximab in Crohn's disease used data from 692 patients in phase 3 studies[120], and found that weight was a significant covariate, despite weight-based dosing. This suggested an inadequate correction of body size by per-kilogram dosing. The volume of distribution/kg decreased with increasing total body weight: under-dosing of low weight individuals may be partly due to this phenomenon.

A meta-analysis of certolizumab pharmacokinetic data from 9 studies carried out in 2157 Crohn's disease patients[121] found that BSA as a covariate contributed more to a pharmacokinetic model than did weight or BMI, by affecting apparent clearance and apparent volume of distribution in a linear fashion; no effect was seen on absorption. The authors commented that "any measure of body size could probably be used".
A correlation was also found between vedolizumab linear clearance and body weight in a meta-analysis including 2554 subjects[122]; the authors commented that measures of body size were the most commonly identified covariates influencing the pharmacokinetics of therapeutic monoclonal antibodies.

Ustekinumab is a monoclonal antibody to the shared interleukin (IL)-12 and IL-23 p40 subunit. One recent phase 3 RCT[123] of ustekinumab in Crohn's disease has reported on pharmacokinetics and immunogenicity; this study was not identified by the search string due to its publication date, but has been included in this analysis as it is the only study reporting pharmacokinetics of ustekinumab in Crohn's disease. Serum levels of ustekinumab 8 weeks after intravenous infusion were approximately three times higher in patients who had received a 6mg/kg intravenous dose compared to those who had received a fixed dose of 130 mg. Studies in psoriasis – an indication with greater clinical experience than Crohn's disease – found that ustekinumab concentrations were lower with increasing weight at both doses of 45 mg and 90 mg[124]. Higher serum levels were associated with better clinical efficacy in both psoriasis and Crohn's disease[123,124].

In a paediatric randomised control trial of adalimumab, patients were dosed by weight, with the standard adult dose (160 mg week 0, 80 mg week 2, 40 mg every other week) for weight ≥40 kg, and half the dose for weight < 40kg. Some patients were randomised after induction

to a 'low dose' maintenance arm in which half the dose of adalimumab was given. Higher baseline body weights were associated with greater adalimumab clearance; median clearance was approximately 50% higher in the fourth quartile (>54 kg) compared with the first quartile (<34 kg)[125].

Body composition effects on outcomes

Twenty-four studies (Table 5) examined the role of body composition in determining clinical outcomes. Two were randomised trials[126,127]. Body composition analysis varied, and the outcome data were heterogeneous. Four studies (n=485) examined body composition as a predictor of post-surgical outcomes, eighteen (n=3104) assessed response to therapy. Anti-TNF drugs, thiopurines, corticosteroids and ustekinumab were the drug treatments used.

Response and loss of response to drug treatment

The largest study, a retrospective cohort of 1176 (818 Crohn's disease), examined responses to azathioprine based on body mass index[128]. No mention was made in that paper of the doses of azathioprine used, nor of thiopurine metabolite testing. The findings, that Crohn's disease patients with a BMI >25 kg/m^2 and treated with azathioprine for less than 3 years experienced fewer flares of disease in the year after discontinuation of azathioprine, were reported in the abstract as showing that: "azathioprine responsiveness depends on body mass index (BMI). The relationship is reciprocal in UC and CD, with a better outcome in UC patients with a BMI<25 and in CD patients with a BMI>25". In fact, no difference in responsiveness to azathioprine commencement was shown between BMI categories in Crohn's disease, as the mean flare rate reduced to zero in both groups (P = 0.676).

A retrospective cohort study of weight-based dosing of azathioprine in children[129] found that 3mg/kg/D was safe, well-tolerated and effective, with 72% maintaining or increasing their dose. 16% of subjects in the cohort stopped therapy due to clinically significant adverse events, the majority being bone marrow toxicity. Drug metabolites were not tested. An early randomised trial of 1.0 mg/kg vs. 2.5 mg/kg in adult patients found a 15% incidence of leukopenia at higher dose; only 3.7% of the low dose arm experienced leukopenia[130]; in neither arm did efficacy measures meet statistical significance[127]. A study of adult patients receiving initial weight-based doing of thiopurines (2.0-2.5 mg/kg azathioprine or 1.0-1.5 mg/kg 6MP), followed by metabolite level testing, identified lower BMI (<18 kg/m^2) by multivariate analysis

as being associated with higher risk of treatment discontinuation[131]. Low-dose azathioprine (<1.0 mg/kg) has been reported as equally efficacious as 1.0-2.0 mg/kg in a Chinese population[132]. The paper posited that ethnicity may be a factor in thiopurine efficacy and toxicity and found that heavier body weight was a factor associated with long-term remission on low dose azathioprine.

Higher BMI was shown to increase the hazard of loss of response for (fixed dose) adalimumab-treated patients in a retrospective cohort study[133], although no significant effect was observed with patients treated with infliximab (dosage of which was weight-based).
In a small prospective cohort study, high BMI and high fat mass (measured by DXA) were associated with reduced response to infliximab[134]. In that study, BMI and FM correlated with post-infusion infliximab levels, which led the authors to comment that infliximab does not appear to distribute in the adipose tissue. Obese infliximab-treated patients in a retrospective analysis[135] were three times likelier to have a flare of Crohn's disease than non-obese patients in a retrospective study, with elevated risk correlating with BMI in a linear fashion.
In a paediatric cohort of Crohn's disease patients[136], (n=12) low BMI z-score was associated with a need for infliximab dose escalation. The authors postulated that low body mass index may identify patients who would benefit from a higher infliximab starting dose.

Our own retrospective analysis of a cohort of 68 inflammatory bowel disease patients[137], using the same CT-based techniques as Ding *et al.* to quantify muscle and fat tissue areas at L3, found that those with less skeletal muscle (than the gender-specific median) were at significant risk of earlier loss of response to anti-TNF drugs.
Data presented in abstract by Ding *et al.*[138] regarding response to anti-TNF drugs in a cohort of 106 Crohn's disease patients demonstrated that patients in the lowest quartile for (pre-treatment) CT-assessed skeletal muscle area at L3 were likelier to have primary non-response to treatment. In a smaller study (n=49) from the same cohort[139], visceral adiposity and low muscle radiodensity (myosteatosis) were identified as risk factors for primary non-response and loss of response, respectively. It may be the case that the significance of these factors became less as the sample size increased.

Ustekinumab showed efficacy in refractory Crohn's disease in a phase 2 RCT at a dose of 6mg/kg with the endpoints being clinical response or remission measured by Crohn's Disease

Activity Index (CDAI)[126]. This dosing schedule was different to that used in psoriasis trials, where fixed-dosing (45 mg if weight <100 kg, 90 mg if weight >100 kg) was used[124].

Obesity and visceral adiposity

A prospective, case-control study of 100 Crohn's disease patients[140] found that the prevalence of obesity was 17% among patients and 12% among age, socioeconomic class and sex-matched controls (difference non-significant [n.s.]). BMI >25 kg/m^2 was present in 40% of patients and 52% of controls (n.s.). Risk factors for increased BMI in Crohn's disease patients identified by regression analysis included age, sedentary lifestyle, lower CDAI and lower white cell count. C-reactive protein and BMI were positively correlated.

A small, prospective cohort study[141] (n = 31, all women) examined the role of visceral adipose tissue in Crohn's disease. MRI analysis, validated by abdominal ultrasound, was used to calculate visceral adipose tissue volumes, with air displacement plethysmography performed to determine total body fat mass and lean body mass. A history of disease and treatment for the preceding five years was recorded, and 6 months of follow-up incorporated indices of disease activity, complications, changes in medications and measurement of cytokines. 19 control subjects were included, matched by age and BMI. The Crohn's disease patients had significantly more visceral adipose tissue than controls (mean 1885 mL vs. 717 mL, P = 0.015), with patients in long-term remission having lower volumes of visceral adipose tissue, and slightly higher values of visceral adipose tissue for patients with "complicated" (penetrating or stricturing) Crohn's disease. The ratio of visceral adipose tissue to fat mass was not affected by cumulative prednisolone dose nor anti-TNF therapy, but higher ratios were associated with increased disease activity in the 6 months after study inception. A paediatric cohort study of 101 Crohn's disease patients with CT analysis of visceral adipose tissue volume[142] found that Crohn's disease patients had more visceral adipose tissue than controls, with higher visceral adipose tissue volume associated with penetrating or stricturing disease (odds ratio [OR] 1.7), hospitalisation in the first year of diagnosis (OR 1.9), more severe disease (OR 1.8), surgery (OR 1.4) and earlier surgery (OR 1.4).

A pilot cross-sectional study of 27 Crohn's disease patients, which did include BIA and anthropometric measures of body composition, found that more than half were overweight or obese, and that increased BMI was associated with increased abdominal pain and reduced wellbeing[143]. The prevalence of obesity was markedly different in a large retrospective cohort

study[144], which reviewed the records of 2065 patients and found only 3% were obese; with obese patients older at initial diagnosis and more prone to penetrating disease, perianal complications, hospitalisation and disease activity. Similarly, another retrospective cohort study including 48 obese Crohn's disease patients[145] found that later age at diagnosis and earlier time to first surgery were associated with obesity.

In a cross-sectional study of Crohn's disease (n=23, with 6 controls) paediatric patients, an association was made between severe Crohn's disease and increased visceral adipose tissue measured by MRI, despite lower BMI[146].

Outcomes after surgery

Body composition as a predictor of outcomes after surgery for Crohn's disease was the subject of three retrospective cohort studies: two used CT scans performed before surgery to determine body composition parameters, and one used bioelectrical impedance analysis. The specified endpoint for the larger study, comprising 269 patients[147], was infective complications within 30 days after surgery. Among other variables such as haemoglobin and albumin levels (which may be markers of disease severity), surgical urgency and high-dose prednisolone use, a higher ratio of subcutaneous to visceral fat was a predictor of postoperative infective complications. Conversely, the other CT-based study (n=72)[148] – using similar methodology to examine different postoperative outcomes – found that endoscopic recurrence at 6 months after surgery was associated with a lower ratio of subcutaneous fat to visceral adipose tissue.

A prospective cohort study of 138 adults which utilised bioelectrical impedance for body composition analysis in patients requiring intestinal resection for Crohn's disease[149], found that skeletal muscle percentage, BMI and body fat percentage increased after a median duration of 26 days of preoperative medical and nutritional management. Multivariate regression analysis with the endpoint of postoperative complications revealed preoperative skeletal muscle percentage as the only significant independent protective factor of those tested, with a threshold of 24.3% identified by ROC curve. A paper from the same group[150] found a 61.4% prevalence of sarcopenia among 114 patients. Patients with sarcopenia had a lower body mass index, lower preoperative levels of serum albumin, and more major complications (15.7% vs 2.3%, P = .027) compared with patients without sarcopenia. Preoperative enteral nutrition and preoperative serum albumin level >35 g/L were protective factors in multivariate analyses.

A small case-control study[151] examined the results of bariatric surgery in morbidly obese patients with active Crohn's disease receiving concomitant or deferred surgical treatment for Crohn's disease. Postoperative weight reduction was similar to 95 control patients, and most patients were able to reduce immunosuppression after surgery. Concomitant ileocolic resection was not associated with increased complications.

Discussion

Methods of body composition analysis

This systematic review found a variety of techniques were used for body composition analysis. Weight and height were the most-reported data and the basis for many of the repeated-measures studies. However, there are significant limitations to these measurements, as body composition of patients with Crohn's disease may differ substantially from that of weight- and height-matched healthy controls, with a poor correlation between BMI and lean mass observed even in clinical remission[1].

Most longitudinal studies using other methods were short-term. DXA was the commonest technology for longitudinal measures, largely in the context of monitoring bone mineral density. DXA is accessible and accurate[152], and provides reproducible regional assessments of lean tissue mass, bone mineral density and fat mass. Regular DXA scanning is recommended for inflammatory bowel disease patients[153], but prevalence of screening is low: only 1 in 5 patients had been screened in a large cohort[154]. Its use as a measure of body composition was less common in this review. Bioelectrical impedance is a widely-available technology that was reported by several studies; its ease-of-use, speed and inexpensiveness make it an accessible form of body composition analysis, although results are calculated based on population data and applicability in disease states is not certain[155]. Systemic errors have been identified in malnourished Crohn's disease patients[156].

In a small number of studies, cross-sectional imaging provided more information regarding anatomical compartments such visceral adipose tissue, as well as extrapolated values for whole body composition. Techniques which have little place in clinical practice, such as protein kinetics, in vivo neutron activation analysis, bromide space studies and total body potassium measurement were reported in only a handful of short-term studies, but provide useful information regarding dynamic short-term responses to treatments for Crohn's disease.

Technologies for performing body composition analysis continue to develop, with different methods more suited to reporting certain variables. Our own comparison of cross-sectional image analysis with DXA for Crohn's disease patients[28] validates measurement of fat mass and fat-free mass, as well as visceral, subcutaneous and intramuscular adipose tissue areas, using previous abdominal imaging. This unlocks a body of existing data, as CT or MRI scans are

frequently performed in Crohn's disease patients; approximately three-quarters of patient in one inception cohort study[157]. However, this technique requires significant operator input, and therefore is not accessible to clinicians and researchers without suitable software and training. Automated algorithms have been developed to accurately quantify adipose tissue areas and volumes[158,159], but these do not yet have a place in clinical practice.

Other methods for determining fat mass and fat-free mass have more mature reporting standards – bioelectrical impedance analysis, DXA and air displacement plethysmography among them. Quantification of anatomical compartments of adipose tissue, particularly visceral adipose tissue and subcutaneous adipose tissue, has not been possible with these latter modalities due to technical limitations. Recently, though, algorithms[160,161] and new proprietary applications[162,163] have been developed which allow estimation of visceral adipose tissue volume from DXA. There are no publications regarding the use of these technologies in patients with Crohn's disease, and adipose tissue compartment measurements in this review were obtained by cross-sectional or volumetric analysis of CT or MRI images, which remain the standard methods[158].

Effects of visceral adiposity and obesity

Obesity, particularly in association with increased waist circumference, is increasingly prevalent in most societies[164]. Abdominal obesity is associated with a low-grade inflammatory state and increased macrophage infiltration of mesenteric adipose tissue[165], with systemic insulin resistance and a pro-inflammatory profile of systemic cytokine release[166,167]. 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 mass of obese visceral adipose tissue[165].

The prevalence of obesity among Crohn's disease patients varied significantly between studies in this review, from 3%-17%[140,144], with some risk factors identified: number of courses of corticosteroids, age, sedentary lifestyle, lower disease activity. In other cohorts[168,169], not included in this review, obesity was found in 18-30%. Among respondents to our questionnaire to members of a national patient support group[52], the self-reported prevalence of obesity in Crohn's disease patients was 13% (unpublished data), and the mean body mass index of 24.7 kg/m^2 was lower than the Australian population mean of 27.9 kg/m^2 for men and 27.2 kg/m^2 for women. This variance is likely to represent a significant difference. Although there is a small systemic bias for underestimation when self-reporting body mass index, in large studies[170] the

difference between measured and self-reported BMI has been shown to be only approximately 0.57 kg/m^2.

Whether obesity is a predisposing factor to inflammatory diseases, including Crohn's disease, is unclear. Large, population-based prospective cohort and nested case-control studies have not shown a consistent association between premorbid obesity and the risk of developing Crohn's disease[171], although obesity at age 18 and magnitude of weight gain from the age of 18 were identified as risk factors in the Nurses' Health Study II[172]. Small numbers of incident diagnoses (9 in the obese group) do mean that results must be interpreted cautiously, but the multivariate-adjusted hazard ratio of 2.33 (95% CI 1.15-4.69) with a comparator group of women with BMI 20-24.9 kg/m^2 at age 18 was significant. In the same cohort, there was no significant association between obesity and increased risk of developing ulcerative colitis. The role of diet in this complex interaction is obscure: obesity, rather than being an initiating factor, may be a manifestation of a high fat or high refined sugar diet – both of which have been identified as risk factors in the development of Crohn's disease[173].

Obesity was associated with earlier loss of response to infliximab[135], earlier surgery[142,144,145] and later age at diagnosis[144,145].

This review identified that visceral adiposity was associated with penetrating or stricturing Crohn's disease and increased disease activity[141,142], primary non-response to infliximab[139], postoperative complications[174] and severe disease in children[142,146].

In Crohn's disease, mesenteric "fat wrapping" of the intestine was recognised as disease-specific by Burril B Crohn[9], and correlates with transmural inflammation[10]. Mesenteric fat in Crohn's disease is infiltrated with immune cells and pre-adipocytes expressing nuclear oligomerisation domains 1 and 2, having the potential to transdifferentiate into macrophages[175], and adipocytes able to function as macrophage-like cells by expressing toll-like receptors and inflammatory mediators. This ability may be beneficial against bacterial invasion, but may also contribute to abnormal intestinal inflammation. Visceral adipose tissue in Crohn's disease is hyperplastic rather than hypertrophic in areas of inflammation[176], and has a different profile of adipocytokine expression than in healthy controls: surgical resection specimens showed overexpression of tumour necrosis factor alpha (TNF-α), leptin, adiponectin, resistin and macrophage migration inhibitory factor (MIF) by mesenteric adipocytes[177]. Patients with

Crohn's disease are known to have a higher ratio of intra-abdominal to total abdominal fat[59], and visceral adipose tissue is the main source of serum TNF-α[178], and a source of C-reactive protein[179], in Crohn's disease. These changes may lead to altered drug kinetics and metabolism: as visceral adipocytes produce TNF-α in Crohn's disease[180], larger visceral adipose tissue volume may be associated with more rapid clearance of anti-TNF drugs. Studies correlating visceral adipose tissue area and anti-TNF drug levels are lacking.

Low skeletal muscle mass

Loss of skeletal muscle in response to inflammatory diseases involves many mediators which cause hypermetabolism and muscle catabolism[181]. The cytokines TNF-alpha, IL-6 and IL-1 beta are among those most often implicated[36], and have been identified as targets of treatment in Crohn's disease. Protein-energy malnutrition, due to anorexia, dietary restriction and malabsorption, is prevalent in Crohn's disease[182-185] and contributes significantly to low skeletal muscle mass[186].

In other disease states, the prognostic implications of low muscle mass have been explored. Loss of muscle mass may be classified in several ways, with cachexia and sarcopenia the most common descriptors. These terms have generally accepted specific definitions, and some papers identified in this search have instead used the less strictly-defined term 'myopenia' to refer to low muscle mass.

Cachexia is defined by an international consensus working group as "a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass"[187]. The Cachexia Consensus Working Group diagnostic criteria are oedema-free weight loss of at least 5% within 12 months in adults (or growth failure in children) in the presence of underlying illness, plus three of: a) decreased muscle strength (lowest tertile), b) fatigue, c) anorexia, d) low fat-free mass index, e) abnormal biochemistry [elevated CRP or IL-6; anaemia; low serum albumin]. BMI and nutritional assessment are insensitive measures for detecting cachexia[188].

Sarcopenia is defined as low muscle mass (more than two standard deviations below a sex- and ethnicity-matched young adult mean), generally in conjunction with reduced muscle function, which may be measured by a validated test such as hand grip strength, four-minute or six-minute walk test[36]. Sarcopenia has been used particularly to describe age-related muscle

wasting[37], but there is no consensus that the definition should be constrained to this context. 'Myopenia' has been suggested as a term to describe the presence of clinically relevant muscle wasting due to any illness and at any age[189], with precise cut-off values not defined.

This review found low muscle mass is prevalent among patients with Crohn's disease[28,49,62,138,139,150,190,191], but few papers incorporated a strict definition of cachexia, or the functional component of sarcopenia. Prognostic implications of low skeletal muscle mass include higher risk of primary non-response[139] or secondary loss of response[137] to anti-TNF drugs, and higher risk of postoperative complications[149,150]. Deficits in skeletal muscle appear to be reversible, with response to Crohn's disease therapy being associated with improvements in muscle strength and function, particularly noted with anti-TNF drugs[54,62,69].

Low bone mineral density

Low bone mineral density was uniformly reported amongst Crohn's disease patients, with disease activity, male hypogonadism, surgery and low body weight being the predominant risk factors. The risk of vertebral fracture is increased in paediatric Crohn's disease patients, even those without corticosteroid exposure[192]. In the retrospective studies identified by this review, corticosteroid use was associated with lower BMD, but this was not able to be dissociated from disease activity. In short term studies, corticosteroid use was not consistently associated with bone loss.

Growth and pubertal development

Exclusive enteral nutrition reduced disease activity and increased muscle mass in several studies. Nutritional measures such as BMI[50] in adults, and height and lean body mass in children[44] showed greater improvement with exclusive enteral nutrition than with corticosteroids; however, clinical response to therapy was consistently identified as the most significant predictor of increased growth velocity[88,89,91-93,96,193]. Permanent growth failure was reported in up to 35% of paediatric subjects in the reviewed literature[194], with Crohn's disease activity and corticosteroid use being identified as risk factors.

Despite the high prevalence of malnutrition and growth delay or failure reported in the studies identified in this review, and the findings that exclusive enteral nutrition is an effective treatment for inflammation and malnutrition in Crohn's disease, a 2013 systematic review of the literature found little evidence from interventional studies to support other specific dietary

recommendations[173]. Published guidelines varied considerably, and were felt to be consensus-based rather than founded on evidence.

Corticosteroids and body composition

Little research has been published regarding the relationship between response to corticosteroids in Crohn's disease and body composition. In an case series from 1966[195] describing the use of corticosteroids and corticotrophin in a cohort of largely post-operative Crohn's disease patients, a variety of prednisolone doses were used, with the authors commenting that surgery was generally necessary and that there was little evidence for the use of corticosteroids. The first randomised, double-blind placebo-controlled trial of corticosteroids for ulcerative colitis was undertaken a decade prior[196], but the first randomised trial in Crohn's disease was the National Cooperative Crohn's Disease Study (1979)[127], which used weight-based prednisolone dosing adjusted according to disease severity. This study was identified by our primary search study, and is one of two placebo-controlled trials cited by a Cochrane systematic review[197] assessing corticosteroids for induction of remission in Crohn's disease; the other trial[198] used weaning doses of prednisolone that were not weight-based. Reflecting the lack of evidence regarding optimal corticosteroid dose choice in Crohn's disease, a prospective, randomised trial examining fixed dosing compared to weight-based dosing of prednisolone is currently recruiting (Clinicaltrials.gov identifier: NCT02392286).

Anti-TNF drugs and body composition

The effects of commencing anti-TNF drugs on body composition were well-characterised: rapid improvement in disease activity and reversal of cachexia were observed. The potentially opposing effects of corticosteroids, reducing inflammatory activity but also negatively impacting lean tissue mass and linear growth, were reflected by more heterogeneous findings. Reduced bone mineral density is prevalent in Crohn's disease; evidence that corticosteroids contribute significantly to this is equivocal, and confounded by underlying disease activity, which appears to be the largest determinant of low BMD.

The immunogenicity of monoclonal antibodies is an important factor in treatment failure[199], with weight-based dosing a contributor: a two-fold difference in anti-infliximab antibody prevalence was observed between patients receiving 5 mg/kg and those receiving 10 mg/kg[200]. Low serum trough drug levels have been demonstrated to be a risk factor for development of anti-drug antibodies in both Crohn's disease and inflammatory arthritis[201]. The studies

identified in this review have shown altered pharmacokinetics with extremes of body composition, with greater drug clearance, altered volume of distribution[120], and lower serum drug levels, in low body weight individuals [117,119]when dosed by weight, as well as in very high weight individuals.

Bhalme et al., in their paper regarding adalimumab pharmacokinetics[133], postulated that two mechanisms may be responsible for lower efficacy of adalimumab in obese individuals: one related to the pharmacokinetic properties of such drugs in obese individuals and the other related to excessive pro-inflammatory adipocytokine production that has been described in the obese. TNF-α is found both in soluble and membrane-bound forms; localisation of the target molecule in inflamed tissues – including visceral adipose tissue – may make rapid saturation difficult at target serum concentrations[202].

While prospective studies comparing efficacy of adalimumab to infliximab are lacking in Crohn's disease, such a trial may have implications for dose selection in subgroups such as the overweight or underweight; particularly if powered appropriately and if drug level monitoring were incorporated, due to the weight-based dosing of infliximab compared to the fixed dose of adalimumab. Phase two studies of anti-TNF drugs in Crohn's disease did not consider differences in body composition in dose selection: for infliximab, a single dose of 5 mg/kg body weight was not inferior to 10mg/kg and 20 mg/kg at inducing clinical response or remission, improving quality of life and reducing CRP[203], in 108 patients with a mean weight of approximately 70 kg. For adalimumab, the CLASSIC-I study enrolled 299 slightly heavier patients (mean weights 74-78 kg), with randomised groups of different induction doses; in this study, the highest dose (160mg week 0, 80mg at week 2) was associated with best early outcomes[204]. In neither study was body size subgroup analysis reported.

Thiopurines and body composition

Despite the central place of thiopurines in the treatment of Crohn's disease, dose-response studies have not been performed[205]. Weight-based dosing at 1.5 mg/kg for 6-mercaptopurine, and 2.5 mg/kg for azathioprine, is recommended in guidelines[29-31]. Previous studies[206,207] have found clinical efficacy correlated with intracellular levels of 6-thioguanine nucleotides, which were not associated with drug dose/kg in the studies identified by this review. Instead, potentially hepatotoxic 6-methylmercaptopurine levels were associated with higher drug doses and higher dose/kg of fat-free mass in our own research[109] and in a paediatric patient group[112],

which may be a contributing factor to the higher rate of treatment discontinuation in underweight patients observed in one study[131].

New therapies

Vedolizumab targets circulating memory T cells, with almost complete binding to the α4β7 ("gut-homing") integrin within hours of infusion. The duration of integrin binding varies according to dose[208], with complete recovery of free α4β7 by day 85 for patients given 0.5 mg/kg, and by day 180 for 2.0 mg/kg. It is licensed for administration as a fixed dose of 300 mg at 0, 2, and 6 weeks and 8-weekly thereafter. The pharmacokinetics paper identified by this systematic review reported a drug half-life in a reference patient (70 kg, serum albumin 4.0 g/dL) of 25.5 days[122], which is longer than anti-TNF antibodies. Linear clearance was found to correlate with body weight, but this effect was not thought likely to have clinical significance unless albumin or weight values were extreme.

Our search strategy was not designed to identify papers pertaining to drugs unavailable for prescription in Crohn's disease, including etrolizumab, JAK inhibitors, mongersen and sphingosine phosphate receptor modulators, but separate literature searches have not uncovered studies regarding interactions between body composition and these medications beyond the pharmacokinetic studies included in the review.

Summary

While the division of the identified papers into subject areas was arbitrary, this approach led to the distillation of several principal themes.

Major themes

- Activity and severity of Crohn's disease is associated with muscle and bone loss
    - These changes are partially reversible with response to treatment
    - Low skeletal muscle mass is associated with
        - treatment toxicity
        - lesser response to treatment
        - more frequent post-operative complications
- Crohn's disease activity is associated with increased visceral adiposity

    - Visceral adiposity is associated with worse post-operative outcomes
- Body composition interacts with drug metabolism and efficacy
    - No dose-finding studies using body composition
- Response to therapy is less with anti-TNF drugs in the context of obesity; this may be due to lower anti-TNF drug levels in obese (higher clearance), and those with very low body weight (higher clearance), or to inflammatory factors specific to obesity

A schematic diagram of the themes identified by this review and their interplay is included (Figure 2.2).

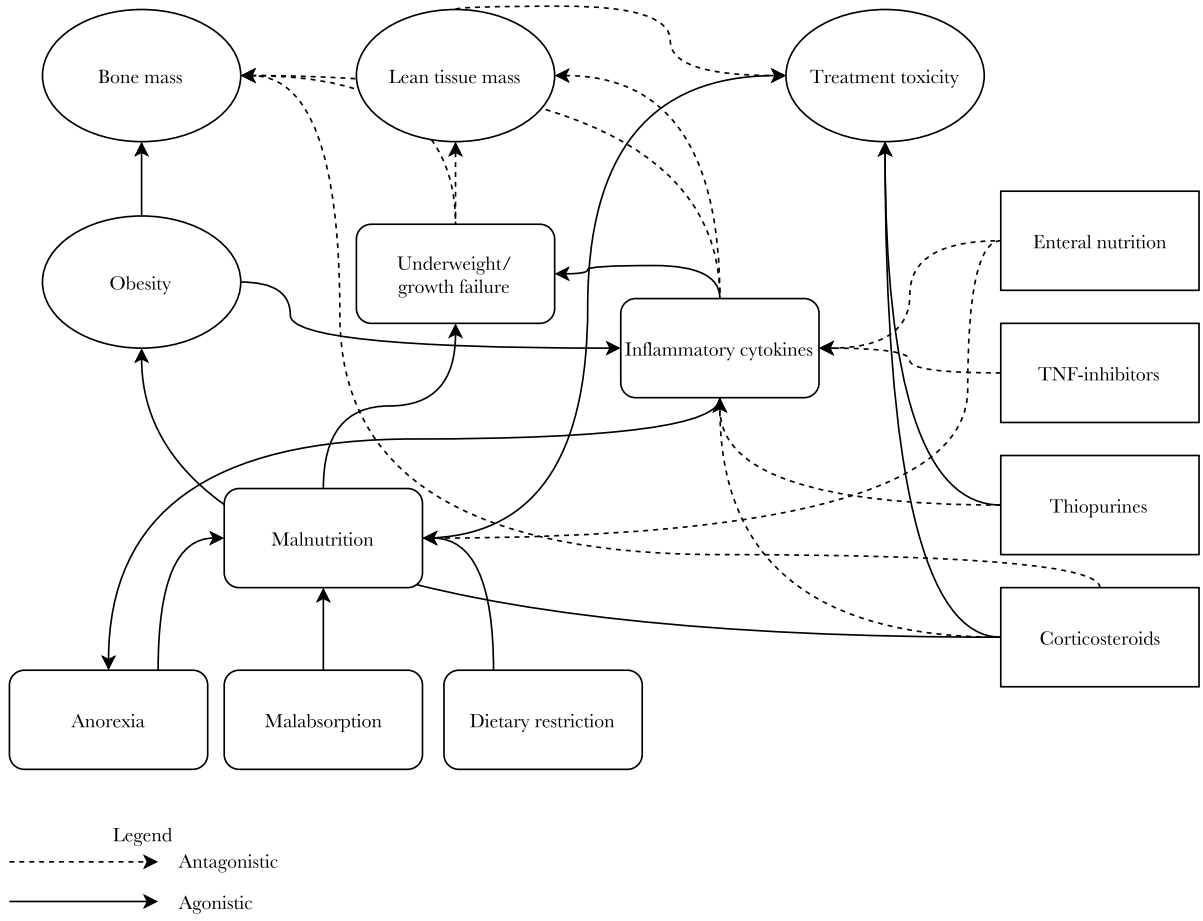


Figure 2.2 Schematic diagram of interactions between body composition and treatment for Crohn's disease

Deficits in the literature and areas for further research

The need for prognostic indicators to guide therapy, avoiding ineffective treatment, medication toxicity and excessive cost is increasing with the advent of new drugs and goals of treatment,

and recent evidence-based consensus guidelines have called for development of a composite predictive index[29]. Due to effects on drug metabolism and pharmacokinetics – and as a marker of disease severity and phenotype – body composition may play an important part in the development of such an index. Similar prognostic indices in cystic fibrosis, oncology and diabetes have been developed from a burgeoning research and policy interest in 'precision medicine': the integration of genomic, proteomic, phenotypic, environmental and patient factors to understand the individual variation within disease states and appropriately target diagnosis and therapy. Prospective trials involving body composition analysis would fulfil a number of the stated aims of the US Precision Medicine Initiative (PMI)[209], in particular:

- *Developing quantitative estimates of risk for a range of diseases by integrating environmental exposures, genetic factors, and gene-environment interactions.*
- *Identifying the determinants of safety and efficacy for commonly used therapeutics.*
- *Discovering biomarkers that identify individuals with an increased risk of developing common diseases.*
- *Using home and mobile health (mHealth) technologies to correlate body measurements and environmental exposures with health outcomes.*
- *Developing new disease classifications and relationships.*

This review of the literature has identified an absence of studies using body composition as a means of optimising drug choice and dosing, despite evidence that body composition affects drug metabolism and efficacy.

Further prospective research is necessary in the sphere of Crohn's disease and body composition, particularly:

- The role of body composition in metabolism of Crohn's disease drug therapies
    - There is an unmet need for pharmacokinetic studies incorporating measurement of body composition compartments
    - Clinical studies assessing response to therapy should incorporate body composition analysis
- Body composition and disease behaviour
    - Further characterisation of the effector mechanisms of muscle and bone loss, and the consequences these changes have on disease outcomes, may help to define phenotypes of Crohn's disease
    - These studies may identify new molecular targets of treatment and may help to appropriately direct the use of present therapies

Conclusion

Crohn's disease is associated with altered body composition as a consequence of inflammation and malnutrition due to dietary restriction and malabsorption. There is bidirectional influence of body composition and treatments for Crohn's disease, with evidence that disease treatment causes alterations in body composition and growth, and that body composition affects pharmacokinetics, drug and metabolite levels and clinical efficacy. There is also evidence that body composition predicts post-surgical outcomes.

There is not widespread, or guideline-based, utilisation of body composition measures in clinical practice.

Incorporation of body composition analysis into therapeutic algorithms may improve the efficacy of existing Crohn's disease treatment strategies, and may allow tailoring of more appropriate therapies in an era when an increasing number of drug classes are available.

Table 1 Treatment effects on body composition

Author, year, country	*Type of study*	*Adult or paediatric*	*Number of patients*	*Treatment group*	*Controls*	*Duration of study*	*Body composition technique*	*Outcome measure*	*Results*
Azcue, 1997, Canada[44]	Prospective cohort	Paediatric	24 CD, 19 anorexia nervosa, 22 healthy controls	Prednisolone vs enteral nutrition	Healthy controls	3 months	anthropometry, BIA, TBK, TBW, bromide space studies, indirect calorimetry	REE, weight, LTM,	Body weight and ideal body weight were significantly lower in patients with Crohn's disease than in healthy controls. Lean tissue was depleted and there was an increase in extracellular water. Per unit of lean body mass, there was no divergence between REE in patients with Crohn's disease and controls, whereas patients with anorexia nervosa had significantly reduced REE. With enteral nutrition, all body compartments and REE increased significantly ($p<0.001$). In a subgroup of age-matched men there was a significant increase in height after three months of enteral nutrition compared with prednisolone ($p<0.01$). Those treated with steroids did not show a significant change in height but did show an increase in all body compartments. However, intracellular water as well as lean body mass accretion were significantly higher in the enteral nutrition group than in the prednisolone group.
Csontos, 2016, Hungary[54]	Prospective cohort	Adult	33 CD, 7 UC	24 ADA, 16 IFX	Repeated measures cohort study	3 months	BIA	BMI, FFM, FM	BMI and muscle parameters increased significantly (BMI: 23.81±7.19 vs. 24.52±7.34, $p<0.001$; FFMI: 17.64±3.00 vs. 18.14±3.08, $p<0.001$; at week 0 vs. 12, respectively). No changes were detected in the fat parameters (BFMI: 6.21±5.20 vs. 6.44±5.27, respectively). There was no significant difference between the effects of adalimumab vs. infliximab on body composition. No significant difference was observed in the extent of changes in parameters whether the patients were on corticosteroids (n=15) or not (n=25) at week 0.
Deepak, 2016, USA[55]	Retrospective cohort	Adult	20	IFX	Repeated measures cohort study	median 447 days	CT abdomen	SAT, VAT, IMAFT, IMAT	At baseline CTE, standardized VAT, standardized RLQ VAT and IMAFT were similar between radiological responders and non-responders, respectively. After treatment initiation, the standardized delta VAT was similar between the 2 groups while the standardized delta RLQ VAT showed a trend towards significance. Delta IMAFT was significantly different between radiological responders and nonresponders.
Dong, 2015, China[42]	Systematic review & metaanalysis	Adult	1442 IBD, 2059 controls	Multiple medical therapies; categorised as "yes"/"no"	Non-IBD controls	NA	Anthropometry	BMI	BMI lower in CD patients than controls; medication increased BMI in CD but not UC, active IBD was associated with lower BMI than remission

Emerenziani, 2015, Italy[56]	Prospective cohort	Adult	8 CD, 10 healthy controls	IFX	Repeated measures cohort study, healthy controls	6 weeks	BIA	FFM, PhA	FFM increased, although not significantly. Phase angle increased.
Franchimont, 2005, Belgium[58]	Prospective cohort	Adult	20 (10 controls)	IFX	Repeated measures cohort study	4 weeks	BIA	BMI, FM	Infliximab significantly induced weight gain at 4 weeks. Fat mass was not significantly altered by infliximab at 1 week and 4 weeks. The percentage of fat mass at 4 weeks did not change as compared with the percentage of fat mass at baseline.
Holt, 2016, Australia[52]	Cross-sectional survey	Mixed	928 (558 CD)	Multiple medical therapies	NA		Self-reported weight, height	BMI	Patients with CD had a self-reported mean body mass index (BMI) of 24.7; for patients with UC, the mean BMI was 24. Difference not statistically significant. The distribution of BMI values was asymmetrical, with a long tail to the right. A BMI <18.5 was reported in 5.8% of respondents with CD and 6.3% of subjects with UC (not significant). Patients who had taken more than 10 courses of steroids were more likely [odds ratio 1.59] to be overweight or obese than those who had taken 0–3 courses of steroids [
Khoshoo, 1996, Canada[45]	RCT	Paediatric	14	Low-fat/high-fat EN	Cross-over study	6 weeks	BIA, Anthropometry	Weight, FM, FFM, skinfolds	Weight increased, as did FFM and triceps skinfolds; PCDAI reduced
Nakahigashi, 2011, Japan[60]	Prospective cohort	Adult	50	IFX	Repeated measures cohort study	10 weeks	Anthropometry	BMI	BMI significantly increased over 10 weeks. The mean increase in BMI was significantly higher in patients who responded to infliximab vs patients who did not (P = 0.03). Further, at weeks 30 and 60, 35 patients (70%) and 33 (66%) were in remission, respectively. The mean increase in BMI was significantly higher in patients who maintained remission vs patients not in remission. Patients with a low baseline BMI (<18.5) and those with small bowel involvement achieved a higher increase in BMI as compared to patients with BMI >18.5 or patients without small bowel involvement.
Parmentier-Decrucq, 2009, France[59]	Prospective cohort	Adult	21	IFX	Repeated measures cohort study	8 weeks	MRI abdomen	BMI, Abdominal fat	A significant homogeneous 18% (15% SAT, 27% VAT) increase in total abdominal fat was observed in the 21 CD patients after infliximab induction therapy (P = 0.027), independently of 6% increase BMI.
Royall, 1995, Canada[49]	Prospective cohort	Adult	30 (30 controls)	EEN	Repeated measures cohort study,	3 weeks	IVNAA, DXA, BIA, TBK	Weight, TBW, FM, TBP	After enteral feeding, body weight increased by 1.9 +/- 0.3 kg (p < .0005). Weight gain was accompanied by an increase in body protein (0.3 +/- 0.1 kg), fat (0.3 +/- 0.1 kg), and water (1.1 +/- 0.4 kg) (all p < .025), and by a nonsignificant increase in total body potassium. The weight gain of

					healthy controls				approximately 2 kg consisted of 65% water, 18% fat, and 18% protein, thus comprising a normal proportion of body composition.
Siffledeen, 2009, Canada[53]	Prospective cohort	Adult	222	Bisphosphonate and corticosteroid	Repeated measures cohort study	2 years	DXA, anthropometry	BMI, BMD, FFM, FM	Patients had an average BMI of 25.2 (S.D. 4.5) and 29.2 (+/- 8.7) percent total body fat (females > males; p<0.05). Total body fat at baseline correlated with lower testosterone/estradiol levels (p<0.05), Increasing age, female gender, and higher lumbar spine bone mineral density. Over 24 months' surveillance, increasing body fat was associated with losses in hip and radial Bone Mineral Density (BMD) (p<0.05). Patients reporting steroid use at 12 or 24 months had a trend towards lower body fat composition. Male corticosteroid users demonstrated significantly lower total body fat at 24 months (-19.1 +/- 10 vs -4.9 +/- 2.5; p<0.05). Disease activity had no effect on changes in body fat. Patients with BMI <25 reported higher corticosteroid use, were younger and more proportionally female. They also had significantly higher levels of vitamin D, but lower lumbar spine and hip BMD. Higher BMI was associated with better BMD, but also with more spinal fractures, lower reported steroid use and lower measured vitamin D levels (p<0.05).
Steiner, 2008, USA[210]	Prospective cohort	Paediatric	31	Corticosteroids	Repeated measures cohort study	2 weeks	Protein kinetics	Protein breakdown/ loss	After corticosteroid therapy in patients with Crohn disease, the rates of appearance of phenylalanine (32%) and leucine (26%) increased significantly, reflecting increased protein breakdown, and the rate of appearance of urea also increased significantly (273%), reflecting increased protein loss
Subramaniam, 2015, Australia[62]	Prospective cohort	Adult	19	IFX	Repeated measures cohort study	25 weeks	MRI muscle volume, strength	Muscle volume and strength	IFX increased muscle volume in both legs from baseline to week 25. IFX also increased muscle strength in both legs from baseline to week 25. Muscle volume gain correlated with male gender (P = 0.003). Significant gains in muscle volume and strength were unrelated to prednisolone use. Serum IL6 levels decreased by week 25 (P = 0.037).
Thomsen, 2014, Denmark[63]	Prospective cohort	Adult	37 (20 UC, 17 CD)	Prednsiolone vs IFX	Repeated measures cohort study	7 days	Functional hepatic nitrogen clearance		At baseline, the FHNC was similar in the 2 treatment groups (36 L/h). After 7 days, prednisolone increased the FHNC by 40% (55 L/h) (P =0.03), whereas infliximab tended to reduce the FHNC by 15% (30 L/h) (P =0.09). The changes in the FHNC differed significantly between the 2 treatment groups (P = 0.01).
Vadan, 2011, Romania[211]	Prospective cohort	Adult	30	IFX	Repeated measures cohort study	12 months	Anthropometry	BMI	The severity of Crohn's disease did not correlate with low BMI but did correlate with Nutritional Risk Index (p =0.001). In all patients that responded to Infliximab treatment progressive weight gain was observed, all

									but one patient reaching normal BMI after one year. Mean weight gain was significantly more elevated (p =0.001) and time needed to reach normal BMI was longer in the undernutrition group (p =0.01). Clinical remission was the principal factor associated with weight gain (p =0.001), while there was no influence of endoscopic remission on nutritional status.
Wiese, USA[212]	2008,	Prospective cohort	Adult	7	IFX	Repeated measures cohort study	6 months	DXA, BIA	BMI, FFM, FM	Overall, patients experienced an increase in BMI after 6 months of infliximab. There was a nonsignificant increase in lean muscle mass and body fat percentage as calculated by DXA. Overall, body fat percentage estimated per bioelectrical impedance increased.
Zhao, China[47]	2015,	Prospective cohort	Adult	61	EEN	Repeated measures cohort study	4 weeks	? Not specified	SMM, Protein mass, REE	A (active phase into remission via EN, n = 21), B (remained in active phase before and after EN, n = 19) and C (in remission before and after EN, n = 21). Patients in group A had a significant increase in SM, protein mass and decrease in resting energy expenditure (REE) per kilogram). There was no significant difference between predicted and measured REE in active CD patients according to the Harris- Benedict equation. There was no linear correlation between the measured REE and CRP, ESR or CDAI in active CD patients.
Zoli, Italy[50]	1997,	RCT	Adult	20 (10 controls)	Elemental diet	10 treated with prednisolone	2 weeks	BIA, Anthropometry	BMI, FFM, FM	BMI increased in ED group, FFM increased in CS group; no other body composition changed were reported

Table 2: Treatment effects on bone mineral density

Author, year, country	*Type of study*	*Adult or paediatric*	*Number of patients*	*Treatment group*	*Controls*	*Duration of study*	*Body composition technique*	*Outcome measure*	*Results*
Abitbol, 2002, France[64]	RCT	Adult	94	Bisodium monofluorophosphate, calcium, vit D, prednisolone	Calcium and Vit D		DXA	BMD	Lumbar BMD increased at 1 year in both groups; there was no difference between placebo and fluoride treated groups. Recent CS treatment did not affect results.
Altowati, 2015, UK[213]	Prospective cohort	Paediatric	17 CD, 19 total	IFX	Cohort study		pQCT	BMD, PCDAI, weight, BMI, bone mineralisation markers, anthropometry	No alteration in BMD after commencement of IFX, even in patients discontinuing steroids.
Azzopardi, 2013, Malta[68]	Cross-sectional	Adult	83	Corticosteroids, anti-TNF, sulfasalazine, 5ASA	None		DXA	BMD	CD diagnosis at young age, long duration of disease, higher cumulative steroid exposure and infliximab use all associated with lower BMD
Bakker, 2013, Netherlands[214]	Prospective cohort	Adult	84	Vit D, Calcium	Cohort study		DXA	BMD	Higher age, male sex, low BMI, and a higher age at diagnosis of CD were associated with low BMD. After mean 4y follow up with Vit D and Ca supplementation, BMD slightly improved.
Burnham, 2004, USA[74]	Cross-sectional	Mixed	104 CD, 233 control	Corticosteroids	Healthy controls		DXA, anthropometry	BMD	Subjects with CD had significantly lower height z score, body mass index z score, and lean mass relative to height compared with controls (all p 0.0001). After adjustment for group differences in age, height, and race, the ratio of BMC in CD relative to controls was significantly reduced in males (0.86; 95% CI, 0.83, 0.94) and females (0.91; 95% CI, 0.85, 0.98) with CD. Adjustment for pubertal maturation did not alter the estimate; however, addition of lean mass to the model eliminated the bone deficit. Steroid exposure was associated with short stature but not bone deficits.
Compston, 1987, UK[76]	Cross-sectional	Adult	51 CD, 75 total	Corticosteroids	None		Single photon absorptiometry, qCT	BMD	BMD positively correlates with BMI, height and weight and negatively with lifetime steroid dose. Osteoporosis was present in 30.6% of subjects.
Cowan, 1997, UK[75]	Cross-sectional	Paediatric	21 CD, 11 UC,	Corticosteroids	Healthy controls		DXA, anthropometry	BMD	Of the children with IBD, 41% had a % BMC less than 1 SD below the mean for the whole body and 47% at the femoral neck. Reduction in % BMC was

			58 controls					associated with steroid usage but not with the magnitude of steroid dose, disease activity, or biochemical markers of bone metabolism.
de Jong, 2002, Netherlands[78]	Cross-sectional	Adult	91	Prednisolone, estrogen,	None	DXA	BMD	A total of 27 patients (30%) fulfilled the World Health Organization criteria for osteoporosis and 46 patients (50%) for osteopenia. Osteoporotic patients used more corticosteroids and had longer duration of disease, lower BMI, and more bowel resections than patients with normal BMD. However, in the linear regression analysis, the only significant independent predictors for BMD of the lumbar spine and femoral neck were BMI and history of bowel resections. BMI and history of resections together accounted for 28% of BMD Z-scores.
de Jong, 2003, Netherlands[79]	Retrospective cohort	Adult	29	Prednisolone, bisphosphonates, Vit D, calcium	Cohort study	DXA	BMD	At baseline, low BMD was present. There was no significant change over the study period despite most patients having active disease requiring CS, and most receiving some bone protecting treatment.
Dinca, 1999, Italy[80]	Prospective cohort	Adult	54 CD, 49 UC, 18 control	Corticosteroids	Healthy controls	DXA	BMD	Reduced BMD more prevalent in CD patients than controls or UC. BMD positively correlated with BMI and negatively correlated with lifetime steroid dose. In UC< steroid use during study period was associated with BMD loss.
Dubner, 2009, USA[69]	Prospective cohort	Paediatric	78	Corticosteroids, IFX, thiopurines, methotrexate	Cohort study	pQCT	BMD	Substantial deficits in trabecular vBMD, cortical bone geometry, and muscle were observed at CD diagnosis. Trabecular vBMD improved incompletely; however, cortical deficits progressed despite improvements in muscle. Glucocorticoids were not associated with bone loss.
Farkas, 2014, Hungary[215]	RCT	Adult	6 CD, 13 UC	Bolus methylprednisolone	Continuous weaning dose methylprednisolone	DXA	BMD, hormonal, metabolic and bone turnover blood tests	Continuous steroid use was associated with weight gain and BMD loss with elevated serum cholesterol and reduced cortisol at the end of treatment, compared with bolus dosing
Laakso, 2014, Finland[81]	Prospective cohort	Paediatric	17 CD, 30 UC	Corticosteroids, anti-TNF, sulfasalazine, 5ASA	Cohort study	DXA, anthropometry	BMD	Cumulative steroid exposure was associated with lower lumbar spine BMD; univariate analysis
Mauro, 2007, Canada[70]	Retrospective cohort	Adult	45	IFX	CD, no IFX	DXA, anthropometry	BMD, anthropometry	The control group (n=30, mean [± SD] 26.7±9 years of age) had a significantly higher increase in body weight between both evaluations (6.26%±8%) than the infliximab group (n=15, 30.6±13 years), which had an increase of 0.3%±7.4%. There was a strong correlation between the final

									weight and lumbar bone mineral content (BMC) in both groups. The infliximab group had a significant increase in lumbar bone area (4.15%±6.6%), BMC (12.8%±13.6%) and bone mineral density (8.13%±7.7%) between both evaluations (interval 22.6±11 months) compared with the control group. The increase in BMC in patients who had received infliximab treatment was significant when com- pared with control patients who had received glucocorticoids (n=8) or had evidence of disease activity (n=13).
Pappa, USA[66]	2011,	RCT	Paediatric	63	Intranasal calcitonin	IBD, received Vit D	DXA, anthropometry	BMD, anthropometry	There was no significant effect of calcitonin treatment. Bone mineral accrual rate during the trial did not lead to normalization of BMD Z-score in this cohort. Factors favouring higher bone mineral accrual rate were lower baseline BMD and higher baseline body mass index Z-score, improvement in height Z-score, higher serum albumin, haematocrit and iron concentration, and more hours of weekly weight-bearing activity. Factors associated with lower bone mineral accrual rate were more severe disease—as indicated by elevated inflammatory markers, need for surgery, hospitalization, and the use of immunomodulators—and higher daily caffeine intake.
Pichler, Austria[71]	2013,	Retrospective cohort	Paediatric	33	IFX	Cohort study	DXA, anthropometry	BMD, PCDAI, weight, BMI, bone mineralisation markers, anthropometry	BMD static after treatment with IFX. Weight, height & BMD z-scores increased, 25OH Vit D increased
Pichler, Austria[72]	2015,	Retrospective cohort	Paediatric	18	ADA	Cohort study	DXA, anthropometry	BMD, PCDAI, weight, BMI, bone mineralisation markers, anthropometry	BMD static after treatment with ADA. Reduction in PCDAI; patients who achieved remission had less deviation in BMI from population mean

Sylvester, 2007, USA[82]	Prospective cohort	Paediatric	58 CD, 18 UC	56-61% received Corticosteroids	Baseline age-matched controls	DXA, anthropometry	BMD, PCDAI, weight, BMI, bone mineralisation markers, anthropometry	BMD z-scores static over 2 year follow-up. Steroid use during study period not associated with lower BMD.
Tobias, 2004, UK[85]	Prospective cohort	Adult	15	Prednisolone	19 CD in remission	DXA	BMD	At 2 months, significant bone loss was found in patients with active disease taking prednisolone, but not in controls. Previous CS use was not significantly associated with baseline bone mineral density, although body weight, site of disease, and dietary calcium deficiency were.
Walther, 2006, Germany[83]	Cross-sectional	Paediatric	90	Corticosteroids	CD, non-IBD controls	DXA, anthropometry	BMD, PCDAI, weight, BMI, bone mineralisation markers, anthropometry	The rate of "osteoporosis" was 8% in girls and 20% in boys. There was a similar proportion of osteoporosis in steroid-naive (12%) and steroid- treated (11%) patients.
Zadik, 2005, Israel[84]	Prospective cohort	Paediatric	24	Oxandrolone, Vit D, calcium, prednisolone, cyclosporine, 5ASA, anti-TNF	CD in remission	Bone sonometry, anthropometry	BMD, PCDAI, weight, BMI, bone mineralisation markers, anthropometry	Bone density reduced for patients with active disease (and on CS), increased for those taking oxandrolone, and increased slightly on some measures for patients in remission

Table 3: Treatment effects on growth

Author, year, country	*Type of study*	*Adult or paediatric*	*Number of patients*	*Treatment group*	*Controls*	*Duration of study*	*Body composition technique*	*Outcome measure*	*Results*
Assa, 2013, Israel[89]	Retrospective cohort	Paediatric	120 (101 CD)	Anti-TNF	NA	median 15 months	Weight, BMI	Growth, response to treatment	Response was associated with improvement in weight and BMI Z-scores but not with linear growth. Responders had a significantly lower weight and BMI Z-scores at initiation of anti-TNFα treatment in compared to non-responders
Borrelli, 2004, Italy[216]	Prospective cohort	Paediatric	18	Infliximab	NA	6 months	Height, weight	Growth, response to treatment	A significant increase in both weight and height Z scores was observed 6 months after beginning of the baseline infusion programme. Moreover, weight and height gain was significantly higher in patients on retreatment rather than in those treated only with three baseline infusions of infliximab.
DeBoer, 2016, USA[217]	Prospective observational	Paediatric	72	Anti-TNF	NA	12 months	DXA, height, weight, sex hormone levels, inflammatory markers, PCDAI	Growth, response to treatment	Sex hormone Z scores increased significantly during the 10-week induction interval. In mixed model regression, PCDAI, cytokine levels, and measures of inflammation were significantly and negatively associated with sex hormone Z scores and with LH and FSH levels. Sex hormone and gonadotropin levels were not associated with body mass index or fat mass Z-scores.
Diamanti, 2009, Italy[218]	Retrospective cohort	Paediatric	28	Infliximab	Mesalazine and azathioprine	Median 10 months	Height, weight, BMI	Growth, response to treatment	In IFX-treated patients, but not controls, mean baseline weight (kg) and BMI values were significantly lower than their final values, and median pCDAI values were significantly higher than their final values. Significant changes in height, REE, and food intake were not found in either group.
Griffiths, 1993, Canada[219]	Retrospective cohort	Paediatric	100	Corticosteroids, nutritional therapy, thiopurines, surgery	NA	Mean 4.9 years	Height, weight	Growth, response to treatment	21% children were below the third centile for height. 40% of children in year one and 33% of children in year two grew less than expected (<4 cm). 49% grew <4 cm/y during two or more of the 4 9 (1.8) years of follow up. Severity of gastrointestinal symptoms was the major factor influencing linear growth velocity. Despite the high prevalence of growth impairment, the subset of children who had reached maturity by the time of the study (n=67) nevertheless maintained their height centile. Growth increments were comparable for surgically treated patients v patients only treated medically and among patients stratified by location of disease.
Hannon, 2011, USA[100]	Randomised control trial	Paediatric	8	rhGH	Cross-over	6 months	DXA, stable isotope measurements	Protein synthesis, accretion of lean mass	Whole-body proteolysis, phenylalanine catabolism, and protein synthesis did not differ during treatment with rhGH vs. placebo. Enteral nutrition suppressed proteolysis and increased protein synthesis similarly during placebo and rhGH treatments.

Heyman, 2008, USA[101]	Prospective cohort	Paediatric	10	rhGH	Untreated age, sex, race and height-matched	12 months	Weight, height, DXA (FFM, FM)	Growth	Mean height velocity in GH-treated patients increased during the year of GH compared to the comparison group. Height Z score increased in the treated group, and weight Z score increased. Bone density revealed an increase of the lumbar spine Z score.
Katznelson, 2003, USA[86]	Case control/cross-sectional	Adult	20 CD, 20 control	NA	Healthy controls	Cross-sectional	BIA, CT	Growth hormone secretion, body composition	Crohn's disease is associated with an increase in central fat accumulation, with more IAF and a higher ratio of intraabdominal to total body fat compared with controls. Although serum GH levels were similar in the two groups, GH contributed significantly to the abdominal fat measurements.
Kim, 2012, Korea[88]	Retrospective cohort	Paediatric	42	"top-down" vs "step-up" therapy with steroids, azathioprine and infliximab	NA	12 months	Weight, height	Weight gain	At 2 months, the Z–score increment for weight was highest in the 'steroid' group, followed by the 'top-down', 'step-up', and 'azathioprine' groups. At one year, the Z–score increment was highest in 'top-down' group, followed by 'steroid', 'azathioprine', and 'step-up' group. There were no significant differences between the four groups in Z–score increment for height and serum albumin during the study period.
Kundhal, 2001, Canada[98]	Retrospective cohort	Paediatric	32	Controlled ileal release budesonide		Up to 12 months	Height, weight	Growth, response to treatment	PCDAI fell to less than 15 (cut-off score remission) in 29%. Six prepubertal responders continued to receive 6 mg CIR budesonide for 6 to 13 months. Five of the 6 experienced only mild or no gastrointestinal symptoms and gained weight. Nevertheless, their mean height velocity was only 2.3 ± 1.0 cm/year, and none grew at a rate of more than 4cm/year whilst receiving CIR budesonide.
Lake, 1985, USA[220]	Prospective cohort	Paediatric	8	Preoperative parenteral nutrition	No preop PN	3 years	Height, weight	Growth, response to treatment	At the time of surgery, all eight patients had growth velocities below the 3rd percentile for age, a pattern which predated surgery for 2 years in five of the eight. In the 1st year postoperatively, seven of the eight had growth velocities greater than the 3rd percentile, with three of four Group A patients demonstrating growth at or exceeding the 50th percentile for age. The average growth velocity (± 1 SD) achieved in Group A in the 1st year was 7.5 (± 2.1) cm/year versus 3.7 (± 0.6) cm/year in Group B ($p < 0.02$). No significant difference was noted in the 3rd postoperative year: 2.5 cm/year in Group A versus 2.2 cm/year in Group B. By the 3rd postoperative year, all eight were Tanner 4 or 5 in sexual development, though bone ages continued to demonstrate approximately a 1-year delay

Malik, UK[94]	2011,	Retrospective cohort	Paediatric	28	Infliximab	NA	18 months (t-6 to t+12)	Height	Height velocity change	Of the 28 cases, 21 (75%) demonstrated a clinical response to infliximab treatment. Overall, height velocity (HV) increased from 3.6 cm/y (0.4–7.8) at T0 to 5.5 cm/y (2.1–9.2) at T + 6 (P = 0.003). In infliximab responders, HV increased from 2 cm/y (P = 0.004) and in the nonresponders, HV remained static at 4.3 cm/y (2.5–8.6) at T0 and 3.0 cm/y (2.0–11.3) (P = 0.701) at T + 6. HV also increased in the subgroup of 13 children who had remained prepubertal from 4.5 cm/y (0.4 – 8) to 5.5 cm/y (3.3 – 8.4) (P =0.050). In the subgroup of 11 children who had a reduction (n =2) or cessation in GC (n =9), HV increased from 1.8 cm/y (0.3 – 8.3) at T0 to 5.6 cm/y (2.2 – 9.2) at T + 6 (P =0.14), whereas those children who did not receive GC during the 12 months had an increase from 3.7 cm/y (0.6 – 6.5) to 6.4 cm/y (2.9 – 9.0) (P < 0.05). HV at T0 and T + 6 showed a significant association with the average alkaline phosphatase during the prior 6 months (r =0.39, P < 0.05). HV did not show any association with individual markers of disease activity.
Malik, UK[90]	2012,	Retrospective cohort	Paediatric	116	Prednisolone, methotrexate, azathioprine, exclusive enteral nutrition, anti-TNF	NA	3 years	Weight, height, BMI	Growth, response to treatment	The clinical, therapeutic and laboratory data for the groups with the worst and best growth outcomes were compared in terms of ΔHtSDS at T1 and T3 (table 2). At T1 the use of methotrexate was significantly associated with better growth (p=0.01), and at T3 the use of prednisolone (p=0.01) and raised ESR (p=0.02) were significantly associated with worse growth. Multivariable regression models were used to determine the association of disease and therapy on growth (HtSDS, WtSDS, BMISDS, HVSDS and ΔHtSDS) at T1, T2, T3 and MF by fitting linear mixed effect models. In the final models, HtSDS was associated negatively with the use of prednisolone (p=0.0001), azathioprine (p=0.0001), methotrexate (p=0.0001) and WtSDS (p=0.0001). HVSDS was associated positively with age (p=0.0001) and WtSDS (p=0.01). ΔHtSDS was associated negatively with the use of prednisolone (p<0.02). BMISDS was associated positively with prednisolone (p=0.0007) and serum Alb (p=0.0001) (table 3).
Malik, UK[193]	2012,	Retrospective cohort	Paediatric	36	Adalimumab	NA	12 months (t-6 to t+6)	Height, weight	Growth, response to treatment	Of 36 cases, 28 (78%) went into remission. Overall 42% of children showed catch up growth, which was more likely in: (i) those who achieved remission (median change in height SDS (ΔHtSDS) increased from −0.2 (−0.9, 1.0) at T0 to 0.2 (−0.6, 1.6) at T+6, (p=0.007)), (ii) in those who were on immunosuppression ΔHtSDS increased from −0.2 (−0.9, 1.0) at T0 to 0.1 (−0.8, 1.3) at T+6, (p=0.03) and (iii) in those whose indication for using

									adalimumab therapy was an allergic reaction to infliximab, median ΔHtSDS increased significantly from −0.3 (−0.9, 1.0) at T0 to 0.3 (−0.5, 1.6) at T+6, (p=0.02). Median ΔHtSDS also increased from −0.4 (−0.8, 0.7) at T0 to 0.0 (−0.6, 1.6) at T+6, (p=0.04) in 15 children who were on prednisolone therapy when starting adalimumab.
Markowitz, 1993, USA[194]	Retrospective cohort	Paediatric	48	Sulfasalazine, corticosteroids, thiopurines, nutritional therapy	NA				Permanent growth failure occurred in 19-35% of subjects, depending upon the method used to assess growth. Overall, 31% (15 of 48) of the subjects had deficits of adult height identified by two or more methods, including 14 of 38 (37%) of those with Crohn's disease but only one of 10 with ulcerative colitis. Duration of corticosteroid use was longer ($p < 0.05$) in growth- impaired subjects. In addition, although 60% of all sub- jects had periods of poor growth that put them in height- for-age percentiles two or more major growth channels below previous percentiles, only 19% remained at these levels upon achieving their final adult heights.
Mason, 2011, UK[97]	Retrospective cohort	Paediatric	8	Testosterone	NA	12 months (t-6 to t+6)	Height	Height velocity change	Seven boys showed an advance of pubertal status. Six boys had a greater than 50% increase in HV; median HV at T0 was 1.6 cm/year (0, 5) com- pared with 6.9 cm/year (1, 11.7) at T6 ($p = 0.005$). C-reactive protein during testosterone therapy had a significant association with HV at T6 ($r = −0.786$; $p = 0.021$).
Mauras, 2002, USA[102]	Prospective cohort	Paediatric	10	Growth hormone	NA	12 months	DXA, calcium kinetic analysis, leucine and glucose isotope studies, substrate oxidation and energy expenditure rates, height, weight	Growth	Body composition changed favourably with increased fat free mass (3 kg, P .001) and decreased percent fat mass (3.5%, P .001) after 4 months of treatment. Rates of whole body protein turnover, oxidation, and synthesis remained invariant, with no changes in substrate oxidation or resting energy expenditure rates. Linear growth velocity increased from 3.5 0.4 cm/yr when the patients were treated with prednisone only, to 7.7 0.9 after 6 months of combined prednisone/rhGH (P .001). The growth velocity was sustained in the 7 patients treated with rhGH for 12 months.
Morin, 1982, Canada[221]	Prospective cohort	Paediatric	10	Exclusive enteral nutrition (elemental formula)	NA	3 weeks of therapy, 12 month follow up	Height, weight, triceps skinfold, mid-arm circumference	Growth, response to treatment	The mean PCDAI whole group was 307.0 ± 23.6 (range: 203 to 413) before and 69.2 ± 11.4 (range: 15 to 114) after the feeding period. Significant increases in body weight, triceps skinfold, mid-arm circumference, serum transferrin and mean percentage of T lymphocytes were also observed.
Motil, 1993, USA[222]	Prospective cohort	Paediatric	69	Corticosteroids	NA	Up to 3 years	Height, weight	Growth, response to treatment	The prevalence of growth failure was 24%, 23%, and 39% by height velocity, Z score, and height-for-age criteria, respectively; deficits were equally prevalent regardless of the stage of pubertal development. A delay in linear

									growth persisted throughout puberty and was not reversed after surgery. Patients who had Crohn's disease were twice as likely to have growth abnormalities than patients who had ulcerative colitis. We detected significant negative associations between linear growth and disease activity but not steroid therapy.
Pfefferkorn, 2009, USA[95]	Prospective cohort	Paediatric	176	86% immunomodulators and 36% infliximab; corticosteroids 77%, 5ASA 61%	NA	2 years	height, weight	Growth, response to treatment	Among therapeutic interventions in the initial 1-year follow-up period, only corticosteroid use was associated with height velocity outcome at 1 year. Subjects whose corticosteroid use extended for 6 months or longer were more likely to demonstrate abnormal height velocity z scores, compared with those with less than 4 months of use (including no use) or 4 to 6 months of use (76% vs 31% and 38%, respectively; $P < 0.001$).
Simon, 2013, France[103]	Randomised control trial	Paediatric	30 on longterm corticosteroids (1 CD)	rhGH	Delayed-start group	t+12 months	Composite index of muscle strength, DXA, MRI, height	Muscle strength, growth	at M6, rhGH therapy did not significantly affect changes in CIMS or CIMS SDSheight the rhGH-treated group had significantly larger changes in height SDS compared with the untreated group. After 1 year of rhGH, height SDS, LM, and MA increased significantly, CIMS increased, and CIMS SDSheight remained within the normal range.
Sinitsky, 2010, Australia[91]	Retrospective cohort	Paediatric	16	Infliximab	NA	12 months	Height, weight	BMI, laboratory and clinical indices	89% of the cohort experienced short-term response following induction. Response was associated with improvement in weight and BMI Z-scores (pb0.001) but not with linear growth. Responders had a significantly lower weight and BMI Z-scores at initiation of
Thayu, 2010, USA[92]	Prospective cohort	Paediatric	78	steroids 34 (74%), methotrexate 11 (24%), 6-mercaptopu- rine 36 (78%), azathioprine 5 (11%), infliximab 13 (28%), and enteral nutrition 9 (20%). Of note, no subject received exclusive enteral nutritional therapy.	Healthy controls	12 months; subset followed up for median 43 months	Weight, height, DXA (FFM, FM)	Change in body composition	LM-ht-Z and FM- ht-Z) improved significantly after diagnosis; however, female patients had persistent LM deficits vs controls (0.50 1.02, P .05). Serum interleukin-6, tumour necrosis factor, and lipopolysaccharide binding protein decreased significantly. Greater increases in LM-ht-Z were associated with infliximab therapy, increases in albumin and decreases in erythrocyte sedimentation rate, interleukin-6, and lipopolysaccharide binding protein. Greater increases in FM-ht-Z were associated with glucocorticoid, methotrexate, and infliximab therapy, and increases in albumin and growth hormone binding protein. Overall, height-Z did not improve; however, greater increases in insulin-like growth factor 1 and decreases in tumour necrosis factor, interleukin-6, and lipopolysaccharide binding protein levels were associated with increases in height-Z.

Walters, 2007, Canada[93]	Retrospective cohort	Paediatric	32	Infliximab	NA	Median 26 months	Height, weight	Growth, response to treatment	n all, 28 of 32 patients tolerated and responded to the induction regimen and 27 responders continued to receive infliximab via regularly scheduled infusions (n 22) or episodically (n 5) for a median of 26 months. Mean standard deviation score (SDS) for height at time of initiation of infliximab therapy was 1.15 1.2 and had declined despite the use of other therapies from 0.44 1.1 at initial diagnosis. Increases in height velocity and stature during infliximab therapy were limited by pubertal stage.
Wong, 2011, UK[104]	Randomised control trial	Paediatric	22 (21 CD)	11 rhGH	10 CD, 1 UC	6 months	Height	Height velocity change	Median HV increased from 4.5 (range, 0.6, 8.9) at base- line to 10.8 (6.1, 15.0) cm/year at 6 month (P = 0.003) in the rhGH group, whereas in the Ctrl group, it was 3.8 (1.4, 6.7) and 3.5 cm/year (2.0, 9.6), respectively (P = 0.58). Median percentage increase in HV after 6 months in the rhGH group was 140% (16.7, 916.7) compared with 17.4% ()42.1%, 97.7%) in the Ctrl group (P < 0.001). There were no significant differences in disease activity and proinflammatory cytokines at baseline and 6 months in both groups and change in bone age for chronological age was also similar in the two groups.

Table 4: Body composition effects on drug dosing

Author, year, country	*Type of study*	*Adult or paediatric*	*Number of patients*	*Treatment group*	*Controls*	*Duration of study*	*Body composition technique*	*Outcome measure*	*Results*
Colombel, 2014, USA[116]	Prospective cohort	Adult	80	Certolizumab	NA	54 weeks	Weight, BMI	Endoscopic remission, drug levels	There was an inverse correlation between baseline body weight and the CZP trough concentration at week 8 (p value given, but not r). These data support a role for body weight as a predictive factor for CZP plasma concentration after a loading dose.
Csontos, 2015, Hungary[113]	Prospective cohort	Adult	18	Adalimumab	NA	12 weeks	BIA	ADA trough levels	ADA trough levels did not differ significantly at week 6 and 12 (8.00±2.9μg/mL vs. 7.73±3.14μg/mL). Three of the patients (6.7%) had suboptimal ADA trough levels, only one of them were detected to have antibodies, he was excluded from further investigations. The changes of adalimumab trough levels correlated with body surface area (r=-0.682; p=0.002). We also found moderate correlation between the variability of trough levels and muscle parameters (FFMI: r=-0.494, p=0.045, SMI: r=-0.508, p=0.038). However, the changes of ADA trough levels did not correlate with BIA fat parameters nor the proportion of extracellular and intracellular fluid (BFMI: r=-0.099 and extracellular/intracellular water r=0.089)
Dassopoulos, 2013, USA[223]	RCT	Mixed	50	Azathioprine dosed according to metabolite levels	Weight-based azathioprine dosing	16 weeks	Weight	Clinical remission, thiopurine metabolite levels	trends towards individualised over weight-based azathioprine dosing, but no statistically significant differences in efficacy, likely due to low statistical power and inability to achieve the target 6TGN concentrations in the individualised arm
Dotan, 2014, Israel[119]	Prospective cohort	Adult	25 CD, 25 UC, 4 NS	Infliximab	NA	NA	BMI, Weight	Pharmacokinetics	The model revealed that the relationship between IFX-CL and body weight is not linear; lower body weight patients actually required a higher milligram per kilogram dose to maintain the same drug exposure
Fasanmade, 2011, USA[120]	Metaanalysis	Mixed	692	Infliximab	NA				Weight affects infliximab PK properties (total CL and total Vd increased with total body weight while per kg CL and Vd decrease with total body weight), V2 decreased as body weight increased, predicting a possible undercompensation for exposure with infliximab dosing per kg weight in lower-weight individuals.

Hämäläinen, 2012, Finland[224]	Prospective cohort	Paediatric	37 (23 CD)	Infliximab	NA	Not specified	Weight	Infliximab levels	Lower body weight and higher level of intestinal inflammation are associated with s-IFX levels during induction.
Holt, 2016, Australia[109]	Cross-sectional	Adult	66	Thiopurine	NA	NA	DXA, CT, Anthropometry	Thiopurine metabolite levels	No correlation was identified between 6TGN and any body composition parameters, absolute drug dose or drug dose/ kg of fat mass, fat-free mass (FFM), subcutaneous adipose tissue area, or visceral adipose tissue area. However, 6MMP correlated with azathioprine dose, thiopurine dose/kg of body weight, and with several body composition parameters.
Hyams, 2012, USA[96]	RCT	Paediatric	192	Adalimumab	Dose stratification	26 weeks	Weight	Clinical remission	Higher ADA doses were associated with higher drug levels; no difference in clinical efficacy was observed between high dose or low dose regimens.
Lie, 2014, Netherlands[114]	Retrospective cohort	Adult	76	Adalimumab	NA	Median 201 days	BMI, Weight	Pharmacokinetics	In a multivariable regression analysis of patient factors influencing week 28 adalimumab levels, the regression model containing CRP at week 28 and BMI at baseline ($r = 0.408$, $p = 0.005$) weakly but significantly predicted week 28 adalimumab levels ($R2 = 0.193$, $P = 0.004$).
Nguyen, 2013, France[112]	Retrospective cohort	Paediatric	86	Thiopurine	NA	median 20 months	Weight	Thiopurine metabolite levels	This study is the first to demonstrate significantly positive correlations between the weight-based azathioprine dosage and the levels of 6-TGN and 6-MeMPN metabolites as well as the 6-MeMPN/6-TGN ratio in paediatric IBD patients, whereas almost all previous studies showed no relationship or only very weak correlations
Poon, 2015, UK[225]	Cross-sectional	Adult	77 CD, 55 UC	Thiopurine	NA	NA	BMI	Thiopurine nucleotide levels	Every 5kg/ m2 increase in BMI was associated with an 8% decrease in 6-TGN (0.92; 95% confidence interval [CI] 0.87–0.98; $p = 0.009$). Obese patients were more likely to have sub-therapeutic 6-TGN levels and a higher methyl mercaptopurine nucleotide [MMPN/TGN] ratio despite a similar dose of thiopurines.
Rosario, 2015, USA[122]	Metaanalysis	Adult	2554 (UC, CD, healthy controls)	Vedolizumab	Healthy controls	NA	Weight	Population pharmacokinetics	Body weight positively correlated with vedolizumab linear clearance. A patient of 120 kg with a serum albumin concentration of 4.0 g/dL had a 19% probability of having CLL greater than the pre-specified criterion for clinical significance. Measures of body size are the most commonly identified covariates influencing the pharmacokinetics of therapeutic monoclonal antibodies. The impact of body weight on vedolizumab CLL is consistent with that reported in population pharmacokinetic analyses of other therapeutic monoclonal antibodies.
Sharma, 2015, USA[125]	Randomised trial	Paediatric	189	Adalimumab	NA	52 weeks	Weight	Pharmacokinetics	Higher baseline body weights were associated with greater adalimumab clearance; median clearance was ≈50% higher in the fourth quartile (>54

									kg) compared with the first quartile (<34 kg). However, due to the wide PK variability, there was considerable overlap in the individual clearance values across body weight groups.
Subramanian, 2014, UK[111]	Retrospective cross-sectional analysis	Adult	106 (55% CD)	Thiopurine	NA	NA	BMI, Weight, body fat index	6TGN levels	After adjustment, a one kilogram increase in weight was associated with a 1.62 unit decrease in 6-TGN levels (95% CI: 0.40 to 2.82, p = 0.0094). Body fat index correlated strongly with weight for both males and females (0.8345 and 0.8860 respectively) and a significant difference was found between BFI for each sex (p < 0.001) with females, on average, having a higher BFI. Weight, BMI and BFI differed significantly across sub-therapeutic, therapeutic and supra-therapeutic 6-TGN groups
Ternant, France, 2008[118]	Retrospective cohort	Adult	33 (30 CD, 3 UC)	Infliximab	NA	Median time from first dose to drug level test 13 months	Weight	Infliximab levels	A two-compartment model was formulated, with both sex and weight were found to significantly influence central volume of distribution (VC): this parameter was higher in men than in women and increased with body weight. An influence of weight on VC was reported for other monoclonal antibodies such as golimumab18 and sibrotuzumab.17 Because VC is similar to plasma volume and this volume increases with body weight, the influence of body weight on VC was expected.
Wade, 2015, Belgium[121]	Metaanalysis	Adult	2157	Certolizumab	NA	NA	Weight, BMI, BSA	Population pharmacokinetics	Of weight, BMI and BSA, BSA most affected clearance and apparent volume of distribution, in a linear fashion; both parameters increased by more than 53% and 49%, respectively, across the range of BSA measurements in the data.
Yip, USA, 2008[107]	Questionnaire to clinicians	Adult	145 respondents	Thiopurine	NA		Weight		Most gastroenterologists aspire to weight-based dosing regardless of checking TPMT. However, more gastroenterologists who checked TPMT, compared to those who did not, reached maximal weight-based dosing for 6-MP (73% versus 54%; P 0.03)

Table 5: Body composition effects on outcomes

Author, year, country	*Type of study*	*Adult or paediatric*	*Number of patients*	*Treatment group*	*Controls*	*Duration of study*	*Body composition technique*	*Outcome measure*	*Results*
Bhalme, 2013, UK[133]	Retrospective cohort	Adult	130	Adalimumab and Infliximab	NA	>3 months	BMI, weight	Loss of response	For those patients on ADA, a Cox proportional hazards model showed that an increased hazard of LOR is related to increases in BMI (P = 0.045). An increase of 1 in BMI corresponds to an increase in hazard of 8.2%. For those patients on IFX, there was no significant effect of BMI upon LOR (P = 0.36).
Blain, 2002, France[144]	Retrospective cohort	Adult	62 obese Crohn's disease (from cohort of 2065)	Multiple medical therapies	124 non-obese CD	Variable follow-up	Weight, height, BMI	Weight change, disease behaviour, disease severity, therapy	Prevalence of obesity in large cohort over 36-year period was 3.6%. Obese patients were older at diagnosis. Perianal disease was more frequent, with shorter time to development of penetrating complications. Active disease and hospitalisation were more likely in obese patients.
Büning, 2015, Germany[141]	Prospective cohort	Adult	31 women	Multiple medical therapies	19 age and BMI-matched women	6 months	BodPod, Height, Weight, BMI, MRI (VAT), abdominal ultrasound	Disease pattern/activity, treatments, cytokines	Patients with CD had higher percentage of FM (37 6 10% versus 31 6 10%, P =0.03), VAT (1885 6 1403 mL versus 941 6 988 mL, P =0.02), and VAT/FM ratio (65 6 24 mL/kg versus 37 6 25 mL/kg, P =0.004) than control women. In patients with CD, VAT/FM ratio was associated with leptin (P =0.009) and interleukin 6 (P =0.032) concentrations, and higher in short-term than in long-term remission (72.6 6 27.1 mL/kg versus 54.8 6 16.1 mL/kg, P =0.079). Patients with CD with stricturing/fistulising disease had a higher VAT/FM ratio than patients with non-stricturing/ non-fistulising behaviour (79 6 0.15 mL/kg versus 63 6 28 mL/kg, P =0.067). A higher baseline VAT/FM ratio was associated with an increased disease activity at follow-up (P =0.029). The ultrasound-determined thickness between the abdominal wall and the aorta was strongly associated with VAT as measured by magnetic resonance imaging
Colombo, 2015, Italy[151]	Case-control	Adult	6	Bariatric surgery	Morbidly obese	Mean 57.8 months	Weight, height	BMI, weight, perioperativ	Perioperative results, in terms of BMI, excess weight loss, and complications after restrictive bariatric surgery, were comparable between obese IBD and control patients.

								e complicatio ns	
Ding, UK[226]	2015,	Retrospective cohort	Adult	49	Anti-TNF	NA	Unspecifi ed	CT (SM, muscle density, VAT)	Primary and secondary loss of response	Patients with visceral obesity were more likely to have PNR [OR 7.42 95%(1.12-49.24) p=0.038]. From the patients that had PNR, 28% had visceral obesity. LOR was present in 18 (37%) patients. Patients with myosteatosis were more likely to have LOR [OR 4.01 95%(1.05-15.22) p=0.042]. From the patients that had LOR, 44% had myosteatosis. None of the other factors (myopenia, age, gender and type of anti-TNF) were associated with LOR or PNR.
Ding, UK[138]	2016,	Retrospective cohort	Adult	106	Anti-TNF	NA	Median 22.65 months	CT (SM, muscle density, VAT)	Primary and secondary loss of response	PNR in 24%. Secondary LOR was identified in 27%. According to body mass index (BMI), 13 (12%) were obese. However, of these, 77% had no visceral obesity. Myopenic patients were more likely to have PNR [OR 4.73 95%(1.81-12.39) p=0.002] on multivariate analysis. In patients with PNR, 15 (57%) were myopenic. No other factors (visceral obesity, myosteatosis, age, gender and type of anti-TNF) were associated with LOR or PNR
Falaiye, USA[136]	2014,	Retrospective cohort	Paediatric	29 (12 CD)	Infliximab	NA	median 923 days	Weight, BMI	Response to therapy, dose escalation	Need for infliximab dose escalation was associated with lower body mass index z score (P = 0.01)
Fuentes, 2003[129]	UK,	Retrospective cohort	Paediatric	107 patients (65 CD)	Azathioprine	NA	mean 3.1 years	Weight	Clinical response, clinical remission, adverse events	A daily dose of 3 mg/kg azathioprine is a safe, well- tolerated and effective maintenance therapy for children with moderate to severe inflammatory bowel disease. For the first time, it has been shown that growth rates in children with the most severe Crohn's disease may not deteriorate, and indeed may improve in the first years following diagnosis using the above regimen. Compared with historical controls, the need for early surgery appears to be reduced.
Harper, USA[135]	2013,	Retrospective cohort	Adult	99 CD, 24 UC	Infliximab	NA	3 years	BMI, Weight	IBD flare	Obese (BMI >30 kg/m2) patients with Crohn's disease were more likely to have an IBD flare than nonobese patients (adjusted hazard ratio [HR]: 3.03, P , 0.001). Increasing weight and BMI were associated with earlier IBD flare in both Crohn's disease (adjusted HR: 1.06 per unit increase in BMI [P = 0.02] and 1.02 per kg increase in body mass [P=0.02]) and

									ulcerative colitis (adjusted HR: 1.3 per unit increase in BMI [P = 0.01] and 1.11 per kg increase in body mass [P = 0.004]).
Hass, 2006, USA[145]	Retrospective cohort	Adult	48 obese Crohn's disease	Multiple medical therapies	100 non-obese CD	median 213 months	Weight, height, BMI	Time to first surgery, age at diagnosis, number of surgeries, and escalation of medical therapy	Obese patients were older at diagnosis and had a shorter time to first surgery than underweight patients
Holt, 2015, Australia[137]	Retrospective cohort	Adult	35 (34 CD)	Anti-TNF	NA	Median 1100 days	CT (VAT, SFA, MFI, SM)	Loss of response	Those patients in the lowest quartile of L4-5 visceral adipose tissue area had a median time to LOR of 636 days, compared with 1100 days in the median 50% (p = 0.0457). The median time to loss of response was shorter for the lowest quartile of skeletal muscle area than for the lowest quartile of body weight or visceral adipose tissue area. Crohn's Disease Activity Index and C-reactive protein were not predictors of loss of response, but those in the lowest quartile of albumin and haemoglobin measures had a shorter mean time to loss of response (p = 0.024 and 0.037 respectively).
Holtmann, 2010, Germany[128]	Retrospective cohort	Adult	1176 (818 CD)	Azathioprine	NA	4 years	BMI	Response to therapy, steroid requirement	Azathioprine responsiveness depends on body mass index (BMI). The relationship is reciprocal in UC and CD, with a better outcome in UC patients with a BMI<25 and in CD patients with BMI>25
Li, 2015, China[227]	Retrospective cohort	Adult	72	Surgery	NA	6 months	CT (VAT, SFA, MFI)	Endoscopic recurrence	The factors associated with postoperative endoscopic recurrence at 6 months after surgery were a high VFA value and MFI values above the median. VFA values were significantly correlated with endoscopic recurrence (r = 0.895, P = 0.040) and endoscopic lesions (r = 0.617, P < 0.0001). Additionally, MFI values correlated well with endoscopic recurrence (r = 0.918, P = 0.02) and endoscopic scores (r = 0.584, P < 0.0001). Multivariate analysis indicated that VFA values above the median (hazard ratio 2.63, 95% CI 1.03–6.74) were predictive of postoperative clinical recurrence in Crohn's disease.

Nic Suibhne, 2012, Ireland	Prospective case-control/cross-sectional	Adult	100	Multiple medical therapies	NA	NA	Height, weight, BMI, skinfold thickness, arm fat area, mid upper arm circumference	Inflammatory markers, disease activity	Overall, 40% of patients with CD were overweight/obese (BMI≥25 kg/m2) compared with 52% of controls (P = 0.206). On regression analysis, higher current BMI was significantly associated with disease specific factors, namely lower disease activity (CDAI) and lower white cell count, suggesting stable disease, as well as older age and lower physical activity. BMI was not significantly associated with the need for surgery or the need for corticosteroids. A novel association between higher BMI and higher CRP was identified.
O'Connor, 2015, Ireland[143]	Cross-sectional	Adult	27	NA	NA	NA	BMI, waist-hip ratio, MUAC, skinfold thickness, BIA	Disease pattern/activity, treatments, abdominal pain, wellbeing	27 patients were recruited in this pilot study. 16 (59%) had BMI >25 and (classified as overweight or obese), 10 had normal BMI and 1 had BMI <18. 32% had body fat stores above normal, 44% within normal range and 24% had low fat stores as measured with BIA. Numbers were too small in this pilot study to establish a relationship between dis- ease pattern and/or activity, those requiring >1 course of steroids in the previous year and those on anti-TNF therapy were more likely to have normal range BMI than the group as a whole. Self reported abdominal pain and decreased well being was highest in patients with an increased BMI.
Petito, 2015, Italy[134]	Prospective cohort	Adult	12 UC, 12 CD	Infliximab	NA	>14 weeks	DXA (FM) and BMI	IFX levels, ATI, response to treatment	Higher BMI and body fat levels were associated to reduced response to IFX. Higher IFX trough levels correlated to retrospective response to IFX. ATI associated to lower IFX trough levels and also post-infusion levels. BMI and body fat levels correlated to IFX postinfusion levels, suggesting that IFX does not distribute in the adipose tissue. Patients under immunosuppressant display higher IFX post-infusion levels and reduced ATI levels.
Qiu, 2015, China[131]	Retrospective cohort	Adult	267	Thiopurine	NA	Median 47.2 months	BMI	Thiopurine adverse events	Low BMI was associated with treatment withdrawal
Sandborn, 2012, USA[126]	RCT	Adult	526 (394 received treatment, 132 placebo)	Ustekinumab	Placebo	Approx 25 weeks	Weight	Clinical response, clinical remission	Patients with moderate-to-severe Crohn's disease in whom treatment with one or more TNF antagonists had failed were more likely to have a clinical response to 6 mg of ustekinumab per kilogram than to placebo. Induction with ustekinumab did not significantly increase the remission rate. For all other secondary outcomes, the efficacy of 6 mg of ustekinumab per kilogram was superior to that of placebo. Lower induction doses of

									ustekinumab generally had a numerical benefit, as compared with placebo, although the differences were not significant.
Summers, 1979, USA[127]	Randomised trial	Adult	113	Azathioprine	1.0 vs 2.5mg/kg Azathioprine	2 years	Weight	Adverse reactions	At a dose of 2.5 mg azathioprine/kg, there was a 15% incidence of leukopenia; at 1 mg/kg, only 3.7% had leukopenia.
Stidham, 2015, USA[147]	Retrospective cohort	Adult	269	Surgery	NA	30 days	CT (VAT, SFA, MFI)	Postoperative infective complications	Bivariate analysis showed subcutaneous-to-visceral fat volume distribution as a predictor of complications. Body mass index, anti-tumour necrosis factor alpha therapies, and immunomodulator use were not predictors of complication. Multivariate modelling demonstrated subcutaneous-to-visceral fat distribution (odds ratio = 2.01; 95% confidence interval, 1.20–3.19; P = 0.006) as a predictor of infectious complication.
Thangarajah, 2014, UK[146]	Prospective, case-control	Paediatric	23	NA	6 healthy controls	NA	MRI (VAT, SAT, SM)	Disease activity	Severe disease is associated with lower muscle mass and higher IAAT. In severe disease despite lower BMI, there is evidence of higher IAAT; this implies that IAAT is mediated by local gastrointestinal inflammation.
Uko, 2014, USA[142]	Retrospective cohort	Paediatric	101 CD	Corticosteroids, anti-TNF	78 age-matched	NA	CT	Disease activity, time to surgery	IBD group had 33% higher VAT than controls after adjusting for body mass index and age. In patients with CD, higher VAT was associated with fistulising or fibrostenotic disease (odds ratio 1.7), CD hospitalizations (OR, 1.9), moderate or severe disease activity scores (OR, 1.8), and shorter intervals from diagnosis to surgery (hazard ratio, 1.4) after adjusting for body mass index and age.
Wu, 2013, China[132]	Retrospective cohort	Adult	77	Azathioprine	NA	≥2 years	Weight	Reduction in Harvey-Bradshaw Index	Among 77 patients, 39 (50.6%) started treatment with <1.0 mg/kg azathioprine and 38 (49.4%) with 1.0-2.0 mg/kg. The remission rate in patients of <1.0 mg/kg group was significantly higher than that in those of 1.0-2.0 mg/kg group. A dose of <1.0 mg/kg azathioprine was more commonly associated with male gender, older age, heavier body weight and L1 location. Adverse events were observed in 21 of 77 patients (27.3%) and no significant difference in occurrence of adverse events or leukopenia between two groups.
Zhang, 2015, China[149]	Prospective cohort	Adult	138	Preoperative management, elective intestinal resection and anastomosis	NA	30 days	BIA	BMI, SM, FM	Preoperative SMP (P=0.002, OR 0.487, 95 % CI 0.307–0.772) and BFP (P=0.036, OR 0.691, 95 % CI 0.490–0.996) were significantly independent protective factors. Notably, only preoperative SMP (P=0.002, OR 0.588, 95 % CI 0.422–0.820) was a significantly independent protective factor for major complications, and our threshold of SMP was 24.3 % (P<0.001, sensitivity 83.7%, specificity 95.9%).

References

1. 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.

2. Behnke AR, Osserman EF, Welham WC. Lean body mass; its clinical significance and estimation from excess fat and total body water determinations. AMA Arch Intern Med. 1953 May;91(5):585–601.

3. Silva AM, Shen W, Wang Z, Aloia JF, Nelson ME, Heymsfield SB, et al. Three-compartment model: critical evaluation based on neutron activation analysis. Am J Physiol Endocrinol Metab. 2004 Nov;287(5):E962–9.

4. Prado CM, Prado CM, Siervo M, Siervo M, Mire E, Mire E, et al. A population-based approach to define body-composition phenotypes. Am J Clin Nutr. American Society for Nutrition; 2014 Jun 1;99(6):ajcn.078576–1377.

5. Baracos V, Caserotti P, Earthman CP, Fields D, Gallagher D, Hall KD, et al. Advances in the Science and Application of Body Composition Measurement. Journal of Parenteral and Enteral Nutrition. 2012 Jan 10;36(1):96–107.

6. Matsuzawa Y. Establishment of a concept of visceral fat syndrome and discovery of adiponectin. Proc Jpn Acad, Ser B. 2010;86(2):131–41.

7. 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.

8. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nat Rev Immunol. 2011 Feb 1;11(2):85–97.

9. Crohn BB, Ginzburg L, Oppenheimer GD. Regional ileitis; a pathologic and clinical entity. Am J Med. 1952 Nov 1;13(5):583–90.

10. 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.

11. Fink C, Karagiannides I, Bakirtzi K, Pothoulakis C. Adipose tissue and inflammatory

bowel disease pathogenesis. Inflamm Bowel Dis. 2012 Aug;18(8):1550–7.

12. 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.

13. 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.

14. Njeh CF, Fuerst T, Hans D, Blake GM, Genant HK. Radiation exposure in bone mineral density assessment. Appl Radiat Isot. 1999 Jan;50(1):215–36.

15. Blake GM, Fogelman I. Technical principles of dual energy x-ray absorptiometry. Semin Nucl Med. 1997 Jul;27(3):210–28.

16. Pietrobelli A, Formica C, Wang Z, Heymsfield SB. Dual-energy X-ray absorptiometry body composition model: review of physical concepts. Am J Physiol. 1996 Dec;271(6 Pt 1):E941–51.

17. Van Der Ploeg GE, Withers RT, LaForgia J. Percent body fat via DEXA: comparison with a four-compartment model. J Appl Physiol. 2003 Feb;94(2):499–506.

18. Glickman SG, Marn CS, Supiano MA, Dengel DR. Validity and reliability of dual-energy X-ray absorptiometry for the assessment of abdominal adiposity. J Appl Physiol. 2004 Aug;97(2):509–14.

19. Bertin E, Marcus C, Ruiz JC, Eschard JP, Leutenegger M. Measurement of visceral adipose tissue by DXA combined with anthropometry in obese humans. Int J Obes Relat Metab Disord. 2000 Mar;24(3):263–70.

20. Kamel EG, McNeill G, Van Wijk MCW. Usefulness of Anthropometry and DXA in Predicting Intra-abdominal Fat in Obese Men and Women. Obesity. Nature Publishing Group; 2000 Jan;8(1):36–42.

21. Snijder MB, Visser M, Dekker JM, Seidell JC, Fuerst T, Tylavsky F, et al. The prediction of visceral fat by dual-energy X-ray absorptiometry in the elderly: a comparison with

computed tomography and anthropometry. Int J Obes Relat Metab Disord. 2002 Jul;26(7):984–93.

22. Park Y-W, Heymsfield SB, Gallagher D. Are dual-energy X-ray absorptiometry regional estimates associated with visceral adipose tissue mass? Int J Obes Relat Metab Disord. 2002 Jul;26(7):978–83.

23. Heymsfield SB, Smith R, Aulet M, Bensen B, Lichtman S, Wang J, et al. Appendicular skeletal muscle mass: measurement by dual-photon absorptiometry. Am J Clin Nutr. 1990 Aug;52(2):214–8.

24. 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.

25. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010 Jul 1;39(4):412–23.

26. Tan BHL, Birdsell LA, Martin L, Baracos VE, Fearon KCH. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. Clin Cancer Res. 2009 Nov 15;15(22):6973–9.

27. Baracos VE, Reiman T, Mourtzakis M, Gioulbasanis I, Antoun S. Body composition in patients with non-small cell lung cancer: a contemporary view of cancer cachexia with the use of computed tomography image analysis. Am J Clin Nutr. 2010 Apr 1;91(4):1133S–1137S.

28. 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.

29. Gomollón F, Dignass A, Annese V, Tilg H, Van Assche G, Lindsay JO, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. J Crohns Colitis. Oxford University Press; 2017 Jan 1;11(1):3–25.

30. Lichtenstein GR, Abreu MT, Cohen R, Tremaine W, American Gastroenterological

Association. American Gastroenterological Association Institute medical position statement on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. Gastroenterology. 2006 Mar;130(3):935–9.

31. Dassopoulos T, Sultan S, Falck Ytter YT, Inadomi JM, Hanauer SB. American Gastroenterological Association Institute technical review on the use of thiopurines, methotrexate, and anti-TNF-α biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. Gastroenterology. 2013 Dec;145(6):1464–78.e1–5.

32. Nielsen OH, Seidelin JB, Ainsworth M, Coskun M. Will novel oral formulations change the management of inflammatory bowel disease? Expert Opin Investig Drugs. 2016 Jun;25(6):709–18.

33. Best WR, Becktel JM, Singleton JW, Kern F. Development of a Crohn"s disease activity index. National Cooperative Crohn"s Disease Study. Gastroenterology. 1976 Mar;70(3):439–44.

34. Irvine EJ, Feagan B, Rochon J, Archambault A, Fedorak RN, Groll A, et al. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. Canadian Crohn's Relapse Prevention Trial Study Group. Gastroenterology. 1994 Feb;106(2):287–96.

35. Summers GD, Deighton CM, Rennie MJ, Booth AH. Rheumatoid cachexia: a clinical perspective. Rheumatology. 2008 Apr 29;47(8):1124–31.

36. Muscaritoli M, Anker SD, Argilés J, Aversa Z, Bauer JM, Biolo G, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". Clin Nutr. 2010 Apr;29(2):154–9.

37. Anker SD, Coats AJS, Morley JE, Rosano G, Bernabei R, Haehling von S, et al. Muscle wasting disease: a proposal for a new disease classification. J Cachexia Sarcopenia Muscle. 2014 Mar;5(1):1–3.

38. Gibson DJ, Burden ST, Strauss BJ, Todd C, Lal S. The role of computed tomography in evaluating body composition and the influence of reduced muscle mass on clinical outcome

in abdominal malignancy: a systematic review. Eur J Clin Nutr. 2015 Oct;69(10):1079–86.

39. Thibault R, Genton L, Pichard C. Body composition: Why, when and for who? Clin Nutr. 2012 Jan 30.

40. Prado CMM, Baracos VE, McCargar LJ, Reiman T, Mourtzakis M, Tonkin K, et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. Clin Cancer Res. 2009 Apr 15;15(8):2920–6.

41. Ali R, Baracos VE, Sawyer MB, Bianchi L, Roberts S, Assenat E, et al. Lean body mass as an independent determinant of dose-limiting toxicity and neuropathy in patients with colon cancer treated with FOLFOX regimens. Cancer Med. 2016 Apr;5(4):607–16.

42. Dong J, Chen Y, Tang Y, Xu F, Yu C, Li Y, et al. Body Mass Index Is Associated with Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. Green J, editor. PLoS ONE. 2015 Dec 14;10(12):e0144872.

43. Ruemmele FM, Veres G, Kolho KL, Griffiths A, Levine A, Escher JC, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. Vol. 8, Journal of Crohn's and Colitis. 2014. pp. 1179–207.

44. Azcue M, Rashid M, Griffiths A, Pencharz PB. Energy expenditure and body composition in children with Crohn's disease: effect of enteral nutrition and treatment with prednisolone. Gut. 1997 Aug 1;41(2):203–8.

45. Khoshoo V, Reifen R, Neuman MG, Griffiths A, Pencharz PB. Effect of low- and high-fat, peptide-based diets on body composition and disease activity in adolescents with active Crohn's disease. JPEN J Parenter Enteral Nutr. 1996 Nov;20(6):401–5.

46. Dignass A, Van Assche G, Lindsay JO, Lémann M, Söderholm J, Colombel JF, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. J Crohns Colitis. 2010 Feb 1;4(1):28–62.

47. Zhao J, Dong J-N, Gong J-F, Wang H-G, Li Y, Zhang L, et al. Impact of enteral nutrition on energy metabolism in patients with Crohn's disease. World J Gastroenterol. 2015 Jan 28;21(4):1299–304.

48. Kaiser KA, George BJ, Allison DB. Re: Errors in Zhao et al(2015), Impact of enteral nutrition on energy metabolism in patients with Crohn's disease. WJG. 2016;22(9):2867.

49. Royall D, Greenberg GR, Allard JP, Baker JP, Jeejeebhoy KN. Total enteral nutrition support improves body composition of patients with active Crohn's disease. JPEN J Parenter Enteral Nutr. 1995 Mar;19(2):95–9.

50. Zoli G, Care M, Parazza M, Spano C, Biagi PL, Bernardi M, et al. A randomized controlled study comparing elemental diet and steroid treatment in Crohn's disease. Aliment Pharmacol Ther. 1997 Jul;11(4):735–40.

51. Steiner SJ, Noe JD, Denne SC. Corticosteroids Increase Protein Breakdown and Loss in Newly Diagnosed Pediatric Crohn Disease. Pediatric research. 2011 Nov;70(5):484–8.

52. Holt DQ, Strauss BJ, Moore GT. Patients with inflammatory bowel disease and their treating clinicians have different views regarding diet. J Hum Nutr Diet. 2016 Jul 14.

53. Siffledeen S, Siminoski S, Jen J, Fedorak F. Lower body fat composition and lower body mass index is associated with corticosteroid use and may not adequately reflect nutritional deficiency in patients with crohn's disease. Can J Gastroenterology. Pulsus Group Inc; 2009;23 IS -:117A.

54. Csontos ÁA, Molnár A, Piri Z, Katona B, Dakó S, Pálfi E, et al. The Effect of anti-TNFα Induction Therapy on the Nutritional Status and Dietary Intake in Inflammatory Bowel Disease. 2016 Mar;25(1):49–56.

55. Deepak P, Takahashi N, Fidler J, Barlow J. P-113 YI Body Fat and Skeletal Muscle Composition Differs in Crohn's Disease Patients Depending on Radiological Response to Medical Therapy. Inflamm Bowel Dis. 2016.

56. Emerenziani S, Guarino MPL, Rescio MP, Balestrieri P, Altomare A, Ribolsi M, et al. Effect of Infliximab Treatment on Body Composition Analysis in Patients with Crohn's Disease

. Digestive and Liver Disease. W.B. Saunders; 2015 Mar 15;47:e115–e208.

57. Barbosa-Silva MCG, Barros AJ, Wang J, Heymsfield SB, Richard N Pierson J. Bioelectrical impedance analysis: population reference values for phase angle by age and

sex. Am J Clin Nutr. American Society for Nutrition; 2005 Jul 1;82(1):49–52.

58. Franchimont D, Roland S, Gustot T, Quertinmont E, Toubouti Y, Gervy M-C, et al. Impact of infliximab on serum leptin levels in patients with Crohn's disease. J Clin Endocrinol Metab. 2005 Jun;90(6):3510–6.

59. Parmentier-Decrucq E, Duhamel A, Ernst O, Fermont C, Louvet A, Vernier-Massouille G, et al. Effects of infliximab therapy on abdominal fat and metabolic profile in patients with Crohn's disease. Inflamm Bowel Dis. 2009 Oct;15(10):1476–84.

60. Nakahigashi M, Yamamoto T. Increases in body mass index during infliximab therapy in patients with Crohn's disease: an open label prospective study. Cytokine. 2011 Nov;56(2):531–5.

61. Vadan R, Gheorghe LS, Constantinescu A, Gheorghe C. The prevalence of malnutrition and the evolution of nutritional status in patients with moderate to severe forms of Crohn's disease treated with Infliximab. Clin Nutr. 2011 Feb;30(1):86–91.

62. Subramaniam K, Fallon K, Ruut T, Lane D, McKay R, Shadbolt B, et al. Infliximab reverses inflammatory muscle wasting (sarcopenia) in Crohn's disease. Aliment Pharmacol Ther. 2015 Jan 8;41(5):419–28.

63. Thomsen KL, Grønbæk H, Dahlerup JF, Aagaard NK, Christensen LA, Agnholt J, et al. Prednisolone but Not Infliximab Aggravates the Upregulated Hepatic Nitrogen Elimination in Patients with Active Inflammatory Bowel Disease. Inflamm Bowel Dis. 2014 Jan;20(1):7–13.

64. Abitbol V, Mary JY, Roux C, Soule JC, Belaiche J, Dupas J-L, et al. Osteoporosis in inflammatory bowel disease: effect of calcium and vitamin D with or without fluoride. Aliment Pharmacol Ther. 2002 May;16(5):919–27.

65. Farkas K, Bálint A, Valkusz Z, Szepes Z, Nagy F. Bolus administration of steroid therapy is more favorable than the conventional use in preventing decrease of bone density and the increase of body fat percentage in …. Journal of Crohn's and …. 2014.

66. Pappa HM, Saslowsky TM, Filip-Dhima R, DiFabio D, Lahsinoui HH, Akkad A, et al. Efficacy and Harms of Nasal Calcitonin in Improving Bone Density in Young Patients With Inflammatory Bowel Disease: A Randomized, Placebo-Controlled, Double-Blind

Trial. Am J Gastroenterol. 2011 Apr 26;106(8):1527–43.

67. Altowati M, Shepherd S, McGrogan P, Russell R. Bone-Muscle Unit Assessment with pQCT in Children with Inflammatory Bowel Disease Following Treatment with Infliximab. ESPE Abstracts. 2015;84:P–1–19.

68. Azzopardi N, Ellul P. Risk factors for osteoporosis in Crohn's disease: infliximab, corticosteroids, body mass index, and age of onset. Inflamm Bowel Dis. 2013 May;19(6):1173–8.

69. Dubner SE, Shults J, Baldassano RN, Zemel BS, Thayu M, Burnham JM, et al. Longitudinal assessment of bone density and structure in an incident cohort of children with Crohn's disease. Gastroenterology. 2009 Jan;136(1):123–30.

70. Mauro M, Radovic V, Armstrong D. Improvement of lumbar bone mass after infliximab therapy in Crohn's disease patients. Can J Gastroenterol. 2007 Oct;21(10):637–42.

71. Pichler J, Hanslik A, Dietrich HW, Aufricht C, Bidmon-Fliegenschnee B. Paediatric patients with inflammatory bowel disease who received infliximab experienced improved growth and bone health. Acta Paediatrica. 2013 Nov 15;103(2):e69–e75.

72. Pichler J. Growth and bone health in paediatric patients with Crohn's disease receiving subcutaneous tumor necrosis factor antibody. WJG. 2015;21(21):6613.

73. Bakker JA. Metabolic and genetic aspects of thiopurine metabolism. PhD thesis, Universiteit Maastricht, 2010.

74. Burnham JM, Shults J, Semeao E, Foster B, Zemel BS, Stallings VA, et al. Whole Body BMC in Pediatric Crohn Disease: Independent Effects of Altered Growth, Maturation, and Body Composition. J Bone Miner Res. 2004 Sep 20;19(12):1961–8.

75. Cowan FJ, Warner JT, Dunstan FD, Evans WD, Gregory JW, Jenkins HR. Inflammatory bowel disease and predisposition to osteopenia. Arch Dis Child. 1997 Apr;76(4):325–9.

76. Compston JE, Judd D, Crawley EO, Evans WD, Evans C, Church HA, et al. Osteoporosis in patients with inflammatory bowel disease. Gut. 1987 Apr;28(4):410–5.

77. World Health Organization. WHO scientific group on the assessment of osteoporosis at

primary health care level. Summary meeting report; 2004.

78. de Jong DJ, Corstens FHM, Mannaerts L, van Rossum LGM, Naber AHJ. Corticosteroid-induced osteoporosis: does it occur in patients with Crohn's disease? Am J Gastroenterol. 2002 Aug;97(8):2011–5.

79. de Jong DJ, Mannaerts L, van Rossum LGM, Corstens FHM, Naber AHJ. Longitudinal study of bone mineral density in patients with Crohn's disease. Dig Dis Sci. 2003 Jul;48(7):1355–9.

80. Dinca M. Evolution of osteopenia in inflammatory bowel disease. Am J Gastroenterol. 1999 May;94(5):1292–7.

81. Laakso S, Valta H, Verkasalo M, Toiviainen-Salo S, Mäkitie O. Compromised Peak Bone Mass in Patients with Inflammatory Bowel Disease–A Prospective Study. J Pediatr. 2014 Jun;164(6):1436–1443.e1.

82. Sylvester FA, Wyzga N, Hyams JS, Davis PM, Lerer T, Vance K, et al. Natural history of bone metabolism and bone mineral density in children with inflammatory bowel disease. Inflamm Bowel Dis. 2007 Jan;13(1):42–50.

83. Walther F, Fusch C, Radke M, Beckert S, Findeisen A. Osteoporosis in Pediatric Patients Suffering From Chronic Inflammatory Bowel Disease With and Without Steroid Treatment. J Pediatr Gastroenterol Nutr. 2006 Jul;43(1):42–51.

84. Zadik Z, Sinai T, Zung A, Reifen R. Longitudinal monitoring of bone measured by quantitative multisite ultrasound in patients with Crohn's disease. J Clin Gastroenterol. 2005 Feb;39(2):120–3.

85. Tobias JH, Sasi MR, Greenwood R, Probert CSJ. Rapid hip bone loss in active Crohn's disease patients receiving short-term corticosteroid therapy. Aliment Pharmacol Ther. 2004 Nov;20(9):951–7.

86. Katznelson L, Fairfield WP, Zeizafoun 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. 2003 Nov;88(11):5468–72.

87. Patel L. Growth and Chronic Disease. Ann Nestlé [Engl]. 2008 Mar 1;65(3):129–36.

88. Kim MJ, Lee WY, Choi KE, Choe YH. Effect of infliximab "Top-down" therapy on weight gain in pediatric Crohn's disease. Indian Pediatr. 2012 Jun 10;49(12):979–82.

89. Assa A, Hartman C, Weiss B, Broide E, Rosenbach Y, Zevit N, et al. Long-term outcome of tumor necrosis factor alpha antagonist"s treatment in pediatric Crohn"s disease. J Crohns Colitis. 2013 Jun;7(5):369–76.

90. Malik S, Mason A, Bakhshi A, Young D, Bishop J, Garrick V, et al. Growth in children receiving contemporary disease specific therapy for Crohn's disease. Arch Dis Child. 2012 Aug;97(8):698–703.

91. Sinitsky DM, Lemberg DA, Leach ST, Bohane TD, Jackson R, Day AS. Infliximab improves inflammation and anthropometric measures in pediatric Crohn's disease. Journal of Gastroenterology and Hepatology. 2010 Apr;25(4):810–6.

92. Thayu M, Denson LA, Shults J, Zemel BS, Burnham JM, Baldassano RN, et al. Determinants of changes in linear growth and body composition in incident pediatric Crohn's disease. Gastroenterology. 2010 Aug;139(2):430–8.

93. Walters TD, Gilman AR, Griffiths AM. Linear Growth Improves during Infliximab Therapy in Children with Chronically Active Severe Crohn's Disease. Inflamm Bowel Dis. 2007 Apr;13(4):424–30.

94. Malik S, Wong SC, Bishop J, Hassan K, McGrogan P, Ahmed SF, et al. Improvement in growth of children with Crohn disease following anti-TNF-α therapy can be independent of pubertal progress and glucocorticoid reduction. J Pediatr Gastroenterol Nutr. 2011 Jan;52(1):31–7.

95. Pfefferkorn M, Burke G, Griffiths A, Markowitz J, Rosh J, Mack D, et al. Growth abnormalities persist in newly diagnosed children with Crohn disease despite current treatment paradigms. J Pediatr Gastroenterol Nutr. 2009 Feb;48(2):168–74.

96. Hyams JS, Griffiths A, Markowitz J, Baldassano RN, Faubion WA, Colletti RB, et al. Safety and efficacy of adalimumab for moderate to severe Crohn's disease in children. Gastroenterology. 2012 Aug;143(2):365–74.e2.

97. Mason A, Wong SC, McGrogan P, Ahmed SF. Effect of Testosterone Therapy for Delayed Growth and Puberty in Boys with Inflammatory Bowel Disease. Horm Res

Paediatr. 2011;75(1):8–13.

98. Kundhal P, Zachos M, Holmes JL, Griffiths AM. Controlled ileal release budesonide in pediatric Crohn disease: efficacy and effect on growth. J Pediatr Gastroenterol Nutr. 2001 Jul;33(1):75–80.

99. Ezri J, Marques-Vidal P, Nydegger A. Impact of Disease and Treatments on Growth and Puberty of Pediatric Patients with Inflammatory Bowel Disease. Digestion. 2012;85(4):308–19.

100. Hannon TS, DiMeglio LA, Pfefferkorn MD, Carroll AE, Denne SC. Effects of recombinant human growth hormone on protein turnover in the fasting and fed state in adolescents with Crohn disease. J Pediatr Endocrinol Metab. 2011;24(9-10):633–40.

101. Heyman MB, Garnett EA, Wojcicki J, Gupta N, Davis C, Cohen SA, et al. Growth hormone treatment for growth failure in pediatric patients with Crohn's disease. J Pediatr. 2008 Nov;153(5):651–8–658.e1–3.

102. Mauras N, George D, Evans J, Milov D, Abrams S, Rini A, et al. Growth hormone has anabolic effects in glucocorticosteroid-dependent children with inflammatory bowel disease: A pilot study. Metabolism. 2002 Jan;51(1):127–35.

103. Simon D, Alberti C, Alison M, Le Henaff L, Chevenne D, Boizeau P, et al. Effects of recombinant human growth hormone for 1 year on body composition and muscle strength in children on long-term steroid therapy: randomized controlled, delayed-start study. J Clin Endocrinol Metab. 2013 Jul;98(7):2746–54.

104. Wong SC, Kumar P, Galloway PJ, Blair JC, Didi M, Dalzell AM, et al. A preliminary trial of the effect of recombinant human growth hormone on short-term linear growth and glucose homeostasis in children with Crohn's disease. Clin Endocrinol (Oxf). 2011 May;74(5):599–607.

105. Chande N, Townsend CM, Parker CE, Macdonald JK. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Chande N, editor. Cochrane Database Syst Rev. Chichester, UK: John Wiley & Sons, Ltd; 2016 Oct 26;10:CD000545.

106. Osterman MT, Kundu R, Lichtenstein GR, Lewis JD. Association of 6-thioguanine

nucleotide levels and inflammatory bowel disease activity: a meta-analysis. Gastroenterology. 2006 Apr;130(4):1047–53.

107. Yip JS, Woodward M, Abreu MT, Sparrow MP. How are Azathioprine and 6-mercaptopurine dosed by gastroenterologists? Results of a survey of clinical practice. Inflamm Bowel Dis. 2008 Apr;14(4):514–8.

108. Dubinsky MC, Lamothe S, Yang HY, Targan SR, Sinnett D, Théorêt Y, et al. Pharmacogenomics and metabolite measurement for 6-mercaptopurine therapy in inflammatory bowel disease. Gastroenterology. 2000 Apr;118(4):705–13.

109. Holt DQ, Strauss BJ, Moore GT. Weight and Body Composition Compartments do Not Predict Therapeutic Thiopurine Metabolite Levels in Inflammatory Bowel Disease. Clin Trans Gastroenterol. 2016 Oct 27;7(10):e199.

110. Poon SS, Asher R, Jackson R, Kneebone A, Collins P, Probert C, et al. Body Mass Index and Smoking Affect Thioguanine Nucleotide Levels in Inflammatory Bowel Disease. J Crohns Colitis. 2015 Jul 27;9(8):640–6.

111. Subramanian S, Poon S, Kneebone A, Asher R, Jackson R, Gregg B, et al. PWE-100 Increasing Weight And Body Mass Index Adversely Affect Thioguanine Nucleotide Levels In Inflammatory Bowel Disease: Abstract PWE-100 Table 1. Gut. 2014 Jun 9;63(Suppl 1):A168.1–A168.

112. Nguyen T-V-A, Vu DH, Nguyen T-M-H, Lachaux A, Boulieu R. Exploring associations of 6-thioguanine nucleotide levels and other predictive factors with therapeutic response to azathioprine in pediatric patients with IBD using multilevel analysis. Inflamm Bowel Dis. 2013 Oct;19(11):2404–10.

113. Csontos CA, Molnár M, Piri P, Katona K, Farkas F, Molnár M, et al. Changes of adalimumab trough levels correlate with body composition parameters. Vol. 3, 21st United European Gastroenterology Week Berlin Germany. Conference Start: 20131012 Conference End: 20131016. SAGE Publications Ltd; 2015 [cited 2016 Aug 9]. pp. A246CY

114. Lie MRKL, Peppelenbosch MP, West RL, Zelinkova Z, van der Woude CJ. Adalimumab in Crohn's disease patients: pharmacokinetics in the first 6 months of treatment. Aliment

Pharmacol Ther. 2014 Sep 28;40(10):1202–8.

115. Hebuterne X, Lémann M, Bouhnik Y, Dewit O, Dupas J-L, Mross M, et al. Endoscopic improvement of mucosal lesions in patients with moderate to severe ileocolonic Crohn's disease following treatment with certolizumab pegol. Gut. BMJ Publishing Group Ltd and British Society of Gastroenterology; 2013 Feb;62(2):201–8.

116. Colombel JF, Sandborn WJ, Allez M, Dupas J-L, Dewit O, D'Haens G, et al. Association Between Plasma Concentrations of Certolizumab Pegol and Endoscopic Outcomes of Patients With Crohn's Disease. Clinical Gastroenterology and Hepatology. 2014 Mar;12(3):423–431.e1.

117. Hämäläinen A, Sipponen T, Kolho K-L. Serum infliximab concentrations in pediatric inflammatory bowel disease. Scand J Gastroenterol. 2012 Dec 18;48(1):35–41.

118. Ternant D, Aubourg A, Magdelaine-Beuzelin C, Degenne D, Watier H, Picon L, et al. Infliximab Pharmacokinetics in Inflammatory Bowel Disease Patients. Ther Drug Monit. 2008 Jul;PAP.

119. Dotan I, Ron Y, Yanai H, Becker S, Fishman S, Yahav L, et al. Patient factors that increase infliximab clearance and shorten half-life in inflammatory bowel disease: a population pharmacokinetic study. Inflamm Bowel Dis. 2014 Dec;20(12):2247–59.

120. Fasanmade AA, Adedokun OJ, Blank M, Zhou H, Davis HM. Pharmacokinetic properties of infliximab in children and adults with Crohn's disease: a retrospective analysis of data from 2 phase III clinical trials. Clin Ther. 2011 Jun 30;33(7):946–64.

121. Wade JR, Parker G, Kosutic G, Feagen BG, Sandborn WJ, Laveille C, et al. Population pharmacokinetic analysis of certolizumab pegol in patients with Crohn's disease. The Journal of Clinical Pharmacology. 2015 Apr 13;55(8):866–74.

122. Rosario M, Dirks NL, Gastonguay MR, Fasanmade AA, Wyant T, Parikh A, et al. Population pharmacokinetics-pharmacodynamics of vedolizumab in patients with ulcerative colitis and Crohn's disease. Aliment Pharmacol Ther. 2015 Jul;42(2):188–202.

123. Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, et al. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. N Engl J Med. 2016 Nov 17;375(20):1946–60.

124. Lebwohl M, Yeilding N, Szapary P, Wang Y, Li S, Zhu Y, et al. Impact of weight on the efficacy and safety of ustekinumab in patients with moderate to severe psoriasis: rationale for dosing recommendations. J Am Acad Dermatol. 2010 Oct;63(4):571–9.

125. Sharma S, Eckert D, Hyams JS, Mensing S, Thakkar RB, Robinson AM, et al. Pharmacokinetics and Exposure–Efficacy Relationship of Adalimumab in Pediatric Patients with Moderate to Severe Crohn's Disease. Inflamm Bowel Dis. 2015 Apr;21(4):783–92.

126. Sandborn WJ, Gasink C, Gao L-L, Blank MA, Johanns J, Guzzo C, et al. Ustekinumab Induction and Maintenance Therapy in Refractory Crohn's Disease. N Engl J Med. 2012 Oct 18;367(16):1519–28.

127. Summers RW, Switz DM, Sessions JT, Becktel JM, Best WR, Kern F, et al. National Cooperative Crohn's Disease Study: results of drug treatment. Gastroenterology. 1979 Oct;77(4 Pt 2):847–69.

128. Holtmann MH, Krummenauer F, Claas C, Kremeyer K, Lorenz D, Rainer O, et al. Significant differences between Crohn's disease and ulcerative colitis regarding the impact of body mass index and initial disease activity on responsiveness to azathioprine: results from a European multicenter study in 1,176 patients. Dig Dis Sci. 2010 Apr;55(4):1066–78.

129. Fuentes D, Torrente F, Keady S, Thirrupathy K, Thomson MA, Walker-Smith JA, et al. High-dose azathioprine in children with inflammatory bowel disease. Aliment Pharmacol Ther. 2003 Apr;17(7):913–21.

130. Singleton JW, Law DH, Kelley ML, Mekhjian HS, Sturdevant RA. National Cooperative Crohn's Disease Study: adverse reactions to study drugs. Gastroenterology. 1979 Oct;77(4 Pt 2):870–82.

131. Qiu Y, Mao R, Zhang S-H, Li M-Y, Guo J, Chen B-L, et al. Safety Profile of Thiopurines in Crohn Disease. Medicine (Baltimore). 2015 Oct;94(41):e1513.

132. Wu J, Gao Y, Yang C, Yang X, Li X, Xiao S. Low-dose azathioprine is effective in maintaining remission among Chinese patients with Crohn's disease. J Transl Med. 2013;11(1):235.

133. Bhalme M, Sharma A, Keld R, Willert R, Campbell S. Does weight-adjusted anti-tumour necrosis factor treatment favour obese patients with Crohn's disease? Eur J Gastroenterol Hepatol. 2013 May;25(5):543–9.

134. Petito V, Schiavoni E, Poscia A, DAmbrosio D, Curro D, Lopetuso LR, et al. Role of BMI, use of immune suppressant and pharmacokinetic of infliximab-pathway in determining prospective and retrospective response to the drug in cohort of IBD patients under maintenance therapy with infliximab. United European Gastroenterol J. Elsevier; 2015;2:Supplement1.

135. Harper JW, Sinanan MN, Zisman TL. Increased body mass index is associated with earlier time to loss of response to infliximab in patients with inflammatory bowel disease. Inflamm Bowel Dis. 2013 Sep;19(10):2118–24.

136. Falaiye TO, Mitchell KR, Lu Z, Saville BR, Horst SN, Moulton DE, et al. Outcomes following infliximab therapy for pediatric patients hospitalized with refractory colitis-predominant IBD. J Pediatr Gastroenterol Nutr. 2014 Feb;58(2):213–9.

137. Holt D, Varma P, Strauss B, Moore G. Low muscle mass at treatment initiation is associated with early loss of response to anti-TNF therapy for Inflammatory Bowel Disease. Journal of Gastroenterology and Hepatology. 2015;30 (Suppl. 3):131.

138. Ding NS, Malietzis G, Lung PF, YIp WM, Penez L, Ganeshanathan T, et al. 186 Body Composition Profile: A Predictor of Therapeutic Outcome in Patients With Moderate to Severe Crohn's Disease. Gastroenterology. 2016 Apr;150(4):S48–9.

139. Ding DN, Malietzis M, Ganeshanathan G, Yip Y, Penez P, Gabe G, et al. Body composition profile is associated with anti-TNF response in Crohn's disease patients. United European Gastroenterol J. SAGE Publications Ltd; 2015;3(5 SUPPL. 1):A597CY–.

140. Nic Suibhne T, Raftery TC, McMahon O, Walsh C, O'Morain C, O'Sullivan M. High prevalence of overweight and obesity in adults with Crohn's disease: Associations with disease and lifestyle factors. J Crohns Colitis. 2013 Aug 1;7(7):e241–8.

141. 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.

142. Uko V, Vortia E, Achkar J-P, Karakas P, Fiocchi C, Worley S, et al. Impact of abdominal visceral adipose tissue on disease outcome in pediatric Crohn's disease. Inflamm Bowel Dis 2014;20(12):2286–91.

143. O'Connor DJ, Sexton G. The relationship of adiposity to disease severity in a Crohn's patient cohort. BMC Proceedings. 2015;9(Suppl 1):A23.

144. Blain A, Cattan S, Beaugerie L, Carbonnel F, Gendre J-P, Cosnes J. Crohn's disease clinical course and severity in obese patients. Clin Nutr. 2002 Feb;21(1):51–7.

145. Hass DJ, Brensinger CM, Lewis JD, Lichtenstein GR. The impact of increased body mass index on the clinical course of Crohn's disease. Clin Gastroenterol Hepatol. 2006 Apr;4(4):482–8.

146. 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.

147. 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 Jun;21(6):1306–13.

148. 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.

149. Zhang W, Zhu W, Ren J, Zuo L, Wu X, Li J. Skeletal Muscle Percentage: A Protective Factor for Postoperative Morbidity in Crohn's Disease Patients with Severe Malnutrition. J Gastrointest Surg. Springer US; 2015 Feb 10;19(4):715–21.

150. Zhang T, Cao L, Cao T, Yang J, Gong J, Zhu W, et al. Prevalence of Sarcopenia and Its Impact on Postoperative Outcome in Patients With Crohn's Disease Undergoing Bowel Resection. JPEN J Parenter Enteral Nutr. 2015 Oct 15;:014860711561205.

151. Colombo F, Rizzi A, Ferrari C, Frontali A, Casiraghi S, Corsi F, et al. Bariatric surgery in patients with inflammatory bowel disease: an accessible path? Report of a case series and

review of the literature. J Crohns Colitis. 2015 Feb;9(2):185–90.

152. Heymsfield SB, Adamek M, Gonzalez MC, Jia G, Thomas DM. Assessing skeletal muscle mass: historical overview and state of the art. J Cachexia Sarcopenia Muscle. 2014 Mar;5(1):9–18.

153. American Gastroenterological Association medical position statement: guidelines on osteoporosis in gastrointestinal diseases. Vol. 124, Gastoenterology. 2003. pp. 791–4.

154. Etzel JP, Larson MF, Anawalt BD, Collins J, Dominitz JA. Assessment and management of low bone density in inflammatory bowel disease and performance of professional society guidelines. Inflamm Bowel Dis. 2011 Oct;17(10):2122–9.

155. Ellis KJ. Human body composition: in vivo methods. Physiol Rev. 2000 Apr;80(2):649–80.

156. Royall D, Greenberg GR, Allard JP, Baker JP, Harrison JE, Jeejeebhoy KN. Critical assessment of body-composition measurements in malnourished subjects with Crohn's disease: the role of bioelectric impedance analysis. Am J Clin Nutr. American Society for Nutrition; 1994 Feb;59(2):325–30.

157. Peloquin JM, Pardi DS, Sandborn WJ, Fletcher JG, McCollough CH, Schueler BA, et al. Diagnostic ionizing radiation exposure in a population-based cohort of patients with inflammatory bowel disease. Am J Gastroenterol. 2008 Aug;103(8):2015–22.

158. Hu HH, Chen J, Shen W. Segmentation and quantification of adipose tissue by magnetic resonance imaging. MAGMA. 2016 Apr;29(2):259–76.

159. Sadananthan SA, Prakash B, Leow MK-S, Khoo CM, Chou H, Venkataraman K, et al. Automated segmentation of visceral and subcutaneous (deep and superficial) adipose tissues in normal and overweight men. J Magn Reson Imaging. 2015 Apr;41(4):924–34.

160. Kaul S, Rothney MP, Peters DM, Wacker WK, Davis CE, Shapiro MD, et al. Dual-Energy X-Ray Absorptiometry for Quantification of Visceral Fat. Obesity (Silver Spring, Md). 2012 Jan 26;20(6):1313–8.

161. Batra A, Zeitz M, Siegmund B. Adipokine signaling in inflammatory bowel disease. Inflamm Bowel Dis. 2009 Dec 1;15(12):1897–905.

162. Ergun DL, Rothney MP, Oates MK, Xia Y, Wacker WK, Binkley NC. Visceral Adipose Tissue Quantification Using Lunar Prodigy. J Clin Densitom. Elsevier; 2013 Jan 1;16(1):75–8.

163. Rothney MP, Xia Y, Wacker WK, Martin F-P, Beaumont M, Rezzi S, et al. Precision of a new tool to measure visceral adipose tissue (VAT) using dual-energy X-Ray absorptiometry (DXA). Obesity. 2013 Jan;21(1):E134–6.

164. Walls HL, Stevenson CE, Mannan HR, Abdullah A, Reid CM, McNeil JJ, et al. Comparing Trends in BMI and Waist Circumference. Obesity (Silver Spring, Md). 2010 Jun 17.

165. 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.

166. Bruun JM, Verdich C, Toubro S, Astrup A, Richelsen B. Association between measures of insulin sensitivity and circulating levels of interleukin-8, interleukin-6 and tumor necrosis factor-alpha. Effect of weight loss in obese men. Eur J Endocrinol. 2003 May 1;148(5):535–42.

167. Karagiannides I, Pothoulakis C. Obesity, innate immunity and gut inflammation. Curr Opin Gastroenterol. 2007 Nov 1;23(6):661–6.

168. Flores A, Burstein E, Cipher DJ, Feagins LA. Obesity in Inflammatory Bowel Disease: A Marker of Less Severe Disease. Dig Dis Sci. Springer US; 2015 Aug;60(8):2436–45.

169. Steed H, Walsh S, Reynolds N. A Brief Report of the Epidemiology of Obesity in the Inflammatory Bowel Disease Population of Tayside, Scotland. Obes Facts. Karger Publishers; 2009;2(6):370–2.

170. Hattori A, Sturm R. The obesity epidemic and changes in self-report biases in BMI. Obesity. John Wiley & Sons, Inc; 2013 Apr;21(4):856–60.

171. Singh S, Dulai PS, Zarrinpar A, Ramamoorthy S, Sandborn WJ. Obesity in IBD: epidemiology, pathogenesis, disease course and treatment outcomes. Nat Rev Gastroenterol Hepatol. 2017 Feb;14(2):110–21.

172. Khalili H, Ananthakrishnan AN, Konijeti GG, Higuchi LM, Fuchs CS, Richter JM, et al. Measures of Obesity and Risk of Crohn's Disease and Ulcerative Colitis. Inflamm Bowel Dis. 2015 Feb;21(2):361–8.

173. Richman E, Rhodes JM. Review article: evidence-based dietary advice for patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2013 Nov;38(10):1156–71.

174. 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.

175. Charrière G, Cousin B, Arnaud E, André M, Bacou F, Penicaud L, et al. Preadipocyte conversion to macrophage. Evidence of plasticity. J Biol Chem. 2003 Mar 14;278(11):9850–5.

176. Kredel LI, Siegmund B. Adipose-tissue and intestinal inflammation - visceral obesity and creeping fat. Front Immunol. 2014;5(3):462.

177. Paul G, Schäffler A, Neumeier M, Fürst A, Bataillle F, Buechler C, et al. Profiling adipocytokine secretion from creeping fat in Crohn's disease. Inflamm Bowel Dis. 2006 Jun 1;12(6):471–7.

178. Desreumaux P. Specific targeting of IL-6 signalling pathway: a new way to treat IBD? Gut. 2000 Oct 1;47(4):465–6.

179. Peyrin-Biroulet L, Gonzalez F, Dubuquoy L, Rousseaux C, Dubuquoy C, Decourcelle C, et al. 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.

180. 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.

181. Roubenoff R, Roubenoff RA, Cannon JG, Kehayias JJ, Zhuang H, Dawson-Hughes B, et al. Rheumatoid cachexia: cytokine-driven hypermetabolism accompanying reduced body cell mass in chronic inflammation. J Clin Invest. American Society for Clinical Investigation; 1994 Jun;93(6):2379–86.

182. Krok KL, Lichtenstein GR. Nutrition in Crohn disease. Curr Opin Gastroenterol. 2003 Mar;19(2):148–53.

183. Gassull MA. Nutrition and inflammatory bowel disease: its relation to pathophysiology, outcome and therapy. Dig Dis. 2003;21(3):220–7.

184. Aghdassi E, Wendland BE, Stapleton M, Raman M, Allard JP. Adequacy of nutritional intake in a Canadian population of patients with Crohn's disease. J Am Diet Assoc. 2007 Sep 1;107(9):1575–80.

185. Nguyen GC, Munsell M, Harris ML. Nationwide prevalence and prognostic significance of clinically diagnosable protein-calorie malnutrition in hospitalized inflammatory bowel disease patients. Inflamm Bowel Dis. 2008 Aug;14(8):1105–11.

186. Gerasimidis K, McGrogan P, Edwards CA. The aetiology and impact of malnutrition in paediatric inflammatory bowel disease. J Hum Nutr Diet. 2011 Aug;24(4):313–26.

187. Evans WJ, Morley JE, Argilés J, Bales C, Baracos V, Guttridge D, et al. Cachexia: a new definition. Clin Nutr. 2008 Dec;27(6):793–9.

188. Elkan A-C, Engvall I-L, Cederholm T, Hafström I. Rheumatoid cachexia, central obesity and malnutrition in patients with low-active rheumatoid arthritis: feasibility of anthropometry, Mini Nutritional Assessment and body composition techniques. Eur J Nutr. D. Steinkopff-Verlag; 2009 Mar 31;48(5):315–22.

189. Fearon K, Evans WJ, Anker SD. Myopenia-a new universal term for muscle wasting. J Cachexia Sarcopenia Muscle. 2011 Mar 25;2(1):1–3.

190. 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.

191. 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.

192. Wong SC, Catto-Smith AGA, Zacharin M. Pathological fractures in paediatric patients with inflammatory bowel disease. Eur J Pediatr. 2013 Oct 17;173(2):141–51.

193. Malik S, Ahmed SF, Wilson ML, Shah N, Loganathan S, Naik S, et al. The effects of anti-TNF-α treatment with adalimumab on growth in children with Crohn's disease (CD). J Crohns Colitis. 2012 Apr;6(3):337–44.

194. Markowitz J, Grancher K, Rosa J, Aiges H, Daum F. Growth failure in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 1993 May;16(4):373–80.

195. Jones JH, Lennard-Jones JE. Corticosteroids and corticotrophin in the treatment of Crohn's disease. Gut. BMJ Group; 1966 Apr;7(2):181–7.

196. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; preliminary report on a therapeutic trial. British Medical Journal. BMJ Group; 1954 Aug 14;2(4884):375–8.

197. Benchimol EI, Seow CH, Steinhart AH, Griffiths AM. Traditional corticosteroids for induction of remission in Crohn's disease. Benchimol EI, editor. Cochrane Database Syst Rev. Chichester, UK: John Wiley & Sons, Ltd; 2008 Apr 16;(2):CD006792.

198. Malchow H, Ewe K, Brandes JW, Goebell H, Ehms H, Sommer H, et al. European Cooperative Crohn's Disease Study (ECCDS): results of drug treatment. Gastroenterology. 1984 Feb;86(2):249–66.

199. Karmiris K, Paintaud G, Noman M, Magdelaine-Beuzelin C, Ferrante M, Degenne D, et al. Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn's disease. Gastroenterology. 2009 Nov;137(5):1628–40.

200. Hanauer SB, Wagner CL, Bala M, Mayer L, Travers S, Diamond RH, et al. Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. Clinical Gastroenterology and Hepatology. 2004 Jul;2(7):542–53.

201. Moss AC, Brinks V, Carpenter JF. Review article: immunogenicity of anti-TNF biologics in IBD - the role of patient, product and prescriber factors. Aliment Pharmacol Ther. 2013 Oct 3;38(10):1188–97.

202. Colombel JF, Feagan BG, Sandborn WJ, Van Assche G, Robinson AM. Therapeutic drug monitoring of biologics for inflammatory bowel disease. Inflamm Bowel Dis. 2012 Feb;18(2):349–58.

203. Targan SR, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. N Engl J Med. 1997 Oct 9;337(15):1029–35.

204. Hanauer SB, Sandborn WJ, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh D, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology. 2006 Feb;130(2):323–33–quiz591.

205. Lichtenstein GR, Hanauer SB, Sandborn WJ. Management of Crohn's Disease in Adults. Am J Gastroenterol. 2009 Jan 6;104(2):465–83.

206. Dubinsky MC, Yang H, Hassard PV, Seidman EG, Kam LY, Abreu MT, et al. 6-MP metabolite profiles provide a biochemical explanation for 6-MP resistance in patients with inflammatory bowel disease. Gastroenterology. 2002 Apr;122(4):904–15.

207. Haines ML, Ajlouni Y, Irving PM, Sparrow MP, Rose R, Gearry RB, et al. Clinical usefulness of therapeutic drug monitoring of thiopurines in patients with inadequately controlled inflammatory bowel disease. Inflamm Bowel Dis. 2011 Jun;17(6):1301–7.

208. Feagan BG, Greenberg GR, Wild G, Fedorak RN, Paré P, McDonald JWD, et al. Treatment of Active Crohn's Disease With MLN0002, a Humanized Antibody to the α4β7 Integrin. Clinical Gastroenterology and Hepatology. 2008 Dec;6(12):1370–7.

209. Hudson K, Lifton R, Patrick-Lake B. The Precision Medicine Initiative Cohort Program–Building a Research Foundation for 21st Century Medicine. Precision Medicine Initiative 2015.

210. Steiner SJ, Pfefferkorn MD, Fitzgerald JF, Denne SC. Carbohydrate and lipid metabolism following infliximab therapy in pediatric Crohn's disease. Pediatric research. 2008 Dec 1;64(6):673–6.

211. Vadan R, Gheorghe LS, Constantinescu A, Gheorghe C. The prevalence of malnutrition and the evolution of nutritional status in patients with moderate to severe forms of Crohn's disease treated with Infliximab. Clin Nutr. 2011 Feb;30(1):86–91.

212. Wiese D, Lashner B, Seidner D. Measurement of nutrition status in Crohn's disease patients receiving infliximab therapy. Nutr Clin Pract. 2007 Dec 31;23(5):551–6.

213. Altowati M, Malik S, Shepherd S, P M, RK R, SF A, et al. Bone-muscle unit assessment with pQCT in children with inflammatory bowel disease following treatment with Infliximab. BA. 2015 Jul 1;:1–2.

214. Bakker SF, Dik VK, Witte BI, Lips P, Roos JC, van Bodegraven AA. Increase in bone mineral density in strictly treated Crohn's disease patients with concomitant calcium and vitamin D supplementation. J Crohns Colitis. 2013 Jun;7(5):377–84.

215. Farkas K, Bálint A, Valkusz Z, Szepes Z, Nagy F, Szűcs M, et al. Bolus administration of steroid therapy is more favorable than the conventional use in preventing decrease of bone density and the increase of body fat percentage in patients with inflammatory bowel disease. J Crohns Colitis. 2014 Feb 13.

216. Borrelli O, Bascietto C, Viola F, Bueno de Mesquita M, Barbato M, Mancini V, et al. Infliximab heals intestinal inflammatory lesions and restores growth in children with Crohn's disease. Digestive and Liver Disease. 2004 May;36(5):342–7.

217. DeBoer MD, Thayu M, Griffin LM, Baldassano RN, Denson LA, Zemel BS, et al. Increases in Sex Hormones during Anti-Tumor Necrosis Factor α Therapy in Adolescents with Crohn's Disease. J Pediatr. 2016 Apr;171:146–52.e1–2.

218. Diamanti A, Basso MS, Gambarara M, Papadatou B, Bracci F, Noto C, et al. Positive impact of blocking tumor necrosis factor alpha on the nutritional status in pediatric Crohn's disease patients. Int J Colorectal Dis. 2009 Jan;24(1):19–25.

219. Griffiths AM, Nguyen P, Smith C, MacMillan JH, Sherman PM. Growth and clinical course of children with Crohn's disease. Gut. 1993 Jul 1;34(7):939–43.

220. Lake AM, Kim S, Mathis RK, Walker WA. Influence of preoperative parenteral alimentation on postoperative growth in adolescent Crohn's disease. J Pediatr Gastroenterol Nutr. 1985 Apr;4(2):182–6.

221. Morin CL, Roulet M, Roy CC, Weber A, Lapointe N. Continuous elemental enteral alimentation in the treatment of children and adolescents with Crohn's disease. JPEN J Parenter Enteral Nutr. 1982 May;6(3):194–9.

222. Motil KJ, Grand RJ, Davis-Kraft L, Ferlic LL, Smith EO. Growth failure in children with inflammatory bowel disease: A prospective study. Gastroenterology. 1993 Sep;105(3):681–

91.

223. Dassopoulos T, Dubinsky MC, Bentsen JL, Martin CF, Galanko JA, Seidman EG, et al. Randomised clinical trial: individualised vs. weight-based dosing of azathioprine in Crohn's disease. Aliment Pharmacol Ther. 2013 Nov 17;39(2):163–75.

224. Hämäläinen A, Sipponen T, Kolho K-L. Serum infliximab concentrations in pediatric inflammatory bowel disease. Scand J Gastroenterol. 2012 Nov 14;:1–7.

225. Poon SS, Asher R, Jackson R, Kneebone A, Collins P, Probert C, et al. Body Mass Index and Smoking Affect Thioguanine Nucleotide Levels in Inflammatory Bowel Disease. J Crohns Colitis. 2015 May 12.

226. Ding NS, Malietzis G, Ganeshanathan T, Yip M, Penez L, Gabe S, et al. Body composition profile is associated with anti-TNF response in Crohn's disease patients. Colorectal Dis. 2015 Sep 23;17:38–101.

227. Li Y, Zhu W. Body Fat Composition Predicts Infectious Complications After Bowel Resection in Crohn's Disease. Inflamm Bowel Dis. 2015 Aug;21(8):E19.

Supplementary material

Table 6 Disease effects on body composition

1. Andreassen H, Rix M, Brot C. Regulators of calcium homeostasis and bone mineral density in patients with Crohn's disease. Scandinavian journal of …. 1998.
2. Ates Y, Degertekin B, Erdil A, Yaman H, Dagalp K. Serum Ghrelin Levels in Inflammatory Bowel Disease with Relation to Disease Activity and Nutritional Status. Dig Dis Sci. 2007 Dec 13;53(8):2215–21.
3. Bechtold S, Alberer M, Arenz T, Putzker S, Filipiak-Pittroff B, Schwarz HP, et al. Reduced muscle mass and bone size in pediatric patients with inflammatory bowel disease. Inflamm Bowel Dis. 2010 Feb;16(2):216–25.
4. Boot AM, Bouquet J, Krenning EP, de Muinck Keizer-Schrama SMPF. Bone mineral density and nutritional status in children with chronic inflammatory bowel disease. Gut. 1998 Feb 1;42(2):188–94.
5. Briet F, Twomey C, Jeejeebhoy KN. Effect of malnutrition and short-term refeeding on peripheral blood mononuclear cell mitochondrial complex I activity in humans. Am J Clin Nutr. 2003 May;77(5):1304–11.
6. 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.
7. Burnham JM, Shults J, Semeao E, Foster B, Zemel BS, Stallings VA, et al. Whole Body BMC in Pediatric Crohn Disease: Independent Effects of Altered Growth, Maturation, and Body Composition. J Bone Miner Res. 2004 Sep 20;19(12):1961–8.
8. Cabré E, Gassull MA. Nutritional and metabolic issues in inflammatory bowel disease. Curr Opin Clin Nutr Metab Care. 2003 Sep;6(5):569–76.
9. Capristo E, Addolorato G, Mingrone G, Greco AV, Gasbarrini G. Body composition in Crohn disease patients: is it a contradictory issue? Scand J Gastroenterol. 1999 Mar;34(3):335–6.
10. Capristo E, Mingrone G, Addolorato G, Greco AV, Gasbarrini G. Glucose metabolism and insulin sensitivity in inactive inflammatory bowel disease. Aliment Pharmacol Ther. 1999 Feb;13(2):209–17.
11. Carlsson E, Bosaeus I, Nordgren S. Body composition in patients with short bowel syndrome: An assessment by bioelectric impedance spectroscopy (BIS) and dual–energy absorptiometry (DXA). Eur J Clin Nutr. 2004 Jun 1;58(6):853–9.
12. Carlsson E, Bosaeus I, Nordgren S. Body composition in patients with an ileostomy and inflammatory bowel disease: validation of bio-electric impedance spectroscopy (BIS). Eur J Clin Nutr. 2002 Jul;56(7):680–6.
13. Casanova MJ, Chaparro M, Molina B, Merino O, Nuevo-Siguairo OK, Dueñas-Sadornil C, et al. 389 Prevalence of Malnutrition and Nutritional Characteristics of Patients With Inflammatory Bowel Disease (IBD). Gastroenterology. Elsevier; 2016 Dec 13;150(4):S89.
14. Costa COPC, Carrilho FJ, Nunes VS, Sipahi AM, Rodrigues M. A snapshot of the nutritional status of Crohn's disease among adolescents in Brazil: a prospective cross-sectional study. BMC Gastroenterol. 2nd ed. BioMed Central; 2015 Dec 8;15(1):172.
15. Csontos ÁA, Molnár A, Lorinczy K. P274 Body composition measurement among IBD patients. Journal of Crohn's and Colitis; 2014.
16. Cuoco L, Vescovo G, Castaman R, Ravara B, Cammarota G, Angelini A, et al. Skeletal muscle wastage in Crohn's disease: A pathway shared with heart failure? Int J Cardiol. 2008 Jul 4;127(2):219–27.
17. de Jong, J D, L M, van Rossum, M LG, M CFH, et al. Longitudinal study of bone mineral density in patients with Crohn's disease. Dig Dis Sci. United States; 2003;48(7):1355–9.
18. Dong J, Chen Y, Tang Y, Xu F, Yu C, Li Y, et al. Body Mass Index Is Associated with Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. Green J, editor. PLoS ONE. 2015 Dec 14;10(12):e0144872.
19. Dubner SE, Shults J, Baldassano RN, Zemel BS, Thayu M, Burnham JM, et al. Longitudinal assessment of bone density and structure in an incident cohort of children with Crohn's disease. Gastroenterology. 2009 Jan;136(1):123–30.
20. Eivindson M, Grønbæk H, Flyvbjerg A, Frystyk J, Zimmermann-Nielsen E, Dahlerup JF. The insulin-like growth factor (IGF)-system in active ulcerative colitis and Crohn's disease: Relations to disease activity and corticosteroid treatment. Growth Hormone & IGF Research. 2007 Feb;17(1):33–40.

21. Gasparetto M. Crohn's disease and growth deficiency in children and adolescents. WJG. 2014;20(37):13219.
22. Geerling BJ, Badart-Smook A, Stockbrügger RW, Brummer RJ. Comprehensive nutritional status in patients with long-standing Crohn disease currently in remission. Am J Clin Nutr. 1998 May;67(5):919–26.
23. Gong J, Zuo L, Guo Z, Zhang L, Li Y, Gu L, et al. Impact of Disease Activity on Resting Energy Expenditure and Body Composition in Adult Crohn's Disease: A Prospective Longitudinal Assessment. JPEN J Parenter Enteral Nutr. SAGE Publications; 2015 Aug;39(6):713–8.
24. Gordon CM. Boning up: exploring bone structure and strength in children with Crohn's disease. Gastroenterology. 2009 Jan;136(1):35–9.
25. Harpavat M, Greenspan SL, O Brien C, Joyce Chang C-C, Bowen AD, Keljo DJ. Altered Bone Mass in Children at Diagnosis of Crohn Disease: A Pilot Study. J Pediatr Gastroenterol Nutr. 2005 Mar;40(3):295–300.
26. Hartman C, Eliakim R, Shamir R. Nutritional status and nutritional therapy in inflammatory bowel diseases. World J Gastroenterol. 2009 Jun 7;15(21):2570–8.
27. Hattar LN, Abraham BP, Malaty HM, Smith EO, Ferry GD. Inflammatory bowel disease characteristics in Hispanic children in Texas. Inflamm Bowel Dis. 2012 Mar;18(3):546–54.
28. Haugeberg G, Vetvik K, Stallemo A, Bitter H, Mikkelsen B, Stokkeland M. Bone Density Reduction in Patients with Crohn Disease and Associations with Demographic and Disease Variables: Cross-sectional Data from a Population-based Study. Scand J Gastroenterol. 2001 Jul 1;36(7):759–65.
29. Hill RJ. Update on nutritional status, body composition and growth in paediatric inflammatory bowel disease. WJG. 2014;20(12):3191.
30. Jahnsen J, Falch JA, Mowinckel P, Aadland E. Body composition in patients with inflammatory bowel disease: a population-based study. Am J Gastroenterol. 2003 Jul 1;98(7):1556–62.
31. Kushner RF, Schoeller DA. Resting and total energy expenditure in patients with inflammatory bowel disease. Am J Clin Nutr. 1991 Jan;53(1):161–5.
32. Laakso S, Valta H, Verkasalo M, Toiviainen-Salo S, Mäkitie O. Compromised Peak Bone Mass in Patients with Inflammatory Bowel Disease–A Prospective Study. J Pediatr. 2014 Jun;164(6):1436–1443.e1.
33. Lee DY, Lewis JD, Shults J, Zemel BS, Long J. 693 The Association of Diet and Exercise With Body Composition in Pediatric Crohn's Disease. Gastroenterology; 2013.
34. Mesker T, van Rheenen PF, Norbruis OF, Uitentuis J, Waalkens HJ, Gonera G, et al. Pediatric Crohn's disease activity at diagnosis, its influence on pediatrician's prescribing behavior, and clinical outcome 5 years later. Inflamm Bowel Dis. 2009 Nov;15(11):1670–7.
35. Middleton JP, Bhagavathula AP, Gaye B, Alvarez JA, Huang CS, Sauer CG, et al. Vitamin D status and bone mineral density in African American children with Crohn disease. J Pediatr Gastroenterol Nutr. 2013 Nov;57(5):587–93.
36. Mingrone G, Benedetti G, Capristo E, De Gaetano A, Greco AV, Tataranni PA, et al. Twenty-four-hour energy balance in Crohn disease patients: metabolic implications of steroid treatment. Am J Clin Nutr. 1998 Jan;67(1):118–23.
37. Müller MJ, Schmidt LU, Körber J, Zur Muhlen A Von, Canzler H, Schmidt FW. Reduced metabolic efficiency in patients with Crohn's disease. Dig Dis Sci. 1993 Nov;38(11):2001–9.
38. Nie Y. Decreased Levels of Serum Omentin-1 in Patients with Inflammatory Bowel Disease. Med Sci Monit. 2015;21:118–22.
39. Oikonomou KA, Orfanidou TI, Vlychou MK, Kapsoritakis AN, Tsezou A, Malizos KN, et al. Lower Fibroblast Growth Factor 23 Levels in Young Adults With Crohn Disease as a Possible Secondary Compensatory Effect on the Disturbance of Bone and Mineral Metabolism. Journal of Clinical Densitometry. 2014 Jan;17(1):177–84.
40. Ruotsalainen E, Salmenniemi U, Vauhkonen I, Pihlajamaki J, Punnonen K, Kainulainen S, et al. Changes in Inflammatory Cytokines Are Related to Impaired Glucose Tolerance in Offspring of Type 2 Diabetic Subjects. Diabetes Care. 2006 Dec 1;29(12):2714–20.
41. Salacinski AJA, Regueiro MDM, Broeder CEC, McCrory JLJ. Decreased neuromuscular function in Crohn's disease patients is not associated with low serum vitamin d levels. Dig Dis Sci. 2013 Jan 31;58(2):526–33.
42. Schmidt S, Mellström D, Norjavaara E, Sundh VS, Saalman R. Low bone mineral density in children and adolescents with inflammatory bowel disease. Inflamm Bowel Dis. 2009 Dec;15(12):1844–50.
43. Schoon EJ, Bollani S, Mills PR, Israeli E, Felsenberg D, Ljunghall S, et al. Bone mineral density in relation to efficacy and side effects of budesonide and

prednisolone in Crohn's disease. Clin Gastroenterol Hepatol. 2005 Feb;3(2):113–21.

44. 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;14(11):1562–8.
45. Semeao EJ, Jawad AF, Stouffer NO, Zemel BS, Piccoli DA, Stallings VA. Risk factors for low bone mineral density in children and young adults with Crohn's disease. J Pediatr. 1999 Nov;135(5):593–600.
46. Sourianarayanane A, Garg G, Smith TH, Butt MI, McCullough AJ, Shen B. Risk factors of non-alcoholic fatty liver disease in patients with inflammatory bowel disease. J Crohns Colitis. 2013 Sep;7(8):e279–85.
47. Sousa Guerreiro C, Cravo M, Costa AR, Miranda A, Tavares L, Moura-Santos P, et al. A comprehensive approach to evaluate nutritional status in Crohn's patients in the era of biologic therapy: a case-control study. Am J Gastroenterol. 2007 Nov;102(11):2551–6.
48. Stephens M, Batres LA, Ng D, Baldassano R. Growth failure in the child with inflammatory bowel disease. Semin Gastrointest Dis. 2001 Oct;12(4):253–62.
49. Sylvester F, Wyzga N, Hyams J. Effect of Crohn's Disease on Bone Metabolism In Vitro: A Role for Interleukin-6 - Sylvester - 2002 - Journal of Bone and Mineral Research - Wiley Online Library. Journal of Bone and …. 2002.
50. Sylvester FA, Wyzga N, Hyams JS, Davis PM, Lerer T, Vance K, et al. Natural history of bone metabolism and bone mineral density in children with inflammatory bowel disease. Inflamm Bowel Dis. 2007 Jan;13(1):42–50.
51. Sylvester FA. Bone protection measures in children and adolescents with IBD. Inflammatory Bowel Disease Monitor. 2012.
52. Sylvester FA. The ABCs (and Ds) of Bone Imaging in Children With Crohn Disease. J Pediatr Gastroenterol Nutr. 2016 Jul 1;63(1):4–5.
53. Szathmári M, Vásárhelyi B, Treszl A, Tulassay T, Tulassay Z. Association of dehydroepiandrosterone sulfate and testosterone deficiency with bone turnover in men with inflammatory bowel disease. Int J Colorectal Dis. 2001 Sep 4;17(2):63–6.
54. Teixeira VS, Velho S, Palmela C, Pia M, Torres J, Glória L, et al. MON-PP129: Disease Phenotype, Nutritional Status and Dietary Intake in Patients with Crohn's Disease. Clin Nutr. Elsevier; 2016 Dec 13;34:S176.
55. Thangarajah D, Chapell KE. Aberrant adipose tissue partitioning with abdominal obesity, defined by MRI, is a hallmark of paediatric Crohn's disease. J Crohns Colitis. JOURNAL OF …; 2016;10(Suppl 1):S362–3.
56. Vaisman N, Dotan I, Halack A, Niv E. Malabsorption is a major contributor to underweight in Crohn's disease patients in remission. Nutrition. 2006 Sep;22(9):855–9.
57. Valentini L, Schaper L, Büning C, Hengstermann S, Koernicke T, Tillinger W, et al. Malnutrition and impaired muscle strength in patients with Crohn's disease and ulcerative colitis in remission. Nutrition. 2008 Jul;24(7-8):694–702.
58. van Langenberg DR, Gatta Della P, Hill B, Zacharewicz E, Gibson PR, Russell AP. Delving into disability in Crohn's disease: Dysregulation of molecular pathways may explain skeletal muscle loss in Crohn"s disease. J Crohns Colitis. The Oxford University Press; 2014 Jul 1;8(7):626–34.
59. van Langenberg DR, Gatta Della P, Warmington SA, Kidgell DJ, Gibson PR, Russell AP. Objectively measured muscle fatigue in Crohn's disease: Correlation with self-reported fatigue and associated factors for clinical application. J Crohns Colitis. 2014 Feb;8(2):137–46.
60. Vidarsdottir JB, Johannsdottir SE, Thorsdottir I, Bjornsson E, Ramel A. A cross-sectional study on nutrient intake and -status in inflammatory bowel disease patients. Nutr J. 2016 Jun 8;15(1):61.
61. Warner JT, Cowan FJ, Dunstan F, Evans WD, Webb D, Gregory JW. Measured and predicted bone mineral content in healthy boys and girls aged 6-18 years: adjustment for body size and puberty. Acta Paediatrica. 2007 Jan 2;87(3):244–9.
62. Wiese D, Lashner B, Seidner D. Measurement of nutrition status in Crohn's disease patients receiving infliximab therapy. Nutr Clin Pract. 2007 Dec 31;23(5):551–6.
63. Wiroth J-B, Filippi J, Schneider SM, Al-Jaouni R, Horvais N, Gavarry O, et al. Muscle performance in patients with Crohn's disease in clinical remission. Inflamm Bowel Dis. 2005 Mar;11(3):296–303.
64. Wong SC, MacRae VE, McGrogan P, Ahmed SF. The role of pro-inflammatory cytokines in inflammatory bowel disease growth retardation. J Pediatr Gastroenterol Nutr. 2006 Aug;43(2):144–55.
65. Zadik Z, Sinai T, Zung A, Reifen R. Longitudinal monitoring of bone measured by quantitative multisite ultrasound in patients with Crohn's disease. J Clin Gastroenterol. 2005 Feb;39(2):120–3.

Chapter 3: Patients with inflammatory bowel disease and their treating clinicians have different views regarding diet

Introduction and context

The patient experience is under-represented in scientific literature regarding management of Crohn's disease, and patients report dissatisfaction regarding the provision of information from their treating clinicians regarding nutrition[1].
In a large international cohort of patients with inflammatory bowel disease, nearly half reported that their doctor did not question them about the impact of symptoms on quality of life[2]. This failure to contextualise the patient's illness may result from a paucity of practice guidelines regarding the management of Crohn's disease aside from medication and surgery. A survey of gastroenterologists regarding their knowledge of aspects of Crohn's disease care revealed nonpharmacological treatment as the component of therapy with the largest gap between current and desired knowledge[3].

The most common question asked by patients with inflammatory bowel disease is: "Doctor, what should I eat?"[4] A thorough, evidence-based response is not always forthcoming.
Recently updated (December 2016) guidelines from the European Society for Parenteral and Enteral Nutrition regarding clinical nutrition in inflammatory bowel disease state: "The review panel and the other discussants do not hide their collective disappointment in the results of the initial systematic review. It has proved remarkably difficult to provide evidence-based and clinically useful conclusions"[5].

Despite the uncertainty underlying professional recommendations regarding diet in inflammatory bowel disease, most patients observe dietary restriction, with two-thirds of respondents in one study reporting avoidance of their favourite foods in order to prevent relapse[6]. In the context of poor quality evidence, but widespread practice, we hypothesised: *That patients with inflammatory bowel disease believe diet is an important influence on their disease and restrict their dietary intake, but that clinicians provide a variety of advice* (hypothesis 1).

Diet and lifestyle are major determinants of body composition[7,8], and malnutrition is a significant contributor to depletions in lean mass and poor bone health, as well as reduced body weight, in Crohn's disease[9]. Conversely, over the past twenty-five years, an increase in the body mass indices of Crohn's disease subjects enrolled in therapeutic trials has been observed[10], mirroring an increase in overweight and obesity in the general population. In the trials analysed, increased weight was associated with increased clinical activity scores and longer disease duration.

A qualitative analysis of clinical practice and patient experience among participants in national groups is described in this chapter of the thesis. Understanding a clinical situation from the patient perspective, and obtaining a snapshot of current practice regarding diet and nutrition in Australia were motivating factors in performing this study. We were interested to know the extent to which members of Crohn's and Colitis Australia believed diet contributed to the pathogenesis and symptomatology of their inflammatory bowel disease, and the nature and prevalence of dietary restrictions. We sought to determine whether any restrictions were based on professional recommendations, and to ascertain links between diet, disease and body composition measures such as self-reported weight and body mass index.

We also questioned clinicians: members of the Dietitians Association of Australia and the Australian Inflammatory Bowel Disease Association provided responses detailing the advice they provided to patients, and their beliefs regarding the role of diet in inflammatory bowel disease. No previous study integrating the distinct viewpoints of patient and clinician regarding diet in inflammatory bowel disease could be identified in the literature.

This chapter highlights the importance of an individualised approach to patient care, as most patients did not feel that they and their treating clinicians shared similar concerns regarding the role of diet.

BDA The Association of UK Dietitians
THE OFFICIAL JOURNAL OF THE BRITISH DIETETIC ASSOCIATION
Journal of Human Nutrition and Dietetics

Journal of Human Nutrition and Dietetics

RESEARCH PAPER

Patients with inflammatory bowel disease and their treating clinicians have different views regarding diet

D. Q. Holt,[1,2,3] B. J. Strauss[2] & G. T. Moore[2,3]

[1]Clinical Nutrition and Metabolism Unit, Monash Health, Clayton, VIC, Australia
[2]School of Clinical Sciences, Monash University, Clayton, VIC, Australia
[3]Department of Gastroenterology & Hepatology, Monash Health, Clayton, VIC, Australia

Keywords
beliefs, Crohn's disease, dietary advice, eating patterns, ulcerative colitis.

Correspondence
D. Holt, Clinical Nutrition and Metabolism Unit, Monash Health, 246 Clayton Road, Clayton, Victoria 3168, Australia.
Tel.: +61 3 95943177
Fax: +61 3 95946250
E-mail: darcy.holt@monashhealth.org

How to cite this article
Holt D.Q., Strauss B.J. & Moore G.T. (2016) Patients with inflammatory bowel disease and their treating clinicians have different views regarding diet. *J Hum Nutr Diet*.
doi: 10.1111/jhn.12400

Abstract

Background: Diet and body composition play unclear roles in the pathogenesis, activity and symptoms of inflammatory bowel disease (IBD). Evidence-based guidance regarding dietary modification in IBD is lacking. We aimed to determine the attitudes of IBD patients and clinicians to diet.
Methods: The present cross-sectional study comprised an online questionnaire distributed to members of a national IBD patient organisation, assessing demographics, anthropometry, disease phenotype and dietary beliefs. Dietitians, gastroenterologists and surgeons were targeted for a similar questionnaire as a result of membership of national professional bodies.
Results: Nine hundred and twenty-eight patients (72.2% female; mean age 39.5 years; age range 5–91 years) responded. Two-thirds of the patients had Crohn's disease. The mean reported body mass index was 24.9 kg m^{-2} and was significantly skewed to the right. Patients who had taken >10 courses of steroids were had a greater probability of being overweight or obese, independent of disease complications. Most patients (71%) assumed that their diet affected their IBD; 61% considered their IBD specialist disregarded the importance of diet. Of the 136 clinicians who responded, the majority felt that diet was a factor in symptoms and intestinal microbiota. More gastroenterologists (44%) than dietitians (17%) considered that diet had a role in the pathogenesis of IBD ($P = 0.003$). Twenty-six percent of patients reported receiving dietary advice from their IBD specialist, whereas 98% of gastroenterologists reported advice provision. Patients received diverse advice. Half of the patients followed recommendations provided by a clinician.
Conclusions: The present study demonstrates that IBD patients consider diet to be important in their disease. IBD clinicians from different disciplines have diverse views of the role of diet. Advice given to patients is heterogeneous, often perceived as inadequate and poorly followed.

Introduction

Although exclusive enteral nutrition has been shown to be effective in the induction of remission of Crohn's disease (CD) [1,2], the role of diet and body habitus in the pathogenesis and activity of inflammatory bowel disease (IBD) is unclear. Protein-energy malnutrition was reported to be prevalent in patients with IBD [3–7], although recently published series [8–12] have shown a 10–55% prevalence of being overweight or obese in patients with IBD. Obesity has been associated with the need for earlier surgery [13] and faster disease progression [14] in patients with CD. Intestinal dysbiosis is a known feature of IBD, and reduced gut microbial gene richness is associated with obesity and inflammation; dietary interventions were shown to increase bacterial gene richness [15,16].

A recent systematic review revealed a lack of clear, evidence-based guidelines regarding dietary modification in

IBD [17]. Some dietary interventions, such as a reduction in fibre or fermentable carbohydrates, may provide symptomatic improvement, although evidence from studies of dietary intervention is limited [18] because randomised controlled trials in this area are lacking and blinding is not possible.

Although there is evidence suggesting that IBD patients consciously modify their diets [19,20], there is sparse literature available regarding the attitudes of treating clinicians to the role that diet plays in IBD. In recently published data, 80–89% of IBD patients considered dietary advice to be important, although only 8–16% felt that their treating clinician had provided sufficient information [21]. The present study aimed to determine the attitudes of IBD patients, as well as clinicians who have frequent contact with IBD patients, regarding the role of diet in the pathogenesis and symptomatology of IBD.

Materials and methods

An anonymous online questionnaire (Google Docs; Google Inc., Mountain View, CA, USA) was advertised to members of the Crohn's and Colitis Australia mailing list. Members of this large national patient support group (with a membership of 3916 in April 2015; personal communication) (Dr Gregory Moore) were asked structured questions regarding demographics, anthropometric data, their IBD phenotype and treatment, and diet-related beliefs (Table 1; see also Supporting infromation, Appendix S1).

A separate anonymous online questionnaire was distributed to members of the Australian Inflammatory Bowel Disease Association (a section of the Gastroenterological Society of Australia comprising members nominating an interest in gastrointestinal tract infection and inflammation) and the Dietitians Association of Australia (Appendix S2).

Statistical analysis

A descriptive analysis was performed with Fishers exact test being used to analyse differences between groups. The D'Agostino & Pearson omnibus normality test was used to assess normality of the continuous data series. Questionnaires remained open for responses from August to December 2012. Only valid responses to each question were included in analyses. $P < 0.05$ was considered statistically significant.

Ethical considerations

The Southern Health (now Monash Health) Human Research Ethics Committee approved the present study (application 11264A).

Table 1 Demographic details, diet-related beliefs and supplement use of Crohn's and Colitis Australia respondents

	N	%
Female	648	72.2
Mean age (years)	39.5 (range 5–91, SD 15.0)	
Crohn's disease	558	63.9
Ulcerative colitis	315	36.1
Montreal classification of Crohn's disease [41]		
A1 (age <16 years)	83	14.7
A2 (age 17–40 years)	369	65.3
A3 (age >40 years)	113	20.0
L1 (ileal)	158	28.0
L2 (colonic)	133	23.5
L3 (ileocolonic)	262	46.4
L4 (isolated upper gastrointestinal)	12	2.1
B1 (not penetrating/stricturing)	229	39.6
B2 (stricturing)	113	19.5
B3 (penetrating)	237	40.9
Weight change subsequent to diagnosis		
None	237	26.5
Loss	244	27.3
Gain	412	46.1
Believe weight change as a result of IBD	471	52.9
Believe weight change as a result of treatment	415	46.8
Believe weight contributes to severity of IBD	219	24.8
Treatment		
Azathioprine	420	41.0
Mercaptopurine	182	17.8
Methotrexate	148	14.5
No immunomodulator	274	26.8
Anti-tumour necrosis factor	233	27.5
Previous IBD surgery	264	30.4
Believe diet affects IBD	679	76.0
Believe IBD specialist places importance in diet	298	34.4
Over the counter supplements		
Vitamin D	245	27.2
Multivitamin	182	20.2
Calcium	167	18.5
Marine omega-3	159	17.6
Iron	117	13.0
Probiotics	70	7.8
Vitamin B	62	6.9
Vitamin C	61	6.8
Vitamin B_{12}	54	6.0
Folic acid	52	5.8
Magnesium	39	4.3
Zinc	39	4.3
Glucosamine	13	1.4
Aloe vera, flaxeed oil, slippery elm, evening primrose oil		<1

% refers to the percentage of respondents to each particular question. IBD, inflammatory bowel disease.

Results

Patient responses

Demographics

There were 928 respondents (72% female; mean age 39.5 years; age range 5–91 years who) who replied to the advertisement for patients with IBD, which is an estimated response rate of 24% (comprising an expected rate of response for an e-mail-based survey without reminders or incentives) [22,23]. In total, 64% were identified as having CD and 36% were identified as having ulcerative colitis (UC) (Table 1).

Most patients described a disease duration of more than 5 years. Patients with CD had a self-reported mean body mass index (BMI) of 24.7 kg m^{-2} (median 23.9 kg m^{-2}, SD 5.1 kg m^{-2}); for patients with UC, the mean BMI was 24.9 kg m^{-2} (median 24.0 kg m^{-2}, SD 5.6 kg m^{-2}; difference not statistically significant). The distribution of BMI values was asymmetrical, with a long tail to the right (skewness: CD 1.060; UC 1.247). A BMI <18.5 kg m^{-2}, meeting the World Health Organization definition of being underweight [24], was reported in 5.8% of respondents with CD and 6.3% of subjects with UC (not significant).

Of the 366 (39%) patients with a BMI >25 kg m^{-2}, 77% considered themselves as overweight, 22% as normal weight and 1% as underweight.

Treatment for inflammatory bowel disease

Of the 44% of patients who gained weight subsequent to their diagnosis of IBD, 67% considered the change to be a result of treatment for IBD (Table 1). Overall, 55% of respondents attributed a change in weight to treatment (58% CD compared to 50% UC; $P = 0.04$) There was no significant difference in BMI between the 39% who had complicated CD (Montreal classification) and those who did not. Patients who had taken more than 10 courses of steroids were more likely [odds ratio 1.59 (range 1.14–2.23)] to be overweight or obese [50.4%; BMI ≥25 kg m^{-2}, mean (SD) 25.72 (6.04) kg m^{-2}] than those who had taken 0–3 courses of steroids [40.0%; BMI ≥25 kg m^{-2}, mean (SD) 23.67 (5.21) kg m^{-2}] ($P = 0.008$). There was no difference between types of IBD and proportion of patients who had taken more than 10 courses of steroids (25.9% CD, 26.2% UC; $P = 0.933$). More than half (51%) of those patients reporting more than 10 courses of steroids considered that they had gained weight subsequent to the diagnosis of IBD compared to 44% of those who had taken fewer than three courses ($P = 0.115$). There was no significant correlation between WHO classifications of BMI (underweight/normal weight/overweight/obese) and rates of surgery for IBD, or the prevalence of complicated (stricturing or penetrating) CD.

Dietary advice and beliefs

One quarter (26%) of patients reported receiving dietary advice from their IBD specialist, whereas 98% of gastroenterologists reported providing dietary advice to patients. The large majority (91%) of patients referred to a dietitian by either their general practioner or specialist had seen a dietitian compared to 46% of all respondents. Significantly more CD patients than those with UC had seen a dietitian (56.1% versus 40.8%; $P < 0.001$). There was no difference in perception of diet (as either healthy or as requiring improvement) between patients who had seen a dietitian and those who had not. Patients who had seen a dietitian were more likely to consider that diet affected their IBD (81.4% versus 72.4%; $P = 0.002$) Half (50%) of patients reported following dietary advice provided by a clinician. Supplement or vitamin use was more prevalent among patients who had seen a dietitian (76.2% versus 69.1%; $P = 0.025$) or a naturopath (81.5% versus 70.8%; $P = 0.005$). Familiarity with a low FODMAP diet (fermentable, oligo-, di-, mono-saccharides and polyols) was reported by 38% of patients; the proportion was twice as high in patients who had seen a dietitian as those who had not ($P < 0.001$). Three-quarters (72%) had used (or were aware of) probiotics (Fig. 1). Almost half of the patients had knowledge of a low residue diet; there was no significant difference in awareness between patients with stricturing disease and those without.

Most patients (71%) considered that diet affected their IBD, with symptoms being worsened by spicy foods in more than half of respondents; high fibre foods, dairy and nuts were similarly implicated. Avoidance of particular foods was more common in patients who had surgery for IBD (84.5% versus 77.1%; $P = 0.033$), with a rate of 93% amongst patients reporting stricturing disease. Food avoidance rates did not differ between CD and UC patients.

The majority (61%) of respondents felt their IBD specialist did not place importance in the role of diet, with significantly fewer UC patients than CD patients considering this to be the case (38.2% versus 26.7%; $P < 0.001$).

Responses from clinicians

The clinician survey was completed by 136 practitioners (including 46 gastroenterologists, 12 surgeons and 73 dietitians; response rates not defined). Half (49%) of the respondents spent less than 10% of their working time with IBD patients. However, the proportion of working time spent on IBD by the respondent gastroenterologists was significantly higher: 39% reported this occupying more than half of their time, with a further 24% reporting one quarter to half their time being occupied.

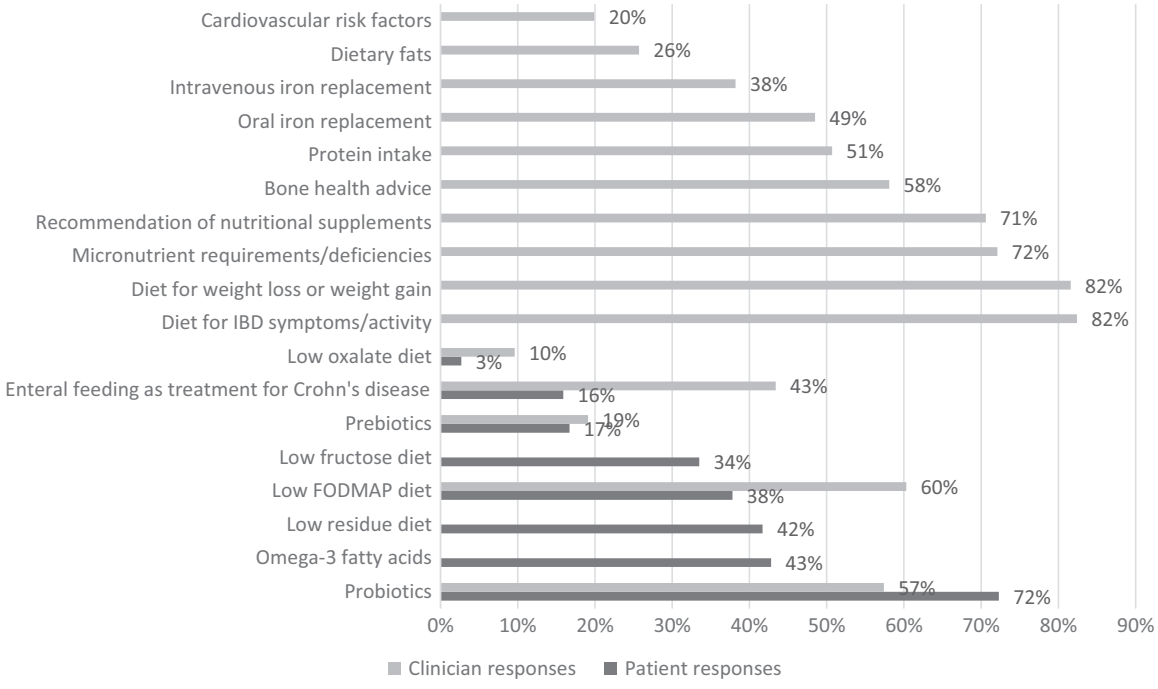


Figure 1 Dietary advice provided by clinicians and received by patients. FODMAP, fermentable, oligo-, di-, mono-saccharides and polyols; IBD, inflammtory bowel disease.

Most (79%) respondents felt that less than one quarter of their IBD patients were overweight or obese. The majority of clinicians felt that diet was a factor in symptoms (94%; 99% of dietitians) and intestinal microbiota (79%; 52% of dietitians); more gastroenterologists (44%) than dietitians (17%) considered diet to have a role in the pathogenesis of IBD ($P = 0.003$). Eighty-two percent of clinicians had advised dietary measures with regard weight loss or gain (Fig. 1), with 72% addressing specific micronutrient deficiencies and 60% providing education about FODMAPs. By contrast to the majority opinion of the patient group, 42% of clinicians considered that they held similar views to their patients regarding the role of diet.

Discussion

The role of diet in IBD may be considered in terms of pathogenesis, symptomatology and nutritional deficiency as a result of malabsorption or dietary restriction.

An analysis of practice guidelines from large dietetic and gastroenterology societies and patient support associations in the USA, Europe and Japan revealed that advice to clinicians regarding micronutrient supplementation was common, although recommendations regarding screening for deficiency varied. Dietary modifications also varied, with common themes of reducing fibre consumption during disease activity and avoidance of dairy if lactose intolerant, although some guidelines suggest the need for a reduction in excess fat, as well as excess or fermentable carbohydrates [25]. This diversity in practical advice was reflected in the responses provided by professionals in the present study.

Although enteral nutrition is an effective treatment for CD, a recent comprehensive review has identified an absence of published data regarding its use in UC [2]. It is not established that the role of diet is different in these types of IBD. We aimed to determine variances in attitude or experience between CD and UC patients. For the majority of categorical and continuous variables identified, there was no significant difference. The only identified distinctions between patient groups were: a higher proportion of CD patients considering a change in their weight was a result of IBD treatment, a lower rate of UC patients having seen a dietitian, and CD patients more often considering that their specialist places importance in the role of diet.

Previous studies have demonstrated the high importance patients with IBD place on the role of diet. In a series of patients surveyed on admission to a French IBD unit, diet was felt to be an initiating factor in the development of IBD by 15.6%, whereas 57.8% considered that food could cause a relapse [19]. A larger proportion of patients in the present study (76%) felt that diet affected

their IBD but, in both studies, over 70% had received dietary advice, and a majority had modified their diets to avoid a disease relapse. The idea that diet played an important role in IBD was more prevalent among patients who had seen a dietitian; this may be either cause or effect. Vitamin or supplement use was higher in patients who had sought dietetic or naturopathic advice. Qualitative analysis in our Australian cohort found that spicy foods, high fibre, dairy and nuts were implicated in worsening symptoms. A variety of foods were considered to contribute to symptoms and these were similar to those reported in another study implicating spicy foods, fat, raw fruits and vegetables, and carbonated beverages [19]. A structured dietary questionnaire administered to a well-described cohort of New Zealand CD patients did not consistently identify foods that were beneficial or detrimental; curry was the most generally detrimental food, and fish, banana and yoghurt were among the most commonly reported beneficial foods [26]. Similar results in terms of dietary preferences were seen in an Internet-based cohort of 2329 American IBD patients [20] and a single-centre survey of CD patients [27]. Yoghurt, bananas, fish and potatoes were among several foods identified as being beneficial in a novel study analysing the diet of subjects with UC in the week prior to a grading sigmoidoscopy; beneficial foods were considered to be those consumed in higher proportions in subjects with low endoscopic activity indices [28]. We found that previous surgery for IBD and stricturing disease were associated with higher incidences of food avoidance.

Dietary restrictions and modifications may lead to suboptimal micronutrient intake. In a study of ambulatory CD patients, diet analysis revealed less than the recommended levels of folate (in 100% of subjects), vitamin C (approximately 40%), vitamin E (almost all subjects) and calcium (approximately 90%) [6], despite an adequate energy intake, normal BMI and mild disease activity. In another cohort, 40–90% of IBD patients had vitamin levels <15th centile of normal [29]. Similar results have been published with respect to a Canadian IBD outpatient population [30]. British patients with UC demonstrated poor adherence to healthy-eating guidelines, although, during flares and treatment, they generally avoided contraindicated foods [31]. In our patient group, awareness of dietary restrictions may explain the widespread (68%) use of supplemental vitamins, minerals or herbal extracts (Table 1).

A significant proportion of patients reported knowledge of diets low in FODMAPs, with 9.2% of respondents using a free text field in the survey to comment on the utility of this diet. Familiarity with this diet was much higher among patients who had seen a dietitian, and this may reflect Australian clinical practice because a majority of clinicians reported providing advice about FODMAPs. There is an evidence basis for this advice: when a recall questionnaire was used in a cohort of IBD patients, it appeared that a reduction in the intake of FODMAPs reduced abdominal symptoms such as pain, diarrhoea, bloating and wind [32]. It has been postulated that increased FODMAP intake in a changing Western diet may explain the rising incidence of CD, implicating diet in disease pathogenesis [33]. Aside from the disease-specific effects of these fermentable carbohydrates, their consumption is strongly associated with worsening symptoms of irritable bowel syndrome [34], which is a condition that is two- to three-fold more prevalent in IBD patients in long-term remission than in the general population [35], although such symptoms may represent occult inflammation [36]. Quality of life improved in a small study evaluating the use of a 'half elemental diet' in CD patients in remission [37]; whether this is the result of a reduction in FODMAP consumption is uncertain. A recent systematic review found very little good-quality evidence regarding the use of indigestible carbohydrates in CD [38]. In a randomised controlled study of fibre supplementation in patients in remission from UC, gut transit time was altered by resistant starch and wheat bran consumption, whereas carbohydrate fermentation and short-chain fatty acid production were unchanged [39]. Similarly, a low FODMAP diet caused a reduction in total bacterial abundance, no effect on relative abundance of bacterial groups with putative health benefits and no effect on increased faecal butyrate excretion [40].

Despite a systematic review showing a reduced BMI in 37% of CD patients and 20% of UC patients [41], the self-reported incidence of an underweight BMI in this large Australian cohort was similar to that reported in the 2011–2012 Australian National Health Survey; rates of being overweight or obese were only slightly lower. The self-reported mean BMI for the general Australian population was 27.9 kg m^{-2} for men and 27.2 kg m^{-2} for women [42]. Steroid use was associated with increased weight, suggesting a drug-related effect because complicated disease in itself was not associated with a significant difference in weight. A high degree of knowledge of CD biology and relevant anatomy has been demonstrated in members of a patient support group [43], providing some validation to responses regarding disease phenotype and treatments in our cohort.

A strength of the present study is the large number of individual responses from members of a national association, matched with clinicians treating the same population. In this patient group, a wide variety of opinions regarding diet existed, and knowledge regarding probiotics, omega-3 fatty acids, low residue and low FODMAP diets was prevalent. However, adherence to dietary advice was poor. This may reflect a lack of efficacy or a paucity of firm evidence.

Conclusions

This present study emphasises that IBD clinicians from different disciplines have diverse views of the role of diet in IBD; for example, gastroenterologists are significantly more likely to place importance in the role of diet in the pathogenesis of IBD. The advice given to patients is heterogeneous, often perceived as inadequate and poorly followed. Further work in this field is needed to provide an evidence base from which to offer the guidance that patients expect.

Transparency statement

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported, that no important aspects of the study have been omitted and that any discrepancies from the study as planned (and registered with) have been explained. The reporting of this work is compliant with STROBE guidelines.

Acknowledgments

We thank Crohn's and Colitis Australia for allowing distribution of the questionnaire hyperlink, as well as the members of each organisation who participated.

Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.
Researchers contributing to this work were funded by the Angela McAvoy AM Fellowship from Crohn's and Colitis Australia, as well as by an Emerging Researcher Fellowship from Monash Health.
DH, GM and BS formulated the questionnaires and designed the study. DH performed the statistical analyses and prepared the manuscript. BS and GM critically revised the manuscript. All authors critically reviewed the manuscript and approved the final version submitted for publication.

References

1. O'Morain C, Segal AW & Levi AJ (1984) Elemental diet as primary treatment of acute Crohn's disease: a controlled trial. *Br Med J (Clin Res Ed)* **288**, 1859–1862.
2. Triantafillidis J-K, Vagianos C & Papalois AE (2015) The role of enteral nutrition in patients with inflammatory bowel disease: current aspects. *Biomed Res Int* **2015**, Article 197167; 1–12.
3. Krok KL & Lichtenstein GR (2003) Nutrition in Crohn disease. *Curr Opin Gastroenterol* **19**, 148–153.
4. Donnellan CF, Yann LH & Lal S (2013) Nutritional management of Crohn's disease. *Therap Adv Gastroenterol* **6**, 231–242.
5. Gassull MA (2003) Nutrition and inflammatory bowel disease: its relation to pathophysiology, outcome and therapy. *Dig Dis* **21**, 220–227.
6. Aghdassi E, Wendland BE, Stapleton M *et al.* (2007) Adequacy of nutritional intake in a Canadian population of patients with Crohn's disease. *J Am Diet Assoc* **107**, 1575–1580.
7. Nguyen GC, Munsell M & Harris ML (2008) Nationwide prevalence and prognostic significance of clinically diagnosable protein-calorie malnutrition in hospitalized inflammatory bowel disease patients. *Inflamm Bowel Dis* **14**, 1105–1111.
8. Sousa Guerreiro C, Cravo M, Costa AR, Miranda A, Tavares L, Moura-Santos P *et al.* (2007) A comprehensive approach to evaluate nutritional status in Crohn's patients in the era of biologic therapy: a case-control study. *Am J Gastroenterol* **102**, 2551–2556.
9. Kugathasan S, Nebel J, Skelton JA *et al.* (2007) Body mass index in children with newly diagnosed inflammatory bowel disease: observations from two multicenter North American inception cohorts. *J Pediatr* **151**, 523–527.
10. Long MD, Crandall WV, Leibowitz IH *et al.* (2010) Prevalence and epidemiology of overweight and obesity in children with inflammatory bowel disease. *Inflamm Bowel Dis* **17**, 2162–2168.
11. Steed H, Walsh S & Reynolds N (2009) A brief report of the epidemiology of obesity in the inflammatory bowel disease population of Tayside, Scotland. *Obes Facts* **2**, 370–372.
12. Nic Suibhne T, Raftery TC, McMahon O *et al.* (2013) High prevalence of overweight and obesity in adults with Crohn's disease: associations with disease and lifestyle factors. *J Crohns Colitis* **7**, e241–e248.
13. Hass DJ, Brensinger CM, Lewis JD *et al.* (2006) The impact of increased body mass index on the clinical course of Crohn's disease. *Clin Gastroenterol Hepatol* **4**, 482–488.
14. Blain A, Cattan S, Beaugerie L *et al.* (2002) Crohn's disease clinical course and severity in obese patients. *Clin Nutr* **21**, 51–57.
15. Cotillard A, Kennedy SP, Kong LC *et al.* (2013) Dietary intervention impact on gut microbial gene richness. *Nature* **500**, 585–588.
16. Albenberg LG & Wu GD (2014) Diet and the intestinal microbiome: associations, functions, and implications for health and disease. *Gastroenterology* **146**, 1564–1572.
17. Richman E & Rhodes JM (2013) Review article: evidence-based dietary advice for patients with inflammatory bowel disease. *Aliment Pharmacol Ther* **38**, 1156–1171.

18. Charlebois A, Rosenfeld G & Bressler B (2015) The impact of dietary interventions on the symptoms of inflammatory bowel disease: a systematic review. *Crit Rev Food Sci Nutr* **10**, 1370–1378.
19. Zallot C, Quilliot D, Chevaux J-B *et al.* (2013) Dietary beliefs and behavior among inflammatory bowel disease patients. *Inflamm Bowel Dis* **19**, 66–72.
20. Cohen AB, Lee D, Long MD *et al.* (2013) Dietary patterns and self-reported associations of diet with symptoms of inflammatory bowel disease. *Dig Dis Sci* **58**, 1322–1328.
21. Wong S, Walker JR, Carr R *et al.* (2012) The information needs and preferences of persons with longstanding inflammatory bowel disease. *Can J Gastroenterol* **26**, 525–531.
22. Sheehan K. B. (2001) E-mail Survey Response Rates: A Review. *Journal of Computer-Mediated Communication* **6**, 0. doi: 10.1111/j.1083-6101.2001.tb00117.x.
23. Edwards P, Roberts I, Clarke M *et al.* (2002) Increasing response rates to postal questionnaires: systematic review. *BMJ* **324**, 1183.
24. World Health Organization (1995) Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. Technical Report Series no. 854. WHO: Geneva.
25. Brown AC, Rampertab SD & Mullin GE (2011) Existing dietary guidelines for Crohn's disease and ulcerative colitis. *Expert Rev Gastroenterol Hepatol* **5**, 411–425.
26. Triggs CM, Munday K, Hu R *et al.* (2010) Dietary factors in chronic inflammation: food tolerances and intolerances of a New Zealand Caucasian Crohn's disease population. *Mutat Res* **690**, 123–138.
27. Zutshi M, Hull TL & Hammel J (2007) Crohn's disease: a patient's perspective. *Int J Colorectal Dis* **22**, 1437–1444.
28. Magee EA, Edmond LM, Tasker SM *et al.* (2005) Associations between diet and disease activity in ulcerative colitis patients using a novel method of data analysis. *Nutr J* **4**, 7.
29. Fernandez-Banares F, Abad-Lacruz A, Xiol X *et al.* (1989) Vitamin status in patients with inflammatory bowel disease. *Am J Gastroenterol* **84**, 744–748.
30. Vagianos K, Bector S, McConnell J *et al.* (2007) Nutrition assessment of patients with inflammatory bowel disease. *JPEN J Parenter Enteral Nutr* **31**, 311–319.
31. Walton M, Walton M, Alaunyte I *et al.* (2014) Do patients living with ulcerative colitis adhere to healthy eating guidelines? A cross-sectional study *Br J Nutr* **112**, 1628–1635.
32. Gearry RB, Irving PM, Barrett JS *et al.* (2009) Reduction of dietary poorly absorbed short-chain carbohydrates (FODMAPs) improves abdominal symptoms in patients with inflammatory bowel disease-a pilot study. *J Crohns Colitis* **3**, 8–14.
33. Gibson PR & Shepherd SJ (2005) Personal view: food for thought – western lifestyle and susceptibility to Crohn's disease. The FODMAP hypothesis. *Aliment Pharmacol Ther* **21**, 1399–1409.
34. Shepherd SJ, Parker FC, Muir JG *et al.* (2008) Dietary triggers of abdominal symptoms in patients with irritable bowel syndrome: randomized placebo-controlled evidence. *Clin Gastroenterol Hepatol* **6**, 765–771.
35. Simrén M, Axelsson J, Gillberg R *et al.* (2002) Quality of life in inflammatory bowel disease in remission: the impact of IBS-like symptoms and associated psychological factors. *Am J Gastroenterol* **97**, 389–396.
36. Keohane J, O'Mahony C, O'Mahony L *et al.* (2010) Irritable bowel syndrome-type symptoms in patients with inflammatory bowel disease: a real association or reflection of occult inflammation? *Am J Gastroenterol* **105**, 1788, 1789–1794.
37. Takagi S, Utsunomiya K, Kuriyama S *et al.* (2009) Quality of life of patients and medical cost of 'half elemental diet' as maintenance therapy for Crohn's disease: secondary outcomes of a randomised controlled trial. *Dig Liver Dis* **41**, 390–394.
38. Lee J, Allen R, Ashley S *et al.* (2014) British Dietetic Association evidence-based guidelines for the dietary management of Crohn's disease in adults. *J Hum Nutr Diet* **27**, 207–218.
39. James SL, Christophersen CT, Bird AR *et al.* (2015) Abnormal fibre usage in UC in remission. *Gut* **64**, 562–570.
40. Halmos EP, Christophersen CT, Bird AR *et al.* (2015) Diets that differ in their FODMAP content alter the colonic luminal microenvironment. *Gut* **64**, 93–100.
41. Bryant RV, Trott MJ, Bartholomeusz FD *et al.* (2013) Systematic review: body composition in adults with inflammatory bowel disease. *Aliment Pharmacol Ther* **38**, 213–225.
42. Australian Bureau of Statistics (2012) Australian Health Survey: First Results, 2011–12. ABS: Canberra.
43. Eaden JA, Abrams K & Mayberry JF (1999) The Crohn's and colitis knowledge score: a test for measuring patient knowledge in inflammatory bowel disease. *Am J Gastroenterol* **94**, 3560–3566.

Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article:
Appendix S1. Inflammatory bowel disease and diet questionnaire.
Appendix S2. Clinician questionnaire: diet and inflammatory bowel disease.

Supplemental material

PATIENT IBD & DIET QUESTIONNAIRE

1. What is your age?

2. What is your gender?
    i. Male
    ii. Female
3. What is your height in centimetres?

4. What is your weight in kilograms?

5. Can you identify your type of inflammatory bowel disease?
    i. Crohn's Disease
    ii. Ulcerative Colitis
    iii. Other:

6. How many years have you had inflammatory bowel disease?
    i. 0-2 years
    ii. 2-5 years
    iii. 5-10 years
    iv. >10 years

7. At what age were you when your inflammatory bowel disease was diagnosed?
    i. Younger than 16 years
    ii. Between 17 and 40
    iii. Older than 40

8. What is the location of your inflammatory bowel disease?
    i. Ulcerative colitis of any extent
    ii. Crohn's Disease of the ileum
    iii. Crohn's Disease of the colon
    iv. Crohn's Disease of the ileum and colon
    v. Crohn's Disease of the upper gastrointestinal tract

9. Have you experienced any of the following complications of Crohn's Disease?
    i. Stricture
    ii. Abscess, fistula
    iii. Neither, but I have Crohn's Disease
    iv. I do not have Crohn's Disease

10. Since your diagnosis, what has happened to your weight?
    (ie. compare your weight now to your weight at diagnosis)
    i. I have gained weight
    ii. I have lost weight
    iii. My weight is the same

11. Do you believe any change in weight is due to inflammatory bowel disease?

i. Yes
ii. No
iii. N/A

12. Do you believe any change in weight is due to treatment for IBD?
    i. Yes
    ii. No
    iii. N/A

13. Do you feel that your weight contributes to the severity of your inflammatory bowel disease?
    i. Yes
    ii. No

14. How do you feel about your weight at the moment?
    i. Underweight
    ii. Normal weight
    iii. Overweight

15. Do you believe that your diet affects your inflammatory bowel disease?
    i. Yes
    ii. No

16. If you believe that diet affects your inflammatory bowel disease, what role do you believe it has?

17. Do you believe that your gastroenterologist/IBD specialist places importance in the role of diet?
    i. Yes
    ii. No

18. Have you received steroids in the past year? (Steroids include medicines like prednisolone and hydrocortisone)
    i. Yes
    ii. No

19. How many times have you received steroids in the past?
    i. 0-3
    ii. 4-5
    iii. 6-10
    iv. >10

20. Have you been treated with Azathioprine, Mercaptopurine or Methotrexate?

21. You may choose more than one option
    i. Azathioprine
    ii. Mercaptopurine
    iii. Methotrexate
    iv. None of these

22. Have you been treated with Infliximab or Adalimumab?
    i. Yes
    ii. No

23. Have you had surgery for inflammatory bowel disease?
    i. Yes

ii. No

24. If you have had surgery, please describe your understanding of the extent of bowel removed...

25. Do you take any dietary supplements or vitamins?
    i. Yes
    ii. No

26. If you do take dietary supplements or vitamins, which do you take?

27. Are there particular foods that you avoid?
    i. Yes
    ii. No

28. If there are particular foods that you avoid, what are they?

29. What do you think of your diet?
    i. Healthy
    ii. Could be improved

30. How often do you see your gastroenterologist/IBD specialist?
    i. Never
    ii. Yearly or less often
    iii. Every 6 to 12 months
    iv. More often than every 6 months

31. Has your specialist given you dietary advice, or referred you to a dietitian? (you may select more than one option)
    i. My specialist has given me dietary advice
    ii. My specialist has referred me to a dietitian
    iii. Neither of the above

32. Has your general practitioner given you dietary advice, or referred you to a dietitian?

33. (you may select more than one option)
    i. My general practitioner has given me dietary advice
    ii. My general practitioner has referred me to a dietitian
    iii. Neither of the above

34. Have you seen a dietitian?
    i. Yes
    ii. No

35. Have you received dietary advice from another health practitioner?
    i. Yes, from a naturopath
    ii. Yes, from another health practitioner
    iii. No

36. Have you followed dietary advice given to you by any of these health practitioners?
    i. Yes
    ii. No

37. If you have followed advice, what advice have you followed - and why?

38. Was there advice you did not follow? What was that, and why did you not follow it?

39. Of which of the following do you have some knowledge or personal experience?
    i. Low FODMAP diet
    ii. Low residue diet
    iii. Probiotics
    iv. Prebiotics
    v. Low fructose diet
    vi. Low oxalate diet
    vii. Elemental diet
    viii. Omega-3 fatty acids
    ix. Enteral feeding as treatment for Crohn's Disease

40. If you have followed one of the above dietary modifications, please describe which, and whether you found it useful.

Clinician questionnaire - diet & IBD

1. What type of clinician are you?
   Multiple answers possible
   i. Gastroenterologist - private practice
   ii. Gastroenterologist - public ± private practice
   iii. Surgeon
   iv. General physician
   v. General practitioner
   vi. Dietitian
   vii. Adult
   viii. Paediatric
   ix. Other

2. What proportion of your working time is spent with patients with IBD?
   i. 0-10%
   ii. 10-25%
   iii. 25-50%
   iv. >50%

3. For how many years have you been at your current level of practice?
   (eg. specialist gastroenterologist/surgeon/general practitioner, etc)
   i. 0-5
   ii. 5-10
   iii. 10-20
   iv. >20

4. Do you believe diet has a role in any of the following aspects of inflammatory bowel disease?

5. Multiple answers possible
   i. Pathogenesis
   ii. Symptoms
   iii. Complications
   iv. Intestinal microbiota
   v. Response to treatment

6. What proportion of your inflammatory bowel disease patients are overweight or obese?
   i.e. body mass index >25
   i. 0-10%
   ii. 10-25%
   iii. 25-50%
   iv. 50-75%
   v. >75%

7. Do you counsel patients on the following?
   Multiple answers possible: tick whichever you regularly explicitly discuss with patients
   i. Diet with relation to Inflammatory Bowel Disease symptoms/activity

ii. Diet with relation to weight loss or weight gain
iii. Diet with relation to particular micronutrient requirements/deficiencies
iv. Recommendation of nutritional supplements
v. Recommendation of probiotics
vi. Recommendation of prebiotics
vii. Role of short-chain carbohydrates/simple sugars (e.g. lactose, fructose, FODMAPs)
viii. Dietary fats
ix. Dietary oxalate
x. Cardiovascular risk factors
xi. Protein intake
xii. Bone health advice
xiii. Enteral feeding/elemental diet
xiv. Oral iron replacement
xv. Intravenous iron replacement

8. Do you believe obesity has significant effects on Crohn's Disease? Please briefly describe.

9. Do you believe you and your patients generally have similar views of the role of diet in Inflammatory Bowel Disease?
    i. Yes
    ii. No

10. If you believe that your views and those of your patients differ in regard to the role of diet in Inflammatory bowel disease, please detail the major difference

Summary and discussion

The findings of the survey were frequently consistent with published literature in this field, but offered a contemporary view of dietary practice for inflammatory bowel disease patients and clinicians in Australia. Widespread knowledge regarding the use of a low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) may be specific to an Australian cohort due to the local development and publication of this dietary intervention[11-13]. Obesity and overweight were less prevalent than in the general Australian population, but were associated with higher cumulative steroid exposure. Unlike some cross-sectional and cohort studies identified in the systematic review, we did not find an association between obesity and rates of surgery or prevalence of complicated Crohn's disease.

Hypothesis 1 *(That patients with inflammatory bowel disease believe diet is an important influence on their disease and restrict their dietary intake, but that clinicians provide a variety of advice)* was supported by this qualitative research: approximately three-quarters of patients believed that diet affected their inflammatory bowel disease and a similar proportion avoided certain foods. Clinicians reported providing a variety of advice, with a minority considering diet a pathogenic factor.

A limitation of this study was the absence of a question regarding the prevalence of body composition testing – whether by routine measurement of height and weight (six-monthly documentation of which is mandatory for prescribing biologic drugs for Crohn's disease in Australia), or by more involved methods such as anthropometry or DXA. Adherence to guidelines recommending periodic DXA[14] in this population-based cohort would be of interest. The use of categorical variables allowed multiple comparisons between different groups, with many analyses not included in the final manuscript.

Modifications to the paper were implemented after peer review, including the omission of some analysis of qualitative data. For example, when patients were asked whether they avoided particular foods, 71% of patients responded: the foods most avoided were represented by a word cloud analysis (Figure 3.1)

Figure 3.1 Pictorial representation of the frequency with which culprit foods were named in response to a question regarding food avoidance; word size is proportional to number of responses (wordle.net)

We are grateful to the membership and organisers of the national bodies involved (Crohn's and Colitis Australia, the Dietitians Association of Australia and the Australian Inflammatory Bowel Disease Association) for their generosity in responding to this questionnaire and for allowing its distribution.

The information received demonstrates a wide variety of belief and dietary practice among patients and clinicians, and emphasises a lack of uniform guidance. The patient perception that clinicians give inadequate consideration to diet may prompt researchers and professional bodies to develop a satisfactory, individualised, approach to the role of diet in inflammatory bowel disease.

Chapter references

1. Guarini A, Biagini S, Capaldi A, Carretto D, Angelis AD, Iudice S, et al. Satisfaction and expectations of patients with inflammatory bowel disease on biologic therapy: a multicenter study. Ann Gastroenterol. 2017;30(1):96–100.

2. Ghosh S, Mitchell R. Impact of inflammatory bowel disease on quality of life: Results of the European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA) patient survey. J Crohns Colitis. 2007 Sep;1(1):10–20.

3. Dupuis M, Marshall JK, Hayes SM, Cytryn K, Murray S. Assessing the educational needs of Canadian gastroenterologists and gastroenterology nurses: challenges to optimal care in Crohn's Disease. Can J Gastroenterol. 2009 Dec;23(12):805–10.

4. Lewis JD, Abreu MT. Diet as a Trigger or Therapy for Inflammatory Bowel Diseases. Gastroenterology. Elsevier; 2016 Oct;0(0).

5. Forbes A, Escher J, Hebuterne X, Kłęk S, Krznaric Z, Schneider S, et al. ESPEN guideline: Clinical nutrition in inflammatory bowel disease. Clin Nutr. 2016 Dec 31.

6. Limdi JK, Aggarwal D, McLaughlin JT. Dietary Practices and Beliefs in Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis. 2016 Jan;22(1):164–70.

7. Andersen RE, Wadden TA, Bartlett SJ, Zemel B, Verde TJ, Franckowiak SC. Effects of Lifestyle Activity vs Structured Aerobic Exercise in Obese Women: A Randomized Trial. JAMA. American Medical Association; 1999 Jan 27;281(4):335–40.

8. Foster Schubert KE, Alfano CM, Duggan CR, Xiao L, Campbell KL, Kong A, et al. Effect of Diet and Exercise, Alone or Combined, on Weight and Body Composition in Overweight-to-Obese Postmenopausal Women. Obesity. Blackwell Publishing Ltd; 2012 Aug 1;20(8):1628–38.

9. Gerasimidis K, McGrogan P, Edwards CA. The aetiology and impact of malnutrition in paediatric inflammatory bowel disease. J Hum Nutr Diet. 2011 Aug;24(4):313–26.

10. Moran GW, Dubeau M-F, Kaplan GG, Panaccione R, Ghosh S. The increasing weight of Crohn's disease subjects in clinical trials: a hypothesis-generatings time-trend analysis. Inflamm Bowel Dis. 2013 Dec;19(13):2949–56.

11. Shepherd SJ, Parker FC, Muir JG, Gibson PR. Dietary triggers of abdominal symptoms in patients with irritable bowel syndrome: randomized placebo-controlled evidence. Clin Gastroenterol Hepatol. 2008 Jul;6(7):765–71.

12. Halmos EP, Power VA, Shepherd SJ, Gibson PR, Muir JG. A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. Gastroenterology. 2014 Jan;146(1):67–75.e5.

13. Gibson PR, Shepherd SJ. Personal view: food for thought - western lifestyle and susceptibility to Crohn's disease. The FODMAP hypothesis. Aliment Pharmacol Ther. 2005 Jun;21(12):1399–409.

14. American Gastroenterological Association medical position statement: guidelines on osteoporosis in gastrointestinal diseases. Vol. 124, Gastoenterology. 2003. pp. 791–4.

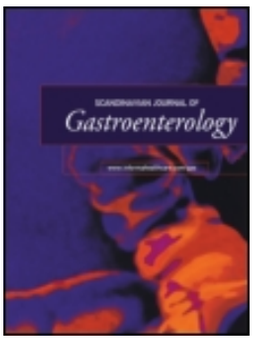
Chapter 4: Body composition analysis using abdominal scans from routine clinical care in patients with Crohn's Disease

Introduction and context

This chapter describes the methodology used to perform body composition analysis for the subsequent component papers of the thesis. While weight and height provide information about nutrition, and have been used to determine drug doses in Crohn's disease, they are relatively insensitive for detecting significantly low muscle mass[1] and low cell mass[2] – which have important negative prognostic implications in inflammatory diseases, and may affect drug metabolism. More accurate body composition analysis generally requires dedicated testing, using techniques that may not be accessible, or involve exposure to ionising radiation[3].

The principle that measurement of tissue areas at a single abdominal cross-section correlates well with total body fat mass and fat-free mass had been validated in other patient groups[4-7] but not in Crohn's disease. We hypothesised that validation of these techniques would be successful in Crohn's disease patients (hypothesis 2: *That cross-sectional abdominal imaging obtained by computed tomography (CT) and magnetic resonance imaging (MRI) during routine clinical care for patients with Crohn's disease allows accurate estimation of body composition parameters*). As most Crohn's disease patients have abdominal scans performed as part of routine clinical care[8], a potential trove of data may be available if the technique is valid in this circumstance. Significantly, this would allow incorporation of retrospective body composition analysis into many existing clinical studies.

From clinical databases, patients who had both whole-body DXA and cross-sectional imaging with CT or MRI were identified. Standard techniques were used to measure the tissue areas, and regression analysis employed to determine relationships between CT or MRI and DXA results. We sought to define a single abdominal level which had the greatest predictive value for estimation of total body fat mass and fat-free mass. We were also interested in the prevalence of osteoporosis and significantly low muscle mass in this cohort



Scandinavian Journal of Gastroenterology

ISSN: 0036-5521 (Print) 1502-7708 (Online) Journal homepage: http://www.tandfonline.com/loi/igas20

Body composition analysis using abdominal scans from routine clinical care in patients with Crohn's Disease

Darcy Quinn Holt, Boyd Josef Gimnicher Strauss, Kenneth K Lau & Gregory Thomas Moore

To cite this article: Darcy Quinn Holt, Boyd Josef Gimnicher Strauss, Kenneth K Lau & Gregory Thomas Moore (2016) Body composition analysis using abdominal scans from routine clinical care in patients with Crohn's Disease, Scandinavian Journal of Gastroenterology, 51:7, 842-847, DOI: 10.3109/00365521.2016.1161069

To link to this article: http://dx.doi.org/10.3109/00365521.2016.1161069

Published online: 22 Mar 2016.

SCANDINAVIAN JOURNAL OF GASTROENTEROLOGY, 2016
VOL. 51, NO. 7, 842–847
http://dx.doi.org/10.3109/00365521.2016.1161069

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Body composition analysis using abdominal scans from routine clinical care in patients with Crohn's Disease

Darcy Quinn Holt[a,b], Boyd Josef Gimnicher Strauss[b], Kenneth K Lau[b,c] and Gregory Thomas Moore[a,b]

[a]Department of Gastroenterology & Hepatology, Monash Health, Victoria, Australia; [b]School of Clinical Sciences, Monash University, Victoria, Australia; [c]Department of Diagnostic Imaging, Monash Health, Victoria, Australia

ABSTRACT

Objective: Crohn's Disease is associated with body composition changes, which have important treatment and prognostic implications. Measurement of body composition usually requires dedicated scanning or measurement, with retrospective analysis of existing datasets impossible. We sought to determine whether single slice analysis of abdominal scans, obtained during routine clinical care, in patients with Crohn's Disease accurately predicts body composition compartments.

Materials and methods: Abdominal CT images of patients with Crohn's disease were analyzed and comparison was made with total body fat-free mass, total body fat mass, femoral neck *t*-score, and other parameters reported from DXA, the reference method.

Results: Thirty-seven subjects were identified, 15 male and 22 female, with a mean age of 43.8 years. There was significant correlation (Pearson $r = 0.923$, $p < 0.001$) between skeletal muscle area from CT and total fat-free mass measured by DXA. Similarly, total body fat mass correlated strongly ($r = 0.928$, $p < 0.0001$) with subcutaneous fat area. In this cohort of ambulatory Crohn's Disease patients, low muscle mass/sarcopenia was prevalent and predictive of lower bone mineral density.

Conclusions: Fat mass, fat-free mass, and appendicular skeletal muscle index can be predicted by analysis of a single CT slice in patients with Crohn's Disease. Similar to published data from healthy subjects, the L3 vertebral body level provided the most robust correlation with most parameters. This study represents the first published use of routinely obtained abdominal imaging to demonstrate this relationship – and to predict body composition components – in patients with inflammatory bowel disease.

ARTICLE HISTORY
Received 28 January 2016
Revised 23 February 2016
Accepted 27 February 2016
Published online 15 March 2016

KEYWORDS
Body composition; bone density; Crohn disease; sarcopenia; tomography

Introduction

Crohn's Disease is a gastrointestinal inflammatory condition associated with malnutrition,[1–4] lower bone mineral density,[5] lower body mass index (BMI), and lower fat-free mass (FFM).[6] Body weight, weight loss, and BMI are insufficiently sensitive to assess FFM.[7,8] In clinical practice, the most accessible [9] and accurate [10] means of determining these body composition compartments is whole body dual-energy X-ray absorptiometry (DXA).

Despite recommendations that patients with inflammatory bowel disease (IBD) undergo regular DXA for monitoring bone mineral density (BMD),[11] screening prevalence is low: approximately one in five patients.[12] However, abdominal computed tomography (CT) scans are often obtained as part of routine care of Crohn's Disease for assessment of disease complications or activity.[13]

In other disease states, such as cancer [14] and obesity,[15] analysis of single slice abdominal CT or magnetic resonance imaging (MRI) images at the level of the third lumbar vertebra (L3) has been shown to highly correlate with FFM as determined by DXA. This correlation has not previously been described in patients with inflammatory bowel disease.

Similarly, evaluation of intra-abdominal fat area in a single CT or MRI slice at the level of the L4–5 intervertebral disc has been shown to correlate highly with total visceral adipose tissue volume.[14,16–18] The use of single-slice abdominal scans to estimate total body skeletal muscle, visceral adipose tissue and subcutaneous adipose tissue as measured by total body MRI scan has shown that the L3 level provides the most robust single scan for estimating all parameters.[19]

We sought to determine whether single slice analysis of CT scans at the L3 and L4–5 levels, obtained as part of routine clinical care in patients with Crohn's Disease, was able to predict body composition compartments with accuracy.

Materials and methods

Patients who had CT scans (Discovery CT 750HD, GE Healthcare, Little Chalfont, UK) and total body DXA (GE Lunar Prodigy, GE Healthcare, Little Chalfont, UK) performed within a 12-month period as part of routine clinical care at a single tertiary health care service (Monash Health, Victoria, Australia) were retrospectively identified by a search of radiology and clinical databases, with a diagnosis of Crohn's disease confirmed by chart review. CT DICOM (Digital Imaging and Communications in Medicine) images at the L3 and L4–5 levels were analysed for body composition by a single experienced operator using SliceOmatic 4.3 (TomoVision, Montreal,

CONTACT Dr Darcy Q. Holt darcy.holt@monashhealth.org Department of Gastroenterology & Hepatology, Monash Health, 246 Clayton Road, Clayton, Victoria 3168, Australia

Canada) according to previously described techniques,[14] and comparison was made with total body FFM, total body fat mass, appendicular skeletal muscle index (ASMI) (lean tissue mass in arms and legs normalised to height [kg/m^2]), femoral neck *t*-score, and other parameters reported from DXA.

Statistical analysis

Pearson correlation coefficients were calculated and multivariate linear regression analysis was performed. Variables included for linear modelling included basic demographic and anthropometric information (age, gender, height, and weight) and the CT measurement with highest correlation to the DXA-measured body composition compartment being estimated. When individual values were missing from the dataset, subjects were excluded from the relevant analysis. Akaike's information criteria [20] were used to discard variables from linear modelling. A Bland–Altman plot was used to evaluate bias and trend of predicting FFM and FM from cross-sectional images compared to DXA measurements. A p value of less than 0.05 was considered significant. GraphPad Prism 6 (GraphPad Software, La Jolla, CA) and R version 3.1.2 (The R Foundation for Statistical Computing, Vienna, Austria) were used.

Ethical considerations

This research was approved by the Monash Health Human Research Ethics Committee (project number 11264A).

Results

Thirty-seven subjects were identified, 15 male and 22 female, with a mean age of 43.8 years (Table 1).

CT scans were obtained for a variety of clinical indications (Table 1).

There was significant correlation (Pearson $r = 0.924$, $p < 0.001$) between the L4–5 skeletal muscle area from CT and total FFM as measured by DXA (Figure 1A); the correlation was equally strong at the L3 level (Table 2). The median time between CT and DXA scans was 21 days; there was no correlation between the interval between scans and the difference between predicted (CT) and measured (DXA) lean tissue mass ($r - 0.124$, p 0.520).

Similarly, total body fat mass showed a high degree of correlation ($r = 0.928$, $p < 0.0001$, n 37) with subcutaneous fat area at an L3 level; correlation was equally strong at the L4–5 level (Figure 1B).

A formula previously described by Mourtzakis, and referenced by Baker,[14,15] for CT-derived FFM was able to predict DXA FFM in this patient group (R^2 0.852, $p < 0.0001$). Likewise, DXA-measured ASMI was predicted by Mourtzakis' formula using measurement of skeletal muscle area at the L3 level (R^2 0.730, $p < 0.0001$).

In these two previously published studies, a statistically significantly older and heavier patient cohort was studied. To ascertain whether closer prediction of DXA measures of body composition may be possible in this Crohn's Disease patient cohort, multivariate linear modelling was used.

Table 1. Characteristics of the study cohort.

		SEM	p (*t*-test male vs. female)
Number (n)	37		
Age (years)	43.8	2.6	
Male	41.1	3.5	
Female	44.7	3.7	0.482
Female (n)	22		
Mean weight (kg)	67.2	3.6	
Male	78.4	6	
Female	59.1	3.6	<0.001
Indication (n)			
Active intestinal inflammation	9		
Pain; no radiological abnormality	6		
Body composition study	6		
Postoperative	5		
Small bowel obstruction without active inflammation	5		
No data available	4		
Pyrexia of unknown origin	1		
Pyelonephritis	1		
Mean BMI (kg/m^2)	23.9	1	
Male	26.1	1.8	
Female	22.4	1.2	0.103
Mean FFM by DXA (kg)	46	2.3	
Male	58.5	3.1	
Female	38.4	1.5	<0.001
Mean ASMI by DXA (kg/m^2)	6.6	0.4	
Male	7.81	0.49	
Female	5.49	0.19	<0.001
Mean L3 skeletal muscle area (cm^2)	128	7.5	
Male	161.9	11.8	
Female	104.8	6.1	<0.001
Mean L4–5 skeletal muscle area (cm^2)	123.9	7.3	
Male	158	11.2	
Female	99.5	5	<0.001
Mean L3 visceral adipose tissue area (cm^2)	97	14.4	
Male	129.6	28.3	
Female	74.8	13.1	0.09
Mean L3 subcutaneous adipose tissue area (cm^2)	171.9	18.8	
Male	182	30.2	
Female	165	24.5	0.66
Mean L4–5 visceral adipose tissue area (cm^2)	92.8	10.7	
Male	111.6	21.2	
Female	79.3	9.7	0.18
Mean L4–5 subcutaneous adipose tissue area (cm^2)	218.7	23.5	
Male	234.4	39.3	
Female	207.6	29.5	0.59

To ascertain and test a specific formula in this setting, subjects were randomly assigned into either a formula-finding cohort (n 19) or a validation cohort (n 18). From the formula-finding cohort, a model incorporating age, gender, weight, height, and skeletal muscle area at L3 level was tested. Using Aikaike's information criteria, weight was discarded. The resulting formula predicted measured FFM from DXA with R^2 of 0.9301, $p < 0.0001$.

$$\begin{aligned}\text{Fat} - \text{free mass} = {} & (0.11687 * \text{L3 skeletal muscle area in cm}^2) \\ & + (0.12883 \times \text{age in years}) \\ & + (34.64221 \times \text{height in m}) \\ & + (4.6485 \text{ if male gender}) - 35.18862\end{aligned}$$

In the validation cohort, this formula had an R^2 of 0.918, $p < 0.0001$ (Figure 1C).

A Bland–Altman plot of the resulting predicted measures for the entire dataset (Figure 2A) suggests that at larger values of FFM, this formula may tend to underestimate the actual value (Pearson r of average vs. difference 0.589, $p < 0.001$), although the bias (+0.005, SD 4.446) is small.

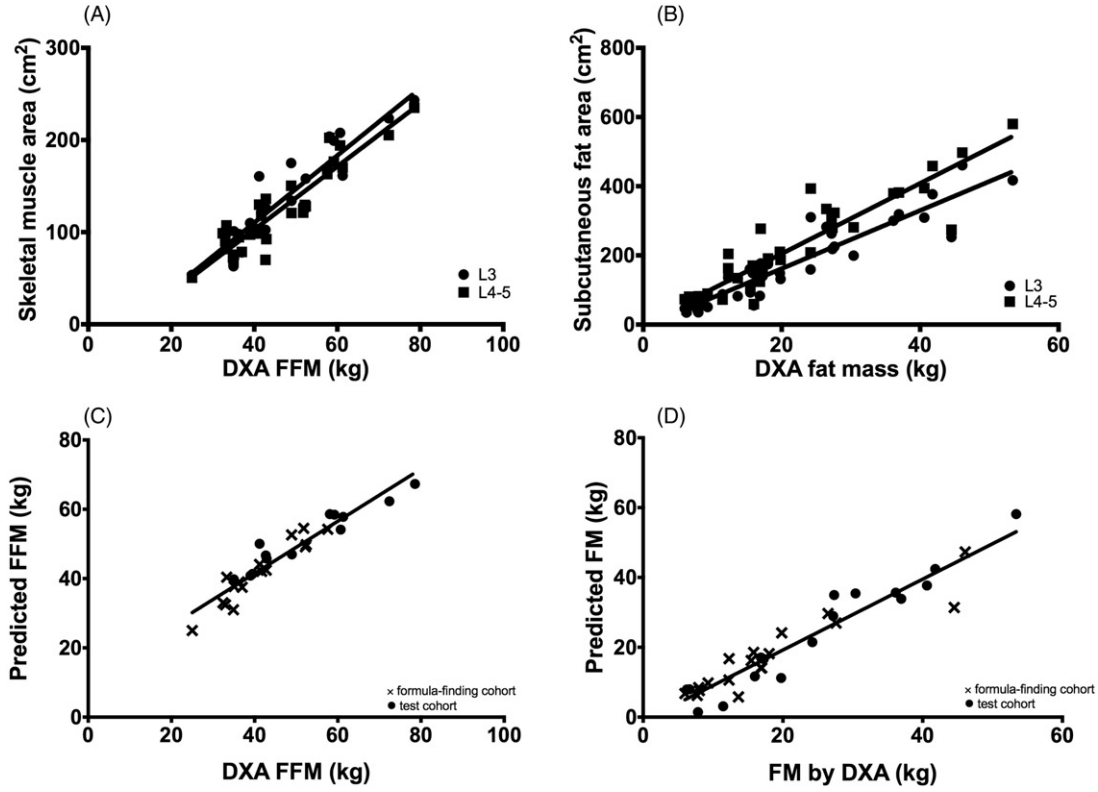


Figure 1. (A) Fat-free mass measured by DXA is predicted by CT-derived skeletal muscle area ($R^2 = 0.85$ for both series of measures, $p < 0.0001$, $n = 29$). (B) CT measurement of subcutaneous fat area at either of two levels predicts total body fat mass by DXA ($R^2 = 0.85$–0.86, $p < 0.001$, $n = 37$). (C) Fitting a derived model of estimating fat-free mass to the validation cohort. (D) Fitting a model for estimating fat mass to the validation cohort.

Table 2. Correlation between CT measurements and DXA-derived parameters (the CT level and area of interest with the highest degree of correlation to DXA parameter in bold type).

	L3		L4–5	
Parameter	Pearson *r*	*p*	Pearson *r*	*p*
FFM	0.923	<0.001	**0.924 (muscle)**	<0.001
Fat mass	**0.928 (SAT)**	<0.001	0.921 (SAT)	<0.001
% fat	**0.866 (SAT)**	<0.001	0.836 (SAT)	<0.001
ASMI	0.87	<0.001	**0.906 (muscle)**	<0.001
LTM	**0.923 (muscle)**	<0.001	0.921 (muscle)	<0.001
Lumbar spine *t*	**0.500 (VAT)**	0.002	0.365 (VAT)	0.029
Femoral neck *t*	**0.651 (muscle)**	<0.001	0.633 (muscle)	<0.001

SAT: subcutaneous adipose tissue; VAT: visceral adipose tissue; muscle: skeletal muscle.

From the formula-finding cohort, a model incorporating age, gender, weight, height, and subcutaneous adipose tissue area at L3 level was tested. No variables were excluded after use of Aikaike's information criteria. The resulting formula predicted measured fat mass from DXA with R^2 of 0.942, $p < 0.0001$.

$$\begin{aligned}\text{Fat mass} &= (0.03377 \times \text{L3 subcutaneous adipose tissue area in cm}^2) \\ &\quad - (0.16216 \times \text{age in years}) \\ &\quad - (6.16599 \text{ if male gender}) \\ &\quad - (24.29556 \times \text{height in m}) \\ &\quad + (0.57833 \times \text{weight in kg}) + 26.49794\end{aligned}$$

In the validation cohort, this model had an R^2 of 0.930, $p < 0.0001$ (Figure 1D).

A Bland–Altman plot (2B) of the difference between predicted fat mass and measured fat mass vs. the average between the two values demonstrated small bias (−0.76, SD 4.32) and did not reveal a trend ($p = 0.237$) towards systematic difference.

Bone mineral density

8.3% of subjects had a lumbar spine *t*-score < -2.5; 14.3% had a femoral neck *t*-score < -2.5. There was a strong correlation between L3 skeletal muscle area and femoral neck BMD (Pearson *r* 0.746, $p < 0.001$), total body BMD (*r* 0.651, $p < 0.001$) and a weaker – although statistically significant – correlation with lumbar spine BMD (*r* 0.355, *p* 0.031). All subjects with femoral neck osteoporosis had lower than median skeletal muscle area.

Sarcopenia

Low muscle mass was prevalent in this cohort. 45.4% of male subjects and 50% of female subjects had a DXA-measured ASMI more than two standard deviations below a young adult population mean, as previously defined.[21] Although the LTMI formula of Mourtzakis had poor sensitivity and specificity for detection of DXA-measured sarcopenia in this cohort (AUROC 0.76, *p* 0.08), we sought to determine whether multivariate linear regression would find a more accurate model: [LTMI = (0.0247 × L4–5 skeletal muscle area in cm²) + (0.01879 × weight in kg) − (3.47054 × height in m) + (0.89309

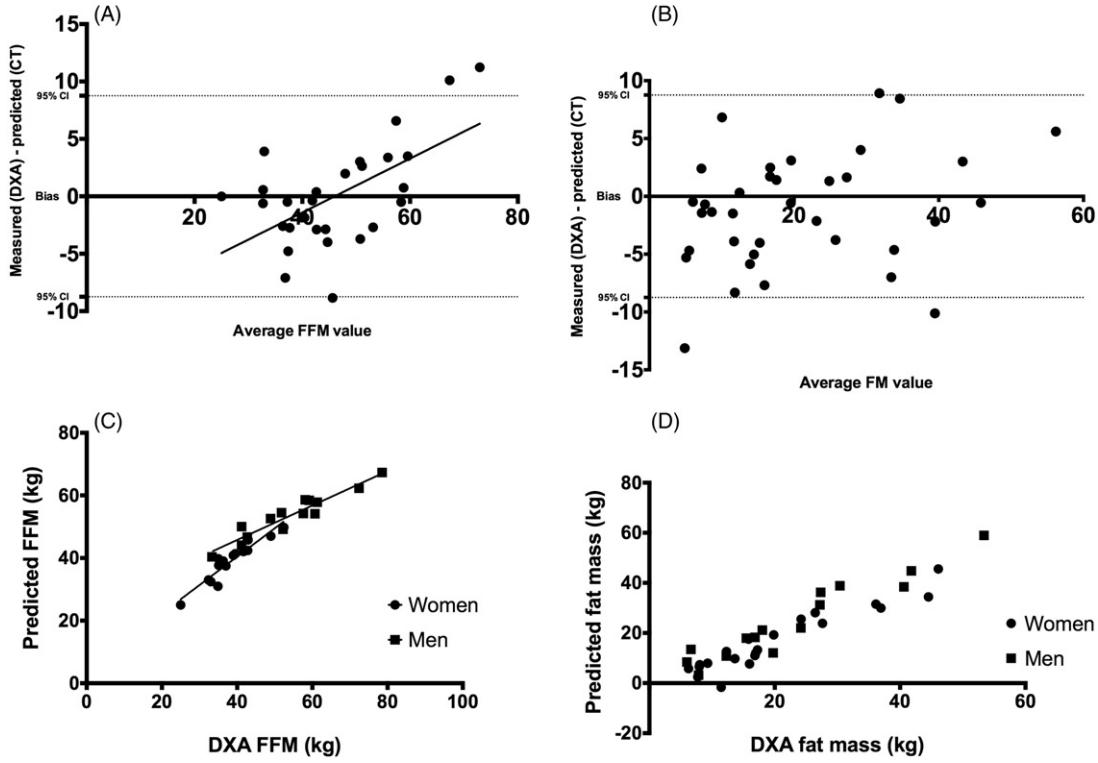


Figure 2. (A) Bland–Altman plot showing the difference between predicted values of fat-free mass and values measured by DXA against the average of the two values with 95% confidence intervals, and linear regression ($R^2 = 0.347$, $p < 0.001$). (B) Bland–Altman plot showing the difference between predicted values of fat mass and values measured by DXA with 95% confidence intervals. (C) Predicted FFM vs. measured FFM in men and women, with linear regression. (D) Predicted fat mass vs. measured fat mass in men and women.

if male gender) + 7.6514] have improved sensitivity and specificity (AUROC 0.86, *p* 0.02).

Obesity

Thirty-nine percent subjects had a BMI greater than 25 kg/m^2 and 19% greater than 30 kg/m^2. The prevalence of sarcopenic obesity, defined as a BMI $\geq$30 kg/m^2 in conjunction with an ASMI <2 SD below young adult mean, was low: only one subject fulfilled these criteria.

Longitudinal studies

A small number of identified subjects had repeated paired scans available for comparison, and in some subjects, changes in body composition had occurred. While only one pair of scans from each subject was included in the main dataset, repeated measurements were analysed with one-way ANOVA to determine that there was no variation in the mean difference between observed measures of skeletal muscle area by DXA and CT-predicted measures ($p = 0.677$).

Male vs. female

While significant differences in body composition existed between male and female subjects (Table 1), the formula for predicting fat mass showed equal applicability in male and female subjects (Figure 2C and D), with linear regression analysis demonstrating no significant difference between the lines ($p = 0.275$). However, the formula for predicting FFM demonstrated a difference between the observed and predicted values in male and female subjects that was of statistical significance ($p = 0.009$). Despite a high degree of accuracy in both genders, model prediction of FFM was slightly better in male subjects (R^2=0.902) than female subjects (R^2=0.885).

Discussion

Analysis of body composition and identification of low FFM may have important implications for prognosis and treatment of patients with IBD and yet, such screening does not form a part of treatment algorithms or recommendations from professional bodies.

A recent systematic review of body composition studies in inflammatory bowel disease found that body composition parameters often varied from population norms, but that detailed analyses and outcome data were scarce;[8] the authors recommend further investigation and publication of better quality data to ascertain the role of body composition analysis in clinical practice.

Sarcopenia – defined as the condition of low muscle mass, strength, and/or function [22] – is prevalent in Crohn's Disease,[8,23–25] with inflammatory cytokines such as tumour necrosis factor alpha (TNF) implicated.[26,27] The TNF antagonist infliximab reverses sarcopenia in Crohn's Disease [25]; early cachexia may also be amenable to treatment of underlying inflammation, nutritional support, orexigenic agents, and exercise.[28–30] In a case-control

study,[24,31] Crohn's Disease patients in clinical remission were three times more likely than healthy controls to have sarcopenia, as defined by an ASMI more than one standard deviation below the young adult mean measured by whole body DXA. Screening for sarcopenia in inflammatory bowel disease may enable more aggressive, and perhaps more effective, early therapy.

Steroid exposure and body composition parameters such as weight, skinfold thickness, BMI, muscle strength, skeletal muscle mass, and ASMI have been associated with altered BMD in patients with IBD.[23,32] Osteopenia has been reported as having a 50% prevalence in patients with Crohn's Disease,[33] with osteoporosis in 30%; a systematic review has shown that 87% of Crohn's Disease patients have a significant reduction in BMD measured by DXA compared to controls.[8] In the patient group reported in our study, a lower incidence of osteoporosis and osteopenia was found, but there was significant correlation between CT measures of body composition and BMD.

Many studies show a reduction in BMI and reduced fat mass in Crohn's disease compared with the general population,[6,34] and in this cohort, rates of overweight and obesity were less than the Australian population (63.4% self-report a BMI $> 25\ kg/m^2$).[35]

Axial CT slices at the L3 level and L4–5 level can be used to estimate fat mass, FFM, and ASMI measured by DXA in patients with Crohn's Disease, allowing analysis of body composition using images otherwise obtained as part of routine clinical care. Although not all paired CT and DXA studies were obtained contemporaneously, the median interval was less than one month; there was no correlation between interval and difference between measured and expected values, suggesting that body composition remained relatively constant during the interval between scans. A limitation of this study is the small number of subjects with both CT and DXA studies performed within the constrained time period. Although robust linear relationships were demonstrated, a larger cohort may have permitted further analysis of gender differences or the role of other variables.

Similar to published data from healthy subjects,[19] the L3 vertebral body level provided the most robust correlation with most parameters, with no significant difference between genders in terms of degree of correlation.

In this cohort of ambulatory Crohn's Disease patients, low muscle mass was prevalent, and was predictive of lower BMD. We have described the first use of routinely obtained abdominal imaging to demonstrate this relationship – and to predict body composition components – in patients with inflammatory bowel disease. This study validates a method of body composition analysis using abdominal scans otherwise obtained as part of routine clinical care in patients with Crohn's Disease.

The technique described may allow not only further research into the role of body composition in inflammatory bowel disease: prospectively, but also by permitting retrospective analysis of existing patient cohorts with accessible CT scans. Possible important applications include optimising drug dosing, predicting treatment response or complications, and improving the accuracy of prognosis.

Disclosure statement

The authors report no conflict of interest.

Funding information

Funding for this work was received from Crohn's and Colitis Australia (the Angela McAvoy AM fellowship) and an emerging researcher fellowship from Monash Health.

References

[1] Krok KL, Lichtenstein GR. Nutrition in Crohn disease. Curr Opin Gastroenterol. 2003;19:148–153.
[2] Alastair F, Emma G, Emma P. Nutrition in inflammatory bowel disease. J Parenter Enteral Nutr. 2011;35:571–580.
[3] Bin CM, Flores C, Álvares-Da-Silva MR, et al. Comparison between handgrip strength, subjective global assessment, anthropometry, and biochemical markers in assessing nutritional status of patients with Crohn's disease in clinical remission. Dig Dis Sci. 2010;55:137–144.
[4] Gassull MA, Cabre E. Nutrition in inflammatory bowel disease. Curr Opin Clin Nutr Metab Care. 2001;4:561–569.
[5] Bernstein CN, Leslie WD, Leboff MS. AGA technical review on osteoporosis in gastrointestinal diseases. Gastroenterology. 2003;124:795–841.
[6] Tjellesen L, Nielsen PK, Staun M. Body composition by dual-energy X-ray absorptiometry in patients with Crohn's disease. Scand J Gastroenterol. 1998;33:956–960.
[7] Kyle UG, Unger P, Mensi N, et al. Nutrition status in patients younger and older than 60 y at hospital admission: a controlled population study in 995 subjects. Nutrition. 2002;18:463–469.
[8] Bryant RV, Trott MJ, Bartholomeusz FD, et al. Systematic review: body composition in adults with inflammatory bowel disease. Aliment Pharmacol Ther. 2013;38:213–225.
[9] Heymsfield SB, Adamek M, Gonzalez MC, et al. Assessing skeletal muscle mass: historical overview and state of the art. J Cachexia Sarcopenia Muscle. 2014;5:9–18.
[10] Reid IR, Ames R, Evans MC, et al. Determinants of total body and regional bone mineral density in normal postmenopausal women – a key role for fat mass. J Clin Endocrinol Metab. 1992;75:45–51.
[11] American Gastroenterological Association medical position statement: guidelines on osteoporosis in gastrointestinal diseases. Gastoenterology. 2003;124:791–794.
[12] Etzel JP, Larson MF, Anawalt BD, et al. Assessment and management of low bone density in inflammatory bowel disease and performance of professional society guidelines. Inflamm Bowel Dis. 2011;17:2122–2129.
[13] Peloquin JM, Pardi DS, Sandborn WJ, et al. Diagnostic ionizing radiation exposure in a population-based cohort of patients with inflammatory bowel disease. Am J Gastroenterol. 2008;103:2015–2022.
[14] Mourtzakis M, Prado CMM, Lieffers JR, et al. 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;33:997–1006.
[15] Baker ST, Strauss BJ, Prendergast LA, et al. Estimating dual-energy X-ray absorptiometry-derived total body skeletal muscle mass using single-slice abdominal magnetic resonance imaging in obese subjects with and without diabetes: a pilot study. Eur J Clin Nutr. 2012;66:628–632.
[16] Shen W, Punyanitya M, Wang Z, et al. Visceral adipose tissue: relations between single-slice areas and total volume. Am J Clin Nutr. 2004;80:271–278.
[17] Shen W, Wang Z, Punyanita M, et al. Adipose tissue quantification by imaging methods: a proposed classification. Obes Res. 2003;11:5–16.

[18] Yoshizumi T, Nakamura T, Yamane M, et al. Abdominal fat: standardized technique for measurement at CT. Radiology. 1999;211: 283–286.
[19] Schweitzer L, Geisler C, Pourhassan M, et al. What is the best reference site for a single MRI slice to assess whole-body skeletal muscle and adipose tissue volumes in healthy adults? Am J Clin Nutr. 2015;102:58–65.
[20] Akaike H. A new look at the statistical model identification. Automatic Control. 1974;6:716–723.
[21] Baumgartner RN, Koehler KM, Gallagher D, et al. Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol. 1998;147:755–763.
[22] Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39:412–423.
[23] Bryant RV, Ooi S, Schultz CG, et al. Low muscle mass and sarcopenia: common and predictive of osteopenia in inflammatory bowel disease. Aliment Pharmacol Ther. 2015;41:895–906.
[24] Schneider SM, Al-Jaouni R, Filippi J, et al. Sarcopenia is prevalent in patients with Crohn's disease in clinical remission. Inflamm Bowel Dis. 2008;14:1562–1568.
[25] Subramaniam K, Fallon K, Ruut T, et al. Infliximab reverses inflammatory muscle wasting (sarcopenia) in Crohn's disease. Aliment Pharmacol Ther. 2015;41:419–428.
[26] Fong Y, Moldawer LL, Marano M, et al. Cachectin/TNF or IL-1 alpha induces cachexia with redistribution of body proteins. Am J Physiol. 1989;256:R659–R665.
[27] Roubenoff R, Roubenoff RA, Cannon JG, et al. Rheumatoid cachexia: cytokine-driven hypermetabolism accompanying reduced body cell mass in chronic inflammation. J Clin Invest. 1994;93:2379–2386.
[28] Haehling von S, Anker SD. Treatment of cachexia: an overview of recent developments. Int J Cardiol. 2014;184:736–742.
[29] Morley JE, Thomas DR, Wilson M-MG. Cachexia: pathophysiology and clinical relevance. Am J Clin Nutr. 2006;83:735–743.
[30] Masuko K. Rheumatoid cachexia revisited: a metabolic co-morbidity in rheumatoid arthritis. Front Nutr. 2014;1(Suppl 3):20.
[31] Blain A, Cattan S, Beaugerie L, et al. Crohn's disease clinical course and severity in obese patients. Clin Nutr. 2002;21:51–57.
[32] Leslie WD, Miller N, Rogala L, et al. Body mass and composition affect bone density in recently diagnosed inflammatory bowel disease: the Manitoba IBD Cohort Study. Inflamm Bowel Dis. 2009;15:39–46.
[33] Bernstein CN, Leslie WD. Review article: osteoporosis and inflammatory bowel disease. Aliment Pharmacol Ther. 2004;19:941–952.
[34] Gearry RB, Irving PM. Biologics for inflammatory bowel diseases in the Asia-Pacific: can we afford to use them, can we afford not to? J Gastroenterol Hepatol. 2009;24:1160–1162.
[35] Australian Health Survey: First Results, 2011–12. ausstats.abs.gov.au. Australian Bureau of Statistics; 2012 Oct. Report No.: 4364.0.55.001.

Summary and discussion

Cross-sectional areas of adipose tissue and skeletal muscle at the level of the third lumbar vertebra correlated highly with total body fat mass and fat-free mass. The regression analysis identified a model incorporating cross-sectional areas and gender, age, weight (for fat mass) and height as being highly predictive of body composition measured by DXA.

These findings validate this technique for use in Crohn's disease patients, and allow analysis of existing datasets. Our hypothesis (hypothesis 2: *That cross-sectional abdominal imaging obtained by computed tomography (CT) and magnetic resonance imaging (MRI) during routine clinical care for patients with Crohn's disease allows accurate estimation of body composition parameters*) was supported. However, the requirement for manual identification of anatomical compartments and specialised software do not lend this method to widespread clinical use.

Limitations of this study include a lack of clinical data, which may have allowed association of body composition parameters with disease activity and duration, biomarkers and medical therapy. Despite this information being unavailable for this validation study, further studies may use this technique in cohorts with more complete data availability to investigate these links. Retrospective analysis does not permit a direction of causality to be established, but this technique may be easily integrated into prospective studies.

We have demonstrated that single-slice image analysis at an L3 level of scans obtained as part of routine clinical care strongly predicts body composition.

Chapter references

1. Seabolt LA, Welch EB, Silver HJ. Imaging methods for analyzing body composition in human obesity and cardiometabolic disease. Annals of the New York Academy of Sciences. 2015 Aug 6;:n/a–n/a.

2. Elkan A-C, Engvall I-L, Cederholm T, Hafström I. Rheumatoid cachexia, central obesity and malnutrition in patients with low-active rheumatoid arthritis: feasibility of anthropometry, Mini Nutritional Assessment and body composition techniques. Eur J Nutr. D. Steinkopff-Verlag; 2009 Mar 31;48(5):315–22.

3. Lustgarten MS, Fielding RA. Assessment of analytical methods used to measure changes in body composition in the elderly and recommendations for their use in phase II clinical trials. J Nutr Health Aging. NIH Public Access; 2011 May;15(5):368–75.

4. 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.

5. Baker ST, Strauss BJ, Prendergast LA, Panagiotopoulos S, Thomas GE, Vu T, et al. Estimating dual-energy X-ray absorptiometry-derived total body skeletal muscle mass using single-slice abdominal magnetic resonance imaging in obese subjects with and without diabetes: a pilot study. Eur J Clin Nutr. 2012 May;66(5):628–32.

6. Gibson DJ, Burden ST, Strauss BJ, Todd C, Lal S. The role of computed tomography in evaluating body composition and the influence of reduced muscle mass on clinical outcome in abdominal malignancy: a systematic review. Eur J Clin Nutr. 2015 Oct;69(10):1079–86.

7. Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge M-P, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. J Appl Physiol. 2004 Dec;97(6):2333–8.

8. Ho IKH, Cash BD, Cohen H, Hanauer SB, Inkster M, Johnson DA, et al. Radiation exposure in gastroenterology: improving patient and staff protection. Am J Gastroenterol. 2014 Aug;109(8):1180–94.

Chapter 5: Weight and body composition compartments do not predict therapeutic thiopurine metabolite levels in inflammatory bowel disease

Introduction and context

Thiopurine drugs are a cornerstone of Crohn's disease treatment, and yet the incidence of adverse effects with their use is significant[1]. Historically, the choice of dose was determined by body weight – although no dose-finding studies were performed in Crohn's disease[2]. Recently, measurement of intracellular concentrations of thiopurine metabolites has entered clinical practice as a means of adjusting drug doses to avoid toxicity and increase efficacy[3], with two metabolites being most associated with outcomes: 6-thioguanine nucleotides (6TGN) exhibiting a therapeutic window[4], and 6-methyl mercaptopurine (6MMP) being associated with hepatotoxicity. Predictors of metabolic profile at the commencement of therapy would guide treatment, especially considering the long time to clinical effect[2].

The use of thiopurine S-methyltransferase (TPMT) genotype testing represents a 'precision medicine' approach to individualised care, and is widely recommended before commencement of thiopurine medications[5]; it is one of the strongest predictors of thiopurine metabolism. The prevalence of functional enzyme activity (homozygous low activity) is approximately 1 in 300[6], with 11% of the population having a heterozygous genotype and intermediate enzyme activity; 89% have a high-activity genotype. Low enzyme activity is associated with toxicity and leukopenia. Aside from TPMT genotype, other determinants of thiopurine metabolism include drug interactions: particularly 5-aminosalicylates, which are commonly prescribed for inflammatory bowel disease and inhibit TPMT, and allopurinol – a xanthine oxidase inhibitor which was designed in the 1950s to improve thiopurine efficacy[7]. Many enzymatic determinants of drug metabolism relate to the distribution of the enzyme in different tissues and to body composition.

There had been no published literature examining the effect of body composition on thiopurine metabolites, and in devising the study described in this chapter we hypothesised: *That weight-based dosing is inferior to dosing by body composition parameters at achieving therapeutic thiopurine metabolite levels* (hypothesis 3).

Body composition may, therefore, allow personalised treatment decisions. To test this theory, we sought to establish the relationships between thiopurine metabolite levels and drug dose, and drug dose divided by weight or body composition compartments in a cohort of patients for whom metabolite level testing and body composition by either DXA, CT or MRI analysis was available.

Citation: Clinical and Translational Gastroenterology (2016) 7, e199; doi:10.1038/ctg.2016.56
 2155-384X/16

www.nature.com/ctg

Weight and Body Composition Compartments do Not Predict Therapeutic Thiopurine Metabolite Levels in Inflammatory Bowel Disease

Darcy Q. Holt, MBBS, FRACP[1,2], Boyd J.G. Strauss, MBBS, PhD, FRACP, FRCPath, FRCP[2] and Gregory T. Moore, MBBS, PhD, FRACP[1,2]

OBJECTIVES: Thiopurine drugs are the most commonly used steroid-sparing therapies in moderate-to-severe inflammatory bowel disease (IBD). Their complex metabolism and their narrow therapeutic windows means that optimal dosing is difficult. However, weight-based dosing is the norm. Similar antimetabolites are dosed by body composition parameters. In IBD, treatment response and toxicity has been shown to correlate with thiopurine metabolite levels. We sought to determine whether weight or body composition parameters predicted therapeutic 6-thioguanine nucleotide (6TGN) or toxic 6-methylmercaptopurine (6MMP) levels.
METHODS: This single-center retrospective cohort study identified 66 IBD patients who had body composition analysis and thiopurine metabolite levels tested. Statistical analysis was performed using Spearman correlation, Kruskal–Wallis, Mann–Whitney, and unpaired *t* tests and receiver-operator operating characteristic curves. A *P* value of <0.05 was considered significant.
RESULTS: No correlation was identified between 6TGN and any body composition parameters, absolute drug dose or drug dose/kg of fat mass, fat-free mass (FFM), subcutaneous adipose tissue area, or visceral adipose tissue area. However, 6MMP correlated with azathioprine dose, thiopurine dose/kg of body weight, and with several body composition parameters.
CONCLUSIONS: No relationship was found between therapeutic metabolite levels and weight or body composition compartments. Higher thiopurine doses, especially in relation to FFM, are associated with higher levels of potentially hepatotoxic 6MMP and shunting toward this metabolite. Conventional weight-based dosing to attain therapeutic metabolite levels appears unreliable and may be replaced by metabolite level testing.

Clinical and Translational Gastroenterology (2016) **7,** e199; doi:10.1038/ctg.2016.56; published online 27 October 2016
Subject Category: Inflammatory Bowel Disease

INTRODUCTION

Azathioprine and its metabolite, 6-mercaptopurine (6MP), are the most commonly used steroid-sparing therapies in moderate-to-severe inflammatory bowel disease (IBD).[1,2] A total of 50–60% of patients respond to these treatments; the remainder will have refractory disease or adverse drug reactions.[3]

The complex metabolism of these drugs and their narrow therapeutic windows means that optimal dosing is difficult. Recent interest in the measurement of intracellular thiopurine metabolites has led to the development of treatment algorithms based on therapeutic 6-thioguanine nucleotide (6TGN) and toxic 6-methylmercaptopurine (6-MMP) levels,[3–6] with a meta-analysis demonstrating an association between the levels of 6TGN and likelihood of clinical response.[7] Combination therapy with allopurinol has been recommended in patients with an elevated 6MMP:6TGN ratio to optimize metabolite levels and treatment response.[8,9] A ratio of >11 has been described as abnormal,[4] with >20 clearly demonstrating skewed metabolism.[10] Sulfasalazine and aminosalicylate (5ASA) drugs, which are commonly prescribed in IBD, inhibit thiopurine S-methyltransferase (TPMT), an intestinal mucosa and liver enzyme, which is important in thiopurine metabolism.[11] This causes elevations of 6TGN in patients receiving concomitant thiopurines and may lower the 6MMP:6TGN ratio.[12]

However, weight-based dosing of thiopurines, without regard to 5ASA coprescription, remains the norm in clinical practice, with measurement of metabolites reserved for those who fail to respond to therapy.[1]

Body composition measurement with bioelectrical impedance analysis predicts pharmacokinetics of a similar antimetabolite fluorouracil more accurately than standard anthropometric parameters,[13] and low lean body mass has been shown to be a significant predictor of fluorouracil toxicity.[14] The most accessible[15] and accurate[16] means of determining whole-body and regional body composition compartments such as fat-free mass (FFM), fat mass (FM), lean tissue mass, and bone mineral density is dual-energy X-ray absorptiometry (DXA). DXA is often indicated for monitoring of bone mineral density in thiopurine-treated patients who may have disease-related malnutrition, cachexia, or significant corticosteroid exposure.[17] Despite recommendations that patients with IBD undergo regular DXA for monitoring bone mineral density,[18] screening prevalence is

[1]Department of Gastroenterology & Hepatology, Monash Health, Clayton, Australia and [2]School of Clinical Sciences, Monash University, Clayton, Australia
Correspondence: Darcy Q. Holt, MBBS, FRACP, Department of Gastroenterology & Hepatology, Monash Health, 246 Clayton Road, Clayton 3168, Australia.
E-mail: darcy.holt@monashhealth.org
Conference presentation: ECCO 2016, Amsterdam, The Netherlands, poster presentation.
Received 14 June 2016; revised 26 August 2016; accepted 13 September 2016

low: approximately one in five patients.[19] However, abdominal computed tomography (CT) scans are often obtained as part of routine care of Crohn's disease.[20] Analysis of a single cross-sectional image from CT or magnetic resonance imaging (MRI) provides an accurate estimate of total body FFM and FM, as well as visceral FM and subcutaneous FM.[21–24] We have validated this technique in patients with Crohn's disease,[25] with high degrees of correlation between CT or MRI and DXA.

Importantly, there are no published data regarding thiopurine metabolite levels and body composition parameters aside from body weight. We sought to determine whether body composition analysis may provide a more accurate means of dosing to achieve therapeutic metabolite levels.

METHODS

All IBD patients who had undergone thiopurine metabolite level testing at a single tertiary care hospital were identified from pathology databases; this was cross-referenced with radiology records. Local practice is to initiate recommended doses of thiopurines (1.0–1.5 mg/kg body weight for 6MP, 2.0–2.5 mg/kg body weight for azathioprine).[26]

Body composition studies were performed using either whole-body DXA or single-slice analysis of abdominal CT scans. DXA scans were performed on a GE Lunar Prodigy DXA scanner (GE Healthcare, Little Chalfont, UK) with reported body composition data, including weight, height, body mass index, body surface area, appendicular skeletal muscle index, appendicular muscle mass, total body FFM, total body FM, percentage body fat, trunk lean tissue mass, trunk FM, android FM, and gynoid FM. From CT and MRI studies obtained as part of routine clinical care, cross-sectional images from the level of the third lumbar vertebra (L3) and L4–L5 intervertebral disc were analyzed by a single experienced operator using SliceOMatic v.4.3 (Tomovision, Montreal, Quebec, Canada) to measure the area of skeletal muscle, subcutaneous visceral adipose tissue, visceral adipose tissue, and intermuscular adipose tissue. Using published techniques,[22–24,27] estimates of total body FM, FFM, appendicular skeletal muscle index, and waist circumference were reported. CT and DXA data was pooled for analyses. Four subjects in this group had contemporaneous CT and DXA scans, which demonstrated a high degree of correlation, consistent with previously published studies[23,25] (for FFM, Spearman $r=0.97$, $P=0.004$). Chart review was used to obtain weight, height, and thiopurine dose at the time of metabolite measurement. Erythrocyte concentrations of 6TGN, 6MMP, and the ratio between these two measures were reported. Thiopurine S-methyltransferase activity phenotype or genotype was not available for many patients. Clinical response was not recorded in this cohort.

Statistics. Prism 6 (GraphPad Software, La Jolla, CA) was used to perform Spearman correlation analysis between variables, with Kruskal–Wallis, Mann–Whitney and unpaired *t* tests as appropriate to determine differences between subjects grouped by category of metabolites. Receiver-operator characteristic curves were used to identify cutoff drug doses. A P value of <0.05 was considered significant.

Table 1 Demographics of thiopurine-treated patients

Indication	*n*
Crohn's disease	52
Ulcerative colitis	14
Gender	
Male	44
Female	22
Drug	
Azathioprine	49
6MP	17
Drug dose (median (IQR))	
Azathioprine	150 (125–200)
6MP	75 (50–75)
5ASA or sulfasalazine prescribed	26 (42%)
Weight (mean ± s.d.)	75.2 ± 17.6
BMI (mean ± s.d.)	25.4 ± 5.0
Age (mean ± s.d.), years	35.6 ± 14.1
Body composition technique	
CT	48
DXA	18

BMI, body mass index; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; IQR, interquartile range; 5ASA, aminosalicylate; 6MP, 6-mercaptopurine.

Ethics. This project was approved by the Monash Health Human Research Ethics Committee (project 15056Q).

RESULTS

Sixty-six IBD patients were identified as having had either a CT, MRI, or whole-body DXA scan and thiopurine metabolite level testing while being treated with azathioprine or 6MP (Table 1). The mean azathioprine dose was 2.18 mg/kg body weight (s.d. 0.71); the mean 6MP dose was 0.92 mg/kg body weight (s.d. 0.33).

Thiopurine metabolite levels. No correlation was identified between 6TGN levels and any parameter of body composition, absolute drug dose, or drug dose/kg of FM, fat free mass, subcutaneous adipose tissue area, or visceral adipose tissue area.

There were no significant differences in mean 6TGN (309.2 (pmol/8×10^8 red blood cells (RBC) ± 237.7 vs. 394.6 ± 233.1, $P=0.164$), 6MMP (2,465.8 (pmol/8×10^8 RBC) ± 3,210.6 vs. 3,542.7 ± 5,884.4, $P=0.403$), and 6MMP:6TGN ratio (11.3 ± 15.9 vs. 9.6 ± 16.8, $P=0.696$) between those who were not prescribed 5ASA or sulfasalazine and the 42% of patients who were; similarly, the thiopurine dose/kg of body weight was not different between these groups.

6MMP levels showed a weak but statistically significant correlation with dose of azathioprine (Spearman $r=0.409$, $P=0.004$), azathioprine dose/kg of body weight ($r=0.489$, $P<0.001$), and dose of 6MP/kg body weight ($r=0.520$, $P=0.032$).

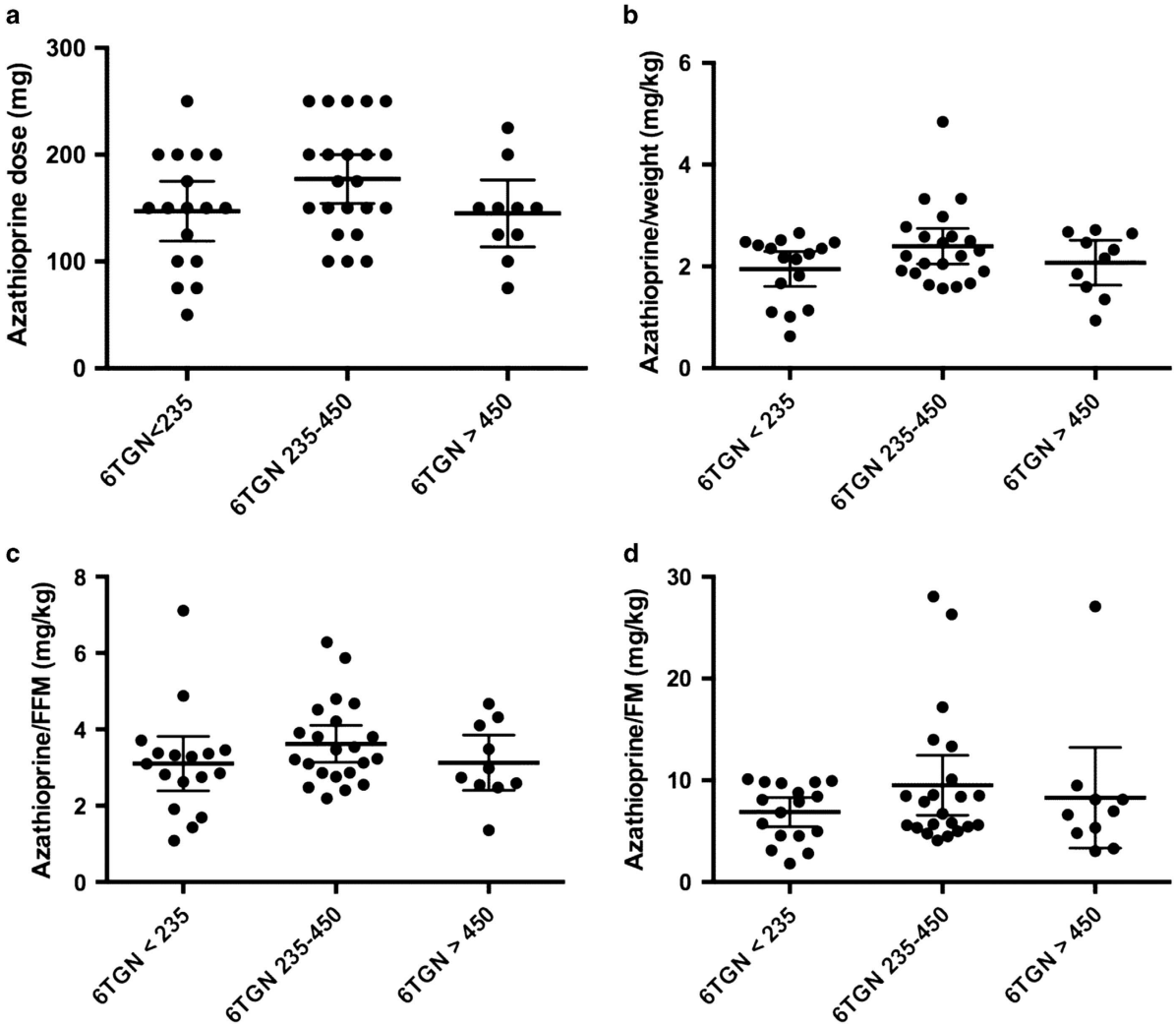


Figure 1 Categories of 6-thioguanine nucleotide (6TGN) levels and dose of azathioprine (the most commonly prescribed thiopurine) (lines: mean ± 95% confidence interval of the mean): (**a**) total azathioprine dose; (**b**) azathioprine dose/kg body weight; (**c**) azathioprine dose/fat-free mass (FFM); (**d**) azathioprine dose/fat mass (FM).

Similarly, there was a weak correlation between 6MMP and several body composition parameters: azathioprine dose/kg of FFM ($r=0.481$, $P<0.001$), azathioprine dose/body surface area ($r=0.507$, $P<0.001$), azathioprine dose/body mass index (BMI) ($r=0.425$, $P=0.002$), and 6MP dose/kg of FFM ($r=0.573$, $P=0.016$), 6MP/BSA ($r=0.513$, $P=0.032$), and 6MP/BMI ($r=0.491$, $P=0.013$).

Using previously defined,[4,28,29] clinically relevant categories of thiopurine metabolites, subjects were classified as having:

(1) Therapeutic 6TGN (6TGN 235–450 pmol/8×10^8 RBC);
(2) Subtherapeutic 6TGN (<235 pmol/8×10^8 RBC);
(3) Supratherapeutic 6TGN (>450 pmol/8×10^8 RBC);

Between these categories, there was no difference in the following parameters: body weight; azathioprine dose; 6MP dose; and dose of either thiopurine per kg of body weight or FM or FFM (Figure 1 and Table 2).

A further two categories were defined utilizing 6MMP levels:
(4) Skewed metabolism,[10] ratio 6MMP:6TGN >20;
(5) Potentially hepatotoxic[5] 6MMP (>5,700 pmol/8×10^8 RBC)
These categories were not mutually exclusive.

Patients with a 6MMP:6TGN ratio >20 had a higher mean azathioprine dose/FFM (4.12 mg/kg ± 0.97 vs. 3.20 mg/kg ± 1.17, $P=0.011$), with a higher median azathioprine dose (200 mg vs. 150 mg; $P=0.03$); mean azathioprine dose/FFM was higher in the group of patients with 6MMP >5,700 pmol/8×10^8 RBC (4.15 mg/kg ± 0.97 vs. 3.21 mg/kg ± 1.18, $P=0.017$) (Figure 2,Table 2).

Anthropometry and body composition categories. Categorization of subjects by weight or muscle mass did not predict metabolite profiles. There was no difference in the levels of 6TGN and 6MMP between patients with a healthy range BMI (18.5–24.9 kg/m^2)[30] and those with BMI ⩾ 25 kg/m^2; ($P=0.484$ for 6TGN and $P=0.484$ for 6MMP) nor for patients with sarcopenia—defined as an appendicular

Table 2 Body composition parameters, drug dosing and clinical categories of thiopurine metabolites

	6TGN < 235	235 ≤ 6TGN ≤ 450	6TGN > 450	*P* value
		Mean ± s.d.		
Weight (kg)	75.7 ± 18.1	75.8 ± 17.7	72.4 ± 17.4	0.96
BMI (kg/m^2)	25.72 ± 5.26	25.37 ± 5.12	24.75 ± 4.47	0.96
BSA (m^2)	1.87 ± 0.22	1.88 ± 0.24	1.83 ± 0.25	0.89
Aza (mg; median (IQR))	150 (100–200)	175 (144–213)	150 (119–163)	0.16
Aza/weight (mg/kg)	1.95 ± 0.64	2.40 ± 0.77	2.07 ± 0.62	0.43
Aza/FFM (mg/kg)	3.10 ± 1.39	3.62 ± 1.08	3.13 ± 1.01	0.30
Aza/FM (mg/kg)	6.88 ± 2.80	9.51 ± 6.64	8.29 ± 6.94	0.64
6MP dose (mg; median (IQR))	50 (38–75)	75 (50–106)	50 (25–75)	0.38
6MP/weight (mg/kg)	0.74 ± 0.18	1.03 ± 0.31	0.79 ± 0.68	0.22
6MP/FFM (mg/kg)	1.26 ± 0.34	1.63 ± 0.58	1.40 ± 1.17	0.63
6MP/FM (mg/kg)	2.44 ± 0.89	3.64 ± 1.54	2.19 ± 2.13	0.38
	(6MMP:6TGN) < 20		(6MMP:6TGN) > 20	*P* value
		Mean ± s.d.		
Weight (kg)	75.9 ± 18.0		70.3 ± 14.0	0.59
BMI (kg/m^2)	25.55 ± 5.14		24.28 ± 3.99	0.59
BSA (m^2)	1.88 ± 0.24		1.81 ± 0.22	0.51
Aza (mg; median (IQR))	150 (118–200)		200 (175–200)	0.03
Aza/weight (mg/kg)	2.09 ± 0.72		2.68 ± 0.45	0.02
Aza/FFM (mg/kg)	3.12 ± 1.17		4.20 ± 0.97	0.01
Aza/FM (mg/kg)	8.01 ± 5.41		10.38 ± 7.29	0.33
6MP dose (mg; median (IQR))	75 (50–75)		62.5 (50–75)	0.97
6MP/weight (mg/kg)	0.89 ± 0.34		1.12 ± 0.06	0.29
6MP/FFM (mg/kg)	1.47 ± 0.60		1.69 ± 0.42	0.62
6MP/FM (mg/kg)	2.98 ± 1.32		4.18 ± 2.98	0.62
	6MMP < 5,700		6MMP > 5,700	*P* value
		Mean ± s.d.		
Weight (kg)	76.9 ± 17.6		65.4 ± 14.3	0.09
BMI (kg/m^2)	25.72 ± 5.06		23.41 ± 4.36	0.20
BSA (m^2)	1.90 ± 0.23		1.73 ± 0.22	0.06
Aza (mg; median (IQR))	150 (125–200)		175 (150–200)	0.36
Aza/weight (mg/kg)	2.10 ± 0.72		2.64 ± 0.50	0.05
Aza/FFM (mg/kg)	3.21 ± 1.18		4.15 ± 0.97	0.02
Aza/FM (mg/kg)	8.07 ± 5.42		10.04 ± 7.35	0.46
6MP dose (mg; median (IQR))	69.6 ± 35.6		66.7 ± 14.4	0.92
6MP/weight (mg/kg)	0.87 ± 0.35		1.13 ± 0.05	0.15
6MP/FFM (mg/kg)	1.44 ± 0.61		1.76 ± 0.32	0.36
6MP/FM (mg/kg)	2.95 ± 1.36		3.90 ± 2.16	0.68

Aza, Azathioprine; BMI, body mass index; BSA, body surface area; FFM, fat-free mass; FM, fat mass; IQR, interquartile range; 6MP, 6-mercaptopurine; 6MMP, 6-methylmercaptopurine; 6TGN, 6-thioguanine nucleotide.

skeletal muscle index (calculated from CT or MRI or measured by DXA) >2 s.d. below a young adult mean (i.e., 7.26 kg/m^2 for men and 5.45 kg/m^2 for women[31]) ($P = 0.429$ for 6TGN and $P = 0.607$ for 6MMP).

DISCUSSION

Optimal dosing of thiopurines in IBD is difficult owing to wide variation in metabolism, relatively long time to efficacy, and the high incidence of adverse effects. There is comparatively little research regarding the pharmacokinetics of thiopurine drugs. Absorption from the gut is variable (5–37%).[32] Area under the curve of plasma mercaptopurine concentration over time has been shown to correlate with clinical response and toxicity in a similar clinical setting,[33] but no correlation exists between oral 6MP dose (in mg/m^2 of body surface area) and area under the curve,[34] implying weight and height may not be significant factors in determining therapeutic dosing. In individual patients, a large degree of variability (up to eightfold) has been observed from day-to-day in area under the curve,[35] which may reflect the variable effect of food intake and metabolic enzyme activity. TPMT activity does not predict preferential metabolism to 6MMP; however, the largest study correlating metabolite profile and TPMT activity found a skewed metabolism at all activity levels.[10] On an individual patient basis, 6TGN levels remain stable throughout the dosing interval.[35] There is considerable interpatient variability in 6TGN levels with thiopurine dosing based on weight[36] or body surface area,[37] with only a weak correlation ($r = 0.28$) demonstrated between thiopurine dose (mg/kg) and 6TGN levels in a group of patients who had ongoing symptoms despite stable thiopurine therapy.[3] A randomized control trial examining clinical outcomes in patients dosed by weight compared with those dosed by metabolite level monitoring found no difference in thiopurine metabolite levels between

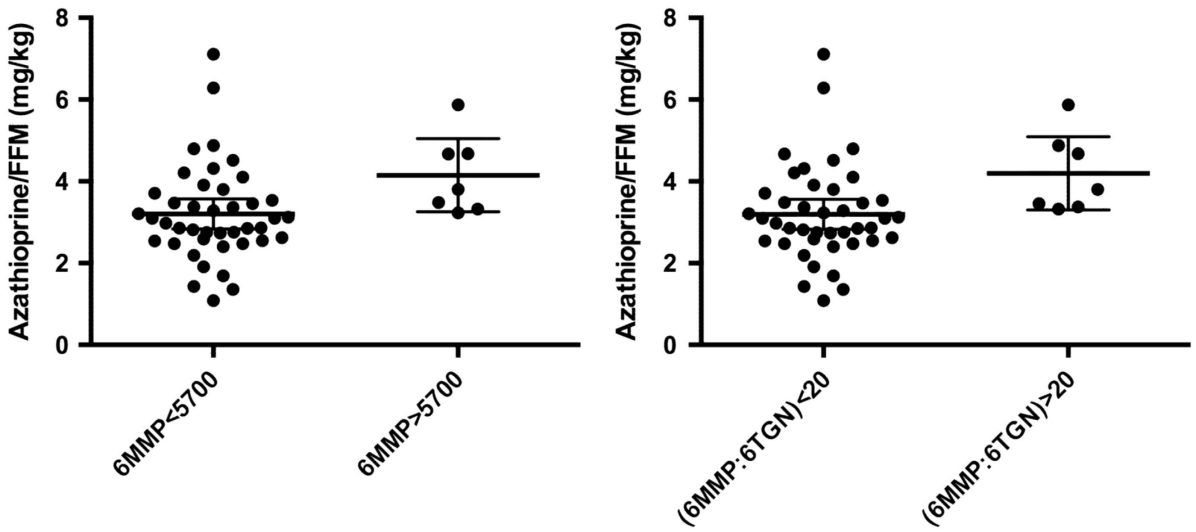


Figure 2 Azathioprine dose per kg of fat-free mass (FFM) by categories of 6-methylmercaptopurine (6MMP) and 6MMP:6TGN (6-thioguanine nucleotide) (lines: mean ± 95% confidence interval of the mean).

groups despite those in the weight-based group receiving more drug; there was no difference in clinical outcomes.[38]

Of interest in our study, the dose of azathioprine per kilogram of body weight—the accepted method of dosing azathioprine in IBD[39]—did not predict whether subjects were likely to have metabolites in the therapeutic range. This finding mirrors similar data from a number of retrospective studies[40] and a recent randomized controlled trial.[38] We found that no other body composition parameter predicted therapeutic metabolites.

This study is novel in seeking to determine a relationship between body composition compartments and thiopurine metabolite levels. Limitations of this retrospective cohort study are the lack of thiopurine S-methyltransferase genotyping or phenotyping, clinical efficacy end points, medication compliance, and data regarding the reason for metabolite testing. Although routine thiopurine dosing according to metabolite levels is becoming more common,[41] some of the subjects may have been tested owing to treatment failure or intolerance—with a possible inherent selection bias toward non-therapeutic or toxic metabolite levels.

A recent retrospective cohort study suggested an inverse relationship between BMI and 6TGN levels,[40] with the authors surmising that adipose tissue distribution of thiopurines may be an important factor in metabolism. Visceral and subcutaneous adipose tissue have distinct metabolic profiles,[42] with cross-sectional measurement predictive of total body volumes.[21,43] However, our analysis did not find a relationship between metabolites and total adipose tissue mass, visceral adipose tissue area, or subcutaneous adipose tissue area or dose of thiopurine divided by these areas.

Prediction of drug toxicity may help to avoid adverse effects causing delayed or discontinued therapy. We found that the likelihood ratio of a 6MMP > 5,700 pmol/8×10^8 RBC was 2.00 at a cutoff azathioprine dose > 3.04 mg/kg FFM (100% sensitivity, 50% specificity, $P = 0.019$). In a similar clinical setting, weight-based dosing was again found not to improve rates of therapeutic 6TGN levels but was associated with shunting toward 6MMP;[41] this finding supports those of our study, although external validation is required owing to potential overlap of subjects between data sets. Identification of patients at higher risk of toxicity by pretreatment anthropometric or body composition measures would be useful: although no such predictors were found in this study, a trend toward lower body weight and BMI in patients with undesirable metabolite profiles further implies that larger relative drug doses may cause shunting toward 6MMP.

No relationship was found between therapeutic metabolite levels and weight or body composition compartments. Higher doses of thiopurines, especially in relation to FFM, are associated with higher levels of potentially hepatotoxic 6MMP and shunting toward this metabolite. Conventional weight-based dosing to attain therapeutic metabolite levels appears unreliable and may be replaced by metabolite level testing.

CONFLICT OF INTEREST

Guarantor of the article: Darcy Q. Holt, MBBS, FRACP.
Specific author contributions: Darcy Q. Holt, Boyd J.G. Strauss and Gregory T. Moore conceived the study. Darcy Q. Holt collected and analyzed the data and wrote the paper, with assistance and revision from Boyd J.G. Strauss and Gregory T. Moore. All authors approved the final version of the article, including the authorship list.
Financial support: This work was funded in part by Crohn's and Colitis Australia (the Angela McAvoy AM fellowship to G.T.M.) and an emerging researcher fellowship to D.Q.H. from Monash Health.
Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Thiopurines are accepted treatment for inflammatory bowel diseases and are conventionally dosed according to body weight.
- ✓ Erythrocyte concentrations of thiopurine metabolites are associated with treatment response or toxicity.
- ✓ Previous small studies have shown a lack of association between thiopurine metabolite levels and dose by body weight, but body composition parameters have not been examined.

WHAT IS NEW HERE

- ✓ This study demonstrates that therapeutic metabolite levels do not correlate with thiopurine dose by body weight or body composition parameters.
- ✓ Potentially hepatotoxic metabolites correlate with dose by weight and fat-free mass.

1. Dignass A, Van Assche G, Lindsay JO *et al.* The second European evidence-based consensus on the diagnosis and management of Crohn's disease: current management. *J Crohns Colitis* 2010; **4**: 28–62.
2. Terdiman JP, Gruss CB, Heidelbaugh JJ *et al.* American Gastroenterological Association Institute Guideline on the Use of Thiopurines, Methotrexate, and Anti–TNF-α Biologic Drugs for the Induction and Maintenance of Remission in Inflammatory Crohn's Disease. *Gastroenterology* 2013; **145**: 1459–1463.
3. Haines ML, Ajlouni Y, Irving PM *et al.* Clinical usefulness of therapeutic drug monitoring of thiopurines in patients with inadequately controlled inflammatory bowel disease. *Inflamm Bowel Dis* 2011; **17**: 1301–1307.
4. Dubinsky MC, Yang H, Hassard PV *et al.* 6-MP metabolite profiles provide a biochemical explanation for 6-MP resistance in patients with inflammatory bowel disease. *Gastroenterology* 2002; **122**: 904–915.
5. Dubinsky MC, Lamothe S, Yang HY *et al.* Pharmacogenomics and metabolite measurement for 6-mercaptopurine therapy in inflammatory bowel disease. *Gastroenterology* 2000; **118**: 705–713.
6. Gearry RB, Barclay ML. Azathioprine and 6-mercaptopurine pharmacogenetics and metabolite monitoring in inflammatory bowel disease. *J Gastroenterol Hepatol* 2005; **20**: 1149–1157.
7. Osterman MT, Kundu R, Lichtenstein GR *et al.* Association of 6-thioguanine nucleotide levels and inflammatory bowel disease activity: a meta-analysis. *Gastroenterology* 2006; **130**: 1047–1053.
8. Sparrow MP, Hande SA, Friedman S *et al.* Allopurinol safely and effectively optimizes tioguanine metabolites in inflammatory bowel disease patients not responding to azathioprine and mercaptopurine. *Aliment Pharmacol Ther* 2005; **22**: 441–446.
9. ANSARI A, Patel N, Sanderson J *et al.* Low-dose azathioprine or mercaptopurine in combination with allopurinol can bypass many adverse drug reactions in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2010; **31**: 640–647.
10. Appell ML, Wagner A, Hindorf U. A skewed thiopurine metabolism is a common clinical phenomenon that can be successfully managed with a combination of low-dose azathioprine and allopurinol. *J Crohns Colitis* 2013; **7**: 510–513.
11. Szumlanski CL, Weinshilboum RM. Sulphasalazine inhibition of thiopurine methyltransferase: possible mechanism for interaction with 6-mercaptopurine and azathioprine. *Br J Clin Pharmacol* 1995; **39**: 456–459.
12. de Graaf P, de Boer NKH, Wong DR *et al.* Influence of 5-aminosalicylic acid on 6-thioguanosine phosphate metabolite levels: a prospective study in patients under steady thiopurine therapy. *Br J Pharmacol* 2010; **160**: 1083–1091.
13. Gusella M, Toso S, Ferrazzi E *et al.* Relationships between body composition parameters and fluorouracil pharmacokinetics. *Br J Clin Pharmacol* 2002; **54**: 131–139.
14. Prado CMM, Baracos VE, McCargar LJ *et al.* Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. *Clin Cancer Res* 2007; **13**: 3264–3268.
15. Heymsfield SB, Adamek M, Gonzalez MC *et al.* Assessing skeletal muscle mass: historical overview and state of the art. *J Cachexia Sarcopenia Muscle* 2014; **5**: 9–18.
16. Reid IR, Ames R, Evans MC *et al.* Determinants of total body and regional bone mineral density in normal postmenopausal women–a key role for fat mass. *J Clin Endocrinol Metab* 1992; **75**: 45–51.
17. Cruz-Jentoft AJ, Baeyens JP, Bauer JM *et al.* Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing* 2010; **39**: 412–423.
18. Clinical Practice Committee, American Gastroenterological Association. American Gastroenterological Association medical position statement: guidelines on osteoporosis in gastrointestinal diseases. *Gastroenterology* 2003; **124**: 791–794.
19. Etzel JP, Larson MF, Anawalt BD *et al.* Assessment and management of low bone density in inflammatory bowel disease and performance of professional society guidelines. *Inflamm Bowel Dis* 2011; **17**: 2122–2129.
20. Peloquin JM, Pardi DS, Sandborn WJ *et al.* Diagnostic ionizing radiation exposure in a population-based cohort of patients with inflammatory bowel disease. *Am J Gastroenterol* 2008; **103**: 2015–2022.
21. Shen W, Punyanitya M, Wang Z *et al.* Visceral adipose tissue: relations between single-slice areas and total volume. *Am J Clin Nutr* 2004; **80**: 271–278.
22. Shen W, Punyanitya M, Wang Z *et al.* Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. *J Appl Physiol* 2004; **97**: 2333–2338.
23. Mourtzakis M, Prado CMM, Lieffers JR *et al.* 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; **33**: 997–1006.
24. Baker ST, Strauss BJ, Prendergast LA *et al.* Estimating dual-energy X-ray absorptiometry-derived total body skeletal muscle mass using single-slice abdominal magnetic resonance imaging in obese subjects with and without diabetes: a pilot study. *Eur J Clin Nutr* 2012; **66**: 628–632.
25. Holt DQ, Strauss BJG, Lau KK *et al.* Body composition analysis using abdominal scans from routine clinical care in patients with Crohn's Disease. *Scand J Gastroenterol* 2016; **51**: 842–847.
26. Siegel CA, Sands BE. Review article: practical management of inflammatory bowel disease patients taking immunomodulators. *Aliment Pharmacol Ther* 2005; **22**: 1–16.
27. Ciudin A, Salvador R, Budoy A *et al.* Measurement of waist circumference for retrospective studies - prospective validation of use of CT images to assess abdominal circumference. *Endocrinol Nutr* 2014; **61**: 147–152.
28. Cuffari C, Theoret Y, Latour S *et al.* 6-Mercaptopurine metabolism in Crohn's disease: correlation with efficacy and toxicity. *Gut* 1996; **39**: 401–406.
29. Cuffari C, Hunt S, Bayless T. Utilisation of erythrocyte 6-thioguanine metabolite levels to optimise azathioprine therapy in patients with inflammatory bowel disease. *Gut* 2001; **48**: 642–646.
30. WHO Consultation on Obesity. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser* 2000; **i–xii**: 1–253.
31. Baumgartner RN, Koehler KM, Gallagher D *et al.* Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol* 1998; **147**: 755–763.
32. Zimm S, Collins JM, Riccardi R *et al.* Variable bioavailability of oral mercaptopurine. Is maintenance chemotherapy in acute lymphoblastic leukemia being optimally delivered? *N Engl J Med* 1983; **308**: 1005–1009.
33. Koren G, Ferrazini G, Sulh H *et al.* Systemic exposure to mercaptopurine as a prognostic factor in acute lymphocytic leukemia in children. *N Engl J Med* 1990; **323**: 17–21.
34. Adamson PC, Balis FM, Steinberg SM *et al.* Pharmacokinetics of mercaptopurine in children with acute lymphocytic leukemia. *N Engl J Med* 1990; **323**: 1565–1566.
35. Bergan S, Rugstad HE, Bentdal O *et al.* Kinetics of mercaptopurine and thioguanine nucleotides in renal transplant recipients during azathioprine treatment. *Ther Drug Monit* 1994; **16**: 13–20.
36. Gardiner SJ, Gearry RB, Begg EJ *et al.* Thiopurine dose in intermediate and normal metabolizers of thiopurine methyltransferase may differ three-fold. *Clin Gastroenterol Hepatol* 2008; **6**: 654–660 quiz 604.
37. Lennard L. The clinical pharmacology of 6-mercaptopurine. *Eur J Clin Pharmacol* 1992; **43**: 329–339.
38. Dassopoulos T, Dubinsky MC, Bentsen JL *et al.* Randomised clinical trial: individualised vs. weight-based dosing of azathioprine in Crohn's disease. *Aliment Pharmacol Ther* 2013; **39**: 163–175.
39. Prefontaine E, Sutherland LR, Macdonald JK *et al.* Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2009: CD000067.
40. Poon SS, Asher R, Jackson R *et al.* Body mass index and smoking affect thioguanine nucleotide levels in inflammatory bowel disease. *J Crohns Colitis* 2015; **9**: 640–646.
41. Goldberg R, Moore G, Cunningham G *et al.* Thiopurine metabolite testing in inflammatory bowel disease. *J Gastroenterol Hepatol* 2015; **31**: 553–560.
42. Ouchi N, Parker JL, Lugus JJ *et al.* Adipokines in inflammation and metabolic disease. *Nat Rev Immunol* 2011; **11**: 85–97.
43. Maislin G, Ahmed MM, Gooneratne N *et al.* Single slice vs. volumetric MR assessment of visceral adipose tissue: reliability and validity among the overweight and obese. *Obesity (Silver Spring)* 2012; **20**: 2124–2132.

Summary and discussion

The lack of an association between 6TGN levels and drug dose, dose/kg weight or dose/kg fat-free mass or fat mass was unexpected – but is consistent with other studies that have not shown a relationship between drug dose/kg weight and 6TGN[8,9]. We were unable to confirm our hypothesis: *That weight-based dosing is inferior to dosing by body composition parameters at achieving therapeutic thiopurine metabolite levels* (hypothesis 3).

This study was novel in the literature, but some limitations do mean that further research in this area would be beneficial. In particular, there was lack of information regarding significant determinants of thiopurine metabolism such as TPMT genotype and 5-aminosalicylate use. Clinical outcome data, and reasons for requesting metabolite testing were also missing. This may have led to a selection bias of patients who were experiencing treatment failure and may have had skewed metabolism.

The finding that 6MMP levels were increased with higher drug doses, and dose/kg fat-free mass, suggests saturable enzyme pathways in the fat-free compartment. An implication of this finding may be that in patients with low fat-free mass, or low body weight, consideration be given to allopurinol and thiopurine co-prescription as an initial strategy. This would avoid a metabolic "shunt" towards 6MMP production. However, a prospective controlled trial including body composition measurement is required to establish the soundness of this approach.

Chapter references

1. Pearson DC, May GR, Fick GH, Sutherland LR. Azathioprine and 6-mercaptopurine in Crohn disease. A meta-analysis. Ann Intern Med. 1995 Jul 15;123(2):132–42.

2. Prefontaine E, Sutherland LR, Macdonald JK, Cepoiu M. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. Sutherland LR, editor. Cochrane Database Syst Rev. Chichester, UK: John Wiley & Sons, Ltd; 2009;(1):CD000067.

3. Goldberg R, Moore G, Cunningham G, Schulberg J, Marsh P, Brown S, et al. Thiopurine metabolite testing in inflammatory bowel disease. Journal of Gastroenterology and Hepatology. 2016 Mar;31(3):553–60.

4. Dubinsky MC, Yang H, Hassard PV, Seidman EG, Kam LY, Abreu MT, et al. 6-MP metabolite profiles provide a biochemical explanation for 6-MP resistance in patients with inflammatory bowel disease. Gastroenterology. 2002 Apr;122(4):904–15.

5. Dassopoulos T, Sultan S, Falck Ytter YT, Inadomi JM, Hanauer SB. American Gastroenterological Association Institute technical review on the use of thiopurines, methotrexate, and anti-TNF-α biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. Gastroenterology. 2013 Dec;145(6):1464–78.e1–5.

6. Lennard L. Clinical implications of thiopurine methyltransferase--optimization of drug dosage and potential drug interactions. Ther Drug Monit. 1998 Oct;20(5):527–31.

7. Elion GB. The purine path to chemotherapy. Science. 1989 Apr 7;244(4900):41–7.

8. Dassopoulos T, Dubinsky MC, Bentsen JL, Martin CF, Galanko JA, Seidman EG, et al. Randomised clinical trial: individualised vs. weight-based dosing of azathioprine in Crohn's disease. Aliment Pharmacol Ther. 2013 Nov 17;39(2):163–75.

9. Poon SS, Asher R, Jackson R, Kneebone A, Collins P, Probert C, et al. Body Mass Index and Smoking Affect Thioguanine Nucleotide Levels in Inflammatory Bowel Disease. J Crohns Colitis. 2015 Jul 27;9(8):640–6.

Chapter 6: Low muscle mass at initiation of anti TNF therapy for inflammatory bowel disease is associated with early treatment failure

Introduction and context

Previous chapters of this thesis have explored weight distribution, dietary beliefs and treatment exposures in a large Australian cohort, and applied validated methods of body composition to a cohort of patients being treated with thiopurine drugs – a mainstay of Crohn's disease treatment. In this chapter, body composition analysis, using methods described in chapter 4, is applied to the clinical situation of anti-TNF maintenance therapy to determine predictors of treatment response.

The place of anti-TNF therapy in current Crohn's disease treatment algorithms and definitions of terms used to denote clinical efficacy are useful to note at this point.
Medical therapy for Crohn's disease involves judicious escalation of immunosuppression, with anti-TNF therapy recommended for patients with high disease activity and poor prognosis, those with steroid-refractory disease or intolerance to corticosteroids and relapsed disease while using immunomodulators[1]. Primary non-response to anti-TNF drugs, defined as a failure to achieve a clinical response following an induction phase, is reported in approximately one third of patients[2]. Secondary loss of response is less well-defined: it has been variously reported as a quantifiable re-emergence of symptoms (for example, a significant rise in Crohn's disease activity index score), or symptoms proven to be due to inflammatory activity, or the need for medical intervention[3]. The rate of secondary loss of response appears to be greater in the first twelve months of therapy, with a more gradual loss of response over subsequent years. Rates of loss of response to infliximab and adalimumab have been reported to range between 23% and 46% at one year, with the majority of patients regaining response after dose-intensification[3]. However, in the Australian context, prescribing restrictions do not permit dose tailoring[4], and local practice may vary from study populations in which this was available. We sought to define loss of response appropriately to a local setting, and examine body composition at the time of anti-TNF induction as a predictor of longer-term outcomes.

Our hypotheses were that a body composition phenotype (such as cachexia, or sarcopenic obesity) may confer worse outcomes in anti-TNF therapy (hypothesis 4: *That body composition parameters predict response to anti-TNF therapy*), and that visceral adipose tissue may be associated with earlier loss of response (hypothesis 5: *That patients with increased visceral adipose tissue mass have a lesser clinical response to anti-TNF therapy*) – if so, this might be due to pharmacokinetic factors such as lower drug levels due to increased expression of TNF in visceral fat[5]. Analysis of visceral adipose tissue area at a single abdominal cross-section has been shown to correlate with volumetric measurement and is an accepted method of assessing visceral adipose tissue mass[6-8].

European Journal of Clinical Nutrition (2017), 1–5

www.nature.com/ejcn

ORIGINAL ARTICLE

Low muscle mass at initiation of anti-TNF therapy for inflammatory bowel disease is associated with early treatment failure: a retrospective analysis

DQ Holt[1,2], P Varma[1], BJG Strauss[2], AS Rajadurai[2] and GT Moore[1,2]

BACKGROUND/OBJECTIVES: Delayed treatment failure occurs in a significant proportion of inflammatory bowel disease (IBD) patients treated with tumor necrosis factor-alpha (TNF) antagonists. Identification of predictors of loss of response (LOR) may help to optimize therapy. We sought to determine whether body composition parameters at the commencement of anti-TNF therapy were associated with earlier treatment failure.

SUBJECTS/METHODS: A retrospective cohort study was performed on 68 patients who had undergone cross-sectional abdominal imaging coincident with the commencement of anti-TNF drugs. Analysis of the images at the third lumbar vertebra was performed using standard techniques to determine cross-sectional areas of skeletal muscle (SM), visceral adipose tissue, subcutaneous adipose tissue and intermuscular adipose tissue. Treatment failure was defined as: post-induction hospital admission or surgery for IBD, escalation of TNF dose or immunosuppressants for clinical LOR, emergence of a new fistula or Crohn's Disease Activity Index (CDAI) >150.

RESULTS: Two-thirds of patients had myopenia. Patients with less than gender-specific median SM area had a median time to failure of 520 (s.d. 135) days compared to 1100 (s.d. 151) days for those with more than median SM area ($P=0.036$). No difference was found in disease duration, inflammatory markers or CDAI between quartiles of SM area. No relation between outcomes and measures of adipose tissue, weight or body mass index was observed.

CONCLUSIONS: Identifying low muscle mass at anti-TNF induction as a risk factor for treatment failure may contribute to a more tailored approach to IBD therapy.

European Journal of Clinical Nutrition advance online publication, 22 February 2017; doi:10.1038/ejcn.2017.10

INTRODUCTION

Monoclonal antibodies to tumor necrosis factor-alpha (anti-TNF drugs) have an established role in the treatment of inflammatory bowel disease (IBD),[1,2] with initial response rates of ~80% in induction and early maintenance studies.[3,4] However, primary non-response to anti-TNF drugs occurs in 13–40% of patients, with ~13% of patients experiencing secondary loss of response (LOR) each year.[5] Predictors of non-response or LOR have been identified, including disease-related characteristics, such as duration and phenotype, smoking status, serological and genetic markers, and immunopharmacological factors.[6] Obesity appears to be associated with earlier LOR to adalimumab[7] and infliximab,[8] for reasons that are not defined. This may be due to pharmacokinetic factors,[9] or a pro-inflammatory state induced by obesity.[10,11] No published studies have examined the role of body composition in clinical response to anti-TNF drugs for IBD. Body composition analysis permits the correlation of physical components—such as visceral adipose tissue, skeletal muscle (SM), total body fat mass (FM) and fat-free mass (FFM)—with clinical outcomes. Analysis of cross-sectional computed tomography (CT) or magnetic resonance imaging (MRI) at a single abdominal level has been demonstrated by a number of authors to provide a reliable estimation of total visceral adipose tissue volume, total body SM mass and total body fat mass as measured by multi-slice volumetric analysis or other technologies such as dual energy X-ray absorptiometry or bioelectrical impedance analysis.[12–20] We sought to determine whether body composition parameters were associated with the anti-TNF drug treatment failure in IBD patients at long-term follow-up.

MATERIALS AND METHODS

A retrospective audit was conducted for all patients with IBD receiving anti-TNF therapy at a tertiary referral center, and from the records of associated gastroenterologists. All patients on anti-TNF therapy with an accurate date for TNF commencement, an abdominal MRI or CT scan contemporaneous with induction and adequate correspondence to determine end-points were included. Prescribing regulations specified standard intravenous dosing of 5 mg/kg of infliximab at weeks 0, 2 and 6, with 8-weekly infusions as maintenance therapy thereafter. Adalimumab was dosed at 160 mg subcutaneously at week 0, 80 mg at week 2, and 40 mg fortnightly thereafter. Analysis of imaging at the level of the third lumbar vertebra was undertaken, as this level has been shown to best predict total body composition.[20] A single experienced operator, blinded to outcomes at the time of analysis, used SliceOMatic v4.3 (TomoVision, Montreal, Canada) software to measure areas of SM, subcutaneous adipose tissue (SAT), intermuscular adipose tissue (IMAT) and visceral adipose tissue (VAT). These methods have been previously described and validated against the standard clinical technique of body composition analysis—dual-energy X-ray absorptiometry—in patients with Crohn's Disease (CD), with formulae developed to estimate appendicular SM index (ASMI), FM and FFM;[13,16] in this study, the formula used for ASMI (kg/m^2) is $0.11 \times$ [L3

[1]Department of Gastroenterology and Hepatology, Monash Health, Clayton, Victoria, Australia and [2]School of Clinical Sciences at Monash Health, Monash University, Clayton, Victoria, Australia. Correspondence: Dr D Holt, Department of Gastroenterology and Hepatology, Monash Health, 246 Clayton Road, Clayton, Victoria 3168, Australia.
E-mail: darcy.holt@monashhealth.org
Received 21 October 2016; revised 28 December 2016; accepted 2 January 2017

SM area/height^2(cm^2/m^2)]+1.17. These values were then expressed as a ratio of the gender-specific mean, and also as height-adjusted indices. Patients with prior exposure to any anti-TNF agent were excluded. Baseline biochemical and clinical data were noted, including steroid and immunomodulatory prescription at the time of anti-TNF commencement; prior steroid exposure was not characterized. LOR was defined as: a post-induction hospital admission or surgery for IBD, escalation of TNF dose or immunosuppressants for clinical LOR, emergence of a new fistula or rising Crohn's Disease Activity Index (CDAI) >150.

Statistics

Statistical analysis was performed with Prism v6 (GraphPad Software, La Jolla, CA, USA) and SPSS statistics v24 (IBM Corp, Armonk, NY, USA). Kaplan–Meier analysis was undertaken, with log-rank test to compare curves, and Fisher's exact test to determine differences between categorical variables with binary outcomes. Spearman correlation coefficients were calculated between continuous variables. Mann–Whitney, Kruskal–Wallis and paired samples *t*-tests were used to compare means between categorical variables. Cox regression analysis was used to identify covariates predicting LOR. ROC curves were used to identify cut-off values. A *P*-value of <0.05 was considered significant.

Ethics

This study was approved by the Monash Health Human Research Ethics Committee (project 16222Q).

RESULTS

From chart review, 211 patients with complete information regarding anti-TNF induction and follow-up were identified. Of these, 68 had suitable abdominal imaging performed around the time of anti-TNF induction (mean 73 days' difference, s.e.m. 71 days). Characteristics of the patients are described in Table 1. Among those meeting the endpoint, hospitalization for LOR occurred in 30.3%, treatment escalation for clinical LOR in 60.6%, surgery in 6.1% and a new fistula in 3.0%. Very few ($n=3$) patients had drug levels or anti-drug antibodies recorded in the medical record at LOR. Median values for body composition parameters are listed by gender in Table 2.

There was no correlation between measures of body composition and biochemical or clinical markers of inflammation. No data were available regarding the prevalence of hypertension, dyslipidemia, hyperglycemia or abnormal liver function. Between those who experienced treatment failure and those who did not, there was no significant difference between mean baseline inflammatory markers, immunomodulator use, type of anti-TNF or gender (Table 3). Multivariate Cox regression analysis identified less than the median SM area (hazard ratio 4.53, $P=0.031$) and adalimumab use as the initial anti-TNF (hazard ratio 2.73, $P=0.030$) as being associated with earlier treatment failure. ASMI, smoking status, years of disease, gender, type of IBD and immunomodulator use were not associated with different times to LOR.

Relationships with SM

Low muscle mass, or myopenia, was prevalent, with calculated ASMI[13] >2 s.d's below a young adult mean[21,22] present in 68.5% of patients. The presence of myopenia was not associated with longer disease duration, although there was a statistical trend toward a weak negative correlation between calculated ASMI and years of disease ($r=-0.268$, $P=0.055$). As the prevalence of myopenia was high in our cohort, internal comparisons were undertaken with an arbitrary cut-off of the median value; SM area was chosen as a single factor to predict response, rather than ASMI, which was a calculated measure incorporating height. A cut-off of 47.62 kg estimated FFM had 100% specificity and 59% sensitivity for identifying subjects with greater than median SM area.

Table 1. Study participants and characteristics

Female sex, *n*	32 (47.1%)
Age, years (mean ± s.d.)	37.6 ± 13.5
Smoking	14 (20.9%)
Type of inflammatory bowel disease	
Crohn's Disease	63 (92.6%)
Ulcerative colitis	5 (7.4%)
Years of disease (mean ± s.d.)	11.6 ± 8.6
Follow-up, days (mean ± s.d.)	809.8 ± 664.3
Anti-TNF drug	
Infliximab	36 (52.9%)
Adalimumab	32 (47.1%)
Indication for anti-TNF	
Refractory Crohn's disease	75.0%
Fistulizing Crohn's disease	19.1%
Acute severe ulcerative colitis	1.5%
Refractory ulcerative colitis	4.4%
Immunomodulator use, *n*	42 (61.8%)
Baseline Crohn's Disease Activity Index score, if applicable (mean ± s.d.)	412 ± 91
Baseline CRP, mg/l (mean ± s.d.)	23.8 ± 31.5
Baseline hemoglobin, g/dl (mean ± s.d.)	13.21 ± 1.74
Baseline albumin, g/dl (mean ± s.d.)	3.64 ± 0.74
Body mass index, kg/m^2 (mean ± s.d.)	24.8 ± 4.7

Patients with less than the gender-specific median SM area experienced treatment failure significantly earlier (Figure 1), despite similar baseline characteristics (Table 3). A median time to failure of 520 (s.d. 135) days was seen in this group, compared to 1100 (s.d. 151) days for those with greater than median SM area ($P=0.031$), hazard ratio 2.062 (95% CI 1.068–3.980). At 24 months, 27.6% of patients with more than median SM area had lost response, compared with 61.7% of those with values less than the median (OR 0.25 (0.09–0.70), $P=0.014$; Figure 2). This effect was seen as a trend at 12 months, but the difference in failure rates (14.7% vs 32.3%, respectively) did not reach statistical significance ($P=0.152$).

Biochemical parameters including CRP and albumin, as well as CDAI, did not correlate with body composition measurements. There was no correlation between the dose of prednisolone used at anti-TNF induction, nor the use of immunomodulators, and SM area. A Kruskal–Wallis test found no difference in SM area between types of LOR.

Relationships with adipose tissue

BMI in the overweight or obese range was observed in 28.0% of patients. There was no difference in Kaplan–Meier survival curves between patients with BMI $\geqslant 25$ kg/m^2 and those <25 kg/m^2, nor between those with BMI $\geqslant 30$ kg/m^2 and those <30 kg/m^2.

There was no difference in time to treatment failure between those with above median VAT or below median VAT, nor between VAT quartiles. Similarly, VAT adjusted for height, and total body fat mass quartiles did not exhibit different time to treatment failure. The ratio of VAT to SAT, or of VAT to total adipose tissue, was not associated with different outcomes, nor with differences in baseline CRP or CDAI.

Anti-TNF drugs only became publicly subsidized for ulcerative colitis (UC) shortly before this cohort was established, and records for few patients were available. Exclusion of the small number of UC patients included in this study did not alter the major findings; robust analysis of this group alone cannot be undertaken due to small sample size.

Table 2. Body composition parameters

	Female (n = 32) median	*IQR*	*Male (n = 36) median*	*IQR*
SM (cm^2)	100.96	86.37–116.95	138.56	127.46–157.91
VAT (cm^2)	55.25	35.61–102.72	60.78	29.34–127.23
SAT (cm^2)	198.98	116.41–317.06	117.26	69.81–182.93
IMAT (cm^2)	3.495	1.608–6.663	3.42	1.383–5.56
ASMI (kg/m^2)	5.44	4.70–5.67	6.51	5.78–7.01
FM (kg)	23.14	18.08–27.55	19.64	16.15–23.70
FFM (kg)	36.35	31.97–41.15	47.63	44.30–53.43

Abbreviations: ASMI, calculated appendicular skeletal muscle index; FFM, calculated total body fat-free mass; FM, calculated total body fat mass; IMAT, intermuscular adipose tissue area; IQR, interquartile range; SAT, subcutaneous adipose tissue area; SM, skeletal muscle area; VAT, visceral adipose tissue area.

Table 3. Baseline characteristics, categories and outcomes ($n = 68$)

	Less than median SM (n = 34)	*Greater than or equal to median SM (n = 34)*	P	*Maintained TNF response (n = 31)*	*Lost TNF response (n = 37)*	P
Age, years (mean ± s.d.)	35.9 ± 14.3	39.4 ± 12.7	0.289	37.2 ± 13.9	38.0 ± 13.3	0.823
Baseline CDAI[a] (mean ± s.d.)	418.3 ± 99.4	406.7 ± 86.8	0.706	417.2 ± 84.8	407.6 ± 99.1	0.753
Baseline prednisolone dose, mg (mean ± s.d.)	13.7 ± 18.2	17.6 ± 20.6	0.45	13.7 ± 17.9	17.3 ± 20.7	0.48
BMI, kg/m^2 (mean ± s.d.)	21.2 ± 3.0	24.9 ± 5.1	0.005	23.3 ± 5.3	23.3 ± 4.1	0.997
Crohn's disease	*n* = 32, 93.9%	*n* = 31, 91.2%	0.514	*n* = 27, 87.1%	*n* = 36, 97.3%	0.17
Female gender	*n* = 16, 47.1%	*n* = 16, 47.1%	1	*n* = 14, 45.2%	*n* = 18, 48.6%	0.811
Immunomodulator use	*n* = 20, 58.8%	*n* = 22, 64.7%	0.803	*n* = 20, 64.5%	*n* = 22, 59.5%	0.803
Montreal classification of Crohn's disease	(Mann–Whitney test for difference between groups)		0.415	(Mann–Whitney test for difference between groups)		0.402
Smoker	*n* = 5, 14.7%	*n* = 9, 36.0%	0.369	*n* = 5, 16.1%	*n* = 9, 24.3%	0.55
Years of disease, years (mean ± s.d.)	11.8 ± 9.6	11.3 ± 7.6	0.24	10.0 ± 8.0	12.89 ± 9.0	0.174

Abbreviations: BMI, body mass index; median SM, gender-specific skeletal muscle area; TNF response, clinical response to infliximab or adalimumab. [a]Crohn's Disease Activity Index: for patients with non-fistulizing CD.

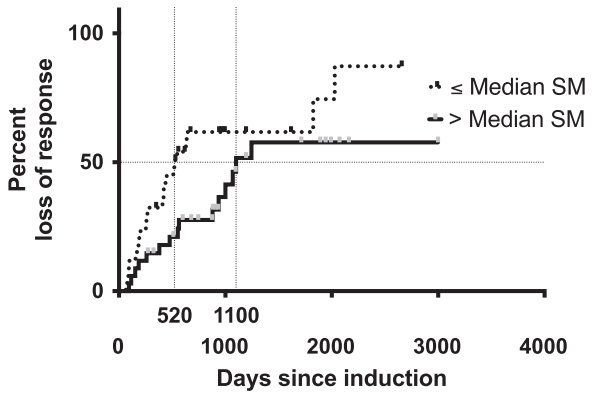


Figure 1. Earlier loss of response observed in patients with low skeletal muscle; median time to failure 520 days (SM ratio < 1) compared to 1100 days (SM ratio $\geqslant 1$; SM ratio, ratio of skeletal muscle area to gender-specific mean).

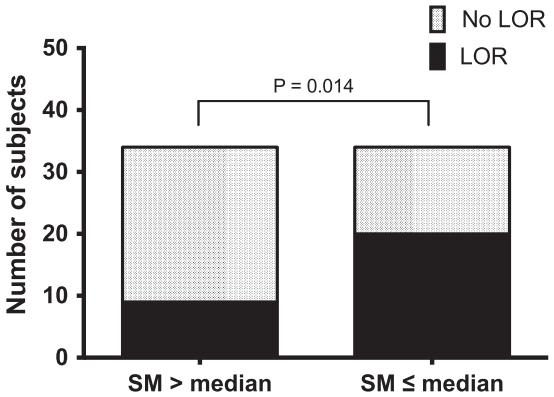


Figure 2. A 24-month treatment failure rate was significantly higher in patients with less than median muscle area (LOR, loss of response).

DISCUSSION

No published study yet has examined the role of body composition compartments to anti-TNF treatment response in IBD, and the novel finding of low muscle mass as a risk factor for poor response warrants further examination in prospective studies. However, in this study, the association observed between low SM mass and early treatment failure does not imply causation. Patients with low SM may have had more severe disease as a cause of sarcopenia or cachexia, with disease phenotype predisposing them to treatment failure. Importantly, however, we were not able to determine any difference in disease duration, inflammatory markers, or CDAI between quartiles of SM area. A prospective study incorporating drug level monitoring and body composition analysis would more completely address the mechanisms of treatment failure. In a systematic review of the literature, there was found to be inconsistent data regarding associations between body composition and disease duration, disease activity and treatments.[23] Infliximab induction for active CD has been shown to improve SM mass and function, suggesting that inflammatory sarcopenia is reversible in this patient group.[24]

Another recent systematic review[5] identified increased BMI as a risk factor for LOR to anti-TNF therapy on the basis of two retrospective cohort studies.[8,25] Proteolytic clearance of

immunoglobulins is generally related to patient weight, with higher weight associated with more rapid clearance in a number of clinical studies.[9,26,27] The mean BMI in our cohort was lower than in these cited studies and BMI did not predict earlier LOR, nor were cut-off values of 25 or 30 kg/m^2 associated with higher rates of treatment failure. This lack of association with BMI—but the finding that low muscle mass confers a negative prognosis—may indicate that the mechanisms of treatment failure involve body composition compartments rather than total body mass. Patients with IBD commonly have reduced muscle mass despite normal BMI.[28] In CD patients, fat distribution may also be altered: expansion of the VAT compartment has been demonstrated, resulting in a four-fold increase in adipocyte number compared to controls[29] and an increased volume of VAT.[30–32]

An observational cohort study found that penetrating or stricturing CD was associated with an increased VAT/FM ratio, and that a high VAT/FM ratio was associated with increased disease activity at follow-up.[30] A higher VAT:SAT ratio (mesenteric fat index (MFI)) has been shown to correlate with a higher incidence of penetrating or stricturing CD.[33] Neither the MFI, nor VAT/FM ratio, were associated with different rates or timing of LOR in our study.

In a prospective study of adalimumab (ADA) in IBD patients, an inverse correlation between muscle-related body composition parameters and variability of ADA levels was noted, suggesting that muscle mass may play a role in anti-TNF pharmacokinetics.[34] A possible mechanism may involve the neonatal Fc receptor (FcRn), which transports maternal IgG across the placenta, and from the intestinal lumen in infants. It is expressed in adult tissues, protecting IgG and albumin from catabolism and transporting IgG across epithelial cells.[35] Expression of FcRn in endothelial tissue[36] and SM[37] may contribute to altered in anti-TNF pharmacokinetics with differences in body composition.

Limitations of this study include its retrospective design, and the associated difficulty in defining primary non-response or secondary LOR according to criteria used in other studies; although there is no consensus definition of these terms in the literature.[38] The absence of routine anti-TNF drug levels and anti-drug antibody testing is another important limitation. Without drug level monitoring, pharmacokinetic mechanisms to explain a relationship between drug efficacy and body composition can only be postulated. The study strengths include the long-term follow-up of a real-world cohort of IBD patients, with defined outcomes. The cumulative rate of LOR in this cohort is similar to previous reports,[38,39] corroborating the outcome measures used. The techniques used for body composition analysis in this paper have been validated in CD patients. More research using existing cohorts of IBD patients treated with anti-TNF drugs is possible using the same methodology and may seek to further elucidate the role of body composition in the treatment of IBD. Determination of patient factors predicting response to treatment can contribute to a more tailored approach to IBD therapy, particularly as new agents with different modes of action become available. Identifying low muscle mass at induction as a risk factor for treatment failure may add to this management algorithm.

CONFLICT OF INTEREST

This work was supported by Crohn's and Colitis Australia (the Angela McAvoy AM Fellowship to GT Moore). DQ Holt has received an emerging researcher fellowship from Monash Health, and honoraria from AbbVie and Janssen.

ACKNOWLEDGEMENTS

We thank the colleagues who have generously contributed data to this study: Dr David Devonshire, Dr Christopher Desmond, Dr Michael Swan, Dr Debra Nathan, Dr Edward Shelton, Dr Ilana Prideaux, Dr Catherine Sorell, Dr Ferry Rusli, Dr Luke Crantock, Dr Anouk Dev, Dr Dilip Ratnam and Dr Stephen Pianko.

REFERENCES

1 Dassopoulos T, Sultan S, Falck Ytter YT, Inadomi JM, Hanauer SB. American Gastroenterological Association Institute technical review on the use of thiopurines, methotrexate, and anti-TNF-α biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. *Gastroenterology* 2013; **145**: 1464–1478. e1–e5.
2 D'Haens GR, Panaccione R, Higgins PDR, Vermeire S, Gassull M, Chowers Y *et al.* The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organization: when to start, when to stop, which drug to choose, and how to predict response? *Am J Gastroenterol* 2011; **106**: 199–212.
3 Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF *et al.* Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002; **359**: 1541–1549.
4 Sandborn WJ, Hanauer SB, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh DG *et al.* Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. *Gut* 2007; **56**: 1232–1239.
5 Ding NS, Hart A, De Cruz P. Systematic review: predicting and optimising response to anti-TNF therapy in Crohn's disease - algorithm for practical management. *Aliment Pharmacol Ther* 2015; **43**: 30–51.
6 Kopylov U, Seidman E. Predicting durable response or resistance to antitumor necrosis factor therapy in inflammatory bowel disease. *Therap Adv Gastroenterol* 2016; **9**: 513–526.
7 Bhalme M, Sharma A, Keld R, Willert R, Campbell S. Does weight-adjusted anti-tumour necrosis factor treatment favour obese patients with Crohn's disease? *Eur J Gastroenterol Hepatol* 2013; **25**: 543–549.
8 Harper JW, Sinanan MN, Zisman TL. Increased body mass index is associated with earlier time to loss of response to infliximab in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2013; **19**: 2118–2124.
9 Dotan I, Ron Y, Yanai H, Becker S, Fishman S, Yahav L *et al.* Patient factors that increase infliximab clearance and shorten half-life in inflammatory bowel disease: a population pharmacokinetic study. *Inflamm Bowel Dis* 2014; **20**: 2247–2259.
10 Karagiannides I, Pothoulakis C. Obesity, innate immunity and gut inflammation. *Curr Opin Gastroenterol* 2007; **23**: 661–666.
11 Blain A, Cattan S, Beaugerie L, Carbonnel F, Gendre J-P, Cosnes J. Crohn's disease clinical course and severity in obese patients. *Clin Nutr* 2002; **21**: 51–57.
12 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; **80**: 271–278.
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; **33**: 997–1006.
14 Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge M-P, Albu J *et al.* Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. *J Appl Physiol* 2004; **97**: 2333–2338.
15 Hu HH, Chen J, Shen W. Segmentation and quantification of adipose tissue by magnetic resonance imaging. *MAGMA* 2016; **29**: 259–276.
16 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; **51**: 842–847.
17 Maislin G, Ahmed MM, Gooneratne N, Thorne-Fitzgerald M, Kim C, Teff K *et al.* Single slice vs volumetric MR assessment of visceral adipose tissue: reliability and validity among the overweight and obese. *Obesity* 2012; **20**: 2124–2132.
18 Baker ST, Strauss BJ, Prendergast LA, Panagiotopoulos S, Thomas GE, Vu T *et al.* Estimating dual-energy X-ray absorptiometry-derived total body skeletal muscle mass using single-slice abdominal magnetic resonance imaging in obese subjects with and without diabetes: a pilot study. *Eur J Clin Nutr* 2012; **66**: 628–632.
19 Xia Y, Ergun DL, Wacker WK, Wang X, Davis CE, Kaul S. Relationship between dual-energy X-ray absorptiometry volumetric assessment and X-ray computed tomography-derived single-slice measurement of visceral fat. *J Clin Densitom* 2014; **17**: 78–83.
20 Schweitzer L, Geisler C, Pourhassan M, Braun W, Gluer CC, Bosy-Westphal A *et al.* What is the best reference site for a single MRI slice to assess whole-body skeletal muscle and adipose tissue volumes in healthy adults? *Am J Clin Nutr* 2015; **102**: 58–65.
21 Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR *et al.* Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol* 1998; **147**: 755–763.
22 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; **83**: 229–239.
23 Bryant RV, Trott MJ, Bartholomeusz FD, Andrews JM. Systematic review: body composition in adults with inflammatory bowel disease. *Aliment Pharmacol Ther* 2013; **38**: 213–225.

24 Subramaniam K, Fallon K, Ruut T, Lane D, McKay R, Shadbolt B *et al.* Infliximab reverses inflammatory muscle wasting (sarcopenia) in Crohn's disease. *Aliment Pharmacol Ther* 2015; **41**: 419–428.
25 Bultman E, de Haar C, van Liere-Baron A, Verhoog H, West RL, Kuipers EJ *et al.* Predictors of dose escalation of adalimumab in a prospective cohort of Crohn's disease patients. *Aliment Pharmacol Ther* 2011; **35**: 335–341.
26 Fasanmade AA, Adedokun OJ, Blank M, Zhou H, Davis HM. Pharmacokinetic properties of infliximab in children and adults with Crohn's disease: a retrospective analysis of data from 2 phase III clinical trials. *Clin Ther* 2011; **33**: 946–964.
27 Mould DR. The pharmacokinetics of biologics: a primer. *Dig Dis* 2015; **33** (Suppl 1): 61–69.
28 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; **41**: 895–906.
29 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; **56**: 577–583.
30 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; **21**: 2590–2597.
31 Katznelson L, Fairfield WP, Zeizafoun 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* 2003; **88**: 5468–5472.
32 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.
33 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; **9**: 684–687. e1.
34 Csontos ÁA, Molnár A, Miheller P. Letter: body surface area and body muscle parameters may influence adalimumab trough levels. *Aliment Pharmacol Ther* 2015; **41**: 700.
35 Kuo TT, Baker K, Yoshida M, Qiao S-W, Aveson VG, Lencer WI *et al.* Neonatal Fc receptor: from immunity to therapeutics. *J Clin Immunol* 2010; **30**: 777–789.
36 Vugmeyster Y, Xu X, Theil F-P, Khawli LA, Leach MW. Pharmacokinetics and toxicology of therapeutic proteins: advances and challenges. *World J Biol Chem* 2012; **3**: 73–92.
37 Fan Y-Y, Neubert H. Quantitative analysis of human neonatal Fc receptor (FcRn) tissue expression in transgenic mice by online peptide immuno-affinity LC-HRMS. *Anal Chem* 2016; **88**: 4239–4247.
38 Ben-Horin S, Chowers Y. Review article: loss of response to anti-TNF treatments in Crohn's disease. *Aliment Pharmacol Ther* 2011; **33**: 987–995.
39 Karmiris K, Paintaud G, Noman M, Magdelaine-Beuzelin C, Ferrante M, Degenne D *et al.* Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn's disease. *Gastroenterology* 2009; **137**: 1628–1640.

Summary and discussion

A hypothesised association between visceral adiposity and early loss of response to anti-TNF drugs was not identified. The proposed pharmacokinetic mechanism of treatment failure in those with excessive visceral adiposity cannot be tested without drug level monitoring, and so the significance of this negative finding is uncertain.

Although disease activity indices (CDAI) and measures of disease duration were recorded, a limitation of the study is that this information was collated retrospectively, using CDAI scores from application documents for subsidised anti-TNF drugs. As such, there is a defined cut-off value for the CDAI (generally greater than 300), and assessments may be biased towards meeting this arbitrary limit in order to meet eligibility criteria for prescription. CDAI itself is a problematic measure, with very wide – up to ten-fold – inter-observer variability in clinical practice[9]. The weights recorded at induction were also often rounded to the nearest ten kilograms, suggesting a variability in drug dose/kg. A suitably powered prospective study may provide more robust multivariate analysis of the effect of visceral adipose tissue, particularly if it included standardised, impartial recording of disease phenotype and activity, and drug level monitoring. Subgroup analysis may also be possible in a larger study; for example, assessing whether obese patients, or those with highest visceral adiposity, have worse outcomes or lower drug levels with fixed-dose adalimumab compared to infliximab, which is dosed by weight.

Two-thirds of patients in this cohort had calculated appendicular skeletal muscle indices more than two standard deviations below a young adult mean (myopenia). This proportion is higher than reported in the cohort described in chapter 4 (45.4% of male subjects and 50% of female subjects), perhaps reflecting more severe body composition changes in those patients meeting eligibility criteria for anti-TNF treatment. The high proportion of myopenic patients prompted the use of the median value as a comparator. Disease duration correlated with low skeletal muscle mass, a finding shown[10] in a cohort of patients with a similar prevalence of myopenia.

Finding that low muscle mass at induction is a risk factor for earlier anti-TNF failure adds to a predictive model of disease behaviour and may help to personalise treatment. Possibly, given that sarcopenia is reversible in Crohn's disease patients[11], body composition analysis at diagnosis may identify those who may benefit from earlier aggressive treatment.

Chapter references

1. Gomollón F, Dignass A, Annese V, Tilg H, Van Assche G, Lindsay JO, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. J Crohns Colitis; 2017 Jan 1;11(1):3–25.

2. Kopylov U, Ben-Horin S, Seidman EG. Therapeutic drug monitoring in inflammatory bowel disease. Annals of Gastroenterology. 2014;(27):1–9.

3. Ben-Horin S, Chowers Y. Review article: loss of response to anti-TNF treatments in Crohn's disease. Aliment Pharmacol Ther. 2011 May;33(9):987–95.

4. Ghaly S, Costello S, Beswick L, Pudipeddi A, Agarwal A, Sechi A, et al. Dose tailoring of anti-tumour necrosis factor-alpha therapy delivers useful clinical efficacy in Crohn disease patients experiencing loss of response. Intern Med J. 2015 Feb;45(2):170–7.

5. Schäffler A, Schölmerich J, Salzberger B Adipose tissue as an immunological organ: Toll-like receptors, C1q/TNFs and CTRPs. Trends in Immunology 2007;28(9):393–9.

6. Hu HH, Chen J, Shen W. Segmentation and quantification of adipose tissue by magnetic resonance imaging. MAGMA. 2016 Apr;29(2):259–76.

7. Schweitzer L, Geisler C, Pourhassan M, Braun W, Glüer C-C, Bosy-Westphal A, et al. Estimation of Skeletal Muscle Mass and Visceral Adipose Tissue Volume by a Single Magnetic Resonance Imaging Slice in Healthy Elderly Adults. J Nutr. American Society for Nutrition; 2016 Oct;146(10):2143–8.

8. Schweitzer L, Geisler C, Pourhassan M, Braun W, Gluer CC, Bosy-Westphal A, et al. What is the best reference site for a single MRI slice to assess whole-body skeletal muscle and adipose tissue volumes in healthy adults? Am J Clin Nutr. 2015 Jul 1;102(1):58–65.

9. de Dombal FT, Softley A. IOIBD report no 1: Observer variation in calculating indices of severity and activity in Crohn's disease. International Organisation for the Study of Inflammatory Bowel Disease. Gut. BMJ Group; 1987 Apr;28(4):474–81.

10. 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.

11. Subramaniam K, Fallon K, Ruut T, Lane D, McKay R, Shadbolt B, et al. Infliximab reverses inflammatory muscle wasting (sarcopenia) in Crohn's disease. Aliment Pharmacol Ther. 2015 Jan 8;41(5):419–28.

Chapter 7: Visceral adiposity predicts recurrence in post-operative Crohn's disease patients

Introduction and context

More than 70% of Crohn's disease patients require surgical resection of affected bowel[1]. However, surgery is not curative. In most cases, disease recurs: with endoscopic recurrence in three-quarters of patients after one year[2], a median time to clinical recurrence of 3-5 years (20-30% at one year[3]) and a median time to repeat surgery of 10-20 years[4]. Strategies to prevent disease recurrence have been developed, with identification of risk factors pivotal to recommending appropriate prophylactic medication. Specific risk factors for recurrence are recognised, such as: cigarette smoking, prior intestinal resection, absence of preventative treatment, penetrating disease at index surgery, perianal disease, and histological features of granulomas in the resection specimen and myenteric plexitis[5].

In a preventative situation, balancing treatment-associated risks and cost requires careful consideration of prognostic factors. As has been demonstrated, body composition is associated with disease duration and severity (systematic review, chapter 2), drug metabolism (chapter 5) and treatment efficacy (chapter 6), it may foretell outcomes after surgery. Body composition analysis would therefore have a position in algorithms determining post-operative management of Crohn's disease patients. To investigate this hypothesis (hypothesis 6: *That body composition parameters predict endoscopic recurrence after surgery for Crohn's disease*), a standardised, thorough, prospectively collected data set with mandated time points for endoscopy would provide the greatest information. For such analysis, we are grateful to the investigators of the POCER (Post-Operative Crohn's disease Endoscopic Recurrence) study[6], performed at St. Vincent's Hospital, Melbourne, for permitting access to the data of this prospective, randomised controlled trial of early endoscopy and treatment escalation. As the POCER study involved treatment escalation with the use of adalimumab – and serum adalimumab levels had been assayed – we also sought to determine a relationship between visceral adipose tissue (or other components of body composition) and drug levels and clinical response. As previously discussed, cross-sectional area of visceral adipose tissue is representative of the total volume of this tissue compartment[7,8]. We postulated that increased visceral adiposity may result in an

excess of adipocyte-derived cytokines such as tumour necrosis factor alpha, and that this may act as an 'antigen sink', resulting in lower concentrations of anti-TNF drugs in Crohn's disease-affected tissues. This was our second hypothesis for this study (hypothesis 7: *That increased visceral adipose tissue is associated with less response to treatment with adalimumab, and with lower serum adalimumab levels*)

The primary outcome measure in the POCER study was the presence of endoscopic recurrence at 18 months. Possible treatment regimens during the study were complex, with subjects assigned a high-risk category if they were active smokers, had perforating disease or previous intestinal resection. High-risk patients were treated from enrolment with metronidazole for three months and for the study duration with a thiopurine, or if intolerant, adalimumab. Low-risk patients were treated with metronidazole. Patients were randomised 2:1 to receive colonoscopy at six months or not, with treatment escalation in those with endoscopic recurrence at six months. Multiple treatment permutations were therefore possible.

AP&T Alimentary Pharmacology and Therapeutics

Visceral adiposity predicts post-operative Crohn's disease recurrence

D. Q. Holt*,†, G. T. Moore*,†, B. J. G. Strauss†, A. L. Hamilton‡,§, P. De Cruz§ & M. A. Kamm‡,§

*Department of Gastroenterology & Hepatology, Monash Health, Melbourne, Vic., Australia.
†Monash University, Melbourne, Vic., Australia.
‡Department of Gastroenterology, St Vincent's Hospital, Melbourne, Vic., Australia.
§University of Melbourne, Melbourne, Vic., Australia.

Correspondence to:
Dr D. Q. Holt, Department of Gastroenterology & Hepatology, Monash Health, 246 Clayton Road, Clayton, Vic. 3168, Australia.
E-mail: darcy.holt@monashhealth.org

Publication data
Submitted 4 November 2016
First decision 16 November 2016
Resubmitted 19 December 2016
Resubmitted 18 January 2017
Resubmitted 7 February 2017
Accepted 7 February 2017
EV Pub Online 28 February 2017

The Handling Editor for this article was Dr Ashwin Ananthakrishnan, and it was accepted for publication after full peer-review.

SUMMARY

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

Aim
To determine whether body composition is 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/height^2 >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 is an independent risk factor for endoscopic recurrence of Crohn's disease after surgery. Sarcopenia correlates with inflammatory biomarkers. Measures of visceral adipose tissue may help to stratify risk in post-operative management strategies.

doi:10.1111/apt.14018

INTRODUCTION

Visceral adipose tissue has distinct metabolic activity, cellular composition, inflammatory infiltrate and cytokine production.[1] 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 condition,[3] and is disease-specific, correlating with transmural inflammation.[4] Inflammatory activity in the submucosal and stromal tissues has been implicated in post-operative Crohn's disease recurrence, with myenteric plexitis a described risk factor for recurrence.[5–8]

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 volume.[10–13] 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 volume.[16] 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 mass.[17] 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 condition,[18] and recurrence after surgery is common, with 48–93% of patients having endoscopic lesions at 1 year post operation.[19] 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 utilisation.[20–23]

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 (400 mg orally twice-daily; dose reduced or discontinued if not tolerated). Patients with prior resections, smokers or those with perforating disease also received azathioprine (2 mg/kg/day) or 6-mercaptopurine (1.5 mg/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 score[29] $\geq$ i2) 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 study,[30] 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 subjects,[31] using software providing results interchangeable with SliceOmatic.[32] 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 formulae,[33] 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 technique.[34]

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, USA) and SPSS statistics 24 (IBM Corp, Armonk, NY, USA). A $P < 0.05$ 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 eight patients who stepped up therapy and those who did not. Steroid use in the pre-operative 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 μg/g ± 964 vs. −1958 μg/g ± 1202, $P = 0.013$). Pre-operative 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 s.d. 0.909] and this value divided by height squared ['visceral adipose tissue/height index' (VHI) (expressed as a proportion of gender mean, with s.d. 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 population.[35]

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/height^2, 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

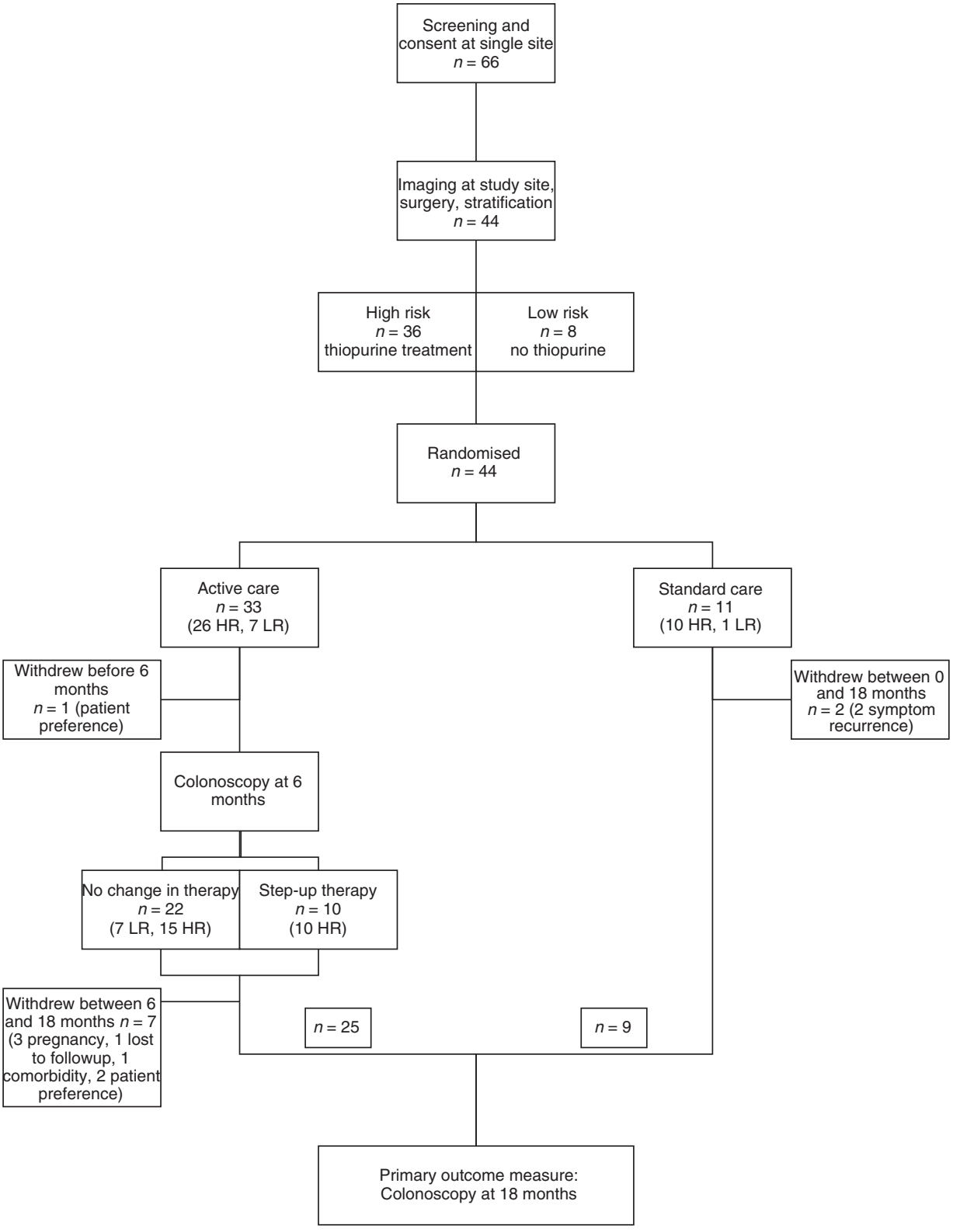


Figure 1 | Trial profile and patient disposition.

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

Table 1 | Characteristics of study participants

Female, *n*	24	54.5%
Age, years ± s.d.	37.8 ± 14.2	
Disease duration (mean ± s.d.)	5.5 ± 4.0	
BMI, kg/m^2 (mean ± s.d.)	23.5 ± 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 (median ± IQR)	56 (22–127)	
Indication for scan, *n*		
Active disease/inflammation	14	
Obstructive/stricture	14	
Penetrating/fistulising	6	
Perianal disease	1	
Information unavailable	9	

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/height^2 value of 51 cm^2/m^2, all eight patients had endoscopic recurrence (Figure 2).

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× (gender mean) had taken steroids at the time of surgery, this was the same proportion as those with VHI ≤1.5× (gender mean) [$P = 0.938$]. The mean VHI was not different between those who had not taken steroids and those who had (30.99 cm^2/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 four 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 five (three female, two male) patients with WC >105 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

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

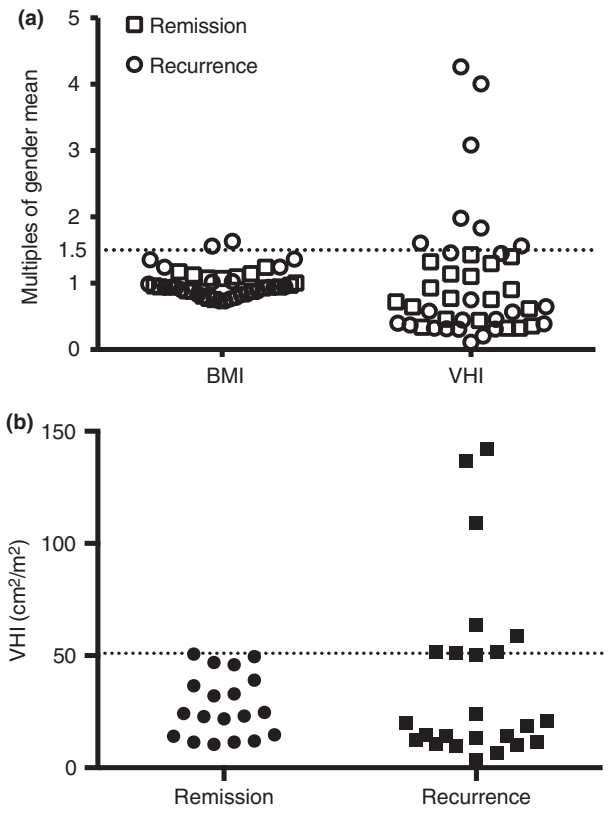


Figure 2 | (a) Values for body mass index (BMI) were clustered around the gender-specific mean. VHI (visceral adipose tissue area/height^2) exhibited a greater range, with all subjects with VHI >1.5 times the gender mean demonstrating endoscopic recurrence; (b) All subjects with visceral adipose tissue area/height^2 (VHI) >51 cm^2/m^2 had endoscopic recurrence.

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 μg/g ± 879 vs. 1095 μg/g ± 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]

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 post-operative recurrence of Crohn's disease,[41] with previous studies associating increased hazard with patient and surgical parameters such as smoking, disease behaviour, resection length and history of previous resection,[19] serology[28, 42] and microbial factors.[26] Prior steroid use has been associated with a reduced risk of post-operative recurrence in a meta-analysis.[43] 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

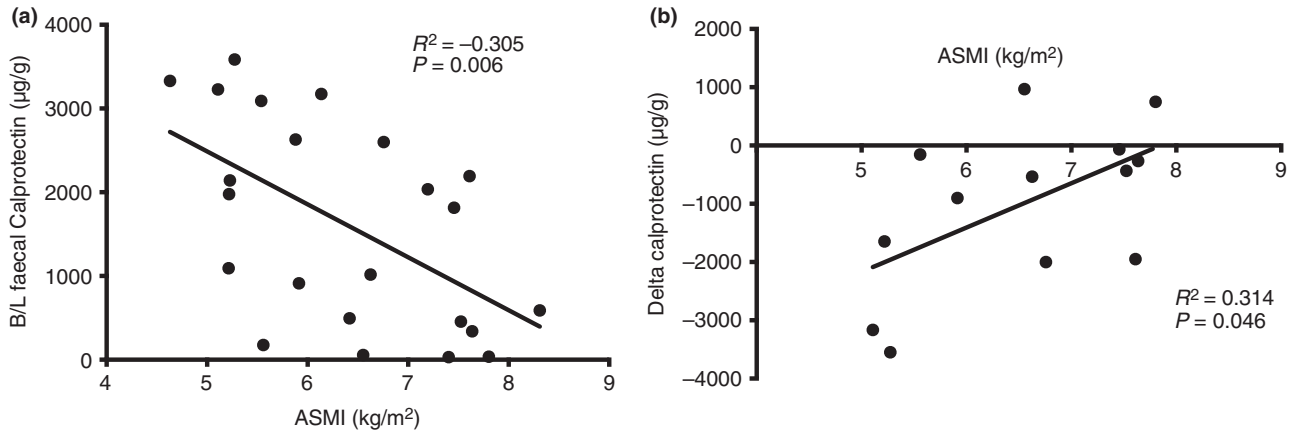


Figure 3 | (a) A negative association between calculated appendicular skeletal muscle index (ASMI) and faecal calprotectin existed, and (b) was consistent across the study period.

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 values[33] 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 pre-determined 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 sarcopenia,[46] with a recent systematic review[47] finding that body composition parameters often varied from population norms, including lower bone mineral density,[48] 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 controls[51] 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 patients,[53] 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 index.[54] 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 analysis.[39] 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 follow-up.[15] High mesenteric fat index, but not BMI nor abdominal circumference, was associated with 30-day morbidity in a retrospective cohort of 143 patients.[55] Conversely, a lower mesenteric fat index has been associated with more post-operative infectious complications in Crohn's disease.[56] 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 ratios,[57] 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 calprotectin.[60] 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 postoperative management strategies.

AUTHORSHIP

Guarantor of the article: Darcy Holt.

Author contributions: 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.

ACKNOWLEDGEMENTS

We thank 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.

Declaration of personal interests: 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.

Declaration of funding interests: This work was supported by Crohn's and Colitis Australia (the Angela McAvoy AM Fellowship to Gregory Moore).

REFERENCES

1. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. *Nat Rev Immunol* 2011; **11**: 85–97.
2. Desreumaux P. Specific targeting of IL-6 signalling pathway: a new way to treat IBD? *Gut* 2000; **47**: 465–6.
3. Crohn BB, Ginzburg L, Oppenheimer GD. Regional ileitis; a pathologic and clinical entity. *Am J Med* 1952; **13**: 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; **79**: 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; **15**: 1499–507.
6. Decousus S, Boucher A-L, Joubert J, *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; **48**: 753–8.
7. Sokol H, Polin V, Lavergne-Slove A, *et al.* Plexitis as a predictive factor of early postoperative clinical recurrence in Crohn's disease. *Gut* 2009; **58**: 1218–25.
8. Bressenot A, Peyrin-Biroulet L. Histologic features predicting postoperative Crohn's disease recurrence. *Inflamm Bowel Dis* 2015; **21**: 468–75.
9. Matsuzawa Y. Establishment of a concept of visceral fat syndrome and discovery of adiponectin. *Proc Jpn Acad Ser B* 2010; **86**: 131–41.
10. Yoshizumi T, Nakamura T, Yamane M, *et al.* Abdominal fat: standardized technique for measurement at CT. *Radiology* 1999; **211**: 283–6.
11. Shen W, Punyanitya M, Wang Z, *et al.* Visceral adipose tissue: relations between single-slice areas and total volume. *Am J Clin Nutr* 2004; **80**: 271–8.
12. Shen W, Wang Z, Punyanita M, *et al.* Adipose tissue quantification by imaging methods: a proposed classification. *Obes Res* 2003; **11**: 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; **33**: 997–1006.
14. Desreumaux P, Ernst O, Geboes K, *et al.* Inflammatory alterations in mesenteric adipose tissue in Crohn's disease. *Gastroenterology* 1999; **117**: 73–81.
15. Büning C, von Kraft C, Hermsdorf M, *et al.* Visceral adipose tissue in patients with Crohn's disease correlates with disease activity, inflammatory markers, and outcome. *Inflamm Bowel Dis* 2015; **21**: 2590–7.
16. Osborn O, Olefsky JM. The cellular and signaling networks linking the immune system and metabolism in disease. *Nat Med* 2012; **18**: 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; **112**: 1796–808.
18. Cosnes J, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology* 2011; **140**: 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; **35**: 625–33.
20. De Cruz P, Kamm MA, Hamilton AL, *et al.* Crohn's disease management after intestinal resection: a randomised trial. *Lancet* 2015; **385**: 1406–17.
21. Wright EK, Kamm MA, Dr Cruz P, *et al.* Cost-effectiveness of Crohn's disease post-operative care. *World J Gastroenterol* 2016; **22**: 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; **18**: 758–77.
23. De Cruz P, Kamm MA, Hamilton AL, *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; **42**: 867–79.
24. De Cruz P, Bernardi MP, Kamm MA, *et al.* Postoperative recurrence of Crohn's disease: impact of endoscopic monitoring and treatment step-up. *Colorectal Dis* 2013; **15**: 187–97.
25. Wright EK, Kamm MA, De Cruz P, *et al.* Measurement of fecal calprotectin improves monitoring and detection of recurrence of Crohn's disease after surgery. *Gastroenterology* 2015; **148**: 938–47; e1.
26. Wright EK, Kamm MA, Wagner J, *et al.* Microbial factors associated with postoperative Crohn's disease Recurrence. *J Crohns Colitis* 2017; **11**: 191–203.
27. Wright EK, Kamm MA, De Cruz P, *et al.* Effect of intestinal resection on quality of life in Crohn's disease. *J Crohns Colitis* 2015; **9**: 452–62.
28. Hamilton AL, Kamm MA, De Cruz P, *et al.* Serologic antibodies in relation to outcome in post-operative Crohn's disease. *J Gastroenterol Hepatol* 2016; doi: 10.1111/jgh.13677 [Epub ahead of print].
29. Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. *Gastroenterology* 1990; **99**: 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; **15**: 370–6.
31. Kullberg J, Brandberg J, Angelhed J-E, *et al.* Whole-body adipose tissue analysis: comparison of MRI, CT and dual energy X-ray absorptiometry. *Br J Radiol* 2009; **82**: 123–30.
32. Bonekamp S, Ghosh P, Crawford S, *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; **32**: 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; **51**: 842–7.
34. Ciudin A, Salvador R, Budoy A, *et al.* Measurement of waist circumference for retrospective studies - prospective validation of use of CT images to assess abdominal circumference. *Endocrinol Nutr* 2014; **61**: 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, *et al.* Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol* 1998; **147**: 755–63.
37. Gallagher D, Visser M, De Meersman RE, *et al.* Appendicular skeletal muscle mass: effects of age, gender, and ethnicity. *J Appl Physiol* 1997; **83**: 229–39.
38. Katznelson L, Fairfield WP, Zeizafoun N, *et al.* Effects of growth hormone secretion on body composition in patients with Crohn's disease. *J Clin Endocrinol Metab* 2003; **88**: 5468–72.
39. Ding Z, Wu XR, Remer EM, *et al.* Association between high visceral fat area and postoperative complications in patients with Crohn's disease following primary surgery. *Colorectal Dis* 2016; **18**: 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; **20**: 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; **39**: 1253–65.
42. Prideaux L, De Cruz P, Ng SC, Kamm MA. Serological antibodies in inflammatory bowel disease: a systematic review. *Inflamm Bowel Dis* 2012; **18**: 1340–55.
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; **28**: 545–56.
44. Regueiro M, Feagan BG, Zou B, *et al.* Infliximab reduces endoscopic, but not clinical, recurrence of Crohn's disease after ileocolonic resection. *Gastroenterology* 2016; **150**: 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; **40**: 322–2.
46. Schneider SM, Al-Jaouni R, Filippi J, *et al.* Sarcopenia is prevalent in patients with Crohn's disease in clinical remission. *Inflamm Bowel Dis* 2008; **14**: 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; **38**: 213–25.
48. Bernstein CN, Leslie WD, Leboff MS. AGA technical review on osteoporosis in gastrointestinal diseases. *Gastroenterology* 2003; **124**: 795–841.
49. Bryant RV, Ooi S, Schultz CG, *et al.* Low muscle mass and sarcopenia: common and predictive of osteopenia in inflammatory bowel disease. *Aliment Pharmacol Ther* 2015; **41**: 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; **33**: 956–60.
51. Peyrin-Biroulet L, Chamaillard M, Gonzalez F, *et al.* Mesenteric fat in Crohn's disease: a pathogenetic hallmark or an innocent bystander? *Gut* 2007; **56**: 577–83.
52. Thangarajah D, Chappell KE, Gale C, *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, *et al.* Visceral fat area is associated with a high risk for early postoperative recurrence in Crohn's disease. *Colorectal Dis* 2015; **17**: 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; **9**: 684–7; 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 ileocolectomy outcomes in Crohn's disease patients. *Dig Surg* 2014; **31**: 219–24.
56. Stidham RW, Waljee AK, Day NM, *et al.* Body fat composition assessment using analytic morphomics predicts infectious complications after bowel resection in Crohn's disease. *Inflamm Bowel Dis* 2015; **21**: 1306–13.

57. Abdou RM, Zhu L, Baker RD, Baker SS. Gut microbiota of nonalcoholic fatty liver disease. *Dig Dis Sci* 2016; **61**: 1268–81.
58. Albenberg LG, Wu GD. Diet and the intestinal microbiome: associations, functions, and implications for health and disease. *Gastroenterology* 2014; **146**: 1564–72.
59. Wu GD, Bushmanc FD, Lewis JD. Diet, the human gut microbiota, and IBD. *Anaerobe* 2013; **24**: 117–20.
60. Reisinger KW, Derikx JPM, van Vugt JLA, *et al.* Sarcopenia is associated with an increased inflammatory response to surgery in colorectal cancer. *Clin Nutr* 2016; **35**: 924–7.
61. Benatti FB, Pedersen BK. Exercise as an anti-inflammatory therapy for rheumatic diseases-myokine regulation. *Nat Rev Rheumatol* 2015; **11**: 86–97.
62. Pedersen BK. Exercise-induced myokines and their role in chronic diseases. *Brain Behav Immun* 2011; **25**: 811–6.

Summary and discussion

This study joins a small literature validating body composition as a risk factor for post-operative recurrence of Crohn's disease. Our finding, that excessive visceral adiposity was associated with endoscopic recurrence, regardless of treatment, was similar to that of a retrospective cohort study[9] published during the preparation of this manuscript. It agreed with our first hypothesis for this study, hypothesis 6: *That body composition parameters predict endoscopic recurrence after surgery for Crohn's disease*. Unfortunately, the number of patients with adalimumab levels was small (seven only), making impossible any analysis of a conjectured inverse correlation between visceral adipose tissue area and adalimumab levels (hypothesis 7: *That increased visceral adipose tissue is associated with less response to treatment with adalimumab, and with lower serum adalimumab levels*).

Other limitations of the study include statistical constraints: as the index of visceral adipose tissue to height (VHI) was not normally-distributed, and as all subjects with a VHI greater than 1.5 times the gender mean had endoscopic recurrence (pseudo-separation of data), it was difficult to incorporate this measure into standard regression analyses. Visual inspection of the distribution of values of VHI compared with body mass index, with outcomes (figure 2), underscores the conclusions of this chapter.
The multiple possible treatments also make determination of interaction between body composition and prophylactic medical therapy for Crohn's disease difficult in a sample of this size. For example, of the 33 subjects in this sample who were randomised to early endoscopy, the seven low-risk subjects all remained in endoscopic remission at six months; six of the 33 patients began the study being treated with adalimumab, and of the twenty treated with thiopurines, 50% were escalated to adalimumab. In this circumstance, multivariable regression analysis was not reliable.

Building a predictive model which incorporated visceral adipose tissue to height index, smoking status, disease factors such as penetrating phenotype, and possibly microbial[10], genetic[11,12], and surgical variables may allow more appropriate and cost-effective use of prophylactic therapies. This model, and the directed therapeutic interventions, will need to be prospectively validated – but this work does demonstrate that body composition is a predictor of risk.

Chapter references

1. Cosnes J, Cattan S, Blain A, Beaugerie L, Carbonnel F, Parc R, et al. Long-term evolution of disease behavior of Crohn's disease. Inflamm Bowel Dis. 2002 Jul;8(4):244–50.

2. 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.

3. Rutgeerts P. Crohn's disease recurrence can be prevented after ileal resection. Gut. 2002 Aug 1;51(2):152–3.

4. Lemann M. Review article: can post-operative recurrence in Crohn's disease be prevented? Aliment Pharmacol Ther. 2006 Oct;24 Suppl 3(s3):22–8.

5. Gionchetti P, Dignass A, Danese S, Magro Dias FJ, Rogler G, Lakatos PL, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 2: Surgical Management and Special Situations. J Crohns Colitis. Oxford University Press; 2017 Feb 1;11(2):135–49.

6. 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.

7. Schweitzer L, Geisler C, Pourhassan M, Braun W, Gluer CC, Bosy-Westphal A, et al. What is the best reference site for a single MRI slice to assess whole-body skeletal muscle and adipose tissue volumes in healthy adults? Am J Clin Nutr. 2015 Jul 1;102(1):58–65.

8. Hu HH, Chen J, Shen W. Segmentation and quantification of adipose tissue by magnetic resonance imaging. MAGMA. 2016 Apr;29(2):259–76.

9. 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.

10. 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.

11. Germain A, Guéant R-M, Chamaillard M, Bresler L, Guéant J-L, Peyrin-Biroulet L. CARD8 gene variant is a risk factor for recurrent surgery in patients with Crohn's disease. Dig Liver Dis. 2015 Nov;47(11):938–42.

12. Fowler SA, Ananthakrishnan AN, Gardet A, Stevens CR, Korzenik JR, Sands BE, et al. SMAD3 gene variant is a risk factor for recurrent surgery in patients with Crohn's disease. J Crohns Colitis. 2014 Aug;8(8):845–51.

Chapter 8: Conclusion

Main findings

The format of this thesis by publication entails discussion of the findings of individual studies, placed in the context of cited existing research, within the text of each chapter. Describing the studies as constituents of a whole body of research, therefore, is the purpose of this concluding chapter. Some repetition of key themes and findings is inescapable, but this synopsis aims to demonstrate an overarching narrative; many previously cited references are omitted in the interests of concision.

The systematic review of the literature in this thesis has revealed multifactorial and bidirectional interactions between body composition and treatment for Crohn's disease. Crohn's disease is associated with particular changes in body composition: loss of muscle and bone, and increased visceral adipose tissue. In turn, these changes have prognostic implications and may predict response to treatment. In an era when 'precision medicine' – an integrative approach combining genomics, proteomics, patient and environmental factors to identify subgroups for the selection of optimal diagnostic tests and treatments – is a policy and research priority, the use of body composition analysis appears to offer much value. However, there are significant deficits in the literature regarding choice of medications based on likelihood of response, optimal dosing of existing and novel therapies, and nutritional and medical protocols to avoid osteoporosis, muscle wasting and impaired muscle function in Crohn's disease. Routine application of body composition analysis may better inform treatment decisions in these areas, but the systematic review has identified that prospective trials examining body composition as a determining factor of treatment are lacking. Many of the drugs used to treat Crohn's disease have not been subject to studies to determine optimal dosage: not at all in the case of corticosteroids, thiopurines and methotrexate, and not in relation to body composition compartments and the effect of body composition on pharmacokinetics for newer therapies such as anti-TNF and anti-integrin agents. There are limited data regarding the effect of physiological, anatomical or functional compartments of body composition on disease-related outcomes.

Precision medicine and personalised medicine are evolutions of a concept that places the individual patient at the centre of the diagnostic process and therapy. Assimilating measures of the patient experience is fundamental to this approach. The questionnaire distributed to members of a national patient support group, described in chapter 3, interrogated beliefs regarding the importance of diet in inflammatory bowel disease. From a large sample, information regarding the distribution of body weight in a contemporary cohort of patients provided a different perspective to historical publications. The prevalence of dietary restriction, the diversity of advice given by practitioners, and the disconnection between patient experience and beliefs and practitioner recommendations highlight the need for a stronger research base in the area of nutrition in inflammatory bowel disease. As one of the major determinants of body composition, quantifying current nutritional practices in an Australian setting provides context for the subsequent research areas of the thesis.

Chapter 4 describes the validation of a technique for utilising existing CT and MRI abdominal imaging to estimate whole-body measures of body composition in Crohn's disease patients. This method had not previously been validated in this context. Low muscle mass was prevalent in the described cohort of Crohn's disease patients, with low muscle mass measured by cross-sectional imaging associated with low bone mineral density measured by DXA.

The next chapter applies the method validated in chapter 4 to a cohort of Crohn's disease patients treated with a cornerstone of therapy, the thiopurine anti-metabolites. As the systematic review identified, there were no dose-finding studies of these medications in Crohn's disease, but current guidelines suggest that the dose should be determined by weight. Moving towards an individualised approach, recent research has shown that intracellular concentrations of thiopurine metabolites are associated with treatment efficacy and toxicity. Thiopurine metabolite testing now forms a part of clinical practice – although prospective trial evidence of its benefit is scarce. Chapter 5 found that the conventional, weight-based, method of thiopurine dosing was not associated with levels of therapeutic thiopurine metabolites, nor was dose adjusted for body composition parameters. Potentially toxic metabolite levels correlated with higher drug doses and lower fat-free mass. This was the first publication evaluating body composition and thiopurine metabolite levels, but the findings are supported by several studies examining the effect of body weight on metabolite levels, and suggest that arbitrary dosing – at less than a threshold level of approximately 3.2 milligrams of azathioprine

per kilogram of fat-free mass, to avoid toxicity – and then adjustment per metabolite testing may be an optimal strategy.

Despite high rates of initial clinical response to anti-TNF drugs, the majority of patients treated with these medications experience loss of response. Chapter 6 explored the effect on clinical outcomes of body composition prior to anti-TNF initiation. No papers regarding anti-TNF drugs and body composition in Crohn's disease have been published. The methods described in chapter 4 were again used. A hypothesised interaction between visceral adipose tissue area and time to loss of response was not found. Low muscle mass relative to a young adult mean was prevalent. Patients with skeletal muscle area lower than the cohort median experienced significantly earlier loss of response to anti-TNF therapy. Clinical patient-specific risk factors, rather than genetic, disease-related or medication-related factors, are scarce. The implications of this finding may be pharmacokinetic – with different doses of anti-TNF required in myopenic patients to achieve therapeutic levels and clinical efficacy – or may highlight the need for earlier intervention to prevent the development of cachexia. The combined use of body composition analysis and drug level monitoring in this circumstance of high inflammatory burden may allow precision use of medical therapy.

An individualised approach to prevent post-operative recurrence of Crohn's disease is already relatively advanced. The POCER study was an interventional trial in which known risk factors for recurrence, such as smoking status, perforating disease and prior surgery were used to stratify subjects, determine initial post-operative medical treatment and allow randomisation to early endoscopy and treatment escalation or standard care. A number of subjects were identified with recent cross-sectional imaging, which permitted body composition analysis. The major finding of this investigation was that large visceral adipose tissue area, particularly when adjusted for gender and height, is associated with endoscopic recurrence. A negative correlation existed between skeletal muscle area and an important biomarker of Crohn's disease activity.

Implications and significance of this research

Elements of this research project address absences of published data in areas identified by a systematic review of the literature. While the findings must be taken in the context of each study design without unwarranted extrapolation, the novel information generated by this research and identification of body composition as a determinant of outcomes in Crohn's disease may

form a basis for further investigation, and development of strategies for optimal individualised medical management.

Patients with inflammatory bowel disease place great importance in their diet but do not believe this concern is shared by their treating clinicians. The qualitative evidence obtained from the questionnaire study in chapter 3 provides a background for developing evidence-based dietary guidelines in an Australian context, as dietary modification was common while specialised advice was often unheeded or not received. Clinicians gave a diversity of advice, which reflects a lack of clear, professionally-endorsed guidance. A higher prevalence of overweight and obesity was reported than in many historical cohorts, which may have implications for dietary recommendations, health policy and treatment choices and costs. A relationship between drug therapy and body composition was suggested by the significant association between repeated courses of corticosteroids and increased weight; this adds to a literature regarding the effect of corticosteroids on body composition and may inform an individualised treatment approach.

The technique of body composition analysis described in chapter 4 had been previously been used in other patient groups, but its validation against the reference standard of DXA in this setting unlocks the possibility of body composition analysis in many existing and well-characterised research cohorts, as most Crohn's disease patients have suitable scans performed as part of their routine clinical care. Retrospective analysis of body composition in existing trial and clinical datasets permits further understanding of the effect of body composition on treatment for Crohn's disease by providing robust data for incorporation into regression analysis, and does so without extraneous radiation exposure or the requirement for subjects to undergo further testing.

Contrary to our hypothesis in chapter 5, the relationship between body composition compartments and thiopurine dose did not correlate with therapeutic metabolite levels. Instead, a relationship between treatment toxicity and low muscle mass relative to drug dose was identified. This may form the basis of further research to offer an improved dosing algorithm.

Low skeletal muscle mass in Crohn's disease patients is associated with greater disease severity and longer duration of illness. It is a reversible state, but prevention, identification and treatment do not form part of present Crohn's disease treatment algorithms. Finding that low

muscle mass, independent of disease duration or clinical phenotype, was associated with earlier loss of response to anti-TNF drugs (chapter 6) has implications for clinical practice. It suggests that early treatment directed at improving muscle mass may have beneficial clinical effects, and that anti-TNF drug efficacy may be affected by muscle mass. Pharmacokinetic, immunological and disease-specific factors may be responsible for this effect, and further research into the interaction between muscle mass and anti-TNF drugs may allow improvements in the use of this medication class.

The post-operative setting provides a unique opportunity to evaluate the efficacy of Crohn's disease treatments and identify risk factors for recurrent disease: standardised systems for grading endoscopic recurrence exist, and endpoints and chronology are easily flagged. The effect of risk factors can be easily studied. Finding that subjects with high levels of visceral adiposity were particularly susceptible to endoscopic recurrence adds to a small list of patient-specific factors known to contribute to risk. This may prompt more aggressive disease therapy after Crohn's disease surgery for patients with greater amounts of visceral fat, and highlights this body composition compartment as an active player in the inflammatory milieu.

Limitations

Perhaps inevitably, research expectations and study designs have changed during this project. From an initial focus on the role of fat-derived cell signals – adipocytokines – in Crohn's disease, the research has moved to encompass more clinical outcomes. This has meant a reliance on retrospective analysis, although two of the studies have examined outcomes after a defined intervention. A weakness of this research is the lack of a prospective, interventional component. The direction of causality cannot be established; although the two-way, complex interactions between Crohn's disease and body composition make this unlikely to be established even in prospective studies. Whereas we may surmise that low muscle mass is a cause of anti-TNF failure due to pharmacokinetic reasons, it may be the case that low muscle mass reflects an underlying refractory disease phenotype (chapter 6).

Selection bias was possible in chapters 5-7, as only patients with relatively contemporaneous abdominal imaging were included in analysis. The clinical indication for the scan may have meant that patients were more unwell, or had a greater incidence of penetrating disease, for example. However, as the comparisons in these studies were internal, this bias may only mean the need for extra caution when extrapolating findings to other groups.

Questionnaire design proved somewhat problematic in chapter 3. While a great deal of data was returned, and gratefully received, analysis of qualitative data was difficult. There were few opportunities to directly compare the responses obtained from patients and those from clinicians, and data interpretation may have been more powerful with the use of more continuous variables to allow correlation analysis rather than an over-reliance on categorical responses. Lessons were learned regarding fundamentals of questionnaire design. No question concerned the prevalence of body composition measurement, by DXA or other methods, in this large cohort, or the likelihood of clinicians to request this. Despite these limitations, further analysis of the large dataset is possible, and there were omissions from the publication after peer review.

The absence of disease outcome measures in chapter 5 is an important limitation. The findings are weakened by the lack of data regarding thiopurine methyltransferase genotype and aminosalicylate co-prescription, both important factors in thiopurine metabolism. This information was not consistently recorded in the cohort being studied, which emphasises the utility of systems of data collection and management in clinical contexts.

Retrospective analysis of a prospective trial has the advantages of carefully recorded data and defined endpoints, however, the complexity of the POCER study and the relatively small number of subjects made subgroup analysis impossible. While the findings of chapter 7 are notable, larger patient numbers and fewer treatment options may have made possible stronger regression analysis to determine the significance of visceral adiposity as a risk factor for endoscopic recurrence of Crohn's disease.

Recommendations for practitioners, and direction of future work

Predictive modelling of Crohn's disease activity and drug effects in individual patients to direct optimal safe, cost-effective treatment is a growing and necessary area of research. Body composition analysis has been relatively neglected in this field of study. Barriers to its prospective use include a lack of incorporation in guidelines, the absence of a single standardised, universally valid method and occasionally esoteric nomenclature. Access to many techniques of body composition can be limited in clinical settings.

Despite these impediments, routinely including body composition analysis in a healthcare setting at the current time may offer benefits to individual patients, by identifying treatable causes of disease-related morbidity such as osteoporosis and sarcopenia. Whole-body DXA provides accurate information regarding components of body composition and is generally available. Periodic DXA scanning is recommended for Crohn's disease patients to assess bone mineral density, but utilisation is poor. Clinicians should feel encouraged to consider greater uptake. Failure to recognise the presence, or effects, of changes in body composition is often due to not looking for them.

The identified lack of strong evidence-based dietary guidelines for inflammatory bowel disease patients should prompt further study into the role of diet in the pathogenesis and symptomatology of Crohn's disease.

Other clinical messages from this research include the suggestion that thiopurine dosing is best guided by metabolite level testing rather than weight-based dosing or dose escalation in underweight subjects, that low muscle mass be considered a risk factor for treatment failure with anti-TNF drugs, and that visceral adiposity may confer extra risk of endoscopic recurrence in post-operative Crohn's disease patients; perhaps indicating greater treatment requirements.

This thesis has identified body composition as a likely component of a composite predictive model of Crohn's disease behaviour and therapeutic requirement. Further research may confirm this, and establish its place in clinical practice. This research may include retrospective analysis of previous study cohorts using the methods described in chapter 4, as well as prospective studies incorporating body composition analysis.

Pharmacokinetic studies and drug trials which incorporate body composition measurement are needed. While a need exists for prospective trials, thiopurines and anti-TNF drugs have well-defined threshold measurements for therapeutic efficacy, with datasets in clinical settings that may allow retrospective analysis. Results would seek to optimise drug selection and dosing in a setting where treatment failure and toxicity are common.

Better understanding of the drivers of muscle and bone catabolism in Crohn's disease, and the disease-related sequelae of these changes, may help to define phenotypes with prognostic implications and may identify new molecular targets of treatment. While much of the literature

identified in the systematic review reported measures of well-described cytokines such as TNF-alpha and interleukin-6, future research will benefit from more accessible genotypic and proteomic analysis to determine links. After identification of a body composition phenotype, genome-wide association studies may provide further information regarding genetic variations that confer susceptibility. Such an approach has already been used in cachexia associated with malignancy and chronic obstructive pulmonary disease.

In the post-operative setting, incorporation of body composition measurement and assessment of visceral adiposity into treatment algorithms may have clinical benefit; this finding should be validated in other cohorts.

Summary

Body composition in Crohn's disease is affected by disease severity and duration with loss of skeletal muscle and bone mineral density, and increased visceral adiposity, being hallmarks of the condition. A diversity of practice regarding the role of diet exists within clinicians treating inflammatory bowel disease and despite patients observing widespread dietary restrictions, their expectations of specific advice are not met by practitioners. Accurate analysis of body composition is possible using abdominal imaging which is frequently obtained as part of routine clinical care. Low skeletal muscle mass is associated with earlier failure of anti-TNF treatment, and potentially hepatotoxic thiopurine metabolite levels, but body composition analysis does not predict therapeutic metabolite levels. Increased visceral adiposity is associated with Crohn's disease recurrence after surgery.

These findings place body composition central to the concept of individualised treatment for Crohn's disease, as a prognostic factor and determinant of drug efficacy and toxicity.

Appendices

Copyright agreements are included as appendices.

Journal of Human Nutrition & Dietetics

Published by Wiley on behalf of British Dietetic Association (the "Owner")

COPYRIGHT TRANSFER AGREEMENT

Date: 2016-05-27

Contributor name: Darcy Quinn Holt

Contributor address: Gastroenterology/Clinical Nutrition & Metabolism Research Fellow Monash Health, Monash Medical Centre 246 Clayton Road, Clayton, Victoria 3168, Australia

Manuscript number: JHND-16-01-0036-OR.R2

Re: Manuscript entitled Patients with inflammatory bowel disease and their treating clinicians have different views regarding diet (the "Contribution")

for publication in Journal of Human Nutrition & Dietetics (the "Journal")

published by John Wiley & Sons Ltd ("Wiley")

Dear Contributor(s):

Thank you for submitting your Contribution for publication. In order to expedite the editing and publishing process and enable the Owner to disseminate your Contribution to the fullest extent, we need to have this Copyright Transfer Agreement executed. If the Contribution is not accepted for publication, or if the Contribution is subsequently rejected, this Agreement shall be null and void.
Publication cannot proceed without a signed copy of this Agreement.

A. COPYRIGHT

1. The Contributor assigns to the Owner, during the full term of copyright and any extensions or renewals, all copyright in and to the Contribution, and all rights therein, including but not limited to the right to publish, republish, transmit, sell, distribute and otherwise use the Contribution in whole or in part in electronic and print editions of the Journal and in derivative works throughout the world, in all languages and in all media of expression now known or later developed, and to license or permit others to do so. For the avoidance of doubt, "Contribution" is defined to only include the article submitted by the Contributor for publication in the Journal and does not extend to any

supporting information submitted with or referred to in the Contribution ("Supporting Information"). To the extent that any Supporting Information is submitted to the Journal for online hosting, the Owner is granted a perpetual, non-exclusive license to host and disseminate this Supporting Information for this purpose.

2. Reproduction, posting, transmission or other distribution or use of the final Contribution in whole or in part in any medium by the Contributor as permitted by this Agreement requires a citation to the Journal suitable in form and content as follows: (Title of Article, Contributor, Journal Title and Volume/Issue, Copyright © [year], copyright owner as specified in the Journal, Publisher). Links to the final article on the publisher website are encouraged where appropriate.

B. RETAINED RIGHTS

Notwithstanding the above, the Contributor or, if applicable, the Contributor's employer, retains all proprietary rights other than copyright, such as patent rights, in any process, procedure or article of manufacture described in the Contribution.

C. PERMITTED USES BY CONTRIBUTOR

1. Submitted Version. The Owner licenses back the following rights to the Contributor in the version of the Contribution as originally submitted for publication (the "Submitted Version"):

> **a.** The right to self-archive the Submitted Version on the Contributor's personal website, place in a not for profit subject-based preprint server or repository or in a Scholarly Collaboration Network (SCN) which has signed up to the STM article sharing principles [http://www.stm-assoc.org/stm-consultations/scn-consultation-2015/] ("Compliant SCNs"), or in the Contributor's company/ institutional repository or archive. This right extends to both intranets and the Internet. The Contributor may replace the Submitted Version with the Accepted Version, after any relevant embargo period as set out in paragraph C.2(a) below has elapsed. The Contributor may wish to add a note about acceptance by the Journal and upon publication it is recommended that Contributors add a Digital Object Identifier (DOI) link back to the Final Published Version.
>
> **b.** The right to transmit, print and share copies of the Submitted Version with colleagues, including via Compliant SCNs, provided that there is no systematic distribution of the Submitted Version, e.g. posting on a listserve, network (including SCNs which have not signed up to the STM sharing principles) or automated delivery.

2. Accepted Version. The Owner licenses back the following rights to the Contributor in the version of the Contribution that has been peer-reviewed and accepted for publication, but not final (the "Accepted Version"):

> **a.** The right to self-archive the Accepted Version on the Contributor's personal website, in the Contributor's company/institutional repository or archive, in Compliant SCNs, and in not for profit subject-based repositories such as PubMed Central, subject to an embargo period of 12 months for scientific, technical and medical (STM) journals and 24 months for social science and humanities (SSH) journals following publication of the Final Published Version. There are separate arrangements with certain funding agencies governing reuse of the Accepted Version as set forth at the following website: http://www.wiley.com/go/funderstatement. The Contributor may not update the Accepted Version or replace it with the Final Published Version. The Accepted Version posted must contain a legend as follows: This is the accepted version of the following article: FULL CITE, which has been published in final form at [Link to final article]. This article may be used for non-commercial purposes in accordance with the Wiley Self-Archiving Policy [http://olabout.wiley.com/WileyCDA/Section/id-820227.html].

b. The right to transmit, print and share copies of the Accepted Version with colleagues, including via Compliant SCNs (in private research groups only before the embargo and publicly after), provided that there is no systematic distribution of the Accepted Version, e.g. posting on a listserve, network (including SCNs which have not signed up to the STM sharing principles) or automated delivery.

3. Final Published Version. The Owner hereby licenses back to the Contributor the following rights with respect to the final published version of the Contribution (the "Final Published Version"):

a. Copies for colleagues. The personal right of the Contributor only to send or transmit individual copies of the Final Published Version in any format to colleagues upon their specific request, and to share copies in private sharing groups in Compliant SCNs, provided no fee is charged, and further provided that there is no systematic external or public distribution of the Final Published Version, e.g. posting on a listserve, network or automated delivery.

b. Re-use in other publications. The right to re-use the Final Published Version or parts thereof for any publication authored or edited by the Contributor (excluding journal articles) where such re-used material constitutes less than half of the total material in such publication. In such case, any modifications must be accurately noted.

c. Teaching duties. The right to include the Final Published Version in teaching or training duties at the Contributor's institution/place of employment including in course packs, e-reserves, presentation at professional conferences, in-house training, or distance learning. The Final Published Version may not be used in seminars outside of normal teaching obligations (e.g. commercial seminars). Electronic posting of the Final Published Version in connection with teaching/training at the Contributor's company/institution is permitted subject to the implementation of reasonable access control mechanisms, such as user name and password. Posting the Final Published Version on the open Internet is not permitted.

d. Oral presentations. The right to make oral presentations based on the Final Published Version.

4. Article Abstracts, Figures, Tables, Artwork and Selected Text (up to 250 words).

a. Contributors may re-use unmodified abstracts for any non-commercial purpose. For online uses of the abstracts, the Owner encourages but does not require linking back to the Final Published Version.

b. Contributors may re-use figures, tables, artwork, and selected text up to 250 words from their Contributions, provided the following conditions are met:

(i) Full and accurate credit must be given to the Final Published Version.

(ii) Modifications to the figures and tables must be noted. Otherwise, no changes may be made.

(iii) The re-use may not be made for direct commercial purposes, or for financial consideration to the Contributor.

(iv) Nothing herein will permit dual publication in violation of journal ethical practices.

D. CONTRIBUTIONS OWNED BY EMPLOYER

1. If the Contribution was written by the Contributor in the course of the Contributor's employment (as a "work-made-for-hire" in the course of employment), the Contribution is owned by the company/institution which must execute this Agreement (in addition to the Contributor's signature). In such case, the company/institution

hereby assigns to the Owner, during the full term of copyright, all copyright in and to the Contribution for the full term of copyright throughout the world as specified in paragraph A above.

For company/institution-owned work, signatures cannot be collected electronically and so instead please print off this Agreement, ask the appropriate person in your company/institution to sign the Agreement as well as yourself in the space provided below, and email a scanned copy of the signed Agreement to the Journal production editor. For production editor contact details, please visit the Journal's online author guidelines.

2. In addition to the rights specified as retained in paragraph B above and the rights granted back to the Contributor pursuant to paragraph C above, the Owner hereby grants back, without charge, to such company/institution, its subsidiaries and divisions, the right to make copies of and distribute the Final Published Version internally in print format or electronically on the Company's internal network. Copies so used may not be resold or distributed externally. However, the company/institution may include information and text from the Final Published Version as part of an information package included with software or other products offered for sale or license or included in patent applications. Posting of the Final Published Version by the company/institution on a public access website may only be done with written permission, and payment of any applicable fee(s). Also, upon payment of the applicable reprint fee, the company/institution may distribute print copies of the Final Published Version externally.

E. GOVERNMENT CONTRACTS

In the case of a Contribution prepared under U.S. Government contract or grant, the U.S. Government may reproduce, without charge, all or portions of the Contribution and may authorize others to do so, for official U.S. Government purposes only, if the U.S. Government contract or grant so requires. (U.S. Government, U.K. Government, and other government employees: see notes at end.)

F. COPYRIGHT NOTICE

The Contributor and the company/institution agree that any and all copies of the Final Published Version or any part thereof distributed or posted by them in print or electronic format as permitted herein will include the notice of copyright as stipulated in the Journal and a full citation to the Journal.

G. CONTRIBUTOR'S REPRESENTATIONS

The Contributor represents that the Contribution is the Contributor's original work, all individuals identified as Contributors actually contributed to the Contribution, and all individuals who contributed are included. If the Contribution was prepared jointly, the Contributor has informed the co-Contributors of the terms of this Agreement and has obtained their written permission to execute this Agreement on their behalf. The Contribution is submitted only to this Journal and has not been published before, has not been included in another manuscript, and is not currently under consideration or accepted for publication elsewhere. If excerpts from copyrighted works owned by third parties are included, the Contributor shall obtain written permission from the copyright owners for all uses as set forth in the standard permissions form or the Journal's Author Guidelines, and show credit to the sources in the Contribution. The Contributor also warrants that the Contribution and any submitted Supporting Information contains no libelous or unlawful statements, does not infringe upon the rights (including without limitation the copyright, patent or trademark rights) or the privacy of others, or contain material or instructions that might cause harm or injury. The Contributor further warrants that there are no conflicts of interest relating to the Contribution, except as disclosed. Accordingly, the Contributor represents that the following information shall be clearly identified on the title page of the Contribution: (1) all financial and material support for the research and work; (2) any financial interests the Contributor or any co-Contributors may have in companies or other entities that have an

interest in the information in the Contribution or any submitted Supporting Information (e.g., grants, advisory boards, employment, consultancies, contracts, honoraria, royalties, expert testimony, partnerships, or stock ownership); and (3) indication of no such financial interests if appropriate.

H. USE OF INFORMATION

The Contributor acknowledges that, during the term of this Agreement and thereafter, the Owner (and Wiley where Wiley is not the Owner) may process the Contributor's personal data, including storing or transferring data outside of the country of the Contributor's residence, in order to process transactions related to this Agreement and to communicate with the Contributor. By entering into this Agreement, the Contributor agrees to the processing of the Contributor's personal data (and, where applicable, confirms that the Contributor has obtained the permission from all other contributors to process their personal data). Wiley shall comply with all applicable laws, statutes and regulations relating to data protection and privacy and shall process such personal data in accordance with Wiley's Privacy Policy located at: www.wiley.com/go/privacy.

[X] I agree to the COPYRIGHT TRANSFER AGREEMENT as shown above, consent to execution and delivery of the Copyright Transfer Agreement electronically and agree that an electronic signature shall be given the same legal force as a handwritten signature, and have obtained written permission from all other contributors to execute this Agreement on their behalf.

Contributor's signature (type name here): Darcy Holt

Date: 28/05/2016

SELECT FROM OPTIONS BELOW:

[X] Contributor-owned work

[ ] U.S. Government work

Note to U.S. Government Employees

A contribution prepared by a U.S. federal government employee as part of the employee's official duties, or which is an official U.S. Government publication, is called a "U.S. Government work", and is in the public domain in the United States. In such case, Paragraph A.1 will not apply but the Contributor must type his/her name (in the Contributor's signature line) above. Contributor acknowledges that the Contribution will be published in the United States and other countries. If the Contribution was not prepared as part of the employee's duties or is not an official U.S. Government publication, it is not a U.S. Government work.

[ ] U.K. Government work (Crown Copyright)

Note to U.K. Government Employees

For Crown Copyright this form cannot be completed electronically and should be printed off, signed in the Contributor's signatures section above by the appropriately authorised individual and returned to

the Journal production editor by email. For production editor contact details please visit the Journal's online author guidelines. *The rights in a contribution prepared by an employee of a UK government department, agency or other Crown body as part of his/her official duties, or which is an official government publication, belong to the Crown and must be made available under the terms of the Open Government Licence. Contributors must ensure they comply with departmental regulations and submit the appropriate authorisation to publish. If your status as a government employee legally prevents you from signing this Agreement, please contact the Journal production editor.*

[ ] Other

Including Other Government work or Non-Governmental Organisation work

Note to Non-U.S., Non-U.K. Government Employees or Non-Governmental Organisation Employees

For Other Government or Non-Governmental Organisation work this form cannot be completed electronically and should be printed off, signed in the Contributor's signatures section above by the appropriately authorised individual and returned to the Journal production editor by email. For production editor contact details please visit the Journal's online author guidelines. *If you are employed by the Department of Veterans Affairs in Australia, the World Bank, the World Health Organization, the International Monetary Fund, the European Atomic Energy Community, the Jet Propulsion Laboratory at California Institute of Technology, the Asian Development Bank, or are a Canadian Government civil servant, please download a copy of the license agreement from http://exchanges.wiley.com/authors/copyright-and-permissions_333.html and return it to the Journal Production Editor. If your status as a government or non-governmental organisation employee legally prevents you from signing this Agreement, please contact the Journal production editor.*

Name of Government/Non-Governmental Organisation:

_____

[ ] Company/institution owned work (made for hire in the course of employment)

For "work made for hire" this form cannot be completed electronically and should be printed off, signed and returned to the Journal production editor by email. For production editor contact details please visit the Journal's online author guidelines. *If you are an employee of Amgen, please download a copy of the company addendum from http://exchanges.wiley.com/authors/copyright-and-permissions_333.html and return your signed license agreement along with the addendum.*

Name of Company/Institution:

_____

Authorized Signature of Employer: _____

Date: _____

Signature of Employee: _____

Date: _____

PUBLISHING AGREEMENT

This is an agreement under which you, the author, assign copyright in your article to Informa UK Limited registered in England under no. 1072954 trading as Taylor & Francis Group, Registered Office: 5 Howick Place, London, SW1P 1WG (hereinafter 'Taylor & Francis') to allow us to publish your article, including abstract, tables, figures, data, and supplemental material hosted by us, as the Version of Record (VoR) in the Journal for the full period of copyright throughout the world, in all forms and all media, subject to the Terms & Conditions below.

Article (the "Article") entitled:	Body composition analysis using abdominal scans from routine clinical care in patients with Crohn's Disease
Article DOI:	10.3109/00365521.2016.1161069
Author(s):	Darcy Quinn Holt, Boyd Josef Strauss, Kenneth K Lau, Gregory Thomas Moore
To publish in the Journal:	Scandinavian Journal of Gastroenterology
Journal ISSN:	1502-7708

STATEMENT OF ORIGINAL COPYRIGHT OWNERSHIP / CONDITIONS

In consideration of the publication of the Article, you hereby grant with full title guarantee all rights of copyright and related rights in the above specified Article as the Version of Scholarly Record which is intended for publication in all forms and all media (whether known at this time or developed at any time in the future) throughout the world, in all languages, for the full term of copyright, to take effect if and when the Article is accepted for publication in the Journal.

ASSIGNMENT OF PUBLISHING RIGHTS

I hereby assign Taylor & Francis with full title guarantee all rights of copyright and related publishing rights in my article, in all forms and all media (whether known at this time or developed at any time in the future) throughout the world, in all languages, where our rights include but are not limited to the right to translate, create adaptations, extracts, or derivative works and to sub-license such rights, for the full term of copyright (including all renewals and extensions of that term), to take effect if and when the article is accepted for publication. If a statement of government or corporate ownership appears above, that statement modifies this assignment as described.

I confirm that I have read and accept the full Terms & Conditions below including my author warranties, and have read and agree to comply with the Journal's policies on peer review and publishing ethics.

Signed and dated: Darcy Quinn Holt, 01 March 2016

Taylor and Francis, 01 March 2016

ASSIGNMENT OF COPYRIGHT: TERMS & CONDITIONS

DEFINITION

1. Your article is defined as comprising (a) your Accepted Manuscript (AM) in its final form; (b) the final, definitive, and citable Version of Record (VoR) including the abstract, text, bibliography, and all accompanying tables, illustrations, data, and media; and (c) any supplemental material hosted by Taylor & Francis. This assignment and these Terms & Conditions constitute the entire agreement and the sole understanding between you and us ('agreement'); no amendment, addendum, or other communication will be taken into account when interpreting your and our rights and obligations under this agreement, unless amended by a written document signed by both of us.

TAYLOR &FRANCIS' RESPONSIBILITIES

2. If deemed acceptable by the Editors of the Journal, we shall prepare and publish your article in the Journal. We may post your accepted manuscript in advance of the formal publication of the VoR. We reserve the right to make such editorial changes as may be necessary to make the article suitable for publication, or as we reasonably consider necessary to avoid infringing third-party rights or breaching any laws; and we reserve the right not to proceed with publication for whatever reason.
3. Taylor & Francis will deposit your Accepted Manuscript (AM) to any designated institutional repository including PubMedCentral (PMC) with which Taylor & Francis has an article deposit agreement; see 4 iv (a) below.

RIGHTS RETAINED BY YOU AS AUTHOR

4. These rights are personal to you, and your co-authors, and cannot be transferred by you to anyone else. Without prejudice to your rights as author set out below, you undertake that the fully reference-linked Version of Record (VOR) will not be published elsewhere without our prior written consent. You assert and retain the following rights as author(s):
    i. The right to be identified as the author of your article, whenever and wherever the article is published, such rights including moral rights arising under § 77, Copyright, Designs & Patents Act 1988, and, so far as is legally possible, any corresponding rights we may have in any territory of the world.
    ii. The right to retain patent rights, trademark rights, or rights to any process, product or procedure described in your article.
    iii. The right to post and maintain at any time the Author's Original Manuscript (AOM; your manuscript in its original and unrefereed form; a 'preprint').
    iv. The right to post at any time after publication of the VoR your AM (your manuscript in its revised after peer review and accepted for publication form; a 'postprint') as a digital file on your own personal or departmental website, provided that you do not use the VoR published by us, and that you include any amendments or deletions or warnings relating to the article issued or published by us; and with the acknowledgement: 'The Version of Record of this manuscript has been published and is available in <JOURNAL TITLE> <date of publication> http://www.tandfonline.com/<Article DOI>.'
        a. Please note that embargoes apply with respect to posting the AM to an institutional or subject repository. For further information, please see our list of journals with applicable embargo periods: PDF | Excel. For the avoidance of doubt, you are not permitted to post the final published paper, the VoR published by us, to any site, unless it has been published as Open Access on our website.
        b. If, following publication, you or your funder pay an Article Publishing Charge for retrospective Open Access publication, you may then opt for one of three licenses: CC BY, CC BY-NC, or CC BY-NC-ND; if you do not respond, we shall assign a CC BY licence. All rights in the article will revert to you as author.
    v. The right to share with colleagues copies of the article in its published form as supplied to you by Taylor & Francis as a digital eprint or printed reprint on a non-commercial basis.
    vi. The right to make printed copies of all or part of the article on a non-commercial basis for use by you for lecture or classroom purposes provided that such copies are not offered for sale or distributed in any systematic way, and provided that acknowledgement to prior publication in the Journal is given.
    vii. The right, if the article has been produced within the scope of your employment, for your employer to use all or part of the article internally within the institution or company on a non-commercial basis provided that acknowledgement to prior publication in the Journal is given.
    viii. The right to include the article in a thesis or dissertation that is not to be published commercially, provided that acknowledgement to prior publication in the Journal is given.
    ix. The right to present the article at a meeting or conference and to distribute printed copies of the article to the delegates attending the meeting provided that this is not for commercial purposes and provided that acknowledgement to prior publication in the Journal is given.
    x. The right to use the article in its published form in whole or in part without revision or modification in personal compilations, or other publications of your own work, provided that acknowledgement to prior publication in the Journal is given.
    xi. The right to expand your article into book-length form for publication provided that acknowledgement to prior publication in the Journal is made explicit (see below). Where permission is sought to re-use an article in a book chapter or edited collection on a commercial basis a fee will be due, payable by the publisher of the new work. Where you as the author of the article have had the lead role in the new work (i.e., you are the author of the new work or the editor of the edited collection), fees will be waived. Acknowledgement to prior publication in the Journal should be made explicit (see below):

        Acknowledgement: This <chapter or book> is derived in part from an article published in <JOURNAL TITLE> <date of publication> <copyright Taylor & Francis>, available online: http://www.tandfonline.com/<Article DOI>

If you wish to use your article in a way that is not permitted by this agreement, please contact permissionrequest@tandf.co.uk

WARRANTIES MADE BY YOU AS AUTHOR

5. You warrant that:
    i. All persons who have a reasonable claim to authorship are named in the article as co-authors including yourself, and you have not

fabricated or misappropriated anyone's identity, including your own.

ii. You have been authorized by all such co-authors to sign this agreement as agent on their behalf, and to agree on their behalf the priority of the assertion of copyright and the order of names in the publication of the article.

iii. The article is your original work, apart from any permitted third-party copyright material you include, and does not infringe any intellectual property rights of any other person or entity and cannot be construed as plagiarizing any other published work, including your own published work.

iv. The article is not currently under submission to, nor is under consideration by, nor has been accepted by any other journal or publication, nor has been previously published by any other journal or publication, nor has been assigned or licensed by you to any third party.

v. The article contains no content that is abusive, defamatory, libelous, obscene, fraudulent, nor in any way infringes the rights of others, nor is in any other way unlawful or in violation of applicable laws.

vi. Research reported in the article has been conducted in an ethical and responsible manner, in full compliance with all relevant codes of experimentation and legislation. All articles which report in vivo experiments or clinical trials on humans or animals must include a written statement in the Methods section that such work was conducted with the formal approval of the local human subject or animal care committees, and that clinical trials have been registered as applicable legislation requires.

vii. Any patient, service user, or participant (or that person's parent or legal guardian) in any research or clinical experiment or study who is described in the article has given written consent to the inclusion of material, text or image, pertaining to themselves, and that they acknowledge that they cannot be identified via the article and that you have anonymized them and that you do not identify them in any way. Where such a person is deceased, you warrant you have obtained the written consent of the deceased person's family or estate.

viii. You have complied with all mandatory laboratory health and safety procedures in the course of conducting any experimental work reported in your article; your article contains all appropriate warnings concerning any specific and particular hazards that may be involved in carrying out experiments or procedures described in the article or involved in instructions, materials, or formulae in the article; your article includes explicitly relevant safety precautions; and cites, if an accepted Standard or Code of Practice is relevant, a reference to the relevant Standard or Code.

ix. You have acknowledged all sources of research funding, as required by your research funder, and disclosed any financial interest or benefit you have arising from the direct applications of your research.

x. You have obtained the necessary written permission to include material in your article that is owned and held in copyright by a third party, which shall include but is not limited to any proprietary text, illustration, table, or other material, including data, audio, video, film stills, screenshots, musical notation and any supplemental material.

xi. You have read and complied with our policy on publishing ethics.

xii. You have read and complied with the Journal's Instructions for Authors.

xiii. You have read and complied with our guide on peer review.

xiv. You will keep us and our affiliates indemnified in full against all loss, damages, injury, costs and expenses (including legal and other professional fees and expenses) awarded against or incurred or paid by us as a result of your breach of the warranties given in this agreement.

xv. You consent to allowing us to use your article for marketing and promotional purposes.

GOVERNING LAW

6. This agreement (and any dispute, proceeding, claim or controversy in relation to it) is subject to English law and the parties hereby submit to the exclusive jurisdiction of the Courts of England and Wales.

Title:	Weight and Body Composition Compartments do Not Predict Therapeutic Thiopurine Metabolite Levels in Inflammatory Bowel Disease
Author:	Darcy Q Holt, Boyd JG Strauss, Gregory T Moore
Publication:	Clinical and Translational Gastroenterology
Publisher:	Nature Publishing Group
Date:	Oct 27, 2016

Creative Commons

The request you have made is considered to be non-commercial/educational. As the article you have requested has been distributed under a Creative Commons license (Attribution-Noncommercial), you may reuse this material for non-commercial/educational purposes without obtaining additional permission from Nature Publishing Group, providing that the author and the original source of publication are fully acknowledged(please see the article itself for the license version number). You may reuse this material without obtaining permission from Nature Publishing Group, providing that the author and the original source of publication are fully acknowledged, as per the terms of the license. For license terms, please see http://creativecommons.org/

BACK CLOSE WINDOW

LICENCE TO PUBLISH

nature publishing group npg

Manuscript Number: 2016EJCN0955R

Journal Name: European Journal of Clinical Nutrition (the "Journal")

Proposed Title of the Contribution: Low muscle mass at initiation of anti TNF therapy for inflammatory bowel disease is associated with early treatment failure: a retrospective analysis (the "Contribution")

Author(s) [Please list all authors, continuing on a separate sheet if necessary]: Darcy Q Holt, Poornima Varma, Boyd JG Strauss, Anton Rajadurai, Gregory T Moore (the "Author(s)")

To: Nature Publishing Group, a division of Macmillan Publishers Ltd ("NPG")

1. In consideration of NPG evaluating the Contribution for publication (and publishing the Contribution if NPG so decides) the Author(s) grant to NPG for the full term of copyright and any extensions thereto, subject to clause 2 below, the exclusive right and irrevocable licence:
   (a) to edit, adapt, publish, reproduce, distribute, display and store the Contribution in all forms, formats and media whether now known or hereafter developed (including without limitation in print, digital and electronic form) throughout the world;
   (b) to translate the Contribution into other languages, create adaptations, summaries or extracts of the Contribution or other derivative works based on the Contribution and exercise all of the rights set forth in (a) above in such translations, adaptations, summaries, extracts and derivative works;
   (c) to licence others to do any or all of the above; and
   (d) to re-licence article metadata without restriction (including but not limited to author name, title, abstract, citation, references, keywords and any additional information, as determined by NPG).
2. Ownership of copyright remains with the Author(s), and provided that, when reproducing the Contribution or extracts from it or the Supplementary Information (defined below), the Author(s) acknowledge first and reference publication in the Journal, the Author(s) retain only the following non-exclusive rights:
   (a) to reproduce the Contribution in whole or in part in any printed volume (book or thesis) of which they are the Author(s);
   (b) they and any academic institution where they work may reproduce the Contribution for the purpose of course teaching;
   (c) to post a copy of the Contribution as accepted for publication after peer review (in a locked word processing file, or a PDF version thereof) on the Author(s)' own web sites, or institutional repositories, or the Author(s)' funding body(s)' archive, six months after publication of the printed or online edition of the Journal, provided that they also link to the Contribution on NPG's web site; and
   (d) to reuse figures or tables created by the Author(s) and contained in the Contribution in oral presentations and other works created by them.
3. The Author(s) grant to NPG for the full term of copyright and any extensions thereto the same rights that have been granted in respect of the Contribution as set out in clause 1 above, in and to all supplementary material in any form (including without limitation images, videos, tables and/or graphs) submitted by the Author(s) to NPG with or in connection with the Contribution ("Supplementary Information") but on a non-exclusive basis.
4. NPG acknowledges that an earlier version of the Contribution and/or Supplementary Information may have been submitted to a pre-print service (in accordance with that service's standard licence terms).
5. The Author(s) warrant and represent that:
   (a) the Author(s) are the sole Author(s) of and sole owners of the copyright in the Contribution and the Supplementary Information and the Contribution and the Supplementary Information is the original work of the Author(s) and not copied (in whole or part) from another work. If however the Contribution or the Supplementary Information includes materials from other sources, the Author(s) warrant they have obtained the necessary rights from the owners of the copyright in all such materials and hereby license to NPG the rights to use such materials in accordance with the grant of rights in clause 1. Copies of all such grant of rights from third parties are attached to this licence;
   (b) all of the facts contained in the Contribution and the Supplementary Information are true and accurate;
   (c) the signatory (the Author or the employer) who has signed this Agreement below has full right, power and authority to enter into this Agreement and grant the rights herein on behalf of all of the Authors;
   (d) nothing in the Contribution or the Supplementary Information is obscene, defamatory, libellous, violates any right of privacy or publicity, infringes any intellectual property rights (including without limitation copyright, patent, database or trademark rights) or any other human, personal or other rights of any person or entity or is otherwise unlawful; and
   (e) nothing in the Contribution or the Supplementary Information infringes any duty of confidentiality which any of the Author(s) may owe to anyone else or violates any contract, express or implied, of any of the Author(s), and all of the institutions in which work recorded in the Contribution or the Supplementary Information was created or carried out, have authorised such publication.
6. The Author(s) authorise NPG to take such steps as it considers necessary at its own expense in the Author(s) name and on their behalf if NPG believes that a third party is infringing or is likely to infringe copyright in the Contribution and/or Supplementary Information including but not limited to initiating legal proceedings.
7. The Author(s) grant NPG the perpetual right to edit, correct, or retract the Contribution and Supplementary Information if NPG considers (in its reasonable opinion) that such actions are required. The Author(s) hereby agree that they shall not object to NPG carrying out any such actions.
8. The Author(s) shall cooperate fully with NPG in relation to any legal action that might arise from the publication of the Contribution and/or Supplementary Information and the Author(s) shall give NPG access at reasonable times to any relevant accounts, documents and records within the power or control of the Author(s).
9. If the Contribution is rejected by NPG and not published, all rights under this licence shall revert to the Author(s).
10. This Agreement shall be governed by and construed in accordance with the laws of England and Wales. The parties irrevocably agree that the courts of England and Wales shall have exclusive jurisdiction to settle any dispute or claim that arises out of or in connection with this Agreement or its subject matter or formation.

Signed for and on behalf of the Author(s): [redacted]

(PLEASE NOTE, ONLY HAND WRITTEN SIGNATURES ARE ACCEPTED)

Print name: Darcy Holt

Date: 04 January 2017

Address:

Department of Gastroenterology & Hepatology, Monash Medical Centre, 246 Clayton Rd, Clayton 3168, Victoria, Australia

Does the Contribution and/or the Supplementary Information contain material from third parties (including previously published images/figures)?

Yes ◯ No ◉ (if yes, please ensure copies of the grant of rights are submitted with this form as indicated in clause 5(a))

Alimentary Pharmacology and Therapeutics

Published by Wiley (the "Owner")

COPYRIGHT TRANSFER AGREEMENT

Date: February 10, 2017

Contributor name: DARCY HOLT

Contributor address:

Manuscript number: APT-1506-2016.R3

Re: Manuscript entitled Visceral Adiposity Predicts Post-Operative Crohn's Disease Recurrence (the "Contribution")

for publication in Alimentary Pharmacology and Therapeutics (the "Journal")

published by John Wiley & Sons Ltd ("Wiley")

Dear Contributor(s):

Thank you for submitting your Contribution for publication. In order to expedite the editing and publishing process and enable the Owner to disseminate your Contribution to the fullest extent, we need to have this Copyright Transfer Agreement executed. If the Contribution is not accepted for publication, or if the Contribution is subsequently rejected, this Agreement shall be null and void.
Publication cannot proceed without a signed copy of this Agreement.

A. COPYRIGHT

1. The Contributor assigns to the Owner, during the full term of copyright and any extensions or renewals, all copyright in and to the Contribution, and all rights therein, including but not limited to the right to publish, republish, transmit, sell, distribute and otherwise use the Contribution in whole or in part in electronic and print editions of the Journal and in derivative works throughout the world, in all languages and in all media of expression now known or later developed, and to license or permit others to do so. For the avoidance of doubt, "Contribution" is defined to only include the article submitted by the Contributor for publication in the Journal and does not extend to any supporting information submitted with or referred to in the Contribution ("Supporting Information"). To the extent that any Supporting Information is submitted to the Journal for online hosting, the Owner is granted a perpetual, non-exclusive license to host and disseminate this Supporting Information for this purpose.

2. Reproduction, posting, transmission or other distribution or use of the final Contribution in whole or in part in any medium by the Contributor as permitted by this Agreement requires a citation to the Journal suitable in form and content as follows: (Title of Article, Contributor, Journal Title and Volume/Issue, Copyright © [year], copyright owner as specified in the Journal, Publisher). Links to the final article on the publisher website are encouraged where appropriate.

B. RETAINED RIGHTS

Notwithstanding the above, the Contributor or, if applicable, the Contributor's employer, retains all proprietary rights other than copyright, such as patent rights, in any process, procedure or article of manufacture described in the Contribution.

C. PERMITTED USES BY CONTRIBUTOR

1. Submitted Version. The Owner licenses back the following rights to the Contributor in the version of the Contribution as originally submitted for publication (the "Submitted Version"):

> **a.** The right to self-archive the Submitted Version on the Contributor's personal website, place in a not for profit subject-based preprint server or repository or in a Scholarly Collaboration Network (SCN) which has signed up to the STM article sharing principles [http://www.stm-assoc.org/stm-consultations/scn-consultation-2015/] ("Compliant SCNs"), or in the Contributor's company/ institutional repository or archive. This right extends to both intranets and the Internet. The Contributor may replace the Submitted Version with the Accepted Version, after any relevant embargo period as set out in paragraph C.2(a) below has elapsed. The Contributor may wish to add a note about acceptance by the Journal and upon publication it is recommended that Contributors add a Digital Object Identifier (DOI) link back to the Final Published Version.
>
> **b.** The right to transmit, print and share copies of the Submitted Version with colleagues, including via Compliant SCNs, provided that there is no systematic distribution of the Submitted Version, e.g. posting on a listserve, network (including SCNs which have not signed up to the STM sharing principles) or automated delivery.

2. Accepted Version. The Owner licenses back the following rights to the Contributor in the version of the Contribution that has been peer-reviewed and accepted for publication, but not final (the "Accepted Version"):

> **a.** The right to self-archive the Accepted Version on the Contributor's personal website, in the Contributor's company/institutional repository or archive, in Compliant SCNs, and in not for profit subject-based repositories such as PubMed Central, subject to an embargo period of 12 months for scientific, technical and medical (STM) journals and 24 months for social science and humanities (SSH) journals following publication of the Final Published Version. There are separate arrangements with certain funding agencies governing reuse of the Accepted Version as set forth at the following website: http://www.wiley.com/go/funderstatement. The Contributor may not update the Accepted Version or replace it with the Final Published Version. The Accepted Version posted must contain a legend as follows: This is the accepted version of the following article: FULL CITE, which has been published in final form at [Link to final article]. This article may be used for non-commercial purposes in accordance with the Wiley Self-Archiving Policy [http://olabout.wiley.com/WileyCDA/Section/id-828039.html].

b. The right to transmit, print and share copies of the Accepted Version with colleagues, including via Compliant SCNs (in private research groups only before the embargo and publicly after), provided that there is no systematic distribution of the Accepted Version, e.g. posting on a listserve, network (including SCNs which have not signed up to the STM sharing principles) or automated delivery.

3. Final Published Version. The Owner hereby licenses back to the Contributor the following rights with respect to the final published version of the Contribution (the "Final Published Version"):

a. Copies for colleagues. The personal right of the Contributor only to send or transmit individual copies of the Final Published Version in any format to colleagues upon their specific request, and to share copies in private sharing groups in Compliant SCNs, provided no fee is charged, and further provided that there is no systematic external or public distribution of the Final Published Version, e.g. posting on a listserve, network or automated delivery.

b. Re-use in other publications. The right to re-use the Final Published Version or parts thereof for any publication authored or edited by the Contributor (excluding journal articles) where such re-used material constitutes less than half of the total material in such publication. In such case, any modifications must be accurately noted.

c. Teaching duties. The right to include the Final Published Version in teaching or training duties at the Contributor's institution/place of employment including in course packs, e-reserves, presentation at professional conferences, in-house training, or distance learning. The Final Published Version may not be used in seminars outside of normal teaching obligations (e.g. commercial seminars). Electronic posting of the Final Published Version in connection with teaching/training at the Contributor's company/institution is permitted subject to the implementation of reasonable access control mechanisms, such as user name and password. Posting the Final Published Version on the open Internet is not permitted.

d. Oral presentations. The right to make oral presentations based on the Final Published Version.

4. Article Abstracts, Figures, Tables, Artwork and Selected Text (up to 250 words).

a. Contributors may re-use unmodified abstracts for any non-commercial purpose. For online uses of the abstracts, the Owner encourages but does not require linking back to the Final Published Version.

b. Contributors may re-use figures, tables, artwork, and selected text up to 250 words from their Contributions, provided the following conditions are met:

(i) Full and accurate credit must be given to the Final Published Version.

(ii) Modifications to the figures and tables must be noted. Otherwise, no changes may be made.

(iii) The re-use may not be made for direct commercial purposes, or for financial consideration to the Contributor.

(iv) Nothing herein will permit dual publication in violation of journal ethical practices.

D. CONTRIBUTIONS OWNED BY EMPLOYER

1. If the Contribution was written by the Contributor in the course of the Contributor's employment (as a "work-made-for-hire" in the course of employment), the Contribution is owned by the company/institution which

must execute this Agreement (in addition to the Contributor's signature). In such case, the company/institution hereby assigns to the Owner, during the full term of copyright, all copyright in and to the Contribution for the full term of copyright throughout the world as specified in paragraph A above.

For company/institution-owned work, signatures cannot be collected electronically and so instead please print off this Agreement, ask the appropriate person in your company/institution to sign the Agreement as well as yourself in the space provided below, and email a scanned copy of the signed Agreement to the Journal production editor. For production editor contact details, please visit the Journal's online author guidelines.

2. In addition to the rights specified as retained in paragraph B above and the rights granted back to the Contributor pursuant to paragraph C above, the Owner hereby grants back, without charge, to such company/institution, its subsidiaries and divisions, the right to make copies of and distribute the Final Published Version internally in print format or electronically on the Company's internal network. Copies so used may not be resold or distributed externally. However, the company/institution may include information and text from the Final Published Version as part of an information package included with software or other products offered for sale or license or included in patent applications. Posting of the Final Published Version by the company/institution on a public access website may only be done with written permission, and payment of any applicable fee(s). Also, upon payment of the applicable reprint fee, the company/institution may distribute print copies of the Final Published Version externally.

E. GOVERNMENT CONTRACTS

In the case of a Contribution prepared under U.S. Government contract or grant, the U.S. Government may reproduce, without charge, all or portions of the Contribution and may authorize others to do so, for official U.S. Government purposes only, if the U.S. Government contract or grant so requires. (U.S. Government, U.K. Government, and other government employees: see notes at end.)

F. COPYRIGHT NOTICE

The Contributor and the company/institution agree that any and all copies of the Final Published Version or any part thereof distributed or posted by them in print or electronic format as permitted herein will include the notice of copyright as stipulated in the Journal and a full citation to the Journal.

G. CONTRIBUTOR'S REPRESENTATIONS

The Contributor represents that the Contribution is the Contributor's original work, all individuals identified as Contributors actually contributed to the Contribution, and all individuals who contributed are included. If the Contribution was prepared jointly, the Contributor has informed the co-Contributors of the terms of this Agreement and has obtained their written permission to execute this Agreement on their behalf. The Contribution is submitted only to this Journal and has not been published before, has not been included in another manuscript, and is not currently under consideration or accepted for publication elsewhere. If excerpts from copyrighted works owned by third parties are included, the Contributor shall obtain written permission from the copyright owners for all uses as set forth in the standard permissions form or the Journal's Author Guidelines, and show credit to the sources in the Contribution. The Contributor also warrants that the Contribution and any submitted Supporting Information contains no libelous or unlawful statements, does not infringe upon the rights (including without limitation the copyright, patent or trademark rights) or the privacy of others, or contain material or instructions that might cause harm or injury. The Contributor further warrants that there are no conflicts of interest relating to the Contribution, except as disclosed. Accordingly, the Contributor represents that the following information shall be clearly identified on the title page of the Contribution: (1) all financial and material support for the research and work; (2)

any financial interests the Contributor or any co-Contributors may have in companies or other entities that have an interest in the information in the Contribution or any submitted Supporting Information (e.g., grants, advisory boards, employment, consultancies, contracts, honoraria, royalties, expert testimony, partnerships, or stock ownership); and (3) indication of no such financial interests if appropriate.

H. USE OF INFORMATION

The Contributor acknowledges that, during the term of this Agreement and thereafter, the Owner (and Wiley where Wiley is not the Owner) may process the Contributor's personal data, including storing or transferring data outside of the country of the Contributor's residence, in order to process transactions related to this Agreement and to communicate with the Contributor. By entering into this Agreement, the Contributor agrees to the processing of the Contributor's personal data (and, where applicable, confirms that the Contributor has obtained the permission from all other contributors to process their personal data). Wiley shall comply with all applicable laws, statutes and regulations relating to data protection and privacy and shall process such personal data in accordance with Wiley's Privacy Policy located at: http://www.wiley.com/WileyCDA/Section/id-301465.html.

[X] I agree to the COPYRIGHT TRANSFER AGREEMENT as shown above, consent to execution and delivery of the Copyright Transfer Agreement electronically and agree that an electronic signature shall be given the same legal force as a handwritten signature, and have obtained written permission from all other contributors to execute this Agreement on their behalf.

Contributor's signature (type name here): Darcy Holt

Date: February 10, 2017

SELECT FROM OPTIONS BELOW:

[X] Contributor-owned work

[ ] U.S. Government work

Note to U.S. Government Employees

A contribution prepared by a U.S. federal government employee as part of the employee's official duties, or which is an official U.S. Government publication, is called a "U.S. Government work", and is in the public domain in the United States. In such case, Paragraph A.1 will not apply but the Contributor must type his/her name (in the Contributor's signature line) above. Contributor acknowledges that the Contribution will be published in the United States and other countries. If the Contribution was not prepared as part of the employee's duties or is not an official U.S. Government publication, it is not a U.S. Government work.

[ ] U.K. Government work (Crown Copyright)

Note to U.K. Government Employees

For Crown Copyright this form cannot be completed electronically and should be printed off, signed in

the Contributor's signatures section above by the appropriately authorised individual and returned to the Journal production editor by email. For production editor contact details please visit the Journal's online author guidelines. *The rights in a contribution prepared by an employee of a UK government department, agency or other Crown body as part of his/her official duties, or which is an official government publication, belong to the Crown and must be made available under the terms of the Open Government Licence. Contributors must ensure they comply with departmental regulations and submit the appropriate authorisation to publish. If your status as a government employee legally prevents you from signing this Agreement, please contact the Journal production editor.*

[ ] Other

Including Other Government work or Non-Governmental Organisation work

Note to Non-U.S., Non-U.K. Government Employees or Non-Governmental Organisation Employees

For Other Government or Non-Governmental Organisation work this form cannot be completed electronically and should be printed off, signed in the Contributor's signatures section above by the appropriately authorised individual and returned to the Journal production editor by email. For production editor contact details please visit the Journal's online author guidelines. *If you are employed by the Department of Veterans Affairs in Australia, the World Bank, the World Health Organization, the International Monetary Fund, the European Atomic Energy Community, the Jet Propulsion Laboratory at California Institute of Technology, the Asian Development Bank, or are a Canadian Government civil servant, please download a copy of the license agreement from http://olabout.wiley.com/WileyCDA/Section/id-828023.html and return it to the Journal Production Editor. If your status as a government or non-governmental organisation employee legally prevents you from signing this Agreement, please contact the Journal production editor.*

Name of Government/Non-Governmental Organisation:

_____

[ ] Company/institution owned work (made for hire in the course of employment)

For "work made for hire" this form cannot be completed electronically and should be printed off, signed and returned to the Journal production editor by email. For production editor contact details please visit the Journal's online author guidelines. *If you are an employee of Amgen, please download a copy of the company addendum from http://olabout.wiley.com/WileyCDA/Section/id-828023.html and return your signed license agreement along with the addendum.*

Name of Company/Institution:

_____

Authorized Signature of Employer: _____

Date: _____

Signature of Employee: _____

Date: _____