INDIRECT CALORIMETRY IN CHRONIC GASTROINTESTINAL CONDITIONS

THE USE OF INDIRECT CALORIMETRY FOR NUTRITION ASSESSMENT IN PATIENTS WITH CHRONIC INFLAMMATORY GASTROINTESTINAL CONDITIONS

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The Use of Indirect Calorimetry for Nutrition Assessments in Patients with Chronic Inflammatory Gastrointestinal Conditions

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Lay Abstract

Little is known about whether chronic inflammatory gastrointestinal conditions (CIGI), such as Celiac Disease (CeD) and Inflammatory Bowel Disease (IBD), alter resting energy expenditure (REE). While energy needs can be estimated using predictive equations (PE), indirect calorimetry (IC) is the gold-standard method for the measurement of energy needs. In this study, we primarily investigated whether there were differences in the measured and estimated energy needs of patients with CIGI. The results showed that most PE were inaccurate for the assessment of energy needs, though the Mifflin St. Jeor and Cunningham formulas showed the best performance. REE comparison of CeD and IBD yielded lower REE in CeD. When factors influencing REE were explored, fat-free mass (FFM), dietary protein intake, and BMI were significant predictors of REE. This research has important implications for patients with CIGI and can inform evidence-based nutritional management and recommendations.

Abstract

Resting energy expenditure (REE) is challenging to predict in chronic inflammatory gastrointestinal conditions (CIGI) such as celiac disease (CeD) and inflammatory bowel disease (IBD). In clinical practice, predictive equations (PE) are often used to provide estimates of REE. However, indirect calorimetry is a gold-standard method for accurate measurement of energy needs.

The central hypothesis for this study was that there would be differences in predicted and measured energy needs in CIGI. We conducted a prospective observational study at an outpatient clinic where REE (kcal/day) was measured by the Q-NRG® Metabolic Cart. This was compared with REE estimated by five commonly used PE (25 kcal/kg, Harris-Benedict, Schofield, Mifflin-St. Jeor and Owen) using paired t-tests (IBM SPSS Version 29.0). REE (kcal/day) and REE adjusted for weight (REE/kcal/kg) were compared in different GI groups using Mann-Whitney U tests.

The study population comprised eighty-seven patients with CIGI (CeD [n=61], IBD [n=10], and Other [n=16]). Mean REE (1462 ± 281) was significantly lower compared with several PE: 1) 25 kcal/kg (1933 ± 536; p <0.001); 2) Harris-Benedict (1552 ± 287; p<0.001); 3) Schofield (1522 ± 282, p=0.01), while higher than Owen (1411 ± 228, p=0.02) and similar to Mifflin St. Jeor (1450 ± 277; p=0.56). REE adjusted for weight (kcal/kg/day) was significantly higher in IBD as compared with CeD patients (22.9 vs 18.2; p=0.04), potentially due to differences in disease activity (16% CeD with active disease vs. 60% IBD with active disease; p=0.0022**)**. Furthermore, fat-free mass (FFM) (r=0.70, p<0.001), BMI (r=0.47, p<0.01), and protein intake (r=0.24, p=0.02)

were important predictors of REE in this cohort. The present results suggest that basal caloric needs are inaccurately predicted by PE, which may have significant implications in the long-term nutritional management of CeD and IBD.

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List of Symbols and Abbreviations

α	Level of statistical significance
ADP	Air Displacement Plethysmography
AEE	Activity energy expenditure
AF	Activity factor
ANOVA	Analysis of variance
ASA24	Automated Self-Administered 24-hour recall
ASPEN	American Society for Parenteral and Enteral Nutrition
ATP	Adenosine triphosphate
BIA	Bioimpedance analysis
BMI	Body mass index
BMR	Basal metabolic rate
CD	Crohn's disease
CeD	Celiac disease
CE	Cunningham equation
CIGI	Chronic inflammatory gastrointestinal
CRP	C-reactive Protein
CT	Computed Tomography
DC	Direct calorimetry
DGP	Deamidated Gliadin Peptide
DLW	Doubly-labeled water
DIT	Diet-induced thermogenesis
DNA	Deoxyribonucleic Acid
DXA	Dual-energy X-ray absorptiometry
EATL	Enteropathy-associated T-cell lymphoma
EOSS	Edmonton Obesity Staging System
FCP	Fecal calprotectin
FFM	Fat free-mass

FM	Fat mass
GFD	Gluten-free diet
GI	Gastrointestinal
GLIM	Global Leadership Initiative on Malnutrition
HB	Harris-Benedict
IBD	Inflammatory bowel disease
IC	Indirect Calorimetry
ICU	Intensive care unit
IEL	Intraepithelial lymphocyte
LM	Lean mass
MNA	Mini-nutritional assessment
MRI	Magnetic Resonance Imaging
MSJ	Mifflin St. Jeor
MUST	Malnutrition Universal Screening Tool
NRS	Nutrition Risk Screening
PAQ	Physical activity questionnaire
PBF	Percent body fat
PG-SGA	Patient-Generated Subjective Global Assessment
RCDI	Refractory Celiac disease (Type I)
RCDII	Refractory Celiac disease (Type II)
REE	Resting energy expenditure
RQ	Respiratory Quotient
SAD	Seasonal Affective Disorder
SGA	Subjective Global Assessment
SPSS	Statistical Package for Social Sciences
TEE	Total energy expenditure
tTG	Tissue transglutaminase
UC	Ulcerative colitis
Q-NRG®	Indirect calorimetry metabolic cart brand

Declaration of Academic Achievement

This is a statement declaring that I have completed all work presented in this thesis under the supervision of Dr. Maria Ines Pinto-Sanchez. Advances in my thesis work were presented at the Farncombe Research in Progress (RIP) during the 2021-2022 and 2022-2023 academic years. I also presented at the International Celiac Disease Symposium (ICDS) on October 21st, 2022, and at Digestive Disease Week (DDW) on May 9th, 2023. I have co-authored a review, *Nutritional Considerations in Celiac Disease and Non-Celiac Gluten/Wheat Sensitivity,* published in the *Nutrients* journal in March 2023. This was an invited review from the Spanish Society of Gastroenterology (Sociedad Española de Gastroenterología) and sponsored by the Spanish Gastroenterology Foundation (Fundacion Española de Gastroenterología), which I have led as a first author as it was significantly related to a portion of my thesis. I have adapted a figure and table from this publication in Chapter 1 of this thesis. All other references to work that is not my own have been cited.

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Chapter One

1. Introduction

This thesis describes the implementation of nutrition assessments and indirect calorimetry in patients with chronic inflammatory gastrointestinal (CIGI) conditions, with a special focus on celiac disease (CeD) and inflammatory bowel diseases (IBD). Chapter One introduces relevant concepts such as malnutrition, energy expenditure, and nutritional status and the importance of conducting nutritional assessments to detect malnutrition in CIGI conditions. In addition, I have reviewed the literature on resting energy expenditure (REE) in CeD and IBD patients using indirect calorimetry and predictive equations, as well as the factors that may influence REE. Finally, the chapter concludes with a rationale for the study, objectives, and hypotheses.

1.1 Malnutrition

Malnutrition refers to deficiencies, excesses, or imbalances in energy or nutrient intake that cause a detrimental impact on function, body composition, and clinical outcomes (Saunders & Smith, 2010). Malnutrition encompasses undernutrition, over-nutrition, and micronutrient deficiencies (Guldan, 2020).

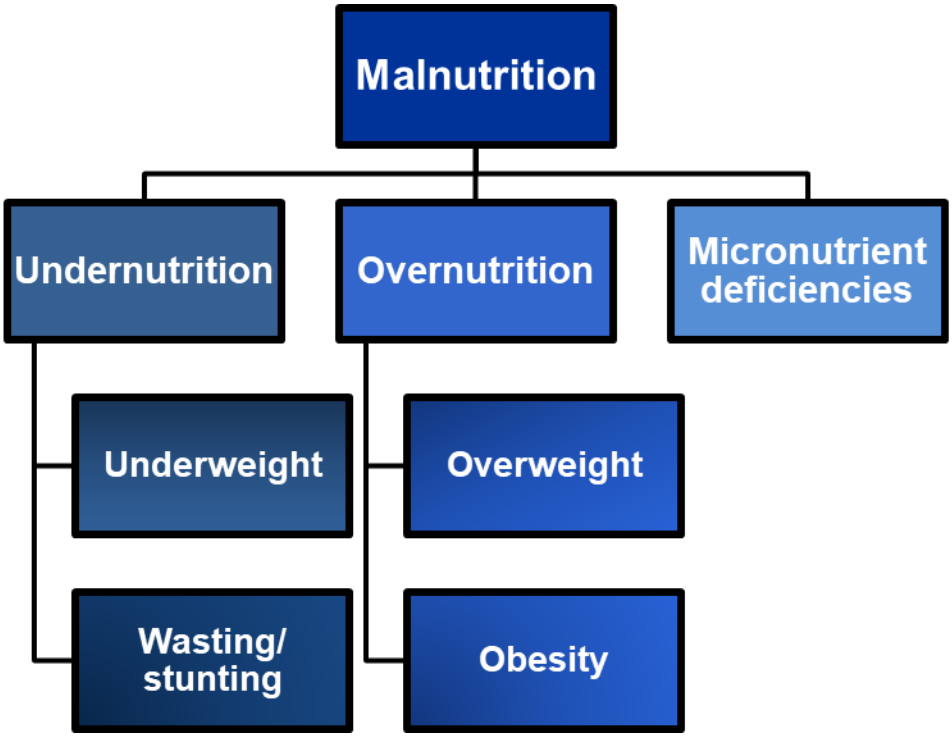

Figure 1.1. An overview of the different forms of malnutrition. Malnutrition includes undernutrition, such as being underweight and stunting; overnutrition, such as overweight and obesity, and micronutrient-related deficiencies.

An underlying condition can impact an individual's ability to meet their energy needs directly, by impacting dietary intake, or indirectly by triggering metabolic and psychological conditions that can increase or decrease nutritional requirements (Schwegler *et al.*, 2010) depending on the presence of inflammation (Cederholm *et al*., 2017). As nutritional status deteriorates, catabolic metabolism is activated. This process, combined with persistent low-grade inflammation, can result in detrimental outcomes, including immune system dysfunction and loss of fat-free mass (Soeters & Schols, 2009). The presence of malnutrition can also impact the efficacy of treatments that may be

required by an individual, including antibiotics, which can lead to physiological stress (Reber *et al.*, 2019). In this state, the sympathetic nervous system is activated, and the endocrine, hematological, and immune systems all respond to the need for increased metabolism. This can result in a hypermetabolic state, meaning an individual has greater energy expenditure and nutritional needs (Reber *et al.*, 2019). Conversely, in a hypometabolic state, an individual's energy expenditure experiences a moderate-severe decrease (Gorr, 2017) which can lead to reduced nutritional needs.

Malnutrition is a common, underrecognized condition correlated with worsened clinical outcomes, increased morbidity and mortality, increased risk of infection, and reduced quality of life (Fan & Cao, 2015). A study conducted by the Canadian Malnutrition Taskforce found that moderate and severely malnourished patients had increased hospital stays within a range of 18-53%, and increased hospital costs by up to 55% (Curtis *et al.*, 2017). Due to changes in nutritional intake, absorption, or energy needs, gastrointestinal (GI) diseases can lead to malnutrition (Klein & Jeejeebhoy, 2002). This was shown in a prospective multi-center cohort study conducted across 18 Canadian hospitals, which found that 45% of patients with GI conditions had malnutrition (Allard *et al.*, 2016). In prioritizing early detection of an individual's nutritional status through nutritional screening and assessments, effective interventions for malnutrition can be facilitated (Kesari & Noel, 2022).

1.11 Nutritional assessments

According to the American Society for Parenteral and Enteral Nutrition (ASPEN), complete nutrition assessments incorporate diagnostic and clinical exams (physical examination), anthropometrics, and evaluate dietary intake Field (Mueller *et al*., 2011). While there is no gold-standard method of diagnosing malnutrition, validated assessment tools are used to assist in the diagnosis (Dijkink *et al.,* 2020). Typically, nutritional screenings are conducted as a preliminary method of routinely determining whether a patient is at risk of malnutrition in an inpatient or outpatient environment (Reber *et al.*, 2019). It is recommended to use nutritional screening tools that evaluate dynamic parameters of nutritional status, such as recent diet and weight changes, disease severity, and present body mass index (BMI) (Reber *et al.*, 2019). Numerous screening tools exist for different patient populations (Van Bokhorst-de van der Schueren *et al.*, 2014). This includes the Mini- nutritional assessment (MNA), Nutritional-risk screening (NRS), and the Malnutrition Universal Screening Tool (MUST). The MUST is a five-step screening tool that healthcare providers can use in a variety of clinical settings to identify whether adult patients are at risk of malnutrition. This tool evaluates risk based on BMI, disease severity, and unintentional weight loss within a 3–6-month time frame. If malnutrition risk is established, it is recommended to conduct nutritional assessments to evaluate nutritional status further.

Nutritional assessment refers to the systematic process of collecting and interpreting information to make decisions about the nature and cause of nutrition-related health issues that affect an individual (British Dietetic Association, 2012). It involves an

in-depth assessment of symptoms, functional capacity, metabolic status, and a physical examination to evaluate nutrition status and determine the presence of a nutrition disorder. Hence, nutritional assessment should be performed by qualified personnel, such as registered dietitians, clinicians, or nurses specialized in nutrition. Various diagnostic criteria and tools are used for nutrition assessment (Allard *et al.*, 2020; Balstad *et al*., 2019; Detsky *et al*., 1987; Guigoz *et al*., 1996; Kondrup *et al.*, 2003; Reber *et al.*, 2019; Rubenstein *et al*., 2001; Weekes *et al.*, 2004). One of the most widely utilized methods is the Subjective Global Assessment (SGA) tool (Detsky *et al.*, 1987). First developed in 1982, the SGA evaluates malnutrition across domains of nutrient intake, gastrointestinal symptoms, weight changes, functional capacity, and metabolic requirements, as well as a physical exam and identifying whether contributing factors may be present. The SGA is often used for its advantages of being inexpensive, non-invasive, and for the ability to determine malnutrition risk without the need for body composition. It has been extensively used for nutritional assessments conducted in hospitals (Allard *et al*., 2020; Curtis *et al.*, 2017; da Silva Fink *et al.*, 2015; Kondrup *et al.*, 2003; Kyle *et al.,* 2006; Makhija & Baker, 2008; Raslan *et al.*, 2011; van Bokhorst-de van der Schueren *et al.*, 2014) and in outpatient settings (Keller *et al.,* 2018; Luong *et al.*, 2020; Makhija & Baker, 2008). The assessment is both objective and subjective (Detsky *et al.*, 1987), and categorical, classifying a patient as well-nourished (SGA-A), moderately malnourished (SGA-B), or severely malnourished (SGA-C) (Detsky *et al*., 1987; Makhija & Baker, 2008). Other tools used in clinical practice include the Patient-Generated Subjective Global Assessment (PG-SGA), which is a self-reported tool based on a modified SGA

(Ottery, 1994; Ottery *et al.,* 2015). Unlike the SGA, the PG-SGA is a continuous—not categorical—assessment that covers weight loss, food intake, nutrition impact symptoms, disease, metabolic needs, activities, functional capacity, and a physical exam (Ottery *et al.*, 2015). The PG-SGA can be used in various patient populations but is primarily used for patients with cancer (Hill *et al.*, 2011). A newer tool for malnutrition diagnosis is the Global Leadership Initiative on Malnutrition (GLIM), which offers a framework for malnutrition diagnosis that combines etiologic and phenotypic criteria to facilitate global comparison of malnutrition assessment tools (Allard *et al.,* 2020). While this tool has good performance and sensitivity and is considered fair validity (Allard *et al.*, 2020), further research is needed to establish clinical relevance (Curtis *et al.*, 2017). For patients with overweight and obesity, tools such as the Edmonton Obesity Staging System (EOSS) can better determine the risk of malnutrition. The EOSS uses a five-stage system of obesity classification based on physical, metabolic, and psychological domains of health. Obesity classes are based on BMI ranges, while stages provide mortality risk using physical, metabolic, and psychological evaluations of an individual's health. Under the EOSS, obese patients are only recommended to lose weight in higher staging categories (Allard *et al.,* 2016; Frings-Meuthen *et al.,* 2021). Despite the variety of tools that can be used for the evaluation of nutritional status, at present, clinical guidelines do not provide specific directions on the tools that should be used in patients with CeD and IBD. Hence, selected tools can be chosen by comparing their advantages and disadvantages, as shown in Table 1.1.

Table 1.1. Tools for Nutritional Screening and Nutritional Assessment (Abdi *et al.*, 2023).

Tools	Components	Advantages	Disadvantages
Nutritional Risk Screening 2002 (NRS-2002)	Used in inpatient setting. Four questions in pre-screening	Simple, well-validated tool Reliable Can be completed within 3-5 minutes	Requires trained staff
Mini Nutritional Assessment (MNA)	Combines nutrition screening and assessment. Covers 4 domains (nutrient intake, anthropometric measurement, global assessment, and subjective assessment)	Quick evaluation tool No biochemical tests required Non-invasive	Useful only in limited patient populations Relies on patient self-assessment
Mini Nutritional Assessment short-form (MNA-SF)	Short version of MNA Covers six items (food intake, weight loss, mobility, psychological stress, neuropsychological symptoms, BMI)	Faster than complete MNA Considered as effective as MNA	Requires MNA when patient has malnutrition risk
Subjective Global Assessment (SGA)	Assesses 7 domains (nutrient intake, weight change, symptoms, functional capacity, metabolic requirement, physical examination and contributing factor)	Non-invasive and inexpensive tool Requires basic training Simple to incorporate in routine follow-ups	Only studied in some populations Does not include biochemical data Allows for subjective determination Need for physical examination
Patient Generated Subjective Global Assessment (PG-SGA)	Patient-generated component (weight history, dietary intake, symptoms, activities, and function), HC provider component (weight loss, disease/nutritional requirements, metabolic demand, and physical exam)	Autonomy for patient Improved patient-clinician interaction Dynamic evaluation of nutritional status	Patients may misinterpret the question Can be difficult to answer honestly Duration of recall can be long for patients
Global Leadership Initiative on Malnutrition (GLIM) criteria	Framework based on phenotypic (non-voluntary weight loss, low BMI, reduced muscle mass) and etiologic (reduced food intake, disease burden/inflammatory condition) criteria	High sensitivity Good performance as a screening tool	Low performance compared with SGA Low specificity False positive risk is high

1.12 Anthropometrics and Body Composition

Anthropometric measures are a vital component of nutrition assessments that evaluate body size and composition. Typically, they involve height and weight, circumferences such as head, arm, calf, waist and hip, and measures of skinfolds including triceps and subscapular (Casadei & Kiel, 2022). An individual's height and weight are used to calculate body mass index (BMI), providing a descriptive index that can be compared with reference values to determine health risks associated with a weight classification (kg/m^2). According to World Health Organization guidelines, an individual can be classified into BMI categories underweight (BMI below 18.5), normal weight (BMI 18.5 to 24.9), overweight (BMI 25.0 to 29.9) and obesity (BMI over 30.0) (World Health Organization, 2021). Obesity can further be categorized as Class I Obesity (BMI 30.0 to 34.9), Class II Obesity (BMI 35.0 to 39.9), or Class III Obesity (BMI over 40.0) (World Health Organization, 2021). While BMI values point to health risks associated with weight status and allow for assessment of changes following nutritional recommendations, sub-parameters of body composition such as fat-mass (FM) and fat-free mass (FFM) cannot be discerned (Holmes & Racette, 2021), requiring tools for their measurement.

Body composition tools have revolutionized anthropometry (Bourgeois *et al.*, 2017). They can be selected based on nutritional goals and conditions that are assessed in each population (Holmes & Racette, 2021). Dual X-ray absorptiometry (DXA) is a highly reliable technique for gauging FM and FFM and bone mineral density. It is considered the preferred method of quantifying body composition. However, it is difficult to obtain

full-body scans for higher stages of obesity using this method, and therefore, may be necessary to resort to half-body DXA, which has not been widely validated (Vatier et *al.,* 2014). Other tools such as Air Displacement Plethysmography (ADP), Bioimpedance analysis (BIA), magnetic resonance imaging (MRI) and Computed Tomography (CT) are all validated, reliable tools that can be used to determine body composition, each with their own set of advantages and disadvantages (Holmes & Racette, 2021). The gold standard methods to assess muscle mass are DXA, computed tomography (CT), and magnetic resonance imaging (MRI), but they can have limited use in clinical practice due to high costs. In addition, DXA and CT involve radiation with associated adverse effects such as a slightly increased risk of cancer development (Damilakis *et al.*, 2013; Silver *et al.,* 2010). BIA can be a valid alternative to DXA due to its lower cost than anthropometric measures (Scaldaferri *et al.*, 2017). Recent advances in digital image analysis tools in the form of 3D body scanners provide a time-efficient, effective and rapid method of determining FM, FFM, and percent body fat (PBF) using infrared cameras (Marra *et al.*, 2019; Silver & Wilson, 2020; Sobhiyeh *et al.*, 2021). A recent systematic review evaluating the reliability of anthropometric measures has found that 61% of studies show greater accuracy of 3D body scanners (Rumbo-Rodríguez *et al.*, 2021). 3D body scanning tools are non-invasive, cost-effective, and easier to use than conventional tools (Bragança *et al.*, 2017; Bretschneider *et al.*, 2009). They typically require 30 seconds to complete a scan (Silver & Wilson, 2020) and are ideal for use with larger patient populations (Treleaven & Wells, 2007).

1.13 Dietary assessment

A registered dietitian or nutrition specialist conducts dietary assessments, which are crucial for determining whether dietary intake is sufficient to meet nutritional needs (Prentice *et al.*, 2011). Dietary assessment is often done through dietary records, 24-h dietary recall (24HDR), and food frequency questionnaires (FFQ and diet histories). Dietary records collected in 24-72 hours are commonly used tools for evaluating nutrient intake. Nutrition analysis software can be used to provide a detailed breakdown of macronutrient and micronutrient composition based on food records (Baranowski, 2012). In contrast, diet history and FFQs facilitate the collection of long-term dietary intake but usually take longer to complete and may be inaccurate due to a reliance on patient memory to note dietary information. At present, dietary records are the preferred tool for dietary assessment, and where sufficient records are available, can even be used to predict usual dietary intake in prospective and retrospective research studies (Baranowski, 2012). In particular, dietary assessments that utilize technology can overcome challenges with collecting data in these methods by improving accuracy and reducing participant burden (Foster *et al.*, 2014). Traditional 24-hr dietary record (24HDR) is administered by interviewers; however, this can be costly and time-consuming (Laramée *et al.*, 2022). Web-based 24HDR methods improve the feasibility of assessing dietary intake in research, are often free, and can be used for larger-scale studies. In Canada, the Automated Self-Administered 24-hour dietary record (ASA24) was modified for use in the Canadian context, with the latest version updated in 2018. The ASA24 uses an Automated Multiple Pass Method (Raper *et al.*, 2004) to obtain dietary intake and

provides an extensive database of 4794 foods whose nutrient composition can be analyzed with 65 nutrients. In a validation study conducted by Kirkpatrick *et al.* assessing the performance of the ASA24 with a 24HDR administered by an interviewer, the ASA24 was not found to have significant differences in diet portion sizes provided to participants in controlled feeding and those measured by the ASA24 (Kirkpatrick *et al.*, 2014). When comparing the true number of items consumed reported in ASA24 as compared with an interviewer-administered Multiple Pass Method, it was shown to have acceptable construct validity (80% vs. 83%; $p = 0.07$). Another study evaluating the ASA24 reported good face validity (Subar *et al.*, 2012). Since its release, ASA24 has been investigated in several studies and can be used with efficacy to obtain patient food records (Kirkpatrick *et al.*, 2014; Laramée *et al.*, 2022; Subar *et al.*, 2012).

1.14 Nutritional status in Celiac disease

Celiac disease (CeD) is a chronic, immune-mediated disorder induced by gluten and characterized by small intestinal enteropathy in genetically susceptible individuals who are positive for HLA-DQ2/ HLA-DQ8 alleles (Catassi *et al.*, 2022). The diagnosis of celiac disease is based on serologic tests that use enzyme-linked immunosorbent assays (ELISA) such as tissue transglutaminase (tTG) and deamidated gliadin peptide (DGP) and confirmed by the presence of villous atrophy in duodenal biopsies (Catassi *et al.*, 2022). tTG is an autoantigen that deamidates gliadin peptides when gluten is consumed, which leads to gluten binding with HLA DQ2/HLA DQ8 molecules on antigen-presenting cells. This results in subsequent antibody production, inflammation of CD8+

T-cell cytokines, and enteropathy of intestinal villi (Adriaanse & Leffler, 2015). tTG IgA tests are widely used due to their high levels of sensitivity and specificity (≥95%) (Leffler & Schuppan, 2010). DGP is a more recent method that also provides high sensitivity and specificity and measures the inflammatory T-cell response in the intestinal mucosa, based on deamidated peptides binding to HLA DQ2/DQ8 antigens (Leffler & Schuppan, 2010). For clinical management of CeD, recent guidelines emphasize the need for follow-up of patients using a team-based approach (Rubio-Tapia *et al.*, 2023).

The only treatment for CeD is adherence to a life-long gluten-free diet (GFD). Most patients improve on a GFD; however, a proportion of CeD have persistent symptoms despite attempting a strict GFD. Some CeD may have a refractory form of the disease, where, in addition to persistent symptoms while adhering to a GDF, they have villous atrophy. Refractory CeD can be classified into Type I (RCDI), which is characterized by a relatively normal intraepithelial lymphocyte (IEL) population, or in the case of Refractory CeD Type II (RCDII), attributed to an abnormal/aberrant IEL pattern that can progress to T-cell lymphoma in 50% of cases (Nijeboer *et al.*, 2013). If not treated, RCDII can develop into a malignant complication—enteropathy-associated T-cell lymphoma (EATL)—within five years (Wierdma *et al.*, 2016).

The immunopathogenesis of celiac disease involves a complex interplay of the innate and adaptive immune systems. The adaptive immune cell response is central to the immunopathogenesis of CeD (Parzanese *et al.*, 2017). Upon intake of gliadin, a component of gluten-protein, individuals genetically predisposed to celiac disease experience damage to the tight junction cells of the small intestine lining resulting in

increased permeability to gliadin peptides (Parzanese *et al.*, 2017). This results in increased passage of gliadin peptides across the epithelial barrier and activation of CD4+ T-lymphocytes, which either stimulate IFN-γ or B-lymphocyte proliferation leading to the production of anti-gliadin and anti-tTG antibodies (Parzanese *et al.*, 2017). The pro-inflammatory cytokine IL-15 stimulates the production of cytotoxic CD8+ T-lymphocytes, inducing enteropathy characteristic of CeD (Troncone *et al.*, 2011). In the innate immune response, α-gliadin peptide P31-43 gliadin modifies the signaling of epithelial cells, alters cell structure, and triggers the release of inflammatory signals. Active transglutaminase 2 (TG2) generates negatively charged gluten peptides (Molberg *et al.*, 1998) which bind to HLA-DQ2 and HLA-DQ8 molecules with high affinity triggering an inflammatory immune response (Kim *et al.*, 2004) of T-cell receptor αβ intestinal epithelial lymphocytes in the intestinal mucosa (Kim *et al.*, 2015). α-gliadin peptide P31-43 also upregulates the expression of IL-15 and induces activation of innate immune response markers CD25 and CD83 (Maiuri *et al.*, 2003).

Intestinal injury in CeD can lead to poor outcomes, which include malnutrition, inflammation, and malabsorption (Rubio-Tapia *et al.*, 2010). Due to the poor quality of common gluten-free foods, individuals with CeD can show energy and nutrition imbalances (Vici *et al.*, 2016). In addition, substrate utilization can be impaired in CeD, with higher carbohydrate oxidation shown in untreated CeD, likely due to increased carbohydrate intake and lipid malabsorption (Capristo *et al.*, 2000, 1997; Mazure *et al.*, 1996). As such, it is necessary to evaluate the nutritional status of CeD patients.

Research on nutritional status in CeD varies based on characteristics of the sample population, such as GFD adherence, age at diagnosis, and whether malabsorption is at play. In the past, CeD was associated with malnutrition, predominantly in the form of undernutrition. Previous studies conducted on CeD patients adopting a GFD have found reductions in bone mineral density, BMI and FM (Bardella *et al.,* 2000; Bodé *et al.*, 1991; Ciacci *et al.,* 2002) compared with healthy controls.

More recently, concurrent with rising BMI in the general population, there has been a shift observed in BMI and body composition of CeD, with an increasingly overweight and obese phenotype (Dickey & Kearney, 2006; Kabbani *et al.,* 2012). In a US-based study, Cheng and colleagues (Cheng *et al.*, 2010) investigated BMI in CeD at diagnosis and following GFD adherence. They reported 66% of patients with CeD and underweight had weight gain, while 54% of patients with CeD and overweight and 47% with CeD and obese had weight loss after a GFD (Cheng *et al.*, 2010). Since individuals with CeD and underweight had weight gain and those with CeD and overweight/obesity had weight loss, they suggested that a GFD was beneficial for nutritional status in CeD. However, given that the analysis was performed on a sample of patients from a prospective database collected between 1981 to 2007, these results may not reflect emerging trends in CeD. A more recent study shows similar BMI and FM in CeD as compared with healthy matched controls (Barone *et al.*, 2016). However, this study focused on a Mediterranean-style GFD, which restricts the applicability of findings. Finally, a recent systematic review and meta-analysis of twenty-five studies reporting body composition in CeD on GFD showed significant increases in FM of CeD patients

compared with FM at baseline and FM of healthy controls, along with a reduction in FFM (Vereczkei *et al.*, 2021). The most recent findings overall indicate an increasingly positive energy balance and weight gain in CeD.

1.15 Nutritional status in IBD

Inflammatory bowel diseases (IBD) refer to chronic, relapsing conditions that predominantly affect the intestines, namely Crohn's disease (CD) and ulcerative colitis (UC) (Endo *et al.*, 2009). CD can cause inflammation in any region of the GI tract, while UC only affects the colon (Bischoff *et al.*, 2020). Malnutrition is a significant concern in IBD, with a prevalence of 65-75% in CD and 18-62% in UC (Scaldaferri *et al.*, 2017). As such, malnutrition tends to be of more concern in CD, even if there is no active flare-up, whilst in UC malnutrition is generally of concern when the disease is active (Bischoff *et al.*, 2020; Forbes *et al.*, 2017). In IBD, disease activity is traditionally assessed using endoscopy (Kim *et al.*, 2022). To monitor changes in disease activity in clinical practice, adjunctive biomarkers assessed include fecal calprotectin (FCP), which shows intestinal inflammation in stool (Ma *et al.*, 2019), or C-reactive protein (CRP), which shows serum levels of acute inflammation (Chen *et al.*, 2020).

Although the pathophysiology mechanisms of IBD are yet to be comprehensively understood, they involve dysregulation of the adaptive and innate immune mucosal response in individuals with genetic susceptibility (Xu *et al.,* 2014). Dysregulation of the mucosal response is attributed to the activation of effector T-cells, proliferation of B-cells and antibodies, and changes to the innate immune system (Xu *et al.,* 2014). Dendritic

cells, IELs, and macrophages detect invading bacteria and launch swift inflammatory responses of the innate immune system. Dendritic cells also activate T-cells, which mediate the adaptive immune system response (Geremia *et al.,* 2014). The adaptive immune response is characterized by atypical, activated T-cell development and an impaired -cell response, which can result in increased inflammatory chemokine and cytokine release, long-term tissue damage and injury to the epithelium, and ultimately lead to apoptosis of enterocytes (Geremia *et al.,* 2014).

Several factors contribute to malnutrition in IBD. Increased risk for malnutrition in this population can be attributed to changes such as decreased dietary intake, loss of nutrients through drug-nutrient interactions, malabsorption, higher energy needs, and inflammation (Donnellan *et al.*, 2013; Goh & O'Morain, 2003). Inflammation induces the release of inflammatory cytokines leading to intestinal damage and malabsorption (Scaldaferri *et al.,* 2017). Due to the compromised integrity of the epithelial lining, there is malabsorption of nutrients and loss of electrolytes secondary to diarrhea during active disease (Scaldaferri *et al.*, 2017). Furthermore, IBD patients often have inadequate dietary intake due to symptoms affecting oral intake and dietary imbalances due to prolonged diet restrictions or fasting due to hospitalization (Hébuterne *et al.*, 2009; Lucendo & De Rezende, 2009). Chronic inflammation or surgery in the intestines can lead to rapid transit time in the bowel, which can cause malabsorption and increased fecal loss (Balestrieri *et al.,* 2020). The severity of malnutrition, in turn, depends on disease severity, activity, and duration (Forbes *et al.,* 2017). Therefore, nutritional assessment is essential for nutritional management in this population (Forbes *et al.,* 2017).

IBD is associated with indicators of malnutrition that include reduced BMI, muscle mass, and functional capacity (Lu *et al.*, 2016; Norman *et al.*, 2006; Valentini *et al.*, 2008). In a recent cross-sectional study evaluating nutritional status by comparing 140 CD with healthy controls, active CD showed lower FM and weight than both inactive CD and control groups (Cioffi *et al.,* 2020). A systematic review and meta-analysis of body composition in IBD, including 631 CD and 295 UC found that BMI was reduced in 37% of CD patients and 20% of UC patients. Alterations in body composition occurred in both IBD groups with reductions in FM in 31% CD and 13% UC. This may partly explain trends showing the rising prevalence of overweight and obese nutritional status in IBD (Singh *et al.,* 2017; Weissman *et al.,* 2021).

Other studies evaluating CD have found changes in substrate utilization, with higher lipid oxidation, lower carbohydrate oxidation, and reductions in diet-induced thermogenesis (Al-Jaouni *et al.*, 2000; Mingrone *et al.*, 1996). This suggests a potential starvation state, which can place strain on other organs such as the liver and alter energy expenditure (Saunders, 2010) thus affecting overall nutritional status.

1.2 Energy expenditure

Evaluating energy needs is a critical step when formulating goals for nutritional management. This is particularly true for individuals unable to regulate their energy intake (Silver *et al.,* 2013). Energy balance can be understood through the first law of thermodynamics, which states that energy can neither be created nor destroyed; hence, quantifying energy taken in and energy expended is essential for evaluating energy needs

(Schoeller, 2009). Total energy expenditure (TEE) encompasses an individual's daily energy needs over a 24-hour period (Westerterp, 2013), with three main components involved: 1) resting energy expenditure (REE), 2) activity energy expenditure (AEE), and 3) diet-induced thermogenesis (DIT). REE can be determined by direct or indirect calorimetry under fasting and resting conditions. The gold standard for measuring TEE under free-living conditions is the doubly labelled water (DLW) method. DLW is a form of indirect calorimetry where an individual's carbon dioxide production is measured from the turnover rates of water-labelled hydrogen and oxygen isotopes (Westerterp, 2017). DIT is the most challenging component of TEE to measure, due to challenges with selecting the characteristics of study meals provided and high variations in physiological responses to foods (Tataranni *et al.*, 1995). To study DIT in a single meal, ventilated-hood systems are used, while respiratory chambers are used for longer exams where participants consume regular meals over the day (Tataranni *et al.*, 1995).

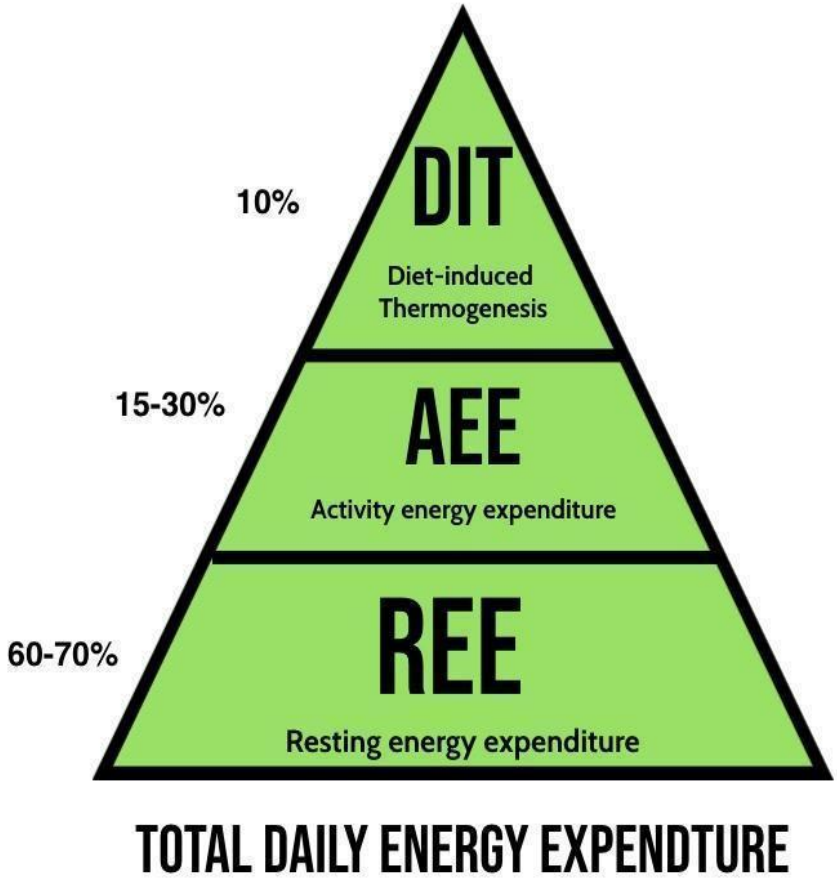

Figure 1.2. Total Daily Energy Expenditure. The subcomponents of daily energy needs are comprised of resting energy expenditure, activity energy expenditure, and diet-induced thermogenesis.

1.21 Resting energy expenditure

Resting energy expenditure (REE) accounts for the most significant component of total energy expenditure (TEE), with 60–80% of TEE determined by REE *(*Capristo *et al*., 1997, Delsoglio *et al.,* 2019; Wong *et al.*, 1996,). REE refers to the amount of energy required to maintain metabolism and essential involuntary physiological functions, such

as respiration, heartbeat, blood pressure, body temperature, and substrate turnover regulation (Delsoglio *et al.,* 2019; Gupta *et al.,* 2017) while an individual is in an inter-prandial state. While many use the term basal metabolic rate (BMR) and REE interchangeably, some authors distinguish BMR and diet-induced thermogenesis (DIT) as sub-components of REE (Delsoglio *et al.*, 2019; Moonen *et al.*, 2021). REE is generally utilized at a rate of 1 kilocalorie/kilogram hourly (Jetté *et al.,* 1990). Skeletal muscle, widely known to be metabolically active tissue, composes 40% of human mass (Nelson *et al.*, 2020) and accounts for 20% of REE in the absence of any activity. Other organs involved in key physiological processes, such as the intestines, liver, brain, kidneys, and heart consume 75% of REE (Klein & Jeejeebhoy, 2002).

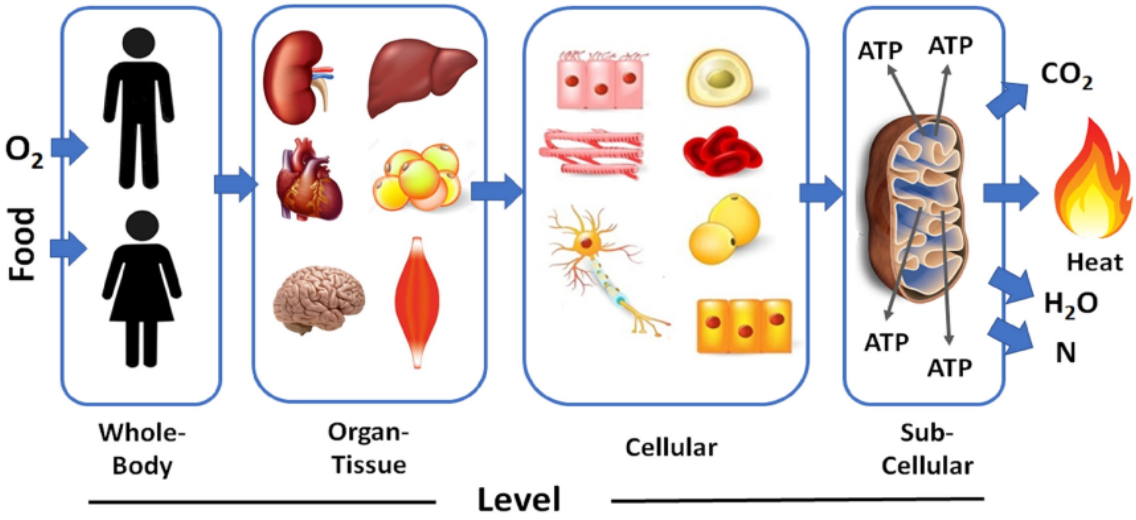

Figure 1.3. Resting energy expenditure (REE). REE is based on energy expenditure generated from biochemical reactions that take place at a subcellular level. Figure adapted from Heymsfield *et al.*, 2021.

1.22 Activity Energy Expenditure

Activity energy expenditure, also known as activity thermogenesis, refers to the amount of energy consumed following any activity of skeletal muscles (Capersen, 1985). AEE constitutes the second most important determinant of TEE, comprising 15-30% depending on whether an individual is inactive, or engages in regular exercise (Poehlman, 1989). Of all components of TEE, AEE has the highest inter-individual differences, due to factors such as body composition, age, height, and activity levels (Plasqui & Westerterp, 2007; Westerterp, 2013). AEE involves energy expended by muscles, including minor movements like shivering and fidgeting (Poehlman, 1989). AEE is also dependent on the weight of the individual's body displaced (Bonomi *et al.*, 2013). Individuals with higher body weight expend greater energy when completing a weight-bearing activity than a lower-weight individual.

Physical activity (PA) is another determinant of AEE, and is based on activity frequency, type, intensity, and duration (Westerp, 2008). Doubly-labelled water (DLW) is a gold-standard method that can be used to measure AEE with accuracy in free-living environment (Bonomi *et al.,* 2010, 2013). This method is preferable to measure AEE for longer durations (7-14 days) and due to high costs, it tends to be used in smaller populations (Yu *et al.*, 2012). Alternatively, motion sensors, such as accelerometers, can be used to quantify physical activity using body movements (Westerterp, 2008). Accuracy of accelerometers is reasonable compared with DLW; however, this can vary depending on the device used and the position worn (Lynch *et al.*, 2019). Unlike DLW,

accelerometers record actual movements so patterns of activity levels can be determined (Plasqui *et al.*, 2013).

When these tools are not readily available, measurement of reported physical activity is through questionnaires— non-invasive, inexpensive tools to determine AEE in free-living conditions (Neilson *et al.,* 2008). Physical activity questionnaires (PAQs) are the most practicable method (Shephard, 2003) as they generate information on physical activity patterns and have long informed recommendations made in population-based epidemiological studies (Ács *et al.*, 2020). For instance, the International Physical Activity Questionnaire (IPAQ) is among the most extensively used validated PAQs and can be used to account for physical activity levels over a 7-day timeframe (Hagströmer *et al.,* 2006; Kim *et al*., 2013). The IPAQ was devised in 1998 to implement a global standard for monitoring physical activity (Craig *et al.,* 2003). While there are both long-form (IPAQ-LF) and short-form (IPAQ-SF) versions of the questionnaire, the original questionnaire authors recommend the use of the 7-item IPAQ-SF for the ease of respondents (Craig *et al.,* 2003). This short-form IPAQ assesses intensity levels, which include sitting, walking, moderate-intense activities, and vigorous-intense activity. SF-IPAQ has been validated in a 12-country study and evaluation has shown acceptable reliability and validity (Spearman's correlation: 0.8; criterion validity: 0.30) (Craig *et al.*, 2003). Based on activity levels, individuals are assigned an activity factor, where values include 1.0-1.1 (bed rest), 1.2 (sedentary), 1.3 (light exercise), 1.5 (moderate exercise), 1.7 (heavy exercise), and 1.9 (very heavy exercise) (El Regal *et al.*, 2016).

1.23 Diet-induced thermogenesis

Diet-induced thermogenesis (DIT) is the smallest component of TEE and REE, and constitutes approximately 10% of TEE (Kreymann *et al.,* 2009). DIT refers to the insulin-mediated, transient increase in energy expenditure that exceeds basal fasting levels in relation to the quantity of energy intake consumed (Westerterp, 2004). Following dietary intake, energy expenditure rises by 10-15% and returns to baseline levels after 8 hours (Ho, 2018). One reason for the increase in energy levels is the digestion, transport and storage of nutrients (Acheson *et al.,* 1984). Differential energy is required for each of these processes with nutrient storage having substantially higher energy needs than digestion and transport (Vernet *et al.,* 1986). The remaining energy is utilized in the storage of glycogen and triglycerides (Ferrannini, 1988).

Theoretically, based on the amount of ATP required for the initial steps of metabolism and storage, the DIT is different for each nutrient. Adenosine triphosphate (ATP) use differs depending on the nutrient consumed, with 0 to 3% required for metabolism and storage of fat, 5 to 10% for carbohydrates, and 20 to 30% for protein (Acheson, 1993). This can partly explain why macronutrient intake affects DIT, with evidence showing that higher protein intake increases DIT, improves satiety, and may subsequently lower energy intake (Halton & Hu, 2004; Westerterp, 2004). Moreover, while protein and carbohydrate oxidation are self-regulated processes (Acheson *et al.,* 1982; Flatt *et al.,*1985), fat oxidation is not induced by fat intake (Schutz *et al.,* 1989). Post-prandial thermogenesis is increased following protein intake by 25%, carbohydrates

by 6% and is lowest following fat intake with an increase of only 3% (Weststrate *et al.,* 1990). The increase in energy expenditure due to DIT can last for 8-10 hours if higher calorie meals over 1,000 kcal are consumed (D'Alessio *et al.*, 1988; Melanson *et al.,* 1998) likely due to inter-individual variation in nutrient digestion, absorption, and gastric emptying (Scott *et al.*, 2007).

1.3 Determining energy expenditure

Energy expenditure (EE) can be 1) measured or 2) estimated. Measurement of EE provides the most accurate energy requirements; however, estimation of EE through predictive equations can be useful in clinical practice. This section will discuss the measurement of energy needs by direct and indirect calorimetry, in addition to the estimation of energy needs using predictive equations.

***Calorimetry**: Calor(latin) = heat / Metrion(greek)= measure*

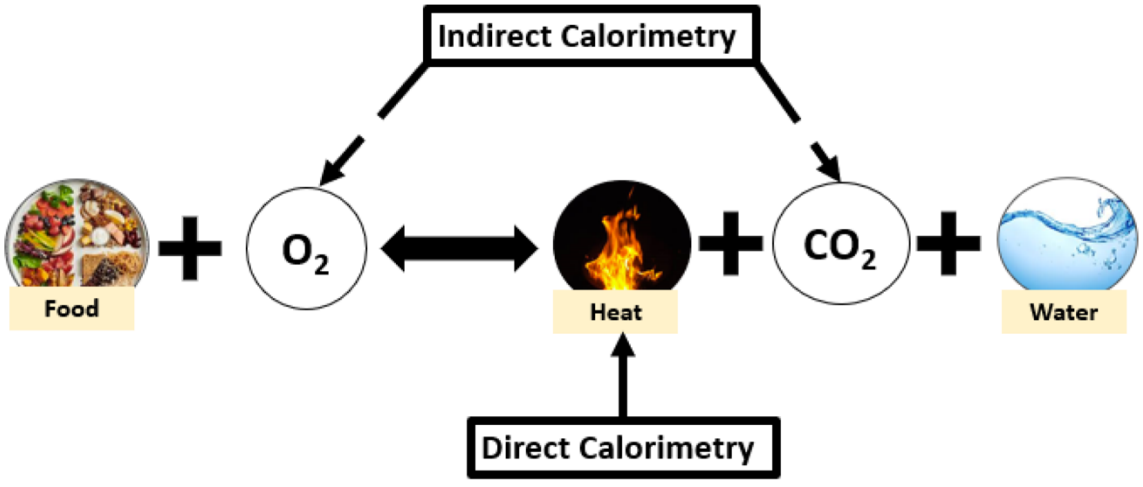

Figure 1.4. Measurement of energy expenditure in direct and indirect calorimetry. To determine energy expenditure, direct calorimetry measures heat while indirect calorimetry measures oxygen (O_2) consumption and carbon dioxide (CO_2) production. (Abdi *et al.,* 2023).

1.3.1 Direct calorimetry

Direct calorimetry measures heat produced and transferred from the body to its surrounding environment (Kenny *et al.,* 2017). Based on the law of energy conservation principle, the quantity of heat produced corresponds to an individual's energy expenditure and metabolic rate (Kenny *et al.,* 2017). The accuracy of measurement depends on study conditions (Ho, 2018). As such, a direct calorimeter should have a closed system to allow for a direct, precise measure of all dissipated metabolic energy without allowing for external transfer (Webb *et al.,* 1988). Our current understanding of human metabolism is based on seminal experiments conducted using direct calorimetry to measure heat in animals (Lodwig & Smeaton, 1974) and led to the development of a respiration calorimeter that could be used to measure metabolic rate in humans (Atwater *et al.,* 1905). However, Webb *et al.* (1988) found that direct calorimeters are unable to account for energy expended during a walking exercise state (Webb *et al.,* 1988) and therefore require a complete resting state (Oshima *et al.,* 2017). While direct calorimeters are a precise tool to measure energy needs, but they are often impractical for use in clinical settings due to the high costs, space, and time associated required (Johnson & Coward-McKenzie, 2001).

1.3.2 Indirect calorimetry

Indirect calorimetry (IC) measures oxygen consumption (VO_2) and carbon dioxide production (VCO_2) to indirectly determine energy expenditure and quantify substrate oxidation (Schoffelen & Plasqui, 2018). It allows for the measurement of energy in both resting and exercise states, and in patients on mechanical ventilation (Delsoglio *et al.,* 2019). IC is a gold-standard method for providing measurement of EE and is recommended for providing optimal nutritional therapy in clinical practice (Delsoglio *et al*., 2019). IC also provides measures of substrate utilization, which refers to the contribution of carbohydrates, proteins and fat to EE during both rest and exercise (Krogh & Lindhard, 1920). Individuals with stable body weight are in a state of energy balance, thus substrate oxidation is reflective of macronutrient intake and amount of body fat storage. However, in individuals with negative energy balance, lipid oxidation is increased (Buscemi *et al.*, 2019).

Underfeeding and overfeeding can lead to malnutrition and other detrimental outcomes (Petros *et al.*, 2016; Singer *et al*., 2011; Wei, 2013), hence, the measurement of energy needs is crucial (Oshima *et al.*, 2017). To measure REE, a ventilated system is used, with a respiration chamber or canopy. Ventilation systems allow for a longer duration measure of energy needs (Singer *et al.,* 2011). Each method has its own advantages and disadvantages. For instance, the use of chambers has been widely validated and produces stable measurements. However, they require a large space to implement and need additional time to be disinfected (Oshima *et al.*, 2017). In contrast, a

canopy minimizes patient discomfort and is less expensive but can be difficult for use in individuals who require oxygen therapy (Oshima *et al.*, 2017). IC in spontaneously breathing patients uses a facemask or ventilated canopy, while in patients requiring mechanical ventilation, the IC system is attached to the ventilator. Another advantage of IC over direct calorimetry is that can be done in both resting and exercise states. Exercise testing measures IC with a mouthpiece, nasal clip, or facemask (Singer *et al*., 2011). The machine uses an Abbreviated Weir's formula (Oshima *et al.*, 2017) to provide resting energy expenditure, calculated as: Resting energy expenditure **(REE) = (3.94 x VO_2) + (1.1 x VCO_2).** IC utilizes a different method of measuring energy needs as compared with DC and is therefore, appropriate for different contexts (Ho, 2018).

IC is particularly beneficial for patients with acute and chronic malnutrition (Delsoglio *et al.,* 2019). It is important to also select an appropriate, validated IC, as there are numerous devices available, and not all provide accurate measures of energy needs (Cooper *et al.*, 2009; Graf *et al.*, 2015; Sundström *et al.*, 2013). Prior to undergoing IC, patients are required to be in a fasting state to prevent the influence of AEE and DIT on REE. The exam should be in an environment with a temperature ideal for the maintenance of body temperature. For accurate measurement to be taken, the validity of a test depends on achieving a steady state, which refers to a 5-minute time frame where the variation of VO_2 and VCO_2 is below 10%. Typically, 20 minutes are required to achieve a steady state (McClave *et al.*, 2003), although this varies depending on the patient. In addition to determining REE, IC provides information on the rate of substrate use through Respiratory Quotient (RQ), which refers to substrate utilization calculated as VCO_2/O_2.

This is an advantage over other methods of determining energy expenditure. The physiological RQ values range from 0.67 to 1.3. RQ values below 0.7 indicate primary lipid oxidation suggestive of underfeeding, while values over 0.95-1.0 denote primary carbohydrate oxidation suggestive of overfeeding. Values between 0.7-0.95 suggest mixed substrate utilization (Matarese, 1997).

Table 1.2. Best Practices for Indirect Calorimetry

Parameter	Best practice	Reference
Fasting	Minimum 5 hour fast observed	Haugen *et al.*, 2007
Steady-state	VO_2 and VCO_2 variability ≤ 10%	McClave *et al.*, 2003
Temperature (°C)	Room temperature (22°- 25°C)	Fullmer *et al.*, 2015
Ventilation (FiO_2, PEEP, Peak ventilatory pressure)	No change before (< 1 hour) or during exam	Achamrah *et al.*, 2021
Position	Supine, no fidgeting, voluntary or involuntary movement	Achamrah *et al.*, 2021 Fullmer *et al.*, 2015
Air leaks	No air leaks (VCO_2/O_2 loss)	Achamrah *et al.*, 2021
RQ	Physiological range between 0.67-1.2	Blauw *et al.*, 2017 Haugen *et al.*, 2007
Machine calibration	Based on IC machine instructions	Graf *et al.*, 2015 Wells *et al.*, 1998
Disinfection	Disinfect breathing apparatus after each test	Oshima *et al.*, 2017 Singer *et al.*, 2020

While many metabolic carts (IC machines) are available, the new generation Q-NRG® are smaller in size and provide accurate measurements (Delsoglio *et al.,* 2020). To investigate the use of Q-NRG® machines over current IC machines, an ESPEN (European Society for Clinical Nutrition and Metabolism) and ESICM (European Society of Intensive Care Medicine) supported study conducted several *in vitro* and *in vivo* research investigations testing healthy volunteers (Delsoglio *et al.,* 2020). Results were compared against reference values from mass-spectrometry, which measures O_2 and CO_2 concentration. In vitro validation of the Q-NRG® found inaccuracy rates as low as 1% for REE, VO_2, VCO_2 and 1.5% for the RQ (Delsoglio *et al.,* 2020). Q-NRG® can also support both spontaneously breathing and mechanically ventilated patients (Q-NRG+®). In a second-phase prospective cross-sectional trial comparing Q-NRG® with another commonly used metabolic cart, the Quark RMR®, results showed that both metabolic carts were comparable in measuring REE through canopy and face-mask mode (Pearson r= 0.96 and r=0.86 respectively) (Dupertuis *et al.*, 2022). Q-NRG® also demonstrated greater time efficiency in canopy mode, allowing 73% of patients to reach a steady state within a 5–15-minute exam, as compared with 40% achieving a steady-state with the Quark RMR®.

While IC is typically used for individuals with critical illnesses or those undergoing surgery, it is also ideal for those with chronic medical conditions (Oshima *et al.,* 2017). IC has been used to measure REE of numerous chronic medical conditions, which include chronic obstructive pulmonary disease (Farooqi *et al.*, 2018), chronic kidney disease (de Oliveira *et al.*, 2018), diabetes (Hugget *et al*., 2003), coronary artery

disease (Schoeller *et al.*, 1990), obesity (Carneiro *et al.*, 2016), anorexia nervosa (Cuerda *et al.*, 2007), arthritis (Metsios *et al.*, 2008), and various neurodegenerative disorders (Çekici & Acar, 2020). Still, IC continues to be underutilized in clinical practice due to factors such as a lack of availability and knowledge of its benefits in nutritional management (De Waele & van Zanten, 2022).

1.3.3 IC in chronic GI conditions

Abnormal function of the GI system affects various physiological processes, such as nutrient delivery, immune cell response, GI motility, the intestinal epithelium, and the composition of gut microbiota, all of which ultimately impact the ability to maintain nutrition (Alberda *et al.*, 2006). Several factors can increase or decrease the amount of energy an individual requires (Gupta *et al.,* 2017). Generally, there may be substantial variations in energy needs in chronic conditions due to alterations in energy metabolism specific to an individual. This can result in hypometabolism, which refers to a lowered metabolic rate, or hypermetabolism, which refers to an increased metabolic rate (Delsoglio *et al.,* 2019) compared to predicted energy needs. When nutrient intake is metabolized, carbohydrate stores are preferred for energy utilization, followed by fat, and last, protein (Alberda *et al.*, 2006). However, in a starvation state, fatty acids are oxidized into ketone bodies for energy, characterizing an RQ of 0.6-0.7 in a starved individual (Alberda *et al.*, 2006). In contrast, substrate utilization leads to accelerated carbohydrate

oxidation in a stress hypermetabolic state, such as critical illness, resulting in an RQ of 0.8–0.9 (Alberda *et al.,* 2006).

Chronic medical conditions such as gastrointestinal and liver diseases (Al-Jaouni *et al.*, 2000; Capristo *et al.*, 1998; Gong *et al.*, 2015; Hill *et al.*, 2011; Kushner & Schoeller, 1991; Rigaud *et al.*, 1993; Sammarco *et al.*, 2017; Sasaki *et al.*, 2010a; Sasaki *et al.*, 2010b; Zoli *et al.*, 1996), short bowel (Fassini *et al.,* 2016), and bariatric surgery (Mirahmadian *et al.,* 2018) can lead to inflammation, impact organ function and modify lean mass leading to changes in metabolism and alterations in resting energy expenditure. This thesis will specifically focus on CeD and IBD, which are well-known chronic gastrointestinal immune-mediated diseases (Pascual *et al.*, 2014).

1.3.3.1 IC in Celiac Disease

The first study investigating REE in CeD was conducted by Capristo *et al*. in 1997, using indirect calorimetry (IC) to compare REE in Italian patients with untreated CeD (n=16), treated CeD (n=18) and a healthy control group (n=20) (Capristo *et al.,* 1997). The authors showed that REE did not vary significantly between groups, when measurements were adjusted for fat-free mass (FFM), REE was significantly higher in both untreated and treated CeD than in controls. A possible explanation given for this was due to reduced muscle mass in CeD.

Later, a longitudinal study performed by this group found that both untreated and treated CeD patients exhibit higher REE, when adjusted for age, sex, fat mass and FFM, compared with a healthy control group (Capristo *et al.,* 2000). In contrast with non-CeD

controls, treated and untreated CeD showed higher REE and carbohydrate oxidation (Capristo *et al.*, 2000, 1997). Although body mass index (BMI) was in the lower normal range in both groups, treated CeD patients had lower fat-free mass (FFM) than untreated CeD and controls. FFM is directly related to metabolism and increased basal metabolic rate; therefore, the reasons for higher REE in treated CeD with lower fat mass are unclear. The authors noted that this observation in untreated CeD could reflect the presence of inflammation-related factors, such as higher migration rates and renewal of epithelial cells and protein synthesis in the intestinal mucosa. A later study by Wierdsma and colleagues (2016) demonstrated that REE changes in refractory CeD when adjusted for weight (Wierdsma *et al*., 2016). This study compared newly diagnosed CeD with Type II refractory CeD (RDCII), and EATL, and provided evidence for higher REE in RCDII patients.

More recently, pilot research conducted in our lab investigated REE in 66 patients with chronic GI conditions. Results showed lower REE in CeD (n=24), as compared with functional GI disorders (n=17), IBD (n=15), and undernutrition (n=10) (Faisal *et al.,* 2022). Following moderate and strenuous exercise testing, EE was significantly higher in CeD compared to all other groups and reduced by 80% compared with predicted EE. PE (Harris-Benedict and 25 kcal/kg) significantly underestimated REE compared to IC. This suggested increased energy needs in CeD; however, given the low sample size of CeD further exploration is needed to better understand metabolic changes in CeD.

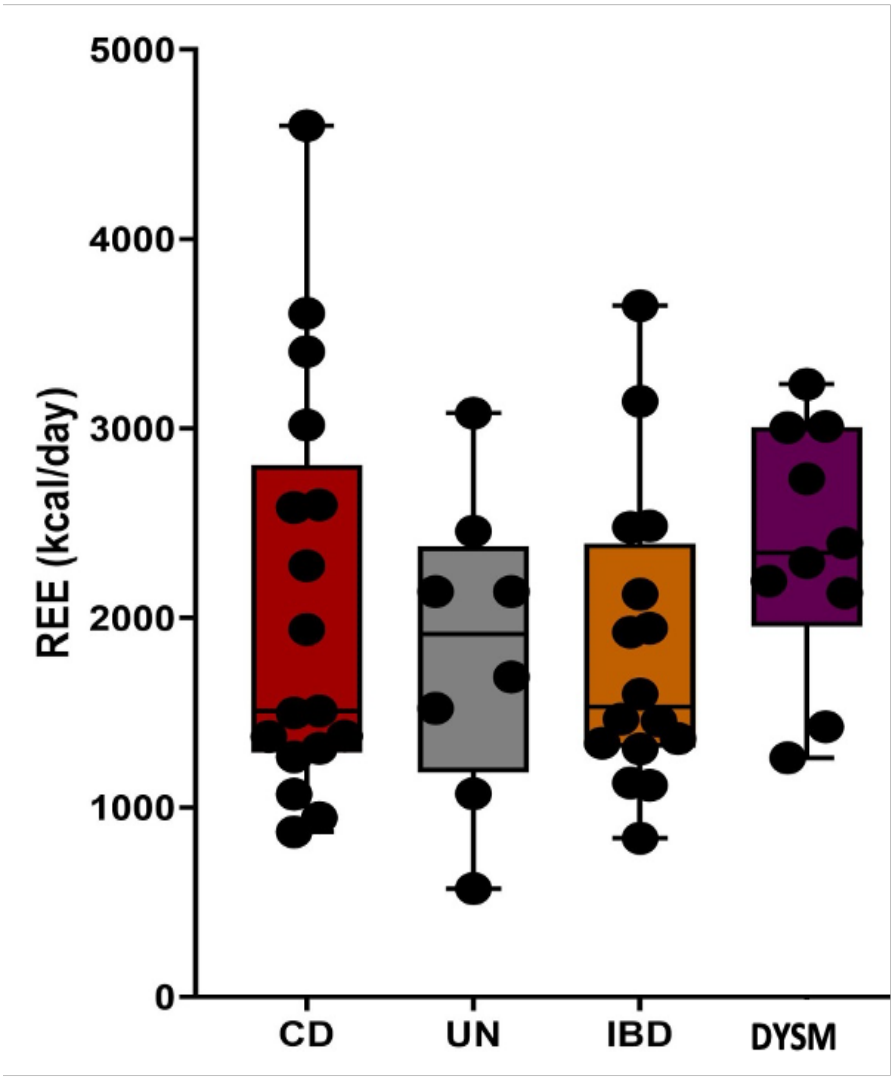

Figure 1.5. Resting energy expenditure (REE) of patients with chronic GI conditions (Figure unpublished). Preliminary findings show higher REE compared with PE (Harris-Benedict and 25 kcal/kg) in patients with celiac disease, IBD, functional GI disorders, and undernutrition due to other causes. Abstract published. (Faisal *et al.*, 2022).

1.3.3.2 IC in Inflammatory Bowel Disease

IBD patients often present with weight loss, and disease activity may contribute to increased resting energy expenditure. Several studies have shown increased REE in IBD (Al-Jaouni *et al.*, 2000; Capristo *et al*., 1998; Gong *et al.*, 2015; R. J. Hill *et al.*, 2011; Kushner & Schoeller, 1991; Rigaud *et al.*, 1993; Sammarco *et al.*, 2017; Sasaki *et al.*, 2010a; Sasaki *et al.*, 2010b; Zoli *et al.*, 1996). However, other studies have shown evidence contrary to these findings (Barot *et al.*, 1981; Chan *et al.,* 1986). Mingrone et *al*. (1996) found lower REE in Crohn's disease patients as compared with controls, however, these findings were reversed when REE was adjusted for lean mass (LM) (Mingrone *et al.*, 1996). Recent research conducted by Bender et *al.* (2020) found that REE decreased in both Crohn's disease and UC patients treated with biologics therapies, which could be attributed to the effects of these therapies on fat tissue, in conjunction with lower physical activity and muscle mass in these patients (Bender *et al.*, 2020). The controversies in this topic point to the need for further research evaluating these differences.

1.3.4 Predictive Equations

Over 200 predictive equations (PE) have been widely used in clinical practice due to their cost-effective method of determining energy expenditure (McClave *et al.*, 2016). Commonly used PE include Harris-Benedict (Harris & Benedict, 1918), Schofield (Schofield, 1985), Owen (Owen *et al.*, 1987, 1986), and Mifflin St. Jeor (Mifflin *et al.,* 1990). Accurate prediction, defined as ±10% of measured REE, has been found in 45-80% of individuals, with an overall tendency of PE to overestimate energy needs (Feurer *et al.,* 1984; Frankenfield *et al.*, 2003; Owen *et al.*, 1986). The Harris-Benedict equation

(HB) is the most extensively used PE and was derived in 1918 to determine REE based on a sample of healthy individuals (Harris & Benedict, 1918). Later, the World Health Organization proposed the Schofield formulas using REE values from twenty-three countries (Schofield, 1985). Thereafter, the Owen formulas were developed using predictive equations in athletic, lean and obese individuals, separately for males (Owen et al., 1986) and females (Owen *et al.*, 1987). Evaluation of the Owen PE show estimated energy within ± 10% measured RMR in 73% of cases (Song *et al.*, 2014). Subsequently, the Mifflin-St. Jeor (MSJ) formula was formulated from a sample of 498 individuals with BMI values ranging from normal weight to severely obese (Mifflin *et al.,* 1990). In an evaluation of 10 validation studies, the MSJ predicted REE within ±10% of the measured REE (Frankenfield *et al.,* 2003). Another predictive method estimates energy requirements using fixed units of kilograms per body weight, which is commonly 25-30 kcal/kg/day (McClave *et al.*, 2016). This is based on ASPEN guidelines which recommend using simple weight-based equations when using IC is not possible.

However, PE are inaccurate as they overestimate or underestimate resting energy expenditure, particularly in underweight and obese individuals (McClave *et al.*, 2016). Furthermore, no PE can be used globally to determine the energy needs of every individual (Frings-Meuthen *et al.,* 2021). Previous research on the use of PE in CeD and IBD populations is limited, and most studies have only evaluated the Harris-Benedict equation. In IBD, there are mixed findings, with most studies showing PE underestimates REE (Chan *et al.*, 1986; Karachaliou *et al.*, 2022; Marra *et al.,* 2020; Stokes & Hill, 1993) though other contradicting results indicate the accuracy of PE when compared with

IC (Barot *et al.*, 1982). Research comparing PE in IBD is scarce, and as noted by Karachaliou and colleagues, most studies differ in methodology and have a small sample size (Karachaliou *et al.,* 2022). In CeD, only one study (Weirdsma *et al.,* 2016) reported inaccuracy of the Harris-Benedict equation in 39% of CD, and 60% in EATL CeD, compared to REE.

Generally, the accuracy of PE is reported between 40-75% compared with IC (McClave *et al.*, 2016). Therefore, due to the accuracy the ease with which testing can be repeated if needed, its relatively inexpensive cost, and its nonintrusive use in testing patients, IC is the preferred method to determine REE (Allard *et al.*, 2016; Mifflin *et al.*, 1990).

1.4 Determinants of Resting Energy Expenditure

The most important predictors of REE are body size, composition, activity level, and dietary intake (Westerterp, 2013). Of these, body composition is reported as the largest contributor, with 60-70% of REE influenced by fat-free mass (FFM) and 5-7% by fat mass (FM) (Johnstone *et al.*, 2005). Underfeeding can reduce REE, likely due to the need for energy conservation (Forbes, 1987; Hall, 2007). In studies comparing REE in fasting and non-fasting states, REE decreases by 100 ± 29 kcal/day ($P < 0.01$) in a fasting state (Heyman *et al.,* 1992). In contrast, overfeeding tends to increase REE, dependent on body composition. In patients with a normal BMI, a minimum of 20% of weight gain is composed of FFM, which is thought to be the cause of an increase in REE (Forbes, 1987; Hall, 2007). Macronutrient composition also impacts REE, with protein found to have a

greater influence on REE. In a randomized controlled trial of 25 healthy participants overeating low-protein, normal protein, and high-protein diets, REE was found to increase significantly in both the normal protein (160 kcal/day [95% CI, 102-218 kcal/day] and the high protein diet groups (227 kcal/day [95% CI, 165-289 kcal/day]) (Bray *et al.*, 2012).

Other factors that can impact REE include age and sex (Owen *et al.*, 1987). Generally, REE decreases with age by a rate of 1-2% each decade (Elia *et al.*, 2000), and in individuals with similar height and weight, REE was reported higher in men than women (Westerterp, 2017). REE is also modulated by the circadian rhythm, where it is lowest late into the night and peaks during the afternoon and evening (Zitting *et al.*, 2018).

Factors impacting REE have not been deeply explored in patients with GI conditions, such as CeD and IBD. However, disease activity may alter REE. For instance, research has shown increased REE in adult CeD before and after adhering to a GFD when compared with control subjects, inferring that disease activity in CeD may have caused an increase (Capristo *et al.*, 2000). Similarly, patients with active CD have increased REE (Gong *et al.,* 2015; Kushner & Schoeller 1991; Rigaud *et al.,* 1993). Additionally, CeD and IBD tend to be associated with anxiety, depression, and a range of GI symptoms (Addolorato *et al.,* 1997; Cao *et al.,* 2019*;* Dorn *et al.,* 2010; Fera *et al.,* 2023*;* Kovács *et al.,* 2007*;* Porcelli *et al.,* 1996) which can impact resting energy expenditure. Investigations into the effects of anxiety disorders hypothesize that sympathetic nervous system activation may increase metabolic rate and REE.

Wymelbeke *et al.* (2004) explored factors associated with higher REE in refeeding of malnourished anorexia nervosa patients using IC. Anxiety was independently linked to the rise in REE ($P < 0.01$) though this was not shown with depressive symptoms ($P < 0.05$) (Van Wymelbeke *et al.*, 2004). A recent preclinical study in mutant $Emx1^{Cre/+}$ mice inducing anxiogenic activation in the brain found that increased basal energy expenditure was due to sympathetic nervous system activation (Xie *et al.*, 2019). Depression has also been hypothesized to alter REE; however, evidence is inconclusive, with some studies reporting no difference in REE between individuals with and without depression (Caroff *et al.,* 1981; Fernstrom *et al.*, 1985) and others showing a decrease in REE of individuals with seasonal affective disorder (SAD) (Gaist *et al.,* 1990). However, further research on whether anxiety and depression affect REE in CIGI is needed.

1.5 Study rationale

IC has been extensively used in ICU for the nutritional management of critically ill patients (Achamrah *et al.,* 2021), and, more recently, in patients with other gastrointestinal conditions, including liver disease (Schneeweiss *et al.,* 1990) and IBD (Al-Jaouni *et al.,* 2000; Capristo *et al.,* 1997; Hill *et al*., 2011; Kushner & Schoeller, 1991; Sammarco *et al.*, 2017; Sasaki *et al.*, 2010), but the evidence in CeD is scarce.

The controversial results and small sample size of current studies in CeD and IBD limit the interpretation of results. Furthermore, there is a need for research focusing on the energy needs of patients with GI conditions in the outpatient setting and how this will improve outcomes in patient care. As part of the nutrition initiative at the Farncombe Institute, the Indirect Calorimetry Clinic has been initiated to conduct an in-depth

nutrition assessment using IC to measure individual energy needs in patients with chronic inflammatory GI disorders identified at risk of malnutrition. In this context, we designed an observational study to determine whether energy needs measured by IC are different from those estimated using predictive formulas in patients with chronic inflammatory GI conditions.

1.51 Study hypotheses

1. There will be differences in the energy needs of patients with chronic inflammatory GI conditions assessed by indirect calorimetry compared to predictive equations.
2. There will be differences in energy needs between different groups of patients with chronic inflammatory GI conditions.
3. Recognizing factors influencing malnutrition will improve the nutrition management of patients with chronic inflammatory GI conditions.

1.52 Aims

1. To assess the differences in energy expenditure estimated by predictive equations compared with those measured by IC (REE).
2. To evaluate current indications of IC to guide decision-making in clinical practice.
3. To assess factors influencing REE in patients with chronic inflammatory GI conditions.

Chapter Two: Methods

2.1 Indirect Calorimetry Clinic

The outpatient Indirect Calorimetry Clinic is part of the Digestive Diseases Clinic and provides an in-depth nutrition assessment for patients with chronic inflammatory GI disorders identified at risk of malnutrition. Concurrently, we have established a prospective registry to collect data for research and quality improvement.

2.2 Study Design

This observational and exploratory study was conducted in the Indirect Calorimetry Clinic at the Digestive Disease Clinic, McMaster University Medical Centre. This study is based on an observational design.

2.3 Study Protocol and Informed Consent

The study protocol for the proposed study was developed in September 2021. The study protocol outlined the creation of a prospective registry for patients undergoing nutrition assessments at the indirect calorimetry clinic. This included the study background, rationale, aims, methods, and future directions. Along with the study protocol, an informed consent form was drafted for patients attending the indirect calorimetry clinic, who then chose to participate in the research study. The informed consent form outlined the purpose of the research study, the benefit of participants contributing to this study—individually and to the fields of gastroenterology and nutrition research—and the potential risks, which were estimated to be minimal since no

intervention would take place. Finally, an introductory handout was created to inform patients about the study procedures before the initial meeting with each patient at the clinic (Appendix A).

2.4 Ethics Submission

The prospective indirect calorimetry registry application began in October 2021. This study has been approved by the Hamilton Integrated Research Ethics Board (HiREB ID# 14164).

2.5 Patient recruitment

Patients were recruited during their regular visits to the IC clinic. The clinic population includes patients diagnosed with Celiac disease (CeD), Intestinal Bowel disease (IBD), Short Bowel disease, or malnutrition due to other GI conditions. To attend the clinic, patients required a referral from a gastroenterologist stating their diagnosis and reason for referral (Appendix B). There were three main reasons given for their referral: 1) suspected malnutrition that requires further assessment; 2) concerns about overnutrition and a goal of weight loss; 3) inability to gain weight and concerns due to a higher metabolic rate. To be included in the study, participants were required to meet the following inclusion criteria: 1) age >18 years; 2) diagnosed with GI conditions (celiac disease, IBD, or malnutrition due to other causes), 3) referred to nutrition/IC clinic, and 4) sign informed consent.

2.6 Sample Size

A sample size calculation was performed on the primary outcome using ClinCalc software (Appendix C) to test the primary hypothesis. Based on a previous study by Stubelj *et al.* (2020) the Mean (SD) REE kcal/day is 1400 ± 256 and 1536 ± 95 using a predictive equation (Stubelj *et al.,* 2020). A statistical power (1-β) of 80% and a statistical significance (α) of 5% are standard values in clinical research studies (Casals-Pascual *et al.*, 2020). Considering this, an adequately powered main trial will require a total sample size of 56 patients per group (α= 0.05 and 1-β=0.8).

2.7 Study measurements

Study measures are included in Table 2.1. below.

Table 2.1. Study Measures

Type of data collected	Data measures
Demographic information	Patient age, gender, weight, and BMI
Referral information	Reason for nutrition assessment Diagnosis at the time of enrolment (e.g., Crohn's disease, ulcerative colitis, Celiac disease, GI dysmotility, malnutrition, pre-operative assessment, other) Disease classification (celiac disease: a) newly diagnosed b) treated celiac disease c) nonresponsive Celiac disease d) refractory Celiac disease; Crohn's: Montreal Classification (Satsangi *et al.*, 2006); UC: Mayo classification (Silverberg *et al.*, 2005); Functional GI disorder: Rome IV (Drossman *et al.,* 2016))
Symptoms	Gastrointestinal symptoms at the time of the test (GSRS questionnaire)[4] (Zigmond & Snaith, 1983) Extra-intestinal symptoms (headaches, skin rash, foggy mind, fatigue, joint pain at the time of the test); anxiety and depression (HADS questionnaire) (Revicki *et al.,* 1998)

Medical history	Medications at the time of the test Smoking history Specific Diet (ex. gluten-free diet, low FODMAPs, lactose-free) Nutritional Support (ex. oral, TPN, enteral nutrition)
Nutrition assessment	SGA rating including nutrition physical exam. Contributing factors (ex. cachexia, sarcopenia) Calorimetry data: baseline VO2, REE, RQ Dietary review: 24-hour ASA Micronutrients (zinc, selenium, chromium, copper, ferritin, iron, vitamin A, E, D, folate), when available Dietitian assessment/conclusions
Dietary review	24-hour food recall (ASA24- Canada-2018) (Kirkpatrick *et al.,* 2014)

2.71 Data collection: Case report form developed in REDCap

To establish a process for secure data collection for the indirect calorimetry study, a case report form was created using REDCap software to record data measures recorded for each participant. The Gastrointestinal Symptom Rating Scale (GSRS), which is a 15-item questionnaire assessing common GI symptoms (Revicki *et al.,* 1997) and the Hospital Anxiety and Depression Scale (HADS), a 14-item questionnaire that evaluates the presence and severity of anxiety and depression (Zigmond & Snaith, 1983), were also stored on REDCap (Appendix D). These scales are validated and have been shown to have acceptable reliability and validity (Andrea *et al.,* 2004; Revicki *et al.*, 1997; Zigmond & Snaith, 1983).

2.72 Automated Self-Administered Recall System (ASA24- Canada-2018)

The ASA24-2018 (Kirkpatrick *et al.,* 2014) was selected as a tool to administer dietary food records for patients attending the Indirect Calorimetry Clinic (Appendix E). An account was created for the study on the ASA-24 website: https://asa24.nci.nih.gov/ entitled 'Indirect Calorimetry Registry'. Study respondent accounts were made with system-generated usernames and passwords. The total number of study respondents was selected to be 250, based on the intended size of the registry. Patients' usernames and passwords were emailed to them before their clinic visit. A paper copy to log dietary intake was also included if their preference was to complete the questionnaire in a paper format. Patients who could not complete their entry online or on paper before the clinic were provided with an iPad to complete their ASA24 in the clinic. A nutrition report that detailed macronutrient and micronutrient intake was generated following a complete 24-hour food record.

2.73 Nutrition assessment

Patients were requested to arrive 30 minutes before their clinic appointment. Once they arrived, they met with the research team to perform the tests and introduce the research study. All patients were tested for clinical purposes, but only those consenting to participate were included in the research study. At the beginning of the clinic, patients had their height and weight measured. Body weight was measured with the clinic digital scale (Health-o-meter Professional, USA), while the patients wore no shoes and light clothes. For ease of input into the indirect calorimetry machine, height, and weight were

converted into centimeters (cm) and kilograms (kg). Patients were then directed to meet with the Registered Dietician (RD). During this component of the visit, they underwent a nutrition-focused physical exam. Their activity factor was determined by answering questions about their physical activity levels using the IPAQ-SF (Craig *et al.*, 2003). The IPAQ-SF assessed the frequency and duration of physical activity (walking; moderate and vigorous levels) over a 7-day time frame (Appendix F). A Subjective Global Assessment (SGA) was completed, and an SGA rating of A, B, or C was recorded in their report (Appendix G). For patients with obesity, the Edmonton Obesity Staging System (EOSS) was used to evaluate their obesity-related comorbidities, where they were assigned as having no risk factors (stage 0), subclinical risk factors (stage 1), established disease (stage 2), severe disease (stage 3), or end-stage disease (stage 4) (Sharma & Kushner, 2009).

2.74 Indirect calorimetry exam

A Q-NRG® metabolic cart (COSMED, US) was used to perform the indirect calorimetry exam. The machine was calibrated at the start of each clinic. Patients underwent IC exams under a canopy while supine, having adhered to fasting for a minimum of 5 hours without consuming any caffeine or stimulants. The exam was conducted for approximately 20-30 minutes, depending on the time taken to reach a steady state.

Patients were reminded to avoid falling asleep during the study to prevent resting energy expenditure (REE) alterations. Steady-state occurred when oxygen consumption

and carbon dioxide production varied by less than 10%, and the RQ changed by less than 5% for a minimum of 5 minutes. The best 5 minutes were selected for the analysis of the REE (kcal/day) and RQ. The abbreviated Weir formula (Weir, 1949) calculated energy expenditure:

$$REE = (3.94 \times VO_2) + (1.1 \times VCO_2)$$

Total energy expenditure (TEE) in kcal/day by incorporating activity levels (El Regal *et al.,* 2016) (Appendix H) and was calculated as follows:

$$Total\ Energy\ Requirements\ (TEE) = Resting\ Energy\ Expenditure\ (REE) + Activity\ factor$$

Predictive equations were subsequently used to compare against REE, as shown in Table 2.2.

Table 2.2. Predictive Equations for Estimation of Resting Energy Expenditure

Equations	Factors included	REE Predictive Equations	
		Men	**Women**
Harris Benedict	Sex, BW (kg), HT (cm), age (year)	66.5 + (13.75 × BW) + (5.003 × HT) - (6.75 × age)	655.1 + (9.563 × BW) + (1.850 × HT - (4.676 × age)
Mifflin St. Jeor	Sex, BW (kg), HT (cm), age (year)	10 × BW+ 6.25 × HT – 5 × age + 5 (kcal/day)	10 × BW) + 6.25 × HT– 5 × age – 161 (kcal/day)
Owen	Sex, BW (kg)	10.2 × BW + 875	7.18 × BW + 795
Schofield	Sex, BW (kg), age (18-30 years)	15.057 × BW + 692.2	14.818 × BW + 486.6
	Sex, BW (kg), age (30-60 years)	11.472 × BW + 873.1	8.126 × BW + 845.6
	Sex, BW (kg), age (> 60 years)	11.711 × BW + 587.7	9.082 × BW + 658.5
25 kcal/kg	BW (kg)	25 kcal/day × BW	25 kcal/day × BW

2.75 Body composition

Body composition was further assessed using a Styku 3D body scanner (Styku, USA). Patients were requested to wear tight-fitting clothing for the scan and tie up their hair if necessary to avoid this impacting body circumference. Once set up, patients stood on the device platform with their arms positioned to make an ‘A-pose.’ They were rotated in a clockwise direction for 30 seconds while the scanner projected infrared light, which was returned to the sensor. Once the scan was complete, a digital report detailing the 3D health scan was generated.

After the assessment, the clinical team met to discuss each case and generated a report on nutrition assessment and recommendations. The referring physician received a nutrition report with a comprehensive nutrition assessment and an indirect calorimetry exam.

2.8 Statistical analysis

Statistical analysis was conducted using Statistical Package for Social Sciences (SPSS version 29.0, IBM) and GraphPad Prism (version 9.5.0, GraphPad Software). Descriptive data measurements on Mean, Median, interquartile range (IQR) and standard deviation (SD) were obtained for continuous variables. Predictive equations were compared with IC REE (kcal/day) using paired t-tests. Patients were divided into BMI groups: normal weight, overweight, and obese, with a one-way ANOVA used to compare REE across groups. Correlations between variables were determined using Spearman's correlation and linear regression. Bland Altman was used to measure the agreement of PE and REE with a twofold standard deviation set as a tolerance limit. Accuracy of PE values were defined as ±10% of IC REE. In instances where data was non-parametric, Mann-Whitney U was used for comparison. Data are presented as Mean ± standard deviation (SD), and when not normally distributed, is presented as Median (IQR). In all tests, a p-value of <0.05 was considered significant.

2.9 Summary

In this chapter, I provided an overview of the establishment of the Indirect Calorimetry clinic and the methods involved in the research study. This includes the study design, clinic procedures, recruitment, data collection and analysis.

Chapter Three: Results

3.1 Study population

Between November 2021 and January 2023, ninety-four patients attended clinic. Of them, eighty-seven patients consented to be enrolled in the study, as shown in Figure 3.1. Patients were subdivided into three groups, based on their gastrointestinal diagnosis at referral. The most common diagnosis was CeD, (n= 61; 70%), IBD (n=10; 10%) and additional patients referred for malnutrition due to other gastrointestinal causes (short-bowel syndrome, pancreatic insufficiency, dysmotility, gastroparesis, neuroendocrine cancer, and dysphagia) were classified into the *Other* category (n=16; 18%).

Patient demographic characteristics, stratified by GI diagnosis, are summarized in Table 1. There was a predominance of female compared with male patients across all groups (80.4% vs 19.6% respectively). Baseline characteristics of age (Median [IQR]) were similar across groups (CeD: 49[37-56]; IBD: 43[34-54]; *Other*: 43[27-57]). Years since diagnosis (Median [IQR]) were longer in IBD (21[16-31]) than in both CeD (6[4-10]) and *Other* patients (6[3-21]). Body weight (kg) (Median [IQR]) was significantly higher in CeD (81.0 [66.9-93.9]) compared with the *Other* group (69.9[48.4-84.3]; p=0.04) though differences were not statistically significant when compared with IBD

(59.0 [IQR: 53.4-83.5]; p=0.08). BMI categories were predominantly in the obese range in CeD (30.0[24.5-33.7]) in contrast with a normal BMI in IBD (20.5[18.9-30.0]; p= 0.03) and an overweight BMI in the Other group (25.6[18.5-33.9]; p=0.1). Most IBD had active disease (60.0%) as compared with CeD (16.4%; p= 0.00022). All other demographics and clinical variables were similar between groups (Table 3.1).

Dietary intake was analyzed from 24-hour food records logged on the ASA24-2018 (Table 3.2). Reported dietary intake was similar across groups, however, statistically significant differences were found in protein intake (g/kg) (p=0.004) which was found to be highest in the *Other* group, and protein intake (g/kg) (p=0.004), which was highest in IBD.

3.2 Comparison of Predictive Equations with Indirect Calorimetry

Bland Altman plots were used to evaluate the agreement of PE and IC by comparing the differences in measurements obtained by these methods. The lowest mean difference was found with the Mifflin St. Jeor equation (Bias: -12.2 kcal/day) and the Owen formula (Bias: - 51 kcal/day). The greatest mean difference was found in the 25 kcal/kg formula (Bias: 478 kcal/day) and the Harris-Benedict formula (Bias: 95 kcal/day), and this is shown in Figure 3.2. Mifflin St. Jeor ($r=0.74$, $p<0.001$) was moderately correlated with IC, followed by Owen and Harris-Benedict ($r=0.73$, $p<0.001$), Schofield ($r=0.70$, $p<0.001$), while the lowest correlation was found in the 25 kcal/kg formula ($r=0.64$, $p<0.001$) (Figure 3.3).

Compared to REE measured by indirect calorimetry (IC), the Harris-Benedict (1552 ± 287, kcal/day; $p<0.001$), Schofield (1522 ± 282 kcal/day; $p=0.01$) and 25 kcal/kg PE (1933 ± 536 kcal/day; $p<0.001$) overestimate energy needs. In contrast, the Owen PE underestimates energy needs (1411 ± 228 kcal/day; $p=0.02$). Only the Mifflin St. Jeor PE (1450 ± 277 kcal/day; $p=0.56$) provided an estimate of energy needs similar to IC, at a group level. These results are shown in Table 3.3.

3.3 Performance of PE According to BMI

One-Way ANOVA comparison was used to assess the performance of PE according to BMI categories. Given the low number of patients with underweight (n=7), for this preliminary analysis, underweight and normal BMI have been grouped into one category ('normal'). The Schofield equation performed best in patients with underweight and normal-weight patients (mean difference: 15 kcal/day; $p<0.001$). In patients with overweight, the Mifflin-St. Jeor formula performed best (mean difference: 18 kcal/day; $p<0.001$). Finally, in patients with obesity, the Owen formula performed best (mean difference: 27 kcal/day; $p<0.001$). When mean differences in each category were compared, the Mifflin-St. Jeor formula was found to perform best overall, with a mean difference of 24.3 kcal/day across the three categories of patient groups. The spread of energy needs (kcal/day) in the five predictive equations are depicted as box plots in Figure 3.4.

3.4 Accuracy of Predictive Equations

When the accuracy of all PE was assessed using the criteria of ±10% of REE, PE performed relatively poorly in varying degrees. The lowest accuracy of a PE was 21% (25 kcal/kg formula), and the highest accuracy was 61% (Mifflin St. Jeor). The accuracy of other PE ranged from 55% in HB to 60% in both the Schofield and Owen formulas. This has been graphically presented in Figure 3.5. To identify overall patterns in the accuracy of each PE, accuracy was evaluated across BMI groups. As illustrated in Figure 3.6, the 25kcal/kg and Owen formulas tended to perform better in normal BMI, while the Harris-Benedict, Schofield, and Mifflin St. Jeor tended to perform better in overweight, and in obesity, Mifflin St. Jeor performed best.

3.51 REE in Patients with Chronic GI Conditions

No differences in REE were found between CeD and IBD, as shown in Figure 3.7A. When REE was adjusted for weight (Figure 3.7B), REE was higher in IBD patients than CeD patients (22.29 vs. 18.24 kcal/kg/day; $p=0.004$).

Subgroup analysis in CeD patients with and without overweight and obesity (Figure 3.8) showed that overweight/obese CeD patients had lower REE compared with CeD with normal weight (median: 17.22 vs 23.30 kcal/kg/day; $p<0.001$).

3.52 Disease activity

To evaluate disease activity in CeD, deamidated gliadin peptide (DGP) and tissue transglutaminase levels were considered against standard reference values (tTg: <4.0 U/mL; DGP: <20.0 U/mL). Spearman's correlation was performed to analyze the

relationship between DGP (u/mL) and tTg (u/mL) with REE (kcal/kg). No correlation was found between DGP (u/mL) (r=0.05; p=0.7) or tTG (u/mL) (r=0.01; p=0.7) with REE (kcal/kg) (Figure 3.9A and 3.9B). Based on these variables, 16.4% of CeD had active disease. There were no differences in REE (kcal/kg) between active CeD (n=10) compared with non-active CeD patients (n=51) (median: 18.54 vs 18.33; p=0.91), as shown in Figure 3.9E. To assess disease activity in IBD, individuals were considered to have active disease if values were elevated above a normal range for C-reactive protein (CRP >10 mg/L) and fecal calprotectin (FCP> 50.0 mg/kg). Based on this criteria, 60% of IBD had active disease. There was no correlation between FCP (mg/kg) (r=0.25, p=0.66) or CRP (mg/L) (r=0.02; p=0.94) with REE (kcal/kg) (Figure 3.9C and 3.9D). The majority of IBD patients had active disease (60%). As shown in Figure 3.9F, there were no differences in REE (kcal/kg) between active (n=6) and non-active (n=4) IBD patients (median REE: 23.45 vs 23.37, respectively; p=0.99).

3.6 Factors Influencing REE in Patients with Chronic GI Conditions

Linear regression was used to evaluate whether factors like age, gender, BMI, FFM, FM, GI symptoms, anxiety (based on HADS-A), and depression (based on HADS-D) were associated with REE. As presented in Table 5, none of these factors were found to be significantly predictive of REE (p>0.05). However, Body mass index (BMI) and fat-free mass (FFM) were positively associated with REE, as depicted in Figure 3.10A and 3.10B. Upon analysis of macronutrient intake with REE (Figure 3.11 A-C), protein was the only macronutrient associated with REE (r=0.24, p=0.002).

3.7 Post-hoc Analysis

To better understand the role of FFM in determining REE, we explored the performance of the Cunningham predictive equation (CE). CE was used to predict REE in a subpopulation of patients (n=17) who had had FFM values reported following a 3D body composition (Styku) exam. The results were compared with REE using Spearman's correlation and a Bland Altman plot, as shown in Figure 3.12. There was a positive moderate correlation between CE and REE (r=0.70, p=0.002), with a low mean difference of 10 kcal/day between CE and REE in this cohort. Accuracy of the CE was 59%.

3.8 Implementation of IC in Clinical Practice

Here, we present a case study to provide a framework for understanding the functionality of the clinic and how IC was used for nutrition assessment.

A 54-year-old male with a diagnosis of ileocolonic Crohn's disease in 1994 and previous bowel resection presented at the clinic. He was referred for weight loss despite his high food intake. His weight was 74.5 kg, and his BMI of 22.5 kg/m^2 was normal. To determine body composition, he underwent a 3D Styku body scan, where his body fat percentage was 30.6%, which was considered high, and his fat-free mass was 49.9 kg, which is classified in the 5^{th}-25^{th} percentile for his age (Pichard *et al.,* 2000). His 24-hour daily food record (ASA24-2018-Canada) showed his dietary intake was 3,888 kcal per day, and he reported that this dietary intake was typical. His most recent fecal calprotectin (stool marker of inflammation), where normal values are <50 mg/kg, was

1,028.3 mg/kg, suggesting active disease. After an IC exam, his REE was 2137 kcal/day (Appendix G). His predictive energy needs, calculated using the Harris-Benedict equation, were 1,696 kcal/day—nearly 500 kcal lower than his measured energy needs. His activity factor (AF) indicated low activity levels, at 1.2; therefore, his total energy expenditure (TEE=REE+AF) was 2565 kcal/day. Despite his reported higher energy intake, his RQ value was 0.68, indicating that he was potentially underfeeding or primarily utilizing lipid substrate oxidation.

The patient was provided with a subjective global assessment of 'B' or at moderate risk of malnutrition, likely in a hypermetabolic state due to CD and likely malabsorption. Therefore, this patient was recommended to modify the quality of his diet and further assess disease activity (Report in Appendix).

3.9 Summary

In this chapter, primary findings that address the study hypotheses have been described. When PE were compared with REE, there were significant differences of up to nearly 500 kcal/day. The performance of PE varied across BMI groups; however, Mifflin St. Jeor emerged as the most accurate formula for patients with GI conditions. BMI was one of the most significant factors to impact REE, as shown by the changes in results of REE in IBD as opposed to CeD when adjusted by BMI, and changes in REE in CeD overweight/obese compared with a normal BMI. In addition to BMI, FFM and protein intake were predictive of REE. It can also be suggested that disease activity may play a role in REE due to salient inter-group differences in disease activity. From the significant

association of FFM with REE compared with all other predictors, a weight-based formula, the Cunningham equation, was used to predict REE in a post-hoc analysis. Although evidence is preliminary, this was shown to have the most similarity with measured REE compared to other commonly used clinical formulas.

Chapter Four: Discussion

Resting energy expenditure (REE) is essential for tailoring appropriate nutritional management in clinical practice. Indirect calorimetry (IC) is a gold standard method for accurate measurement of energy needs; however, predictive equations (PE) are often used in patients with chronic inflammatory gastrointestinal conditions (CIGI). In this study, when individuals with different GI conditions were compared, IBD patients had lower BMI compared with the CeD and the Other group. Similar findings were reported by previous studies and attributed to the high levels of malabsorption and malnutrition that characterize IBD (Capristo *et al.*, 1998). In contrast, patients with CeD are overweight, which contradicts the notion that CeD has difficulty achieving sufficient energy intake. Although patients with overweight/obesity may be overrepresented in this study due to referral bias, our results are in agreement with recent reports showing rising obesity rates in individuals with CeD (Villanueva *et al.*, 2020). A US-based study evaluating CeD BMI across 360 hospitals reported that nearly 50% of patients with CeD had obesity and suggested that positive energy balance following disease remission may be of greater importance in CeD (Drosdak *et al.*, 2022).

In this study, we investigated REE in patients with CIGI by comparing measured energy needs with predicted energy needs based on commonly used PE (25 kcal/kg, Harris-Benedict, Mifflin St. Jeor, and Owen). Our results showed that the estimation of energy needs based on PE is relatively inaccurate compared to measured REE in patients with chronic inflammatory GI conditions. Few studies have been performed conducting IC specifically for patients with chronic inflammatory GI conditions, despite evidence that these conditions often alter REE (Al-Jaouni *et al.*, 2000; Capristo *et al.*, 2000, 1997, 1998; Hill *et al.*, 2011; Kushner & Schoeller, 1991; Sammarco *et al.*, 2017; Sasaki *et al.*, 2010; Schneeweiss *et al.*, 1990). PE also assumes normal body composition and may not be suitable for patients with GI conditions due to disease effects (Barot *et al.*, 1980.) Despite limitations, PE are often used in clinical practice due to their convenience and simplicity. Yet, due to their use of estimates to provide energy needs, they can often lead to biased recommendations. The results of this study show that no PE provides the exact measure of REE; however, some PE perform better than others. At a group level, Mifflin St. Jeor has the closest estimate of REE. The results of this study can be related to the nature of the population included in this analysis, given that most patients attending the clinic (73%) are overweight. This finding is in accordance with previous studies that indicate Mifflin St. Jeor has the most accuracy in overweight and obese individuals (Frankenfield *et al.*, 2005; Weijs, 2008). Research by Namazi *et al.* evaluating REE using IC and common PE in 98 normal and overweight females found that MSJ had the lowest mean bias (-2.97 kcal/day) and highest accuracy (80%) (Namazi *et al.*, 2016). Thus far, this is the first study comparing Mifflin St. Jeor with REE in CeD patients, and based on

our results, MSJ is preferred in CeD with overweight or obesity. Properly powered final analysis will help establish whether MSJ should be used in lieu of Harris-Benedict in IBD and other GI conditions.

When differences in REE of different groups of patients with varied GI conditions were analyzed, we found no significant differences between CeD and IBD (Figure 3.7A). However, once the REE was adjusted for weight, IBD patients had significantly higher REE compared with CeD patients (Figure 3.7B). This preliminary result is in agreement with previous work conducted on IBD patients. In a study by Sasaki *et al.* comparing REE of 16 CD patients with eight healthy controls, significant differences in REE were not found (Sasaki *et al.*, 2010a). However, REE adjusted for body weight was significantly higher in CD than in healthy controls (24.4 ± 2.4 kcal/kg/day vs 21.3 ± 1.7 kcal/kg/day; p=0.003). Similarly, in another study by Sasaki *et al.* comparing REE in 13 UC patients with ten healthy controls, significant differences between groups were only found when REE was adjusted for weight (26.4 ± 3.6 vs 21.8 ± 1.7; p= 0.001) (Sasaki *et al.,* 2010b). While a larger sample size of IBD patients is needed to provide more conclusive evidence, these findings suggest higher energy requirements in IBD, which is relevant for the nutrition management of this population. In CeD, one study has compared REE with REE adjusted for body weight (kg). Wiersdma *et al.* showed no differences in REE between newly diagnosed CeD, RCDII and EATL, even when adjusted for weight (Wiersdma *et al.*, 2016). Further research on the differences in REE (kcal/day) and REE (adjusted for body weight) is needed to assess differences in CeD and IBD better.

A comparison of REE in CeD patients with normal weight and overweight/ obesity yielded a novel finding showing that overweight/obese CeD patients have lower REE than normal CeD. The previous suggests a potentially hypometabolic state in patients with this comorbidity, possibly contributing to their current nutritional status. Guidelines for the nutritional management of CeD note that recommendations for caloric intake differ based on the severity of malabsorption. As such, individuals with CeD may be given nutritional recommendations for nutrient intake calculated as 1.5 times the REE (See & Murray, 2006). However, our results illustrate that CeD can vary in response to GFD and disease remission and may often achieve positive energy balance and weight gain. Furthermore, overestimation of REE can have greater consequences in individuals with CeD and overweight/obesity, impacting their metabolism and energy prescription. This reinforces the importance of proper individualized nutritional assessment with accurate measurement of energy needs in CeD and recommendations tailored based on individual requirements and current nutritional status.

An analysis of factors potentially influencing REE found that age, gender, GI symptoms, anxiety, and depression are not significantly associated with REE in CIGI. Previous research has consistently found age and gender differences in REE (Geisler *et al.,* 2016; Hölzel *et al.,* 2021) though this effect is not observed in our population. Studies have shown that REE tends to decline with age (Blanc *et al.*, 2004; Elia *et al.*, 2000; Hölzel *et al.*, 2021; Roberts & Dallal 2005). This has been proposed to be attributed in part to age-related reductions in FFM and diminished response of the sympathoadrenergic nervous system with age (Bell *et al.*, 2001). Research has also shown lower REE in

women as compared with men due to correspondingly lower FFM/lean muscle mass (Afghani & Barrett-Connor, 2009; Blanc *et al.*, 2004; Buchholz *et al.*, 2001). A large study measuring REE in 522 healthy individuals even demonstrated lower REE in women than men, independent of body composition (Arciero *et al.*, 1993). Although findings from our study have not supported the effects of these common contributors to REE, this may be due to the heterogeneous GI population studied. Additional study is needed to explore whether these factors and others, may affect REE in each subpopulation included.

In our study, based on initial results which showed significant inter-group differences in the proportion of CeD and IBD with active disease, it can be speculated that increased disease activity may play a role in REE, since IBD showed a substantially higher rate of active disease and higher REE. However, further investigation into the role of intra-group differences in REE based on differences in disease activity does not support the role of disease activity in REE as hypothesized (Figure 3.9). In CeD, our results differ from previous studies reporting that untreated CeD patients have increased REE due to disease activity (Capristo *et al.*, 2000). However, there are two possible reasons to explain this finding. Monitoring disease activity in CeD poses some difficulty, and it is essential to note that the present evidence relies on serologic tests. As pointed out by others, using serologic tests such as tTG and DGP to evaluate disease activity provides a measure of the adaptive immune response. Still, it does not directly measure intestinal inflammation (Leffler & Schuppan, 2010). Furthermore, the lack of observed impact on REE based on disease activity may be due to the low number of active CeD (n=10) in this

study population. Preliminary analysis in our cohort also showed that REE is similar between active and non-active IBD. These findings can be explained by other studies demonstrating that CRP levels may not always be associated with disease activity (Moscandrew & Loftus, 2009; Schoepfer *et al.*, 2009). Research evaluating REE of IBD patients by Takaoda and colleagues show no significant correlation between CRP and REE in IBD patients (Takaoka *et al*., 2015). Moreover, CRP measures acute inflammation and is therefore not disease-specific (Chen *et al.,* 2020). Research has shown that individuals with active IBD can have normal CRP levels and that, due to genetics, the level of CRP varies in individuals with identical inflammation conditions (Fagan *et al.,* 1982). In examining disease activity, we also assessed the influence of FCP on REE. Although the findings agreed with previous reports in IBD patients, it should be noted that the low number of patients—and thus potential Type II error—does not allow for a consistent conclusion. Final analysis at the end of the study will be important to clarify the role of disease activity on REE in IBD patients. Therefore, conducting future research with an adequately powered population will be essential to confirm these results.

One interesting result is the positive association of BMI and FFM with REE, which has also been previously reported in healthy individuals (Geisler *et al.,* 2016; Johnstone *et al.*, 2005). Based on this finding, we conducted a posthoc analysis using the Cunningham equation (CE) (Cunningham, 1980) to evaluate whether FFM measured by a 3D body scan (Styku) can be used to predict more accurate REE. While our results are based only on the small subgroup of patients who have undergone this test, given the low mean bias of -10.4 kcal/day, CE was most similar to REE at a group level than all other

PE assessed, including the MSJ formula. Although the accuracy of CE was lower than MSJ (59% vs 61%), this can be attributed to the lower sample of individuals assessed for the CE analysis, as a previous study comparing REE and common PE in 90 adult athletes showed higher accuracy in CE as compared with MSJ (ten Haaf & Weijs, 2014). Taken together, the results suggest that CE may potentially provide more precise measurements compared with other PE. This is relevant, as 3D body scans are non-invasive, less expensive, and require a very short time for testing compared to IC. Therefore, if efficacy is proven in a larger population, CE can be used to predict energy requirements in patients with GI conditions when IC is not available.

Our analysis has also found an association between protein intake and REE, but not in carbohydrate and fat intake. In line with results showing that protein intake contributes to the greatest increase in DIT (Raben *et al.*, 2003), protein also affects REE more than other macronutrients (Bray *et al.*, 2015). This may contribute to the differences observed in REE (kcal/kg) across different GI groups, where IBD was shown to have higher REE than CeD and reported higher protein intake (g/kg). This finding also matches our results, demonstrating that FFM contributes most to REE since protein plays a crucial role in maintaining muscle mass. The results of our study showing the influence of protein on REE in the context of CIGI have direct implications for the nutritional management of this population. The present findings are promising and relevant for decision-making in the nutrition management of individuals with CIGI.

4.2 Strengths

This research has several key strengths. This is the first study to evaluate REE in different cohorts of patients with GI conditions using indirect calorimetry. Our preliminary results suggest differences in REE of CeD and IBD patients mainly driven by BMI, diet, and body composition and highlight the need for a better understanding of potential drivers of malnutrition in CeD and IBD. In establishing a nutrition assessment clinic and recruiting patients with chronic GI conditions exclusively from the clinic, the findings are directly relevant to this understudied patient population. Additionally, the prospective observational study design allowed for a better understanding of nutrition in our GI population and generated new research questions. Furthermore, this study involves a multi-disciplinary care team using validated tools to assess nutrition in GI patients accurately. This illustrates the importance of a team-based, personalized medicine approach in providing effective clinical care for individuals with chronic GI conditions.

4.3 Limitations

While this study has strengths, we acknowledge some limitations. First, study recruitment was slightly lower than expected due to initial pandemic-related closures in the clinic and patient no-shows and cancellations, particularly in the IBD population. However, this is also related to different timing in recruitment, as IBD recruitment began six months after CeD patients. This is expected to resolve over time as more IBD patients are presently being referred to the clinic. When assessing REE in CIGI, it is possible that factors such as body temperature and both daily and seasonal variation impact this population. Furthermore, although every effort was made to determine whether CeD and

IBD patients had active or inactive disease, based on tests performed closest to the date of their IC exam, the time between the tests and IC exam varied and was therefore not uniform across all patients. To overcome this limitation, disease activity will be prospectively collected at a scheduled time for all patients moving forward. Finally, using self-reported dietary records carries a risk of social desirability bias (Hebert *et al.,* 1995), in which individuals may feel the need to under or over-report their diet to avoid criticism.

4.4 Future directions

We will continue to recruit more IBD patients for a properly powered study and conduct a more in-depth analysis by comparing the performance of PE according to GI condition and exploring REE in Crohn's disease and Ulcerative colitis. Given the yet unanswered questions on disease activity and resting energy expenditure in chronic GI conditions, further analysis should consider the effects of disease activity in depth. Finally, future studies, including the assessment of DIT and exercise tests using IC rooms, will be essential to measure TEE more accurately in patients with CGIC.

4.5 Conclusion

In conclusion, predictive equations (PE) are inaccurate compared to measured energy needs in patients with chronic GI conditions (CIGI). This has potential clinical implications, as PE are widely used in clinical practice and can mislead energy prescription. Indirect calorimetry is a valuable tool to provide accurate measurements of energy requirements in this population and should be the preferred method for

determining REE, when available. Moreover, in CIGI patients with overweight and obesity, the Mifflin St. Jeor formula provide greater accuracy and should be preferred in these populations. Finally, a variety of factors influence REE in patients with GI conditions, including the type of disease, nutritional status, dietary protein intake, and body composition, which are relevant for the nutrition management of this population. Our results provide some tentative initial evidence that disease activity is of salience when considering REE of CIGI groups. However, future studies that account for disease activity in greater depth will need to be undertaken.

TABLES

Table 3.1. Demographic Characteristics of Patients Enrolled

Characteristics	CeD (*n*=61)	IBD (*n*=10)	Other (*n*=16)[2]	P-value
Gender (male: female)	13:48	2:8	2:14	0.7
Age (years)[1]	49(37-56)	43(34-54)	43(27-57)	0.5
Height (m)[1]	1.65(1.6-1.7)	1.70(1.58-1.77)	1.61(1.54-1.68)	0.1
Years since diagnosis	6(4-10)	21(16-31)	6(3-21)	**0.0002**
Body weight (kg)[1]	81.0(68.2-93.8)	65.6(53.4-83.5)	69.1(48.4-84.3)	0.05
BMI (kg/m^2)[1]	30.0(24.5-33.7)	20.5(18.9-30.0)	25.6(18.5-33.9)	0.07
tTG levels(u/mL)[1]	2.0(2.0-3.1)	-	-	-
DGP levels (u/mL)[1]	5.0(5.0-5.2)	-	-	-
CRP levels (mg/L)[1]	-	6.9(5.0-28.95)	-	-
FCP levels (mg/kg)[1]	-	116.8(5.2-385.8)	-	-
Active disease (%)	16.4	60.0	-	**0.0022**

[1] Values expressed as Median (IQR)

[2] Includes SBS, IBS, pancreatic insufficiency, dysmotility, gastroparesis, neuroendocrine cancer, and dysphagia.

Table 3.2. Dietary Intake of Patients

Dietary record	CeD (*n* = 61)	IBD (*n*=10)	Other[3] (*n*=16)	P-value
Total caloric intake (kcal/day)[1]	1778.7 ± 717.4	1714.7 ± 1058.5	1628.9 ± 987.1	0.73
Protein (%)[1]	17.6 ± 5.6	18.6 ± 5.4	15.4 ± 5.2	0.09
Protein (g/kg)[2]	0.80 ± 0.2	0.95 ± 0.3	1.0 ± 0.4	**0.04**
Carbohydrates (%)[1]	47.6 ± 10.7	46.7 ± 11.4	50.0 ± 15.7	0.19
Carbohydrates (g/kg)[2]	3.8(3.3-4.5)	4.4(3.6-5.4)	4.4(3.6-6.3)	0.08
Fibre (g/kg)[2]	0.2(0.2-0.3)	0.3(0.2-0.4)	0.3(0.2-0.4)	0.05
Fat (%)[1]	32.8 ± 9.6	34.4 ± 8.7	34.5 ± 12.3	0.7
Fat (g/kg)[2]	0.23(0.22-0.31)	0.32(0.25-0.39)	0.30(0.25-0.43)	**0.04**
[1] Values expressed as Mean ± SD				
[2] Values expressed as Median (IQR)				
[2] Includes SBS, IBS, gastroparesis, pancreatic insufficiency, dysmotility, congenital esophageal atresia				

Table 3.3. Performance of Predictive Equations

Variable	Mean ± SD (kcal/day)	95% Confidence Interval	p-value[1]
Measured			
REE	1462 ± 281	-	-
Predicted			
25 kcal/kg	1933 ± 536	1822 to 2059	<0.001
Harris-Benedict	1552 ± 287	1494 to 1620	<0.001
Schofield	1522 ± 282	1459 to 1584	0.01
Mifflin St. Jeor	1450 ± 277	1389 to 1511	0.56
Owen	1411 ± 228	1360 to 1461	0.02
Cunningham[2]	1438 ± 185	1343 to 1534	0.82

[1] p- values obtained by paired t-test analysis
[2] Compared with REE in a sub-group of patients (n=17)

Table 3.4. Performance of Predictive Equations According to BMI

REE (kcal/day)[1]	Normal weight	Overweight	Obese	p-value[2]
Measured				
REE (kcal/day)	1298 ± 277	1489 ± 200	1578 ± 268	<0.001
Predicted				
25 kcal/kg	1390 ± 297	1877 ± 190	2401 ± 352	<0.001
Harris-Benedict	1339 ± 232	1540 ± 192	1734 ± 247	<0.001
Schofield	1283 ± 165	1507 ± 181	1715 ± 255	<0.001
Mifflin St. Jeor	1230 ± 223	1431 ± 190	1631 ± 227	<0.001
Owen	1246 ± 179	1407 ± 177	1541 ± 206	<0.001

[1] Values expressed as Mean ± SD
[2] One-way ANOVA comparison

Table 3.5. Predictors of Resting Energy Expenditure

Predictors	Regression Analysis[1]
Age	*F=0.7, p=0.4*
Gender	*F=1.3, p=0.3*
GI symptoms	*F= 3.6, p=0.06*
Anxiety	*F=0.4, p=0.5*
Depression	*F=0.5, p=0.5*
[1] *P-values obtained by simple linear regression*	

FIGURES

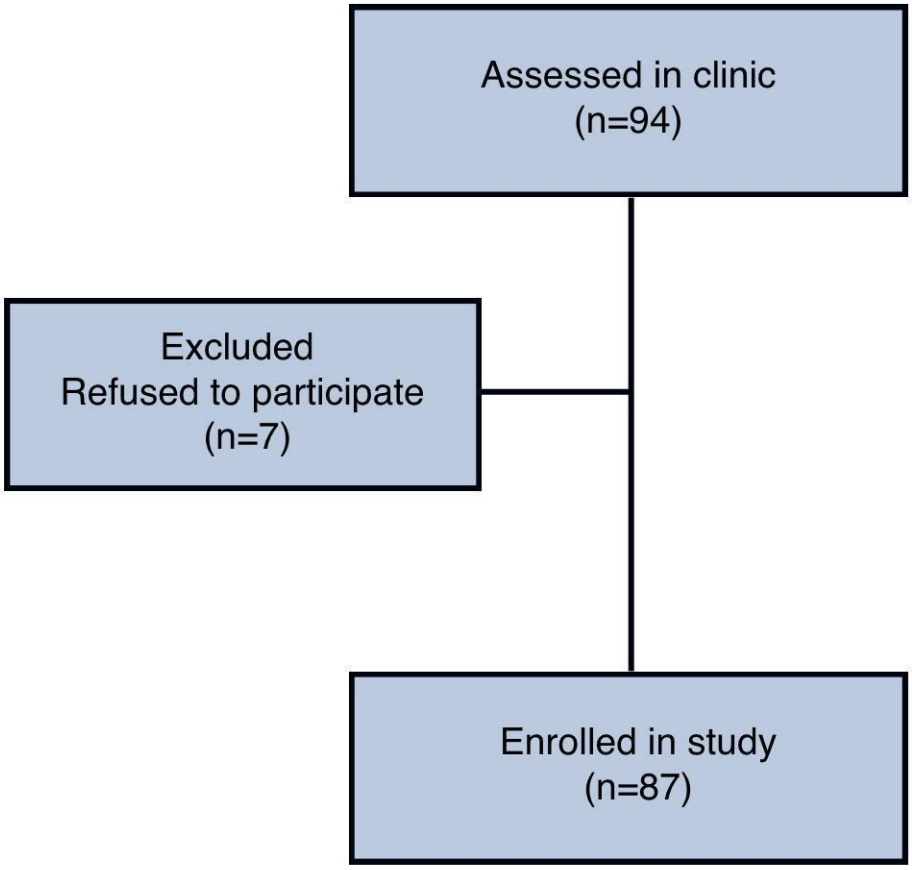

Figure 3.1. Study recruitment of patients attending the indirect calorimetry clinic. Patients with chronic inflammatory gastrointestinal conditions who received a referral were assessed in clinic (n=94). Upon meeting the study inclusion criteria and consenting to study participation, patients were enrolled (n=87).

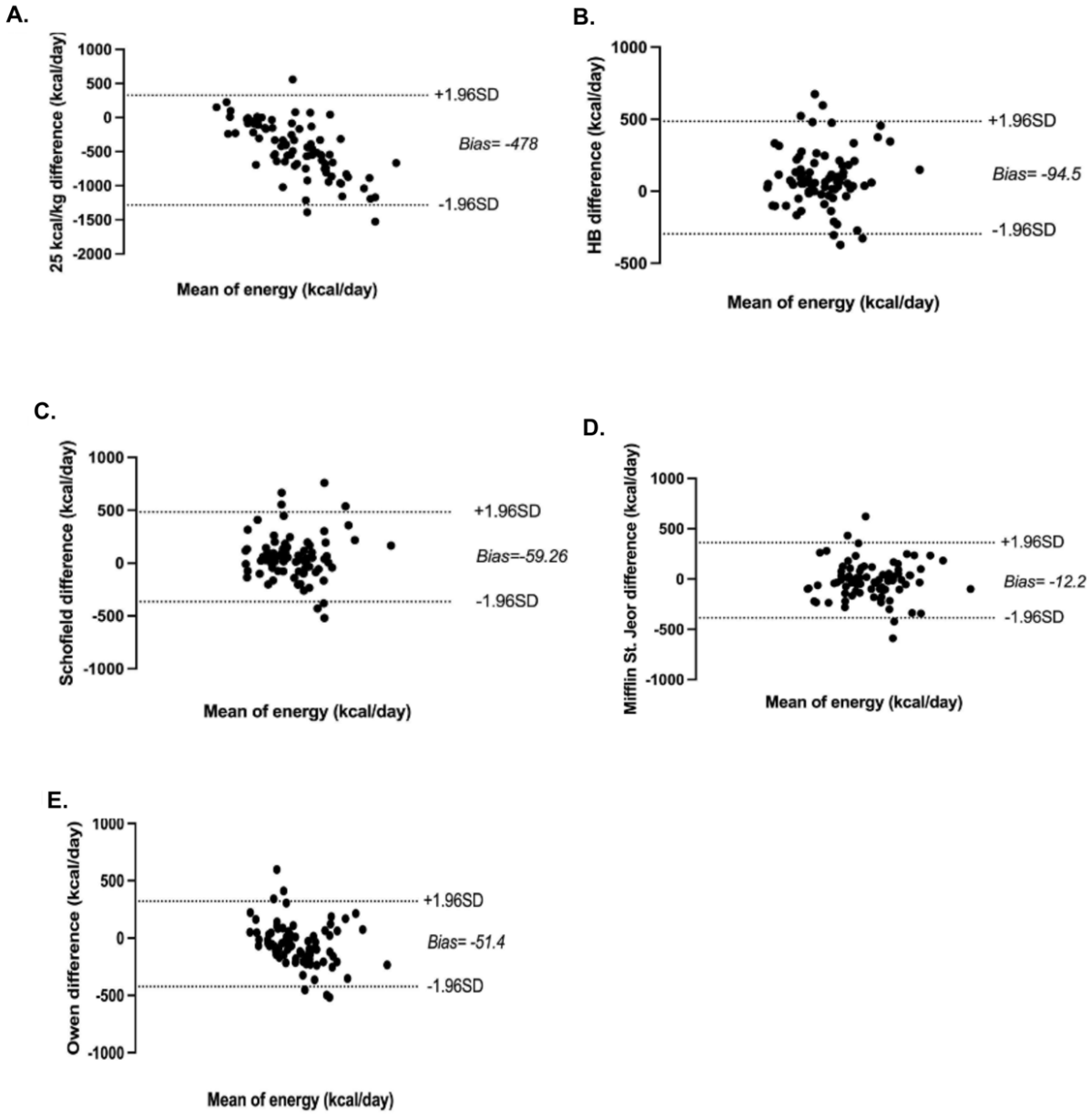

Figure 3.2. Bland-Altman Plots Comparing Predictive Equations with REE. The Bland-Altman plots show concordance and differences in energy needs estimated by predictive equations (PE) against resting energy expenditure (REE) measured with a Q-NRG® indirect calorimeter. PE compared are the 25 kcal/kg formula (A), the Harris-Benedict formula (B), the Schofield formula (C), the Mifflin-St. Jeor formula (D), and the Owen formula (E). Mean bias is shown, and limits of agreement (± 1.96 SD) are depicted by dotted lines.

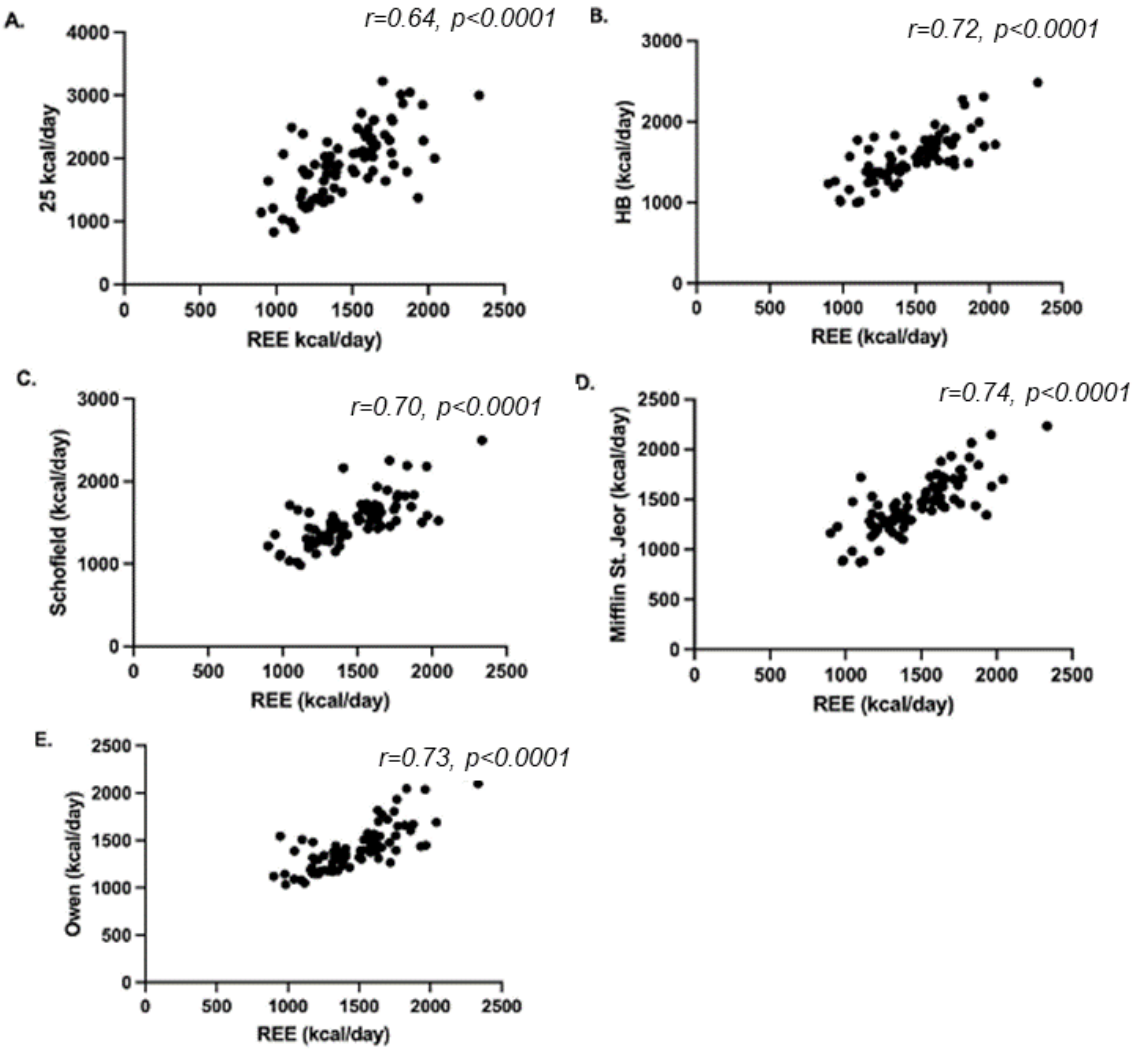

Figure 3.3. Correlation of Predictive Equations with REE. Correlation of predictive equations (PE) with resting energy expenditure (REE) measured with a Q-NRG® indirect calorimeter are represented using Spearman's coefficients of correlation. PE compared are the 25 kcal/kg formula (A), the Harris-Benedict formula (B), the Schofield formula (C), the Mifflin-St. Jeor formula (D), and the Owen formula (E). All p-values are statistically significant.

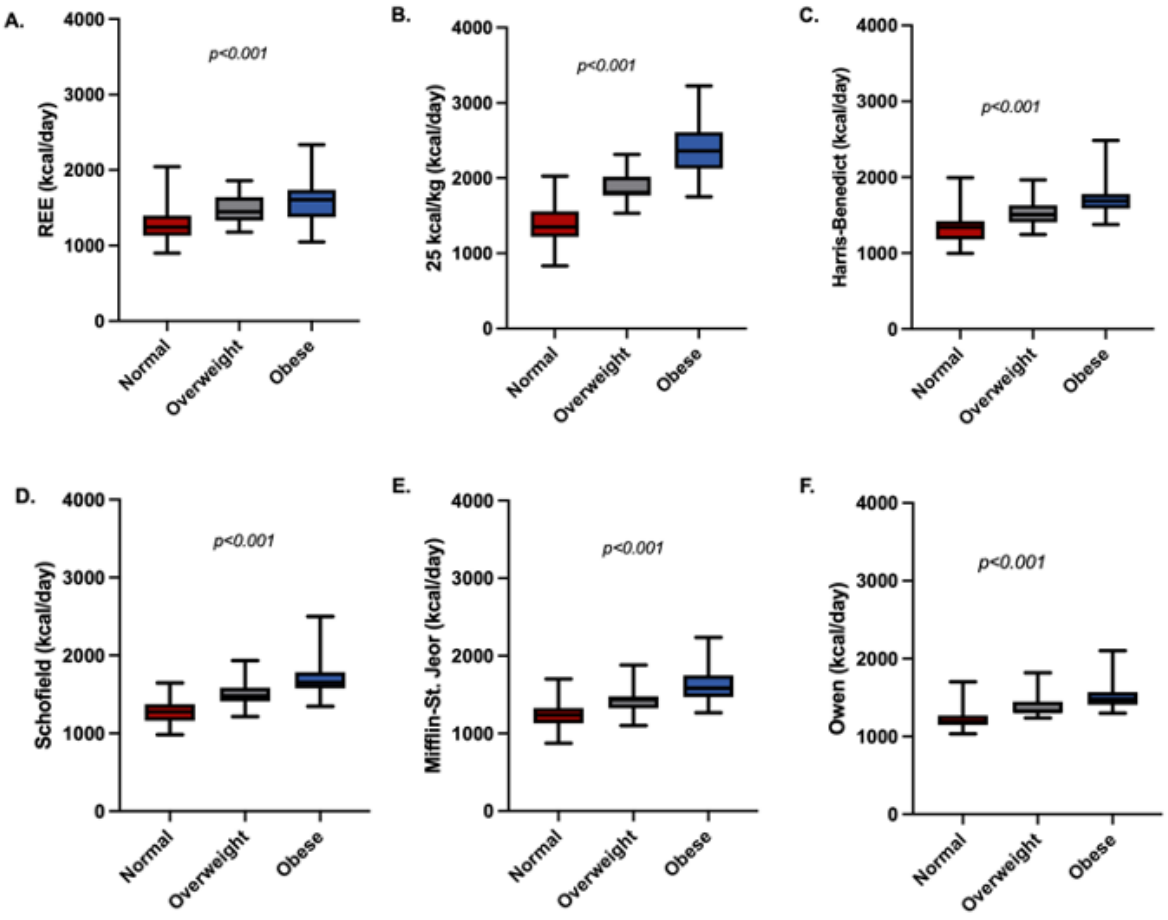

Figure 3.4. Comparison of PE Performance Across BMI Groups. Box plots of REE (kcal/day) in patients with chronic inflammatory gastrointestinal conditions (n=87) grouped by BMI (kg/m^2) classification (normal, overweight, and obese) are displayed. REE measured by indirect calorimetry corresponds as a reference (A) contrasted with REE predicted by the 25 kcal/kg formula (B), the Harris-Benedict formula (C), the Schofield formula (D), the Mifflin-St. Jeor formula (E), and the Owen formula (F). All p-values are statistically significant.

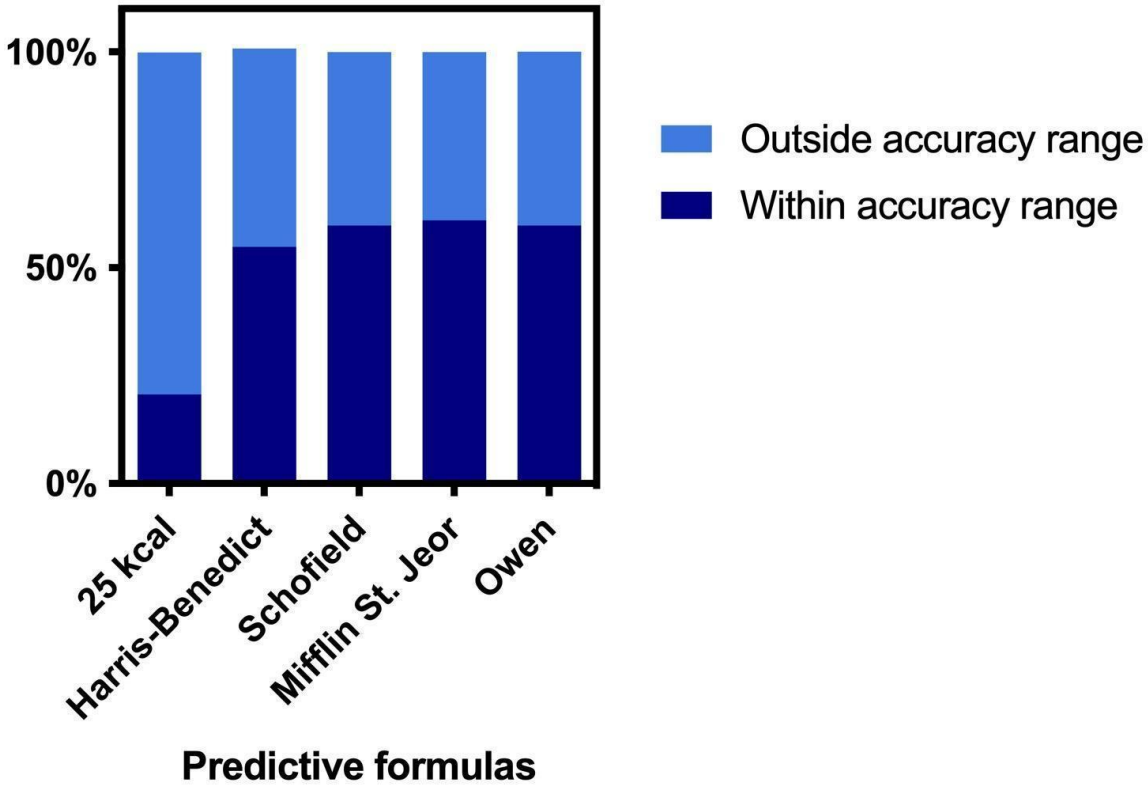

Figure 3.5. Accuracy of All Predictive Equations. The proportion of predictive equations (PE) within ±10 % of measured REE is shown. PE were considered accurate within ±10 % of measured REE and outside the accuracy range if they exceeded ±10 % of measured REE.

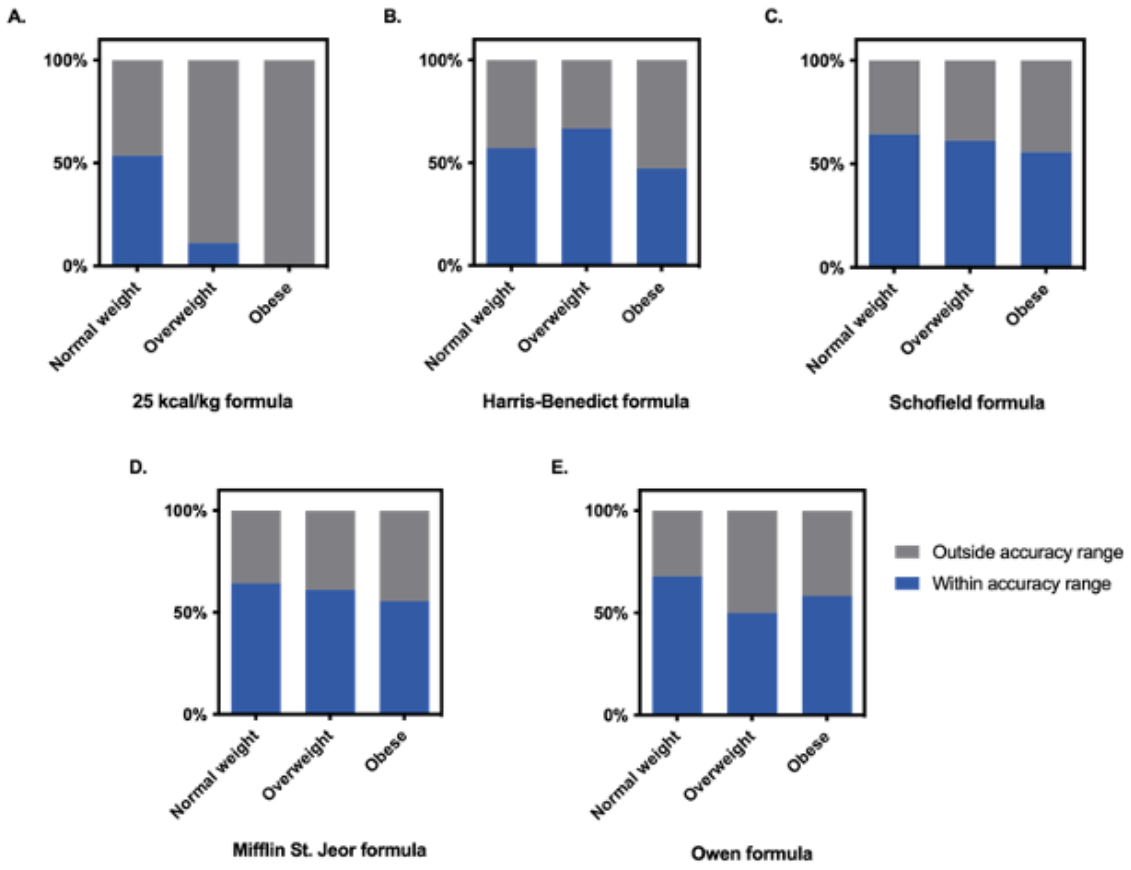

Figure 3.6. Accuracy of Predictive Equations According to BMI Groups. The proportion of predictive equations (PE) within ±10 % of measured REE is shown based on BMI (kg/m^2) classification (normal, overweight and obese). PE were considered accurate within ±10 % of measured REE and outside the accuracy range if they exceeded ±10 % of measured REE. PE compared are the 25 kcal/kg formula (A), the Harris-Benedict formula (B), the Schofield formula (C), the Mifflin St. Jeor formula (D) and the Owen formula (E).

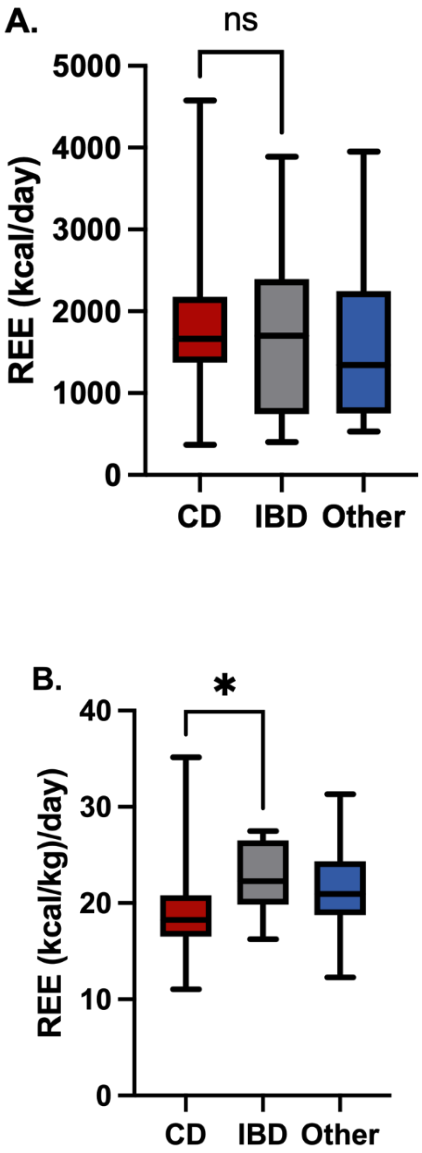

Figure 3.7. REE in Patients with Chronic GI Conditions. Box plots of REE (kcal/day) (A) and REE adjusted for body weight (kg) (B) in patients with celiac disease (CeD) (n=61), inflammatory bowel disease (IBD) (n=10) and referred for malnutrition due to other causes (n=16) are displayed. P-values <0.05 were considered statistically significant.

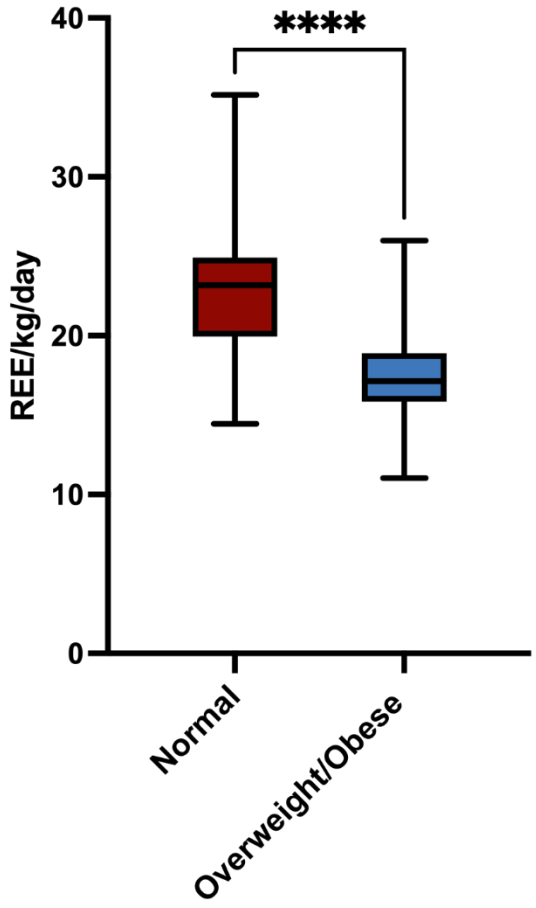

Figure 3.8. REE in Patients with Celiac Disease. A box plot of resting energy expenditure (REE) adjusted for body weight (kg) in patients with celiac disease (CeD) (n=61) grouped by BMI (kg/m^2) classification (normal, overweight/obese) is depicted. The difference in REE between normal CeD and overweight/obese CeD was considered statistically significant ($p<0.001$).

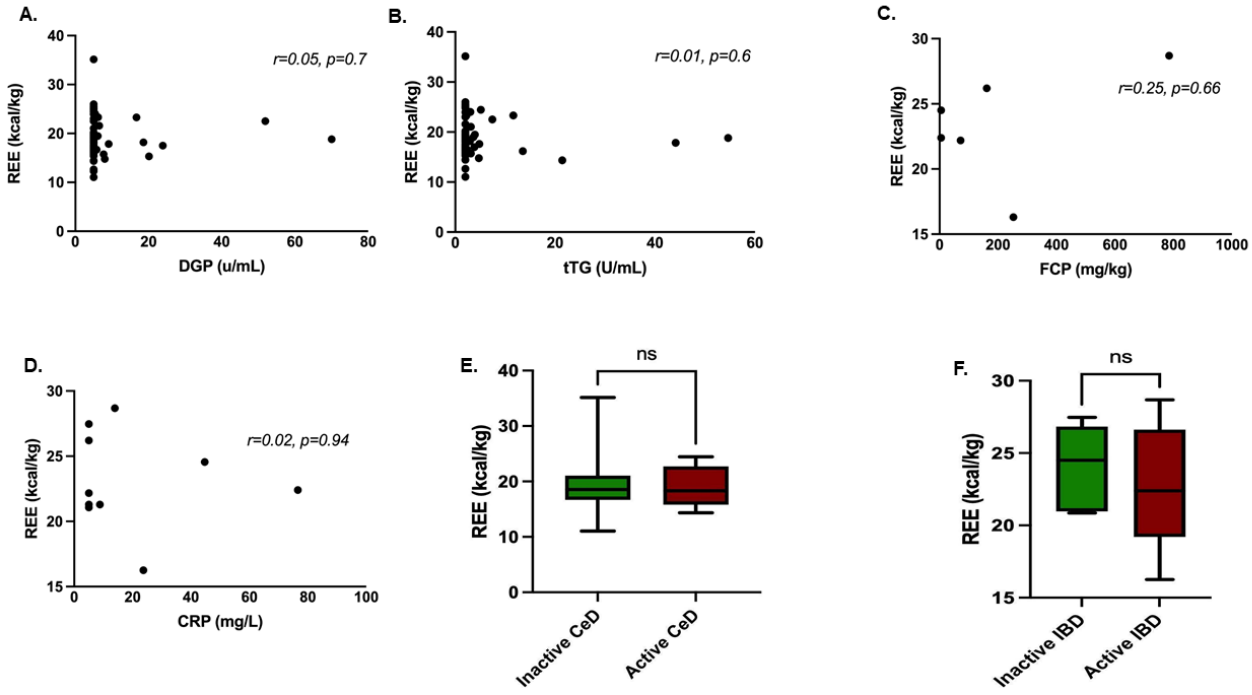

Figure 3.9. Disease Activity and Resting Energy Expenditure. Disease activity was evaluated in celiac disease (CeD) based on the correlation of deamidated gliadin peptides (DGP) (u/mL) (A) and tissue transglutaminase (tTg) (u/mL) (B) with resting energy expenditure (REE) adjusted for weight (kcal/kg), and CeD were classified as active or inactive based on DGP and tTg (E). In inflammatory bowel disease (IBD) disease activity was assessed based on the correlation of fecal calprotectin (FCP) (mg/kg) (C) and C-reactive protein (CRP) (mg/L) (D) with REE (kcal/kg) and IBD were classified as inactive or active (F) based on FCP and CRP. All p-values were not significant ($p > 0.05$).

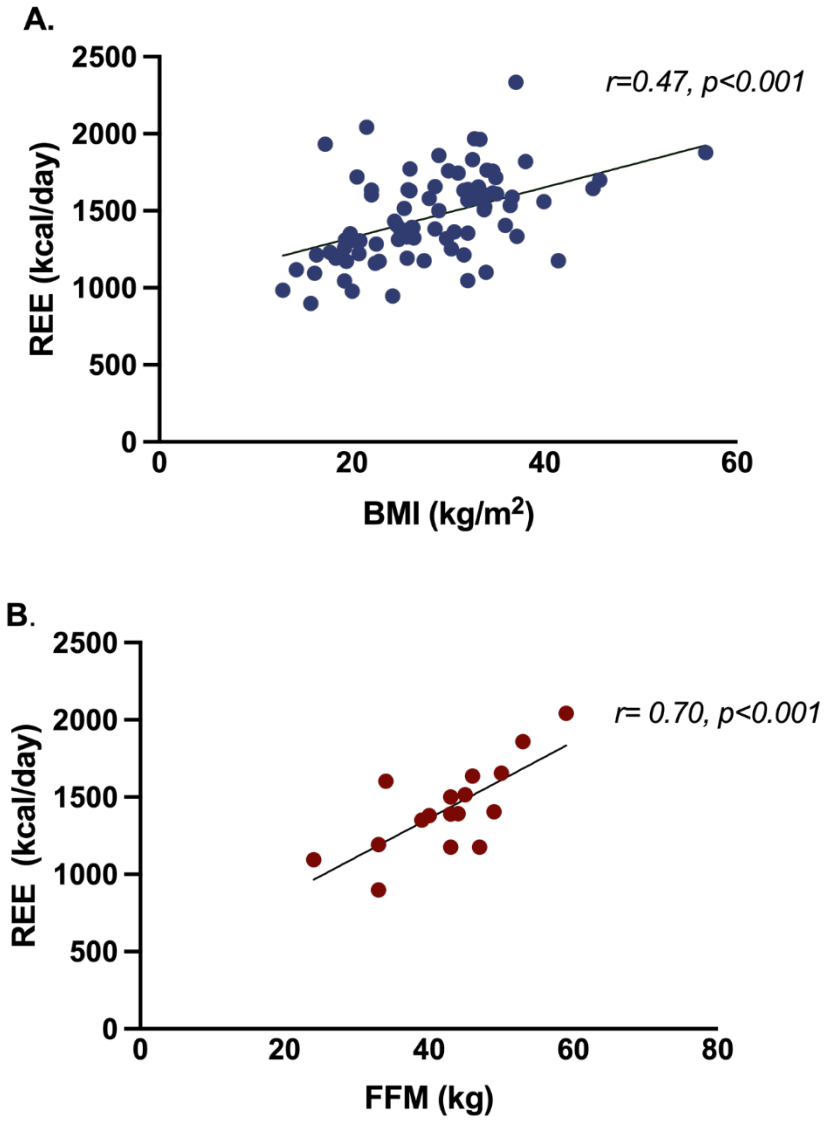

Figure 3.10. Association of BMI and FFM with REE. Simple linear regression of resting energy expenditure (REE) with body mass index (BMI) (A) and fat-free mass (B) are shown. All p-values are included.

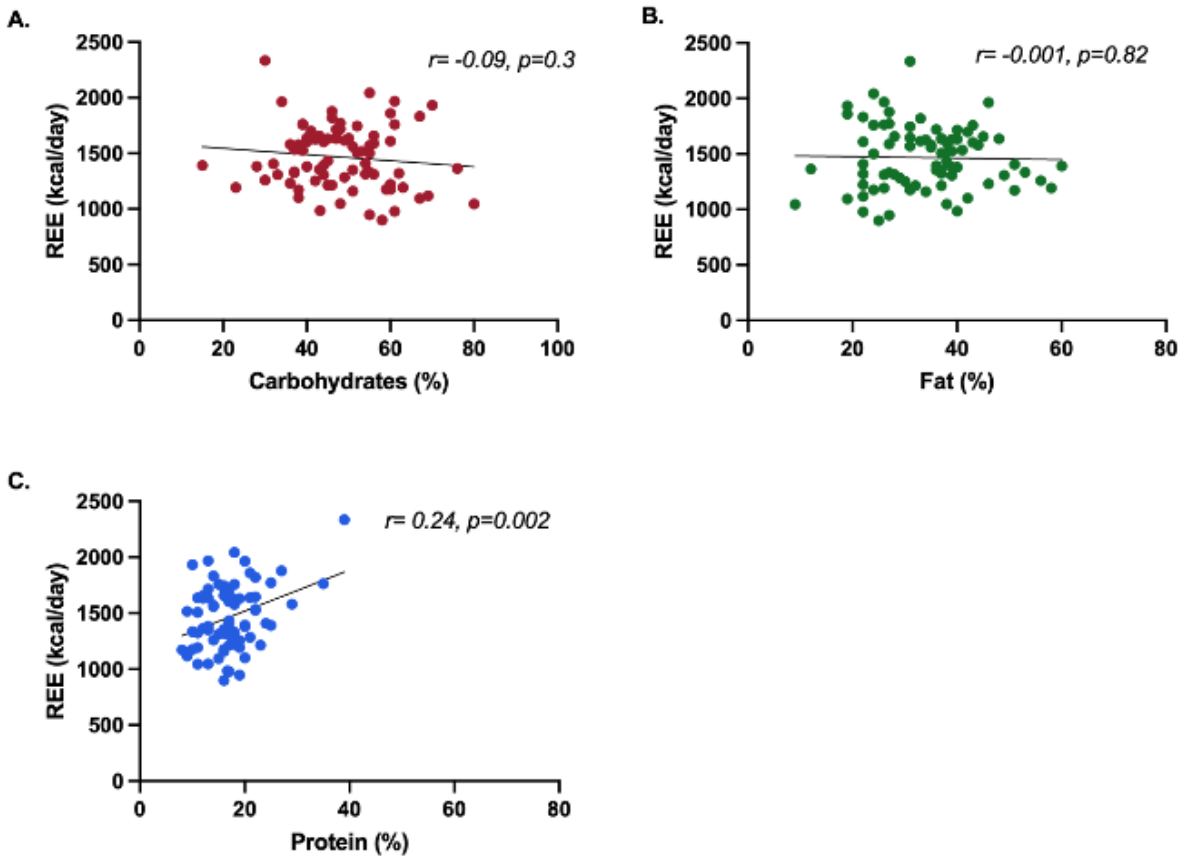

Figure 3.11. Association of Macronutrient Intake With REE. Simple linear regression of resting energy expenditure (REE) with reported macronutrient intake for carbohydrates (A), fat (B), and protein (C) are shown. P-values <0.05 are considered statistically significant.

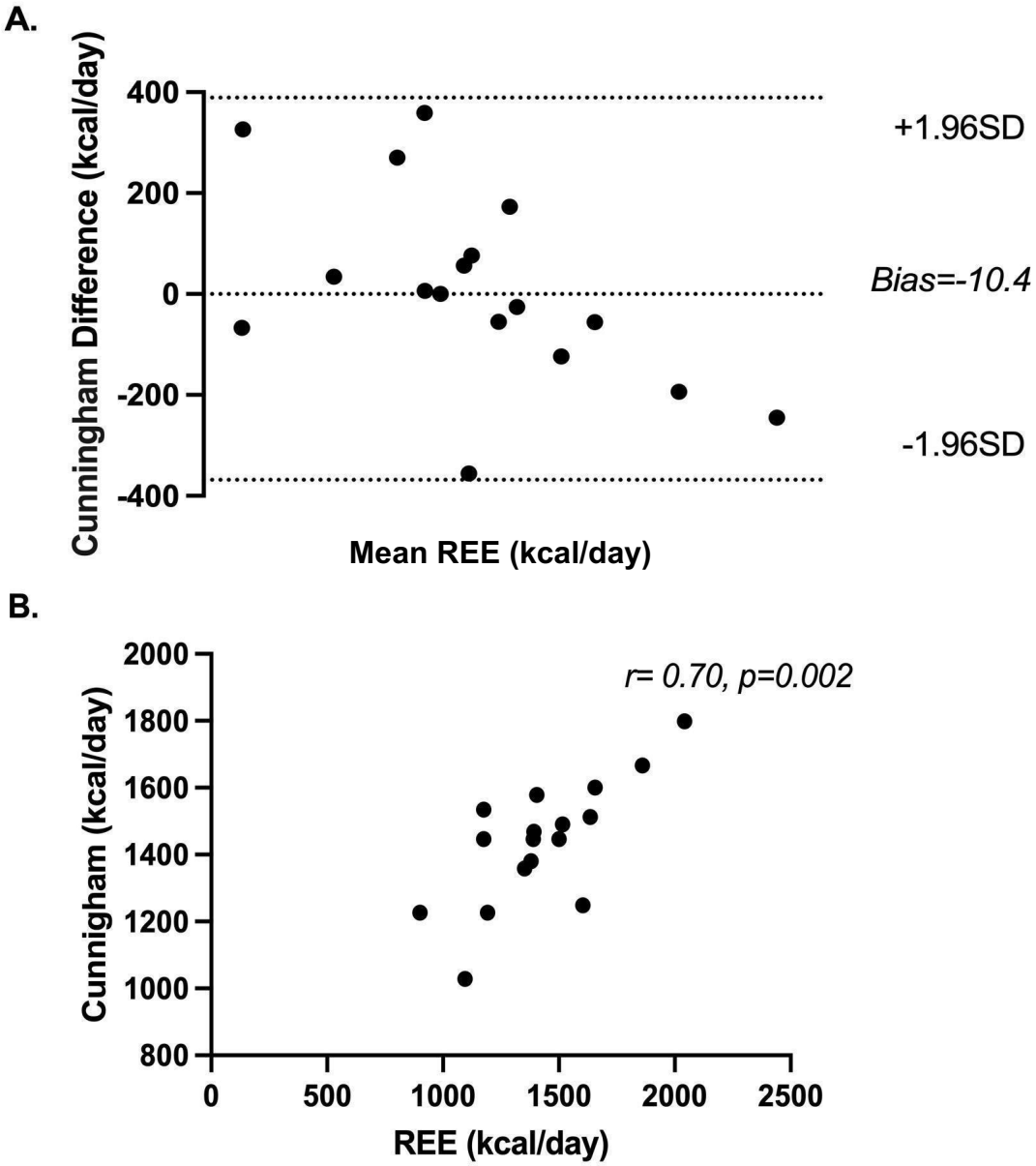

Figure 3.12. Post-hoc Analysis. The Cunningham formula was assessed using a Bland-Altman plot (A). Mean bias is represented, and limits of agreement (± 1.96 SD) are depicted by dotted lines. The correlation of the Cunningham formula with REE is shown (B), using Spearman's coefficients of correlation. The p-value is considered statistically significant ($p<0.005$).

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Chapter 6: Appendix

Appendix A: Clinic Handout

Indirect Calorimetry Handout

McMaster University Health Sciences

Hamilton Health Sciences

WHAT TO EXPECT IN THE NUTRITION ASSESSMENT/INDIRECT CALORIMETRY CLINIC

What will your visit look like?

- ✓ After registration at the front desk, you will meet with Miss. Fardowsa Abdi and you will be asked to complete some questionnaires to assess your dietary intake (ASA24), symptoms (GSRS) anxiety and depression (HADS). We encourage you to complete the questionnaires the day before the clinic by accessing the following links:
  1) https://asa24.nci.nih.gov/
  2) https://redcapfarncombe.mcmaster.ca/surveys/?s=9HX8DHLPCP
- ✓ You will meet with the nutrition fellow and dietitian to perform the following:
  1) An interview for nutrition assessment
  2) A physical examination
  3) Indirect calorimetry testing

What is indirect calorimetry?

- Indirect calorimetry (IC) is the most accurate method to measure your energy needs
- It is a non-invasive tool that measures the amount of oxygen you consume, and the amount of carbon dioxide you produce while you are breathing
- During this test, you will be asked to lie down on an examination bed. A transparent canopy or ventilated hood will be placed over your head (see picture below)
- The test takes approximately 20 minutes
- The test results will provide a daily caloric target, which can be used by your doctor and/or dietitian to help you meet your nutrition and weight management goals

Indirect Calorimetry Handout

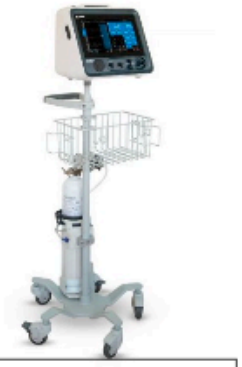


Image source: Medical Expo

Figure 1. The metabolic cart QNRG is used to measure the indirect calorimetry.

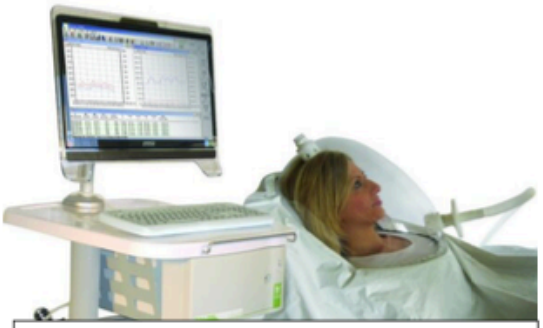


Image source: Wikipedia Commons

Figure 2. A patient is shown under the ventilated hood connected to the metabolic cart. Baseline energy expenditure of the patient is measured on the machine monitor.

What are some do's and don'ts when you are undergoing this test?

- ✓ DO:
  - Ensure you begin the test without having consumed food, calorie-containing drinks, or caffeine within the last 4 hours
    - Please disclose if you eat anything within this period of time
  - Stay awake as much as possible—even a light rest can alter your energy expenditure
  - Try to relax as you undergo the test
    - If you hear unusual or loud sounds, do your best to maintain calm
- ✓ DON'T:
  - Fall asleep

What is SGA and what does it entail?

- SGA stands for Subjective Global Assessment
- It is a simple bedside method used to diagnose malnutrition and identify those who would benefit from nutrition care
- You will discuss the following:
  - history of recent food intake
  - weight history
  - gastrointestinal symptoms (i.e., nausea, vomiting, diarrhea)
  - physical examination of your legs, back, and abdomen to detect signs of muscle wasting, fat depletion or edema (swollen ankles or back)

What else will we discuss?

- Medications you are taking
- More details on your ASA24 for accurate records
- Height & weight
- Handgrip strength using a dynamometer

Image Source: Shutterstock

Figure 3. A dynamometer assessing handgrip strength is shown above.

When should I expect to receive the results of my nutrition assessment?

✓ A report and recommendations based on the nutrition assessment and indirect calorimetry testing will be sent to your doctor within 2 weeks. You should expect to discuss the results of this assessment in the next visit arranged with your doctor.

Appendix B: Patient Referral Form

McMaster University Health Sciences

Hamilton Health Sciences

FARNCOMBE

Patient's last name First name

Address-Street City Postal code

Telephone Ext

Date of birth (yyyy/mm/dd) Age Gender M F

HIN Family physician

Patient Referral Form- Nutrition Assessment & Indirect Calorimetry Clinic

Referring Physician: _____

Date of Referral: DD/MM/YYYY _____

Reason for Referral: (Check all that Apply)

- Suspicion for Malnutrition: _____
- Goal for Weight loss: _____

Assessment of Metabolic Rate: _____

Other (describe)_____

Main GI Diagnosis:

- CELIAC DISEASE: __YES __NO

- Date of Diagnosis: _____
- Biopsy Proven: __YES __NO
- On Gluten Free Diet: __YES __NO
- Celiac Controlled?: __YES __NO

- INFLAMMATORY BOWEL DISEASE: __YES __NO

- Type of IBD: __Crohn's Disease __Ulcerative Colitis __Mixed
- Date of Diagnosis: _____
- Biologic Therapy: __YES __NO
- Clinical Remission: __YES __NO
- Prior Resection: __YES __NO Please Describe: _____

CROHN'S DISEASE CLASSIFICATION

- Age at Diagnosis (years): _____
- Location of Disease: __ILEAL; __COLONIC; __ILEOCOLONIC; __ ISOLATED UPPER DISEASE
- Behavior: __NON-STRICTURING, NON-PENETRATING; __STRICTURING; __PENETRATING; __PERIANAL DISEASE
- Harvey-Bradshaw Index: __General Well Being; __Abdominal Pain; __Number of Liquid stools per day; __Abdominal Mass; __Complications; __ TOTAL SCORE

ULCERATIVE COLITIS CLASSIFICATION

- Extent: __ Ulcerative Proctitis; __ Left-Sided UC (distal to splenic flexure); __ Extensive (Proximal to splenic flexure)
- MAYO Score: __Stool frequency; __Rectal Bleeding; __Mucosal Appearance at Endoscopy; __Physician rating of disease activity; __ Total Score

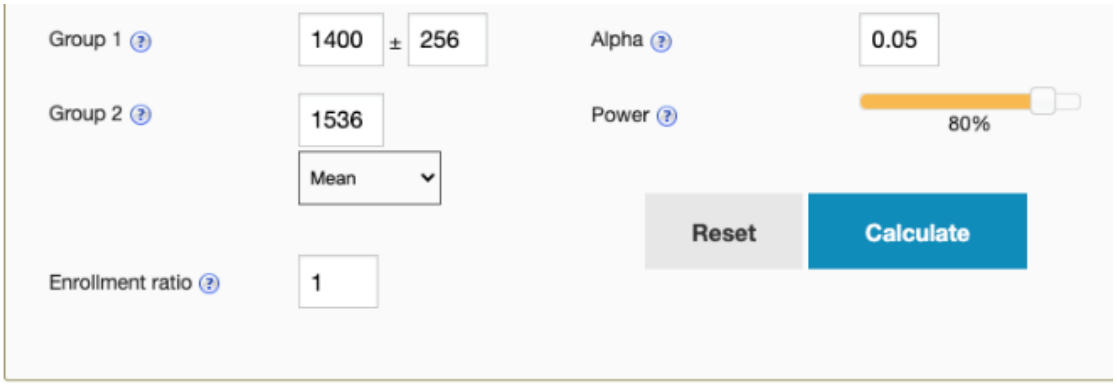
-SHORT BOWEL: __ YES __ NO

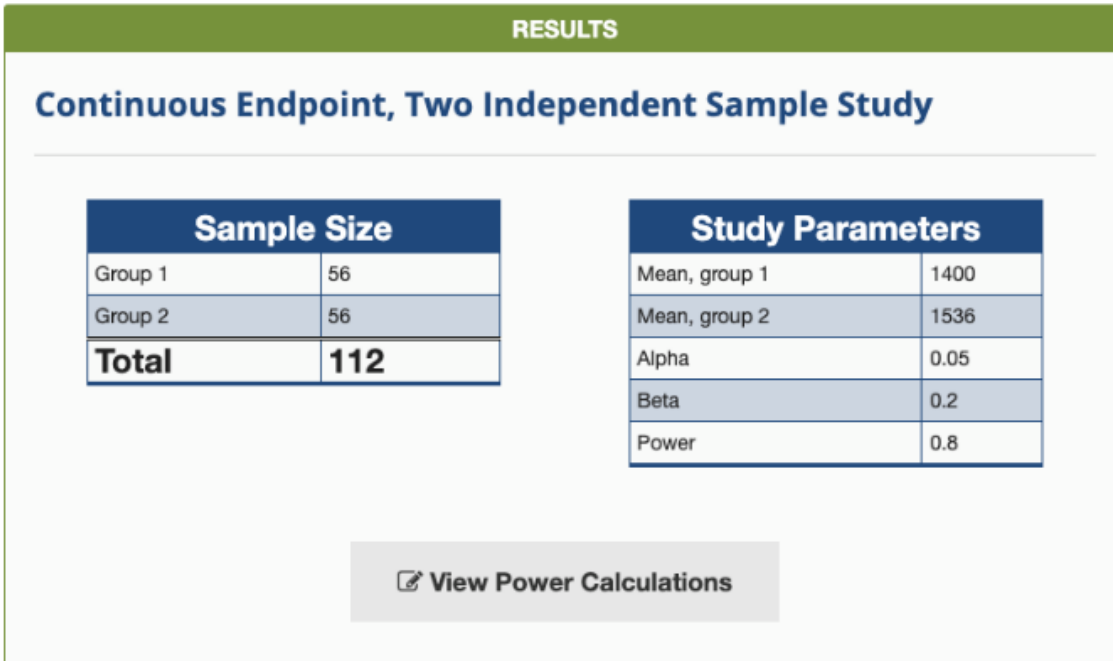
- Approx. Length of Small Bowel: _____
- Colon in Continuity: __YES __NO
- Ostomy: __Duodenostomy ___Jejunostomy ___ Ileostomy ___Colostomy
- Etiology of Short bowel: __ Ischemia __Trauma __Malignancy __IBD ___Other (Please describe): _____

COMMENTS: SIGNATURE: _____ DATE: _____

PLEASE COMPLETE FORM AND FAX TO: (905)-526-0594 ATTN: DR. M INES PINTO-SANCHEZ

Appendix C: Sample Size Calculation





Appendix D: HADS and GSRS Questionnaires

Accessed online at: https://redcapfarncombe.mcmaster.ca/surveys/?s=9HX8DHLPCP

Appendix E: ASA-24

Accessed online at: https://asa24.nci.nih.gov/

Appendix F: International Physical Activity Questionnaire Short Form (IPAQ-SF)

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

   _____ **days per week**

   ☐ No vigorous physical activities → ***Skip to question 3***

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

   _____ **hours per day**

   _____ **minutes per day**

   ☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

   _____ **days per week**

   ☐ No moderate physical activities → ***Skip to question 5***

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you have done solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

_____ **days per week**

☐ No walking → ***Skip to question 7***

6. How much time did you usually spend **walking** on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

This is the end of the questionnaire, thank you for participating.

SHORT LAST 7 DAYS SELF-ADMINISTERED version of the IPAQ. Revised August 2002.

Appendix G: Subjective Global Assessment (SGA)

Subjective Global Assessment Form

MEDICAL HISTORY

Patient name: _____ Date: _____/_____/_____

NUTRIENT INTAKE

1. ☐ No change; adequate
2. Inadequate; duration of inadequate intake _____
   ☐ Suboptimal solid diet ☐ Full fluids or only oral nutrition supplements ☐ Minimal intake, clear fluids or starvation
3. **Nutrient Intake in past 2 weeks***
   ☐ Adequate _____ ☐ Improved but not adequate _____ ☐ No improvement or inadequate _____

WEIGHT

Usual weight _____ **Current weight** _____

1. **Non fluid weight change past 6 months** Weight loss (kg) _____
   ☐ <5% loss or weight stability ☐ 5-10% loss without stabilization or increase ☐ >10% loss and ongoing
   If above not known, has there been a subjective loss of weight during the past six months?
   ☐ None or mild ☐ Moderate ☐ Severe
2. **Weight change past 2 weeks*** Amount (if known) _____
   ☐ Increased ☐ No change ☐ Decreased

SYMPTOMS (Experiencing symptoms affecting oral intake)

1. ☐ Pain on eating ☐ Anorexia ☐ Vomiting ☐ Nausea ☐ Dysphagia ☐ Diarrhea
   ☐ Dental problems ☐ Feels full quickly ☐ Constipation
2. ☐ None ☐ Intermittent/mild/few ☐ Constant/severe/multiple
3. **Symptoms in the past 2 weeks***
   ☐ Resolution of symptoms ☐ Improving ☐ No change or worsened

FUNCTIONAL CAPACITY (Fatigue and progressive loss of function)

1. No dysfunction
2. Reduced capacity; duration of change _____
   ☐ Difficulty with ambulation/normal activities ☐ Bed/chair-ridden
3. **Functional Capacity in the past 2 weeks***
   ☐ Improved ☐ No change ☐ Decrease

METABOLIC REQUIREMENT

High metabolic requirement ☐ No ☐ Yes

PHYSICAL EXAMINATION

Loss of body fat	☐ No	☐ Mild/Moderate	☐ Severe
Loss of muscle mass	☐ No	☐ Mild/Moderate	☐ Severe
Presence of edema/ascites	☐ No	☐ Mild/Moderate	☐ Severe

SGA RATING

☐ **A** Well-nourished Normal

☐ **B** Mildly/moderately malnourished Some progressive nutritional loss

☐ **C** Severely malnourished Evidence of wasting and progressive symptoms

CONTRIBUTING FACTOR

☐ **CACHEXIA** - (fat and muscle wasting due to disease and inflammation) ☐ **SARCOPENIA** - (reduced muscle mass and strength)

*See page 2 SGA Rating for more description.

April 2017

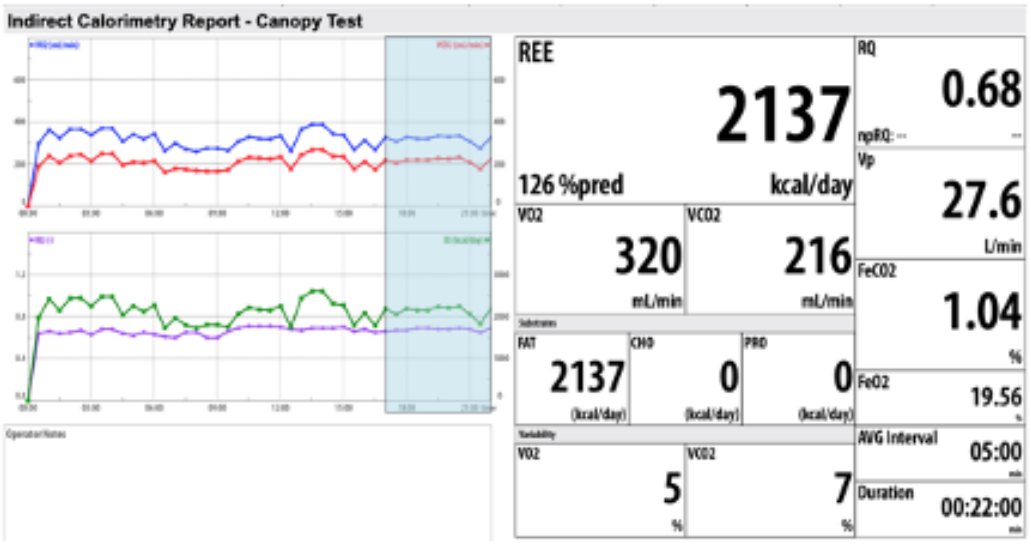
Canadian Malnutrition Task Force* | le Groupe de travail canadien sur la malnutrition*

Appendix H: Activity Factor

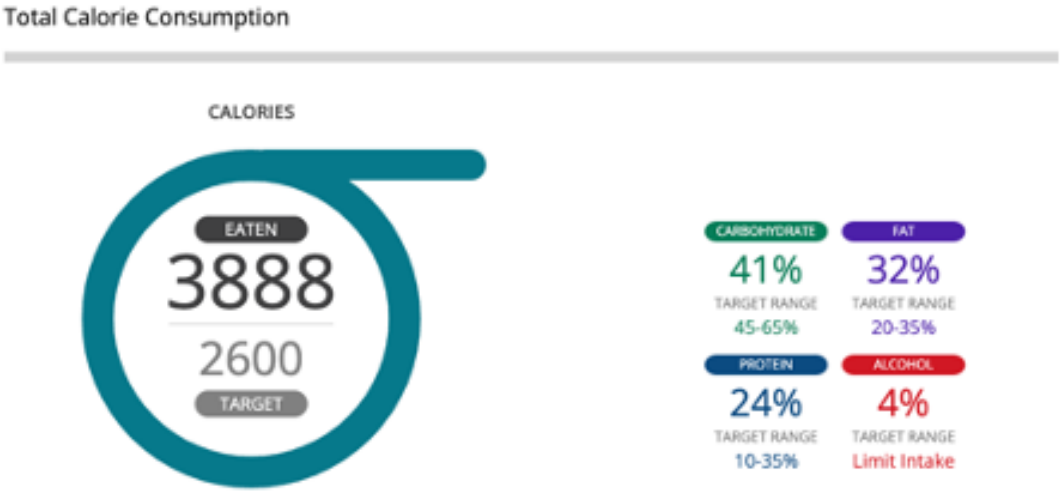
Activity Level	Activity factor
Bed rest (Bed-ridden- Unconscious	1.0-1.1
Sedentary (Little to no exercise)	1.2
Light exercise (1-3 days per week)	1.3
Moderate exercise (3-5 days per week)	1.5
Heavy exercise (6-7 days per week)	1.7
Very heavy exercise (twice per day, extra heavy workouts)	1.9

Appendix I: Case Study Reports

i.



ii.



iii. Progress Notes [redacted]

INDIRECT CALORIMETRY

Indication for Referral/Nutrition Goals: Suspicion for malnutrition in context of Crohn's disease. To assess for metabolic rate to target caloric goals.

Nutrition Assessment:
Weight changes: Most recent documented weight 74.5 kg, usually weight kg: 77 weight loss < 5%, Ideal body weight 66 kg.
[redacted].
BMI: 22.5 kg/m2- Normal
[redacted]
Nutrition Intake (24ASA): 3888 kcal/day; 229 g protein (24%); 41% Carb; 24% Fat
Current symptoms limiting oral intake: None

Results of Indirect Calorimetry:
Period: 22 total measured time
Technical limitations: None. Steady state was reached (Variability <10%, average time >5mins)
Resting Energy Expenditure: 2137 kcal/day
Predicted Energy Expenditure: 1696 kcal/day
RQ: 0.68; Primarily lipid substrate utilization and is a sign of underfeeding

Activity Factor: 1.2
Total Energy Requirements: 2564 Kcal/day
Body composition:
Percentage of body fat: 33.6%
Percentage of lean mass: 66%
Abdominal Waist: 94.6

Given this diagnosis we have made the following recommendations:
1) Encourage patient to monitor food intake to ensure consistency in caloric intake
2) To work with RD [redacted] in optimizing his diet- appointment booked [redacted] Food records confirmed he is eating over his nutritional daily needs. Therefore, we consider a possible malabsorptive syndrome in this patient. [redacted] active disease beyond the ileum which may be contributing to his hypermetabolic state.
3) Ensure adequate exercise at least 150 minutes of moderate to vigorous activity a week