Optimizing Muscle Health in Patients with Colorectal Cancer through Targeted Nutrition Intervention

by

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Abstract

Patients with cancer are nutritionally vulnerable and at risk of low muscle mass (MM), a primary nutrition problem that independently predicts poor prognosis. Targeted nutrition interventions to optimize muscle health should focus on adequate energy and protein. Many patients alter their diet but may not consider the corresponding impact on muscle health.

Three studies are presented as part of the Protein Recommendation to Increase Muscle (PRIMe) pilot trial. Patients newly diagnosed with stage II-IV colorectal cancer were randomized to a diet containing 1 g/kg/day) or a 2 g/kg/day protein for 12 weeks and supported with individualized nutrition counselling. Study 1 included baseline data to characterize total energy expenditure (TEE) and resting energy expenditure (REE) by calorimetry chamber of these patients. Energy expenditure was compared with energy intake recommendations and commonly used predictive equations. Predictors of TEE and REE were also investigated.

Study 2 informed the feasibility of a diet containing 2 g/kg/day versus 1 g/kg/day of protein to halt MM loss (evaluated as appendicular lean soft tissue [ALST] index [ALSTI]) and assessed potential effects on maintaining physical function (Short Physical Performance Battery test). The feasibility of sustaining a 2 g/kg/day diet and the potential effects of the diets on anthropometrics, body composition, physical activity, energy expenditure, nutritional status, and quality of life were also assessed.

Study 3 included baseline data that aimed to understand if and why dietary changes were made by patients. Patients' beliefs pertaining to food intake post diagnosis and dietary changes that had the potential to impact muscle health were explored using audio-recorded one-on-one

semi-structured interviews that were coded inductively and analyzed using qualitative content analysis.

Study 1 included 31 patients (56±10 years; body mass index [BMI]: 27.9±5.5 kg/m^2; 67.7% male; 74.2% stages II/III colon cancer). TEE (2074±337 kcal/day) did not differ from the lower recommended intake in cancer (25 kcal/kg/day) but was below the upper bound of 30 kcal/kg/day (-430±322 kcal/d; $p<0.001$). TEE was variable (21-32 kcal/kg/day) and most patients (n=18) had TEE outside of the recommended intake range. REE was higher than predicted by the Mifflin-St. Jeor (145±144 kcal/day; $p<0.001$) and Harris-Benedict (78±147 kcal/day; $p=0.006$) equations for the group. ALST, sex, rectal cancer, and presence of an ostomy were among predictors of TEE and REE. In models adjusted for sex, ALST and tumor location were independently predicted TEE (both $p<0.05$). ALST independently predicted REE when adjusted for sex and tumor location ($p<0.001$).

Study 2 included 50 patients (57±11 years; BMI: 27.3±5.6 kg/m^2; 60% males; 78% colon; 64% stage III). A 2 g/kg/day diet was not feasible (mean intake: 1.6±0.5 g/kg/day) although individually, 35.3% of patients (n=6) in this diet group attained 2.0 g/kg/day. This level of protein intake was observed in 8.7% of patients (n=2) in the 1 g/kg/day group. Difference between groups trended towards significance for MM (ALSTI 2 g/kg/day group: 8.2±1.8 kg/m^2; 1 g/kg/day group: 7.2±1.2 kg/m^2; mean difference: -0.9 kg/m^2; 95% confidence interval: -1.9 to 0.1 kg/m^2; $p=0.065$) but were not observed for physical function. Irrespective of diet allocation, a 1.0 g/kg/day increase in protein intake appeared to result in 1.6% increase in ALSTI (β: 1.572; 95% CI: -0.243, 3.387; $p=0.090$). Positive associations between protein intake and physical function and nutritional status scores were noted.

Study 3 included 29 patients (57±10 years; 62% male; 59% stage III) who reported varied degrees of dietary change that stemmed from internal and external influences. Four main themes emerged to describe dietary decisions after diagnosis: (1) Medical Influences: eating to live; (2) Health Beliefs: connecting lived experiences with new realities; (3) Static Diets: no changes post-diagnosis; and (4) Navigating External Influences: confluence of personal agency and social constraints.

Key findings of this thesis were that energy recommendations, which impact MM, are variable and not an all-encompassing approach to optimize muscle health in patients with cancer. We showed that increased protein intake through targeted nutrition intervention positively impacted muscle health but that a target of 2.0 g/kg/day was not feasible for patients. Prior to nutrition intervention, patients altered their dietary choices based on the degree to which dietary decisions provided a sense of control over physical ramifications of cancer. Overall, this research is a step towards designing definitive trials to assess targeted nutrition interventions to optimize muscle health in cancer.

Preface

This thesis is an original work by Katherine Leslie Ford. The research project, of which this thesis is a part, received research ethics approval from the Health Research Ethics Board of Alberta - Cancer Committee, Decreasing the Burden of Sarcopenia in Cancer through Targeted Nutrition Intervention: A Feasibility Study (HREBA.CC-15-0193), initially approved on March 7, 2016. This study complied with the standards on the use of human participants in research.

This preface is an overview of the work completed in partial fulfillment of the requirements of a Ph.D.; it is complemented by more detailed and extensive prefaces at the beginning of each chapter. Some of the research conducted for this thesis uses data that was previously collected by other researchers, as described in chapter-specific prefaces.

Dr. Carla Prado's Campus Alberta Innovation Program (CAIP) Chair in Nutrition, Food and Health funded the work presented in this thesis. Recruitment and data collection for **Chapters 4, 5, and 6** were initiated by Claire Trottier (Lead Lab Coordinator, Prado Lab) and other members of the research group prior to me joining the team. Upon my arrival, I was responsible for data collection, management, and analysis. Data collection continued to also be supported by a research coordinator.

All work presented in this thesis was critically assessed for intellectual content by my supervisor, Dr. Carla Prado, my supervisory committee members, Dr. Sunita Ghosh and Dr. Michael Sawyer, and external examining committee members, Dr. Kate Storey (University of Alberta) and Dr. Bruno Gualano (University of São Paulo). Information included in some chapters have led to submitted or published journal articles or book chapters.

Journal articles:

Ford KL, Arends J, Atherton PJ, Engelen MPKJ, Goncalves TJM, Laviano A, Lobo DN, Phillips SM, Ravasco P, Deutz NEP, Prado CM. The importance of protein sources to support muscle anabolism in cancer: an expert group opinion. *Clinical Nutrition.* 2022; 41(1):192-201. *Located in Chapter 2*.

Ford KL, Prado CM, Weimann A, Schuetz P, Lobo DN. Unresolved issues in perioperative nutrition: A narrative review. *Clinical Nutrition.* 2022;41(7):1578–1590. *Located in Chapter 2*.

Ford KL, Orsso CE, Kiss N, Johnson SB, Purcell SA, Gagnon A, Laviano A, Prado CM. Dietary choices following a cancer diagnosis: A narrative review. *Nutrition.* Online ahead of print. DOI: 10.1016/j.nut.2022.111838. *Located in Chapter 2.*

Ford KL, Sawyer M, Trottier C, Ghosh S, Deutz N, Siervo M, Porter Starr K, Bales C, Roitman Disi I, Prado CM. Protein Recommendation to Increase Muscle (PRIMe): Study protocol for a randomized controlled pilot trial investigating the feasibility of a high protein diet to halt loss of muscle mass in patients with colorectal cancer. *Clinical Nutrition ESPEN*. 2021;41:175-85. *Located in Chapter 3.*

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Book chapters:

Ford KL, Oliveira CLP, Ramage S, Prado CM. Protocols for the use of indirect calorimetry in clinical research. In Betim Cazarin CBB (Ed.), *Basic Protocols in Foods and Nutrition*. New York, NY: Springer US; 2022. p. 265-291. *Located in Chapter 2 and Appendix 1*.

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Abbreviations

μSV: micro Sieverts

η^2: eta squared

AICR: American Institute for Cancer Research

ALST: appendicular lean soft tissue

ALSTI: appendicular lean soft tissue index

ANCOVA: analysis of covariance

AR-1: autoregressive model 1

ASM: appendicular skeletal muscle

AT: activity thermogenesis

BEE: basal energy expenditure

BMI: body mass index

BW: body weight

CAPOX: drug combination of capecitabine and oxaliplatin

CC: calf circumference

CI: confidence interval

CO_2: carbon dioxide

CRC: colorectal cancer

CT: computed tomography

DIAAS: Digestible Indispensable Amino Avid Score

DRI: dietary reference intake

DXA: dual-energy X-ray absorptiometry

EE: energy expenditure

EORTC QLQ C-30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30

FAACT: functional assessment of anorexia/cachexia treatment

FFM: fat-free mass

FM: fat mass

FOLFIRI + BEVA: drug combination of leucovorin calcium, fluorouracil, and irinotecan hydrochloride plus bevacizumab

FOLFIRI: drug combination of leucovorin calcium, fluorouracil, and irinotecan hydrochloride

FOLFOX: drug combination of Leucovorin calcium, fluorouracil, and oxaliplatin

GEE: generalized estimating equation

HNRU: Human Nutrition Research Unit

HR: hazard ratio

HU: Hounsfield units

IMAT: intermuscular adipose tissue

IPAQ-SF: International Physical Activity Questionnaire – Short Form

IQR: interquartile range

kcal/day: kilocalories per day

L3: third lumbar vertebra

LOA: level of agreement

LST: lean soft tissue

mL: millilitre

MET: metabolic equivalent of task

MM: muscle mass

MPB: muscle protein breakdown

MPS: muscle protein synthesis

mREE: measured resting energy expenditure

mSY: milli Sieverts

mTEE: measured total energy expenditure

O_2: oxygen

OR: odds ratio

PAL: physical activity level

PDCAAS: Protein Digestibility Corrected Amino Acid Score

PG-SGA: Patient-Generated Subjective Global Assessment

pREE: predicted resting energy expenditure

PRIMe: Protein Recommendation to Increase Muscle

QoL: quality of life

RDA: recommended dietary allowance

REE: resting energy expenditure

SD: standard deviation

SE: standard error

SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

SPPB: Short Physical Performance Battery

TEE: total energy expenditure

TEF: thermic effect of food

TNM: tumor, node, metastasis

$\dot{V}CO_2$: volume of carbon dioxide

$\dot{V}O_2$: volume of oxygen

WCRF: World Cancer Research Fund

Chapter 1 Introduction

1.1 Thesis Organization

This thesis has been prepared as a paper format according to specifications provided by the Faculty of Graduate Studies and Research at the University of Alberta. Following the Introduction is a Literature Review (**Chapter 2**), 4 individual manuscript-style chapters (**Chapters 3–6**), and a Discussion and Conclusions section (**Chapter 7**). A preface precedes **Chapters 3, 4, 5**, and **6** with a brief description of each study and collaborators' contributions. Related figures and tables are provided at the end of each chapter.

1.2 Rationale

Cancer is a leading cause of morbidity and mortality with an estimated 18 million new cases diagnosed in 2020 [1]. Globally, colorectal cancer (CRC) is the third most diagnosed cancer and the second cause of cancer-related mortality [1]. Low muscle mass (MM) is a condition that is prevalent in cancer, including CRC, regardless of disease stage, and is associated with decreased physical function, poorer health-related quality of life, increased risk for treatment toxicity, delayed treatment, surgical complications, and shorter survival [2-13]. Chemotherapy is routinely used to treat stages II–IV CRC [14] and can accentuate muscle loss [9, 15]. Muscle depletion in cancer is a multifactorial process driven by an imbalance in muscle protein synthesis and breakdown favoring the latter, yet muscle loss may not be an inevitable part of the cancer trajectory [16]. Despite accelerated catabolism, patients with cancer retain anabolic potential, regardless of disease stage [17, 18].

It is increasingly apparent that muscle loss is the primary nutritional problem experienced by oncology patients [19]. Optimal provision of energy and protein is essential to prevent or halt MM loss. Energy intake should match energy expenditure (EE) to promote weight maintenance [20] and avoid unintentional weight loss that is often coupled with MM depletion [21] while protein intake should be sufficient to negate depletion of amino acid reserves [22, 23]. Despite evidence of altered metabolism [24-28], energy recommendations in cancer (25–30 kcal/kg body weight [BW]/day) are not different from healthy populations and this may be due to the very limited number of studies that have objectively assessed total energy expenditure (TEE) in patients with cancer [24-26, 29]. Energy expenditure of patients with CRC has been

characterized and was not accurately captured by current recommendations [24]. This may be due in part to the high variability of physical activity levels observed in this population [24]. The literature pertaining to resting energy expenditure (REE) in persons with cancer is more extensive although heterogeneity of methods and reporting standards [28] and inaccurate assessments techniques [30] hinder our understandings of REE across the spectrum of disease. Both TEE and REE relate to body composition suggesting that lean soft tissue (LST), which includes MM, is of important consideration [24, 31]. The gold standard to assess TEE and its selected components is a calorimetry chamber [32] although this approach has not been used in patients with CRC or in any cancer cohort in >25 years [25].

In addition to optimal energy intake, specific nutrients play an important role in muscle health, particularly protein [29, 33-36]. If dietary protein is not sufficient, muscle will self-sacrifice in times of need [37, 38]. Protein intake in patients with cancer varies; many do not meet the minimum recommended intake of 1.0 g/kg/day or the target intake of 1.2–1.5 g/kg/day [39-42]. The latest published guidelines suggested the need to explore the feasibility of a higher protein (2.0 g/kg/day) diet on patient outcomes (e.g., the extent to which it can sustain MM) in this population [29].

Optimizing nutritional status through targeted energy and protein intakes is essential for muscle health yet patients may underestimate the severity of nutrition-related conditions [43] and not consider the importance of nutrition when making dietary choices. A cancer diagnosis can act as a catalyst for lifestyle changes [44]. In turn, patients are prone to dietary changes that may not align with oncology nutrition recommendations [29] such as reducing or eliminating animal products from their diet [45, 46]. Nutrition is of importance to people with cancer and many patients alter their diet in an attempt to cure the cancer or alleviate symptoms [47] but may not consider the impact of dietary choices on muscle health.

1.3 Purpose

The overarching purpose of this research was to explore a targeted nutrition intervention to optimize muscle health in patients newly diagnosed with CRC. We sought to characterize energy expenditure, assess different doses of protein on muscle health, and understand the determinants of dietary intake. In turn, a deeper understanding of determinants of dietary intake

in patients with cancer can inform, and may impact, the success of similar nutrition interventions in the future.

1.4 Research Questions

The research questions for this thesis were:

In patients being treated for a new diagnosis of stages II-IV CRC:

1. What is their TEE and REE, and do they differ from energy intake recommendations?
2. What is the variability and the predictors of TEE and REE?
3. Is a diet containing 2 g/kg/d of protein feasible to consume?
4. What are the potential effects of a diet containing 2 g/kg/day versus 1 g/kg/day of protein on muscle health?
5. Are dietary changes that have the potential to impact muscle health made post-diagnosis?
6. What drives dietary decision-making and ultimately dietary intake related to muscle health?

1.5 Objectives and Hypotheses

The above-mentioned research questions are answered within **Chapters 4-6** using data from a randomized controlled pilot trial. **Chapters 4** and **6** present secondary analyses of the trial using baseline data only. **Chapter 5** presents the main randomized controlled trial findings.

1.5.1 Total 24-hour Energy Expenditure Assessed by Calorimetry Chamber in Patients with Colorectal Cancer (Chapter 4)

In patients being treated for a new diagnosis of stages II-IV CRC:

Objectives:

a. To characterize TEE and REE by calorimetry chamber.
b. To compare measured TEE by calorimetry chamber to energy intake recommendations in cancer (25–30 kcal/kg/day) and the dietary reference intake (DRI) equation for healthy populations.
c. To compare measured REE (mREE) to common predictive equations.

d. To investigate predictors of TEE and REE.

Hypotheses:

a. Measured TEE and mREE would not differ from energy intake recommendations, but wide individual variability would be observed.

b. Weight, sex, stage of disease, and muscle (i.e., LST) would independently predict TEE and REE.

1.5.2 Assessing the Feasibility and Impact of Protein Intake on Muscle Mass and Physical Function in Patients with Colorectal Cancer: Findings from a Randomized Pilot Trial (Chapter 5)

In patients being treated for a new diagnosis of stages II-IV CRC:

Primary Objective:

a. To inform the feasibility of utilizing a 2 g/kg/day compared with a 1 g/kg/day diet to halt MM loss.

Secondary Objective:

a. To assess potential effects of a diet containing 2 g/kg/day compared with 1 g/kg/day of protein on maintaining physical function.

Exploratory Objectives:

a. To assess the feasibility sustaining a 2 g/kg/day diet during cancer treatment and to compare the potential effects of a 2 g/kg/day compared with a 1 g/kg/day diet on anthropometrics, body composition, physical activity, energy expenditure, nutritional status, and quality of life.

Hypotheses:

As recommended by the *Consolidated Standards of Reporting Trials (CONSORT) 2010 Statement: Extension to Randomized Pilot Trials*, formal hypothesis testing was not conducted [48-50].

1.5.3 Drivers of Dietary Choice Following a Diagnosis of Colorectal Cancer: A Qualitative Study (Chapter 6)

In patients being treated for a new diagnosis of stages II-IV CRC:

Objectives:

a. To understand if and why dietary changes were made by patients starting chemotherapy.
b. To learn about patients' beliefs pertaining to food intake following a CRC diagnosis.
c. To understand if patients made dietary changes that had the potential to impact muscle health.

Hypotheses:

a. This was a hypothesis-generating study that can be useful for tailoring future quantitative studies.

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Chapter 2 Literature Review

2.1 Preface

The section of this chapter that describes energy metabolism has been modified from a published book chapter and reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature Springer eBook. Ford KL, Oliveira CLP, Ramage SM, Prado CM. Protocols for the Use of Indirect Calorimetry in Clinical Research. In: Betim Cazarin CB, editor. Basic Protocols in Foods and Nutrition. New York, NY: Springer US; 2022. p. 265-91. [65]. Copyright (2022). I was responsible for the review and analysis of the literature and writing the first draft. All co-authors provided critical contributions and reviewed the manuscript for intellectual content.

The section of this chapter that describes body composition includes information modified from a paper published in Clinical Nutrition (Ford KL, Prado CM, Weimann A, Schuetz P, Lobo DN. Unresolved issues in perioperative nutrition: A narrative review. 2022;41(7):1578–1590). As an author of this article, I retain the right to include it in a thesis or dissertation; permission from the publisher is not required. I was responsible for creation of the visual components (tables and figures), the majority of the content, and reviewing full manuscript for intellectual content. Any components of this thesis that were adapted from the above publication were from sections where I was responsible for conducting the literature review and writing the first draft.

The section of this chapter that describes nutrition as a therapy to support muscle health in cancer is modified from an open access paper distributed under the terms of the Creative Commons CC-BY license and previously published as Ford KL, Arends J, Atherton PJ, Engelen MPKJ, Gonçalves TJM, Laviano A, et al. The importance of protein sources to support muscle anabolism in cancer: An expert group opinion. Clin Nutr. 2022;41:192-201. Within this article, I was responsible for the review of the literature, critical analysis, and writing the first draft of the manuscript. All co-authors provided critical contributions and reviewed the manuscript for intellectual content.

The section of this chapter that describes determinants of dietary choice is modified from a published paper in Nutrition (Ford KL, Orsso CE, Kiss N, Johnson SB, Purcell SA, Gagnon A, Laviano A, Prado CM. Dietary choices following a cancer diagnosis: A narrative review. Nutrition. 2022. Online ahead of print. DOI: 10.1016/j.nut.2022.111838). Within this manuscript, I was responsible for the review and critical analysis of the literature and writing the first draft of the manuscript. All co-authors provided critical contributions and reviewed the manuscript for intellectual content.

2.2 Patients with Cancer as a Nutritionally Vulnerable Population

As highlighted in **Chapter 1**, individuals with cancer are nutritionally vulnerable due to the disease and treatment effects which put them at increased risk for disease-related malnutrition [1], **Figure 2.1**. Older age, weight loss, type of cancer, and advanced stage of disease are among factors that increase risk for malnutrition in cancer [2, 3]. A distinguishing element and diagnostic criterion of malnutrition is low muscle mass (MM) [4], a body composition phenotype [5] that is often observed in patients with cancer, regardless of body size and adiposity [6, 7]. Low MM in cancer is associated with decreased physical function, poorer health-related quality of life, risk of treatment toxicity, delayed treatment, risk of infection, increased medical costs, and shorter survival [8-16], **Figure 2.2**. Muscle loss negatively affects prognosis and is the primary nutritional problem in patients with cancer [17].

Skeletal muscle is a metabolically active endocrine organ, the largest amino acid reserve in the human body, and any imbalance between energy (i.e., caloric) and nutrient (e.g., protein) intake and respective requirements will cause alterations to body composition [18, 19]. Targeted nutritional therapies to optimize muscle health in cancer should thus focus on adequate energy and protein intakes [17, 20, 21]. Despite the prevalence of low MM and associated negative clinical outcomes, oncology patients underestimate the presence and severity of these conditions [22]. Many patients alter their diet in attempt to cure the cancer or alleviate symptoms [23] but may not consider the impact of dietary choices on muscle health.

Colorectal cancer (CRC) is the third most diagnosed cancer globally and the second cause of cancer-related mortality [24]. Improved screening has led to decreased incidence of CRC in countries such as Canada, but this trend is largely masked by the increasing rates of CRC in adults <50 years of age [24, 25]. Despite the wide age-range at time of diagnosis, low MM is observed in ~50% of patients with CRC [26]. Our laboratory has been dedicated to better understanding nutritional status, including energy metabolism and body composition, of patients with CRC for over a decade. Our group was the first to measure total energy expenditure (TEE) of patients with primarily early-stage CRC in free-living conditions (using doubly labelled water) and showed variability that was not reflective of energy recommendations in cancer [27]. Importantly, earlier work also showed that low MM was prevalent regardless of disease stage or body size and was an independent predictor of survival in patients with solid tumors of the

respiratory or gastrointestinal tract [6], which has also been confirmed in patients with earlier stages of CRC [28]. The work presented in this thesis builds and expands on past findings and is a step towards better understanding aspects of nutritional assessment and intervention of patients with CRC, with a particular focus on muscle health.

2.3 Energy Metabolism

The human body survives on energy supplied by oxidation of macronutrients obtained through diet or hydrolysis of body stores when exogenous energy is insufficient [29]. Energy homeostasis (i.e., energy balance) is achieved when the difference between energy intake and energy expenditure (EE) is chronically nil [30]. Weight maintenance is possible when energy balance is maintained over time although clinical conditions can cause disruptions to energy homeostasis, in-turn causing unintentional weight change. The latter, specially weight loss, should not be neglected given the negative associations between survival and low body mass index (BMI) [31], weight loss (independent of body weight [BW]) [32], and malnutrition [33] in patients with cancer.

Understanding energy expenditure is essential to promote energy homeostasis in oncology. The major physiological components of TEE include resting energy expenditure (REE), thermic effect of food (TEF), and activity thermogenesis (AT) [30]. Resting EE is the largest component of TEE, contributing approximately 60-70% of daily EE depending on an individual's physical activity levels [34]. Resting EE represents the amount of energy required to maintain vital bodily functions at rest while awake, in a fasting state, and in a thermoneutral environment [30]. Assessment under such conditions ensures that the TEF and AT are not accounted for, providing an accurate REE valuation [35]. Although the terms REE and basal energy expenditure (BEE) are often used interchangeably, these energy metabolism components are not synonymous. The difference between REE and BEE pertains mainly on how they are assessed. Basal energy expenditure is usually ~10% lower than REE, with the difference representing the energy expended during arousal [36, 37]. Resting EE or BEE are commonly assessed yet TEE determines energy requirements and objective data on TEE in patients with cancer is limited [27, 38, 39].

2.3.1 Energy Expenditure in Cancer

Current oncology nutrition guidelines are based on the notion that patients with cancer have similar metabolic demands to healthy individuals thus energy intake recommendations (25–30 kcal/kg/day) [20] parallel those for healthy adults. Studies of TEE in patients with small cell lung cancer [38] or cachexia and advanced pancreatic cancer [39] suggested that patients with cancer have lower measured TEE compared with values predicted for healthy adults [20]. Lung and pancreatic cancers have the highest prevalence of low MM (70% and 56%, respectively) [26] which could be altering the energy metabolism profiles of these patients. Changes to physical activity levels are another plausible explanation for observed differences, especially given that REE has been shown to be increased in patients with cancer [20]. Notably, this dose-dependent or additive effect of physical activity on TEE is controversial and has been challenged by the constrained TEE model, especially in the context of negative energy balance [40]. The constrained TEE model suggests the positive correlation between physical activity and TEE has a stronger relationship in persons with low levels of physical activity whereas TEE plateaus in persons with higher levels of physical activity when body size and composition are considered [41]. To our knowledge, this model has not been studied in patients with cancer. The metabolic nature of cancer varies by type and stage of disease and can also influence TEE and REE, resulting in altered energy metabolism [42]. The disease promotes secretion of cancer-derived factors (e.g., parathyroid hormone, myostatin, and activins) that interact with the host immune system [43]. The nature of the disease stimulates secretion of pro-inflammatory cytokines including interleukin-1, interleukin-6, and tumor necrosis factor [43]. Systemic inflammation is commonly observed in cancer and is one factor that may directly or indirectly affect EE, likely through skeletal muscle breakdown and the ubiquitin-proteasome pathways [43, 44].

Beyond the impact of the disease, energy expenditure is also affected by factors such as genetics, age, sex, menstrual cycle, body composition, physical activity, diet composition, health status, medications, and environmental stimuli [45]. Generally, REE is higher in men than in women even after adjusting for confounding variables such as age, body composition, and activity levels [46, 47]. External factors such as diet composition are also able to affect EE. In fact, the energy expended to digest, absorb, process, and store dietary protein is 25-30% of the energy content of the meal, followed by carbohydrates (6-8%) and fat (2-3%) [48]. In addition to

diet composition, medications can affect EE by affecting respiration or heart rate, leading to increased or decreased EE. Anti-asthmatic drugs such as salbutamol have been found to increase oxygen and carbon dioxide [49]. Conversely, β-blockers have been shown to decrease EE related to their activity, decreasing skeletal muscle sympathetic nerve activity and resting heart rate [50, 51] Additionally, anti-seizure drugs [52], antidepressants [53], and corticosteroids [54] have been found to decrease EE. Therefore, if indirect calorimetry is used in a research design that includes repeated measures, the above-mentioned factors should be considered to ensure that captured change is truly representative of the change in EE and that the effect of measurement error is minimized.

2.3.2 Predicting Energy Expenditure in Cancer

Indirect calorimetry offers a precise prediction of REE in the clinical setting but creates challenges due to the accessibility of equipment, cost, time, and required skills associated. Predictive equations offer clinicians the ability to predict EE on an individual level as a part of nutritional assessment, albeit with sub-optimal accuracy and preciseness, especially in clinical conditions such as cancer [55]. The most common and clinically relevant predictive equations include those by Harris and Benedict [56], Mifflin-St Jeor [57], Owen [58, 59], and the World Health Organization/Food and Agriculture Organization/United Nations University [60, 61]. Comparing measured REE (mREE) to predicted REE (pREE) is a method used to categorize metabolic status. A quintessential study by Boothby & Sandiford (1922) showed that 85% of persons (n=8614) with varying conditions had REE within 10% of that predicted by Harris Benedict equation [62]. Thus, Boothby et al. suggested that normometabolism is mREE/pREE between 90-110%; mREE/pREE <90% is considered hypometabolism; and mREE/pREE ≥110% is considered hypermetabolism [62].

Variable metabolic profiles are observed in cancer although these should be interpreted with caution given that predictive equations are validated in healthy populations and have proven to be inaccurate in cancer [55]. Notwithstanding this limitation, studies classify metabolic status using predictive equations. A study of 179 older adults with a solid tumor had REE assessed by indirect calorimetry (Fitmate VM®) and predicted by the Harris-Benedict equation [63]. Almost half of patients (47%) were hypermetabolic while 18% were hypometabolic [63]. Notably, the majority (82%) of patients presented with metastatic disease [63]. A study (n=21) by Purcell et al

found that half of patients with CRC presented with hypermetabolism when mREE was assessed by indirect calorimetry and pREE by Mifflin-St. Jeor equation [27]. A separate study by the same group assessed REE by various equations capered to indirect calorimetry in patients (n=125) with various cancer types and found pREE by Miffllin St-Jeor equation had the smallest limits of agreement (–21.7% to 11.3% or –394 to 203 kcal/day) and was accurate (within 10% of mREE) in ~65% of patients [55]. An integrative systematic review included 15 studies that assessed the accuracy of predictive equations compared with mREE by indirect calorimetry in patients with solid tumors and found heterogeneous results amongst studies and low accuracy regardless of tumor location or type of anti-cancer therapy [64]. This review brought to light the variability of pREE vs mREE in cancer although some limitations were noted including that the breadth of past research [65] and the unique fluctuating clinical course observed in patients with cancer [66] were not fully captured.

Energy metabolism may be altered in cancer when body composition shifts occur. As further discussed below, muscle is a lean tissue organ that is of relevance for non-lipophilic drug distribution and metabolism [67]. A prospective cohort study of older patients with a solid tumor receiving anti-cancer treatment (n=179) was the first to elucidate a relationship between REE and the risk of early dose-limiting toxicity [63]. Multivariate analysis showed that hypermetabolism (defined as mREE/pREE >110%; measured by indirect calorimetry and predicted by Harris Benedict equation) was an independent predictor of early limiting toxicity (adjusted OR: 2.44; 995% CI: 1.02 – 5.80; p=0.012) [63]. Alterations to EE in cancer can promote malnutrition or nutritional risk [68, 69] and warrant accurate assessment techniques.

2.3.3 Indirect Calorimetry as a Method to Assess Energy Expenditure

Human energy needs are assessed by measuring an individual's EE by calorimetric or non-calorimetric methods [36]. Several devices are available to assess EE through indirect calorimetry although only those relevant to this thesis will be discussed in detail herein. Additional indirect calorimetry devices available for the research and clinical settings and important considerations for their use are summarized in **Table 2.1** [70].

Resting EE assessment by indirect calorimetry provides the most accurate value and is considered the clinical standard for evaluating and monitoring EE [71]. Indirect calorimetry is an evidence-based calorimetric method that measures the products of respiration: oxygen (O_2) and

carbon dioxide (CO_2). Using the volume of O_2 and CO_2 (VO_2 and VCO_2, respectively), the amount of energy released in the combustion of substrates (metabolism) is estimated [36]. Several energy metabolism components can be assessed using indirect calorimetry, including TEE and its major components (i.e., REE, TEF, and AT).

Indirect calorimetry is based on known amounts of heat generated per liter of O_2 and CO_2 consumed and produced when macronutrients are oxidized [36, 72, 73]. Because the oxidation of different macronutrients results in distinct VO_2 and VCO_2, indirect calorimetry estimates substrate oxidation rates, caloric equivalents for macronutrients, and EE [72, 73]. Several scientists have dedicated their work to develop equations for the estimation of EE based on measurements of O_2 and CO_2 [74, 75]. One of the most commonly used equations to estimate REE using indirect calorimetry is the abbreviated Weir equation [74]:

$$\text{REE (kcal/day)} = (3.941 \times VO_2\ [\text{L/min}] + 1.106 \times VCO_2\ [\text{L/min}]) \times 1440\ \text{min/day}$$

The abbreviated Weir equation was designed with the notion that although nitrogen is a product of substrate oxidation, it is neither consumed nor produced during respiration and thus EE can be accurately estimated without consideration for nitrogen (i.e., requiring correction for protein) [74]. For persons consuming diets containing 10-14% of calories from protein, the error observed when discounting nitrogen in the EE equation would be less than 1 in 500 [74]. Alternatively, the error ensued by discounting nitrogen equates to 1% for every 12.3% of calories represented by protein [74].

Indirect calorimetry obtains volumes of O_2 and CO_2 through total collection (rigid or flexible system), open-circuit (ventilated or expiratory collection), confinement (respiratory chamber), or closed-circuit systems [36]. Open-circuit calorimeters are a common type of indirect calorimetry devices used to assess REE in both clinical and research settings and include metabolic carts (with a facemask, mouthpiece, or canopy hood to capture gas exchanges) or whole-room calorimetry chambers [37].

2.3.3.1 Calorimetry Chambers

Calorimetry chambers are highly accurate and precise albeit rare and resource-intensive [37, 76]. Given these characteristics, it is not surprising that globally there are less than 45 centers that house calorimetry chambers [76]. Calorimetry chambers employ indirect calorimetry

methods to a whole room, allowing the patient to move freely about the space and engage in activities of daily living over a prolonged period of time [76]. This controlled setting allows for quantification of nitrogen intake (e.g., nutrient analysis) and losses (e.g., 24-hour urinary nitrogen) and subsequently, the use of Weir's equation [74]:

$$\text{EE (kcal/day)} = (3.941 \times \dot{V}O_2\,[\text{L}] + 1.106 \times \dot{V}CO_2\,[\text{L}]) - (2.17 \times \text{urinary nitrogen [g/day]})$$

A small study of patients with unresectable small-cell lung cancer (n=5) validated a tracer method against EE derived from a 24-hour stay in a calorimetry chamber [38]. Mean group-level EE derived from the calorimetry chamber was 1902 ± 373 kcal/day. Physical activity level defined as the ratio of 24-hour EE to basal metabolic rate was 1.232 ± 0.069 [38]. Sex-specific details and EE (kcal/kg/day) were not investigated in this study [38]. To our knowledge, calorimetry chambers have only been used to assess 24-hour EE in patients with cancer on one occasion [38], as such, more research is needed to enhance our understanding of 24-hour energy expenditure of patients being treated for CRC. This data would contribute essential information needed to optimize caloric intake during targeted nutritional interventions to support muscle health.

2.4 Body Composition

Muscle is a metabolically active endocrine organ that represents approximately 40% of human body composition [77]. Any imbalance between energy and nutrient (e.g., protein) intake and respective requirements will cause alterations to body composition [18, 19], which refers to the science of individual tissues that make up the human body. Body components are typically summed by evaluating total body mass (i.e., weight) and overall BW is frequently characterized using BMI. These approaches for individual body description do not depict quantities or changes in specific tissue compartments [78]. For example, change in weight or BMI does not quantify shifts in individual body tissues and similarly, weight stability does not imply that tissue masses are stable [14, 78]. Alterations to body composition are especially notable in non-homeostatic conditions but require assessment beyond total BW to gain a deeper understand the impact on overall health, including nutritional status [78].

2.4.1 Body Composition Abnormalities in Cancer

Muscle is a key regulator of whole-body metabolism, the largest amino acid reserve in the human body, and will self-sacrifice in times of need (e.g., inadequate exogenous protein intake) [77, 79]. Low MM is an important, yet often neglected, consideration in oncology clinical practice [80]. It is often referred to as sarcopenia which is defined as low muscle strength in combination with low muscle quantity and physical performance [81]. In cancer, sarcopenia is typically disease-related (i.e., secondary sarcopenia) as opposed to age-related (i.e., primary sarcopenia) [81]. Despite these definitions, most oncologic research that assesses body composition has focused on muscle loss alone [80]. Consequences of low MM in cancer are summarized in **Figure 2.2** and include physical impairment or disability, poorer health-related quality of life, risk of treatment toxicity, delayed treatment, disease progression, and shorter survival [8-14]. Muscle loss negatively affects prognosis and is the primary nutritional problem in patients with cancer [17].

The chronic systemic inflammatory nature of cancer is among reasons why alterations to body composition, including loss of MM, are observed in cancer [82]. The impact of chronic inflammation can be compounded by bed rest and acute inflammation experienced by oncology patients requiring surgery, resulting in an environment conducive to muscle catabolism [82]. Most patients, especially diagnosed with stages I-III CRC, have surgery to remove the primary tumor. Bed rest, interruptions to nutritional intake, and prolonged fasting are observed in the surgical setting and can negatively impact muscle health [83]. In addition to surgery, most patients with stages II-IV CRC are treated with anti-cancer therapies including chemotherapies. Although these treatment regimens are typically dosed based on body surface area calculations, contemporary research suggests that dosage based on MM could present a patient-centered approach to treatment that decreases incidence of dose-limiting toxicity [84]. A systematic review aimed to evaluate the effect of MM on dose-limiting toxicity of different chemotherapy regimens commonly used to treat patients with colorectal cancer [84]. Of the 10 studies included, 3 presented a toxicity cut-off value based on LST (2 for 5-fluorouracil; 1 for oxaliplatin-based regiments) while the remainder presented associations between body composition-derived metrics and dose limiting toxicity [84]. Due to heterogeneity of methods used amongst included studies, quantitative data could not be synthesized [84]. Nonetheless, increased use of body

composition metrics in the oncologic setting shows promising results for personalized dosing and improve treatment tolerability, especially in cancers with elevated prevalence of obesity and/or increased adiposity such as CRC [28].

Obesity is a risk for cancer and specifically for CRC. A recent study of n=800 patients showed that those with a BMI ≥30 kg/m^2 were at increased risk (adjusted odds ratio [OR]: 1.27; 95% confidence interval [CI]: 1.06-1.53) of developing CRC compared to patients with a BMI in the normal or overweight range [85]. A study of patients (n=725) with mixed cancer types (>30% CRC) showed that 60% presented with an elevated BMI (>25 kg/m^2) at time of diagnosis and >40% presented with low MM and muscle quality [86]. It is known that BMI and BW are not directly indicative of adiposity or body composition. The presence of increased adiposity in combination with low MM is termed sarcopenic obesity and is a body composition phenotype associated with worse clinical outcomes compared to each condition experienced in isolation [87, 88]. The focus of this thesis is on the muscle although the impact of adipose tissue, including visceral and subcutaneous, and adipose tissue radiodensity on survival and other clinical outcomes in cancer should be acknowledged and have been detailed by others [28, 89-92].

It is now understood that body composition can change without a change in BW, thus indicating that BW is not a sensitive marker of MM depletion [14]. A study of 1921 patients with stage I-III CRC found that >50% of patients were weight stable 15 months post-diagnosis but low MM (prevalence: 8.5%; 95% CI: 3.6–10.6%) and muscle quality (prevalence: 13.5%; 95% CI: 11.1–15.9%) were observed regardless [14]. Sex differences were observed whereby sarcopenia (p=0.04) and myosteatosis (p=0.001) were more prevalent in weight stable women [14]. A systematic review and meta-analysis of patients with CRC (total patients=8572) showed that patients with myosteatosis had a significant increased risk of mortality on multivariate analysis (HR: 1.55; 95% CI: 1.23 – 1.96; p<0.00001) [93]. The effect of myosteatosis on survival was independent of the presence of low MM on multivariate analysis (sarcopenia HR: 1.28; 95% CI: 1.09 – 1.49; p=0.002 vs. myosteatosis HR: 1.38; 95% CI: 1.07 – 1.80; p=0.001) [93].

2.4.2 Methods to Assess Anthropometry and Body Composition

Several methods to assess anthropometry and body composition exist; selection of the most appropriate method or technique depends on the outcome of interest and availability/practicality of the equipment needed. Assessment techniques, each with their advantages and disadvantages as described in detail elsewhere [78, 94], includes the measurement of lengths (e.g., height, ulna), circumferences (e.g., waist, calf), and/or skinfold thicknesses for anthropometry and body volume; total body water; body elements; impedance; and imaging for body composition. In settings where multiple techniques are available, data can be combined to assess body composition via multicompartment modelling [95].

2.4.2.1 Anthropometry

Anthropometry can be used as a surrogate indicator of body composition at the whole-body level using predictive equations [96]. Standardized protocols and repeated measures should be applied to anthropometric assessments to decrease the measurement error inherent to predictive equations [97]. Nonetheless, the use of anthropometric valuations in predictive equations of body composition should not discount the innate limitations to this approach including the applicability of predictive equations to the population in which they were validated and the measurement approached uses for the predicted value [97]. Anthropometry has low time and financial cost although its ability to act as a surrogate marker of body composition parameters lacks accuracy. A study of 127 Brazilian adults ≥60 years of age evaluated the use of anthropometric measures and equations to estimate percent body fat in comparison with dual-energy X-ray absorptiometry (DXA) [98]. Equations to predict percent body fat based on circumferences and BMI showed differences between the estimated and measured values (i.e., constant error) of –5.3% to 29.68% [98]. Calf circumference (CC) was shown to be a reliable surrogate estimate of muscle when adjusted for BMI and/or presence of edema in a large cohort (n=17,789) of representative American adults [99, 100]. A BMI-adjusted CC approach was defined in attempt to eradicate the cofounding effects of adiposity on this anthropometric measurement [99]. For patients who present with a BMI outside of the normal range (18.5–24.9 kg/m^2), an adjustment factor should be applied to the CC measurement (BMI <18.5 kg/m^2: CC + 4 cm; BMI 25.0–29.9 kg/m^2: CC – 3 cm; BMI 30.0–39.9 kg/m^2: CC – 7 cm; BMI ≥40 kg/m^2: CC – 12 cm) [99]. These findings offer a clinically feasible alternative to body composition

assessment but require further evaluation across varying populations. Whenever possible, predicted values used to assess body composition should be replaced with measured covariates (e.g., via imaging techniques) [97].

2.4.2.2 Dual-Energy X-Ray Absorptiometry

Dual-energy X-ray absorptiometry is a technique used to assess body composition at the molecular level [78]. This method offers insight into body composition for the whole-body and segmental-body compartments (i.e., head, trunk, arms, and legs) and provides estimates of bone mineral content, fat and lean soft tissues (LST) [101]. These body compartments are calculated based on the resistivity of tissues to 2 photon energy levels (low and high) emitted from X-ray beams. The resistivity of tissues provides attenuation values that are used to distinguish between tissues (i.e., high attenuation for bone and low attenuation for fat) [102]. Bone mineral density is then calculated by summing the pixels containing bone and using a known coefficient of attenuation for bone [101].

Dual-energy X-ray absorptiometry offers the ability to evaluate appendicular LST (ALST), commonly referred to as appendicular skeletal muscle (ASM), by summing the LST found in the arms and the legs [78]. The LST within these limbs is composed primarily of skeletal muscle, with the remainder of LST accounted for by water and fibrotic and connective tissues [103]. Given that ALST accounts for >75% of whole-body muscle [104], appendicular LST provides a surrogate marker to whole-body MM [105]. At the whole-body level, LST from DXA includes organ, fibrotic, and other tissues [103]. Thus, in cases of abnormal tissue presence (e.g., tumor) within the trunk of the body, it is especially important to consider ALST as a surrogate marker of whole-body MM [106].

Body composition assessments by DXA employ assumptions including constant hydration status and that LST is only found in bone-free pixels [95, 101]. Shifts in intramuscular solutes (e.g., creatine, glycogen) can cause alterations in total body water that result in implausible acute changes to LST [107]. Despite older adults having higher amounts of total body water and less LST, acceptable error (<2% precision error) in FFM is still observed across the age spectrum on repeat scans [108]. Implementation of standardized assessment protocols can further reduce biological variability between scans [108]. Dual-energy X-ray absorptiometry is a unique technique wherein precision standards are set for use in longitudinal trials that

evaluate outcomes of interest following an intervention. The International Society of Clinical Densitometry specifies that for use in interventional trials, DXA precision (coefficient of variation) is <2% for LST, <3% for fat mass (FM), and <2% for percent fat [109]. These values were derived based on the 75th percentile of combine precision studies reviewed by the International Society of Clinical Densitometry [109]. The precision, safety, low patient burden, and feasibility of DXA are features that suggest it may be an appropriate reference standard (not to be confused for gold standard) for assessing LST in clinical and research settings [110].

The accuracy of DXA decreases at the extremes of the BMI spectrum and may overestimate FM in persons classified as having a low BMI and underestimate FM in persons whose body type is classified as high BMI [95, 109, 111]. Additionally, DXA as a body composition technique has a weight restriction although newer devices with increased weight capacity (e.g., >600 lbs) are available [112]. It should be noted that even if weight is within the acceptable range, the accuracy of DXA-derived estimates of body composition are more prone to error with increased body thickness [112]. The amount of radiation endured in a DXA scan is minimal (1-7 micro Sieverts [μSV]) [102] and is comparable to radiation exposure incurred during activities of daily living [95]. DXA is thus considered safe for research purposes and for repeated assessments [78] and presents a viable assessment technique to monitor longitudinal response to targeted nutritional interventions.

2.5 Nutrition as a Therapy to Support Muscle Health in Cancer

Nutritional interventions to treat muscle-related conditions or abnormalities is an area of interest in the literature. A scoping review on future research found that 20% of ongoing trials investigating the impact of nutrition on muscle health were focused on patients with cancer [113]. Early and continued optimization of nutritional status, including meeting energy and protein requirements [20, 114], is crucial to optimize BW and composition and to prevent/minimize negative health outcomes (e.g., muscle loss) that are often observed in cancer. Isocaloric (energy balance) diets are especially important in cancers such as CRC that exhibit a high prevalence of patients who present with normal weight or overweight/obesity and are at risk of weight gain during treatment in the curative setting [32, 115, 116]. Ultimately, other interventions to support muscle health in cancer may not succeed without adequate energy and protein intake [117].

2.5.1 Protein Intake and Muscle Mass

Whole-body skeletal MM is dependent on rates of muscle protein synthesis (MPS) and muscle protein breakdown (MPB), collectively termed muscle protein turnover [118, 119]. In a healthy state, MPS and MPB are constantly changing in relation to food intake to maintain MM [119]. To achieve muscle anabolism (i.e., growth), MPS on average must chronically exceed MPB to obtain a positive net protein balance. The homeostatic state of muscle protein turnover is disrupted in pro-inflammatory conditions such as cancer [119, 120]. Upregulation of ubiquitin-proteasome/autophagy pathways [121] and a decline in MPS [122] results in increased degradation of intracellular proteins and subsequently loss of MM [44, 123]. Reduced protein intake because of inflammation-related anorexia and the adverse effects of cancer therapy further contribute to muscle loss [124, 125].

The nutritional value of protein is determined by the quantity and quality of constituent amino acids [126]. Amino acids are the dietary anabolic drivers of MM accretion but vary in quality and do not equally promote anabolism [127, 128]. The Protein Digestibility Corrected Amino Acid Score (PDCAAS) is indicative of essential amino acid content and digestibility of proteins [129]. Since the PDCAAS was developed, another measure of protein quality was introduced: The Digestible Indispensable Amino Acid Score (DIAAS) [130]. Notably, these scores do not suggest true skeletal muscle anabolic response to a particular amino acid but do provide a proxy method of quality comparison between proteins [131]. Dietary proteins have varying amino acid profiles whereby animal-based proteins offer greater anabolic stimuli when compared with plant-based alternatives [131-133].

2.5.1.1 Anabolic Potential and Protein Source in Cancer

The anabolic potential of skeletal muscle during cancer is controversial; studies indicate both anabolic resistance [134, 135] and retained anabolic potential [134, 136-138]. Animal-based proteins are of major importance during active cancer treatment to preclude detrimental loss of muscle and promote muscle anabolism. Only a few amino acid kinetic studies investigated whole-body protein synthesis and balance in cancer over the last decade [134, 139-141], as reviewed by Antoun & Raynard [142]. Previously Bozetti & Bozetti [143] reviewed the same topic and cited studies that suggested increased [144-146] or decreased/no change [145] whole-body protein synthesis. Although these studies forecast the effects of mimicking whole-food

diets on muscle change, translating results from amino acid kinetics to whole-body anabolism is difficult, as whole-body protein turnover does not necessarily equate to skeletal muscle protein anabolism [142].

A systematic review of protein intake and MM maintenance in patients with cancer types that have a high prevalence of low MM found that attenuation of muscle during treatment is possible with a higher protein diet [21]. Studies (n=8) of patients (n=554) with head and neck, lung, and esophageal cancer were included. Muscle loss during cancer treatment was observed in patients with protein intake below 1.2 g/kg/d whereas patients who achieved a mean intake of at least 1.4 g/kg/d maintained muscle [21]. Notably, methods to assess body composition varied across studies; high-quality research is needed to better understand optimal protein dosing for MM maintenance in cancer.

The role of the mTOR pathway in mediating amino acid-induced skeletal muscle anabolism is well-established. Nevertheless, the mTORC1 pathway is also involved in negative forms of anabolism, including tumor growth, such that some fear nutritionally-derived anabolic stimuli (e.g., protein) may also fuel or be associated with tumor growth [147]. Despite amino acids having heterogeneous effects on tumor growth in humans, the effect of protein intake on tumor growth has not been substantiated [148]. In general, international guidelines on nutrition in cancer acknowledge that theoretical arguments suggesting that nutrition feeds the tumor are not supported by evidence and should not be a reason to alter nutrition delivery [20].

2.5.1.1.1 Considerations and Current Evidence of Animal- and Plant-Based Protein Intake During Cancer Treatment

One of the 10 World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) recommendations for prevention of cancer is to follow the remaining 9 recommendations for those diagnosed with cancer [149]. Translating dietary recommendations for prevention of cancer to patients with active cancer may provide insufficient nutritional targets and, therefore, suboptimal nutritional status. Once a diagnosis of cancer is made, the goals of nutritional intake likely shift and may not necessarily parallel the recommendations for cancer prevention and post-treatment (survivors), **Figure 2.3**.

When considering protein sources, one concern regarding an exclusively, or even predominantly, plant-based diet during active treatment of cancer is the feasibility of obtaining adequate dietary amino acid intake to sustain functional muscle reserves, especially given the high risk of malnutrition in this population [1] (**Figure 2.4**). Cancer therapy is frequently accompanied by nutrition impact symptoms (e.g., nausea, anorexia, taste alterations) that can affect food intake and compound muscle catabolism [150, 151]. Early satiation can also contribute to decreased oral intake and may be influenced by nutrients in the diet (e.g., protein, fiber). As discussed, protein intake is essential for muscle health in cancer, although caloric intake is also vital for optimizing nutrition in this vulnerable population. In older adults, essential amino acid supplementation has been proposed as a complementary measure, in addition to protein intake, that does not impact satiety, optimizes the ability to meet nutritional requirements, and promotes muscle health [152]. The efficacy of essential amino acid supplementation requires further investigation in clinical settings, including cancer. Similarly, although the satiating effect of protein has been studied in other populations, how a predominantly plant- vs. animal-based diet affects satiety is unknown in people with cancer or at risk of malnutrition [153]. Regardless of satiating effects, a larger volume of plant-based proteins than animal-based products is required to obtain adequate amino acid intake [154]. It follows that the higher quality of animal-based proteins provides adequate protein intake from a smaller volume of food [131], as shown in **Figure 2.5**.

Despite some insight into protein intake in this population, studies investigating protein quality or types of protein consumed are lacking [20]. In healthy middle-aged women, those consuming ~68% of their protein from animal sources (animal:plant protein intake ratio 2.09) had significantly higher MM compared with vegetarians consuming ~55% of their protein from animal sources (animal:plant protein intake ratio 1.23) [155]. Given the scarcity of research on optimal ratio of protein sources in cancer, interpretations can be drawn from studies in populations at similar risk of malnutrition as those undergoing treatment of cancer to provide insight and a starting point into appropriate nutrition needed to optimize health in cancer. In older adults with comorbidities, at least 65% of protein intake from high-quality protein (i.e., animal-based protein) is needed to avoid malnutrition [156]. Additionally, factors similar to those seen in people undergoing treatment of cancer (e.g., missing a meal, taste alterations) were

independently associated with inadequate intake of ≥1 essential amino acid and subsequently greater risk of malnutrition [156]. Given the paucity of this type of research in cancer and the similarity in malnutrition risk and nutrition impact symptoms between populations, inferences could be drawn suggesting minimum of 65% of protein intake from animal sources may be as an optimal starting point to support muscle anabolism for people undergoing active cancer treatment. Future trials should seek to discover the optimal animal:plant protein ratio to support MM in cancer.

Ongoing trials are investigating protein needs [157] and the clinical impact of increased protein [158, 159] or amino acid [160, 161] intake on muscle in people with cancer [113]. The impact of protein on muscle strength is also an important consideration in cancer given that muscle weakness can occur without loss of MM [120]. A review that focused on nutritional interventions for muscle strength in cancer found no studies that compared plant- with animal-based diet interventions [162]. Clinical trials related to protein source and muscle anabolism in cancer primarily focused on MPS and MPB rather than whole-body lean mass response and its impact on clinical outcomes. A paradox exists in current research whereby humans consume predominately whole foods, yet research has focused on specific amino acids and their contribution to muscle protein turnover. Pragmatic studies employing the influence of protein sources and differing doses of protein on whole-body skeletal muscle anabolism are needed to guide future nutrition recommendations [20].

In catabolic disease states such as cancer, the attributes of animal-based proteins contribute to optimal nutrition care and can be safely included in the diet although various reasons (ethical, religious, planetary, health, etc.) for choosing a plant-based diet exist. Those already consuming a balanced exclusively or predominantly plant-based diet may achieve adequate nutritional intake to support health, although appropriate knowledge of diet diversity is needed to ensure higher protein needs are met [163, 164]. Initiating an unbalanced exclusively or predominantly plant-based dietary pattern during active treatment of cancer may impact negatively on the ability to achieve optimal protein intake. In contrast, a dietary pattern that combines protein from animal- and plant-based sources may present the most suitable option for optimal health, although more research is needed to investigate diets focused on animal protein and/or different levels of protein. Importantly, regardless of protein sources in the diet, exercise

is a viable proponent of a multimodal approach to supporting muscle health in cancer. It is safe during and after treatment and recommended [20, 165]. The role of resistance exercise and nutrition to mitigate muscle loss in pro-catabolic states has been extensively reviewed, emphasizing the importance of a multimodal approach to muscle health [166-168].

2.5.2 Protein in Nutrition Oncology Guidelines (During Curative or Palliative Cancer Treatment)

Protein intake in cancer is highly variable, and many patients do not meet the minimum recommended intake [169-172]. Nutritional oncology guidelines recommend a minimum intake of 1.0 g protein/ kg/d but suggest a target consumption of 1.2-2.0 g/kg/d [20]. These guidelines are similar to those for older adults, which recommend at least 1.0-1.2 g/kg/d, acknowledging that those with acute or chronic illness require more protein (1.2-1.5 g/kg/d) [173]. Given that targeting guideline-based protein levels with individualized nutrition support improves clinical outcomes in cancer [174] and that increased total protein intake in adults over the age of 65 years (similar to the median age of a cancer diagnosis) has a protective effect [175], it appears that total protein intake should be a co-primary consideration in addition to protein quality. Notably, historical concerns regarding the supposed negative impact of protein on kidney health are unfounded. Higher protein intakes (≥2.0 g/kg/d) are safe for people with healthy kidney function [20, 126] and may reduce mortality in critically ill patients [176], although those with pre-existing kidney disease should maintain a lower intake [177, 178].

Protein intake recommendations in cancer are notably higher than the recommended dietary allowance (RDA) of 0.8 g/kg/d for the healthy population, determined by nitrogen balance studies [179]. These studies primarily used high-quality proteins with a PDCAAS of 1.0 (e.g., animal-based proteins or soy protein isolate) [131, 179-181]. Based on the methodology used to determine the RDA, this value should be considered a minimum amount needed to attain nitrogen balance rather than an amount sufficient to promote muscle maintenance or anabolism [126]. Conversely, the recommendations for patients with cancer are primarily based on expert opinions given the paucity of studies that investigated nitrogen balance or the impact of protein intake on clinical outcomes [20]. As oncology recommendations were derived from protein metabolism studies [20, 134, 182, 183], the guidelines also acknowledge that the optimal amino acid composition for patients with cancer remains unknown [20].

The risk of malnutrition varies in people with cancer [1], especially between the curative and palliative setting [4]. Nutritional interventions to combat malnutrition commonly focus on increased energy intake to address low BW although the potential benefit of protein is also present given the association of low MM with malnutrition [4]. Studies employing isotopic tracer methods are needed to determine specific amino acid requirements in oncology settings [17]; for example, the indicator amino acid oxidation method is one technique that could be used to determine total protein requirements in a non-invasive manner [184]. Additionally, challenges of understanding optimal protein quantity and amino acid composition for MM maintenance or anabolism are compounded by gut dysfunction, which is observed in patients with cancer, resulting in decreased protein digestion of oral food intake and absorption [185, 186]. The reduction in protein digestion negatively impacts systemic amino acid availability and leads to increased quantity of undigested proteins in the colon [185, 186]. The latter can alter microbial metabolism and generate harmful metabolites which may negatively affect muscle health [185, 186].

2.6 Nutrition-related Decision Making in Cancer

The impact of cancer on dietary intake is an essential consideration as optimized nutrition status plays an important role in cancer-related outcomes [20, 114, 174, 187, 188]. Optimizing nutritional status through targeted energy and protein intakes is essential for muscle health yet patients may underestimate the severity of nutrition-related conditions [22] and not consider the importance of nutrition when making dietary choices. For many patients, receiving a diagnosis of cancer is a motivator for positive behavioural alterations, including changes in dietary intake [189]. Patients and their families may seek information to inform dietary choices [189, 190] but are challenged with the abundant availability of conflicting and erroneous cancer-related information, particularly from online and social media sources [191, 192]. In turn, patients are prone to dietary changes that may not align with oncology nutrition recommendations [20] such as reducing or eliminating animal products from their diet [193, 194]. In order to provide evidence-based and patient-oriented nutrition information and education, practitioners must first gain a solid understanding of determinants of dietary choice throughout the cancer continuum. Despite the plethora of factors that influence dietary choices in cancer, post-diagnosis dietary choices are not fully understood.

Post-diagnosis dietary changes have been studied primarily in women with breast cancer in European countries [195]. Reported changes typically included decreased red and processed meat intake and increased consumption of fruit and vegetables [195, 196]. These changes align with recommendations for cancer prevention [197, 198] but were implemented post-diagnosis and may not meet the nutrition guidelines for patients with cancer [20]. Data on dietary decision making post-diagnosis are lacking and would provide practitioners with an enhanced understanding of patient information needs and reasons for dietary choices.

Dietary choices are determined by several complex factors. For brevity and clarity, determinants of dietary choice have been broadly divided into internal (e.g., biological, psychological) and external (e.g., economic, social, physical environments) factors [199, 200]. Examples of internal factors that are primarily biological in nature include hunger, satiety, taste, energy balance, and genetics whereas psychological factors may include attitudes, beliefs, and knowledge. External factors are diverse and can include socio-economic status, cost, marketing, and policy (economic environment); friends, family, peers (social environment); and home, work/school, and access to food procurement (physical environment) [199, 200]. The influence of external factors on food choice can be partially self-controlled (e.g., through changes to social environment) although the omnipresence of certain factors (e.g., physical and cultural environments) are less controllable [199]. Understanding the determinants of dietary choice is therefore important in designing targeted strategies to improve nutritional status.

Given the dynamic nature of cancer and its treatments, select factors that influence dietary choices can be transient or changing (e.g., nutrition impact symptoms) and result in varied dietary intake [201, 202]. Symptoms such as fatigue, neuropathy, nausea, anorexia, and taste alterations are common [203] and can lead to altered dietary choices and subsequently impaired nutrient intake [202]. Symptoms from cancer and its treatment may also alter environmental determinants of dietary choice including the ability to purchase, prepare, and consume foods [204]. Factors such as taste preferences, nutrition knowledge, socio-economic status, geography, culture, and traditions also influence dietary choices for all populations [201, 202, 205-207] but may be further affected by the disease. For example, taste can be impacted by anti-cancer treatment, patients living in remote areas may have to travel to urban centers for treatment (changing the physical environment), and traditions may be altered due to treatment

side effects. In addition to dietary implications, the psychological impact of a cancer diagnosis can motivate patients to make positive lifestyle changes [208]. As a result, self-induced behavioral modifications that impact dietary choices are catalyzed with the goal of positive dietary change and a commitment to improve health [189].

Most patients are motivated seek nutrition information to educate themselves to make informed dietary choices [190]. Common sources of nutrition information include physicians, family/friends, and mass media [190, 209]. Non-evidence based guidance on nutrition and cancer—readily available online—may influence dietary change [191]. One-third of cancer-related social media articles contain misinformation and of those, nearly 80% contain harmful information [192]. Financial incentives are also prevalent in online cancer nutrition information and much of the content contains prevention, treatment, or curative content claims [210]. Patients are thus likely to face conflicting information from various sources and may in turn acquire nutrition-related fallacies that self-guide dietary choices [211]. Although evidence-informed nutrition is viewed as important by many patients, more than half do not discuss nutrition with a health care professional at any point during cancer trajectory [212].

2.6.1 Changes to Dietary Choices Post-Diagnosis

A longitudinal study of patients in the Netherlands with stage I-III CRC (n=1072; 63% male) quantified modifications to dietary and physical activity patterns at time of diagnosis, 6 months, and 2 years post-diagnosis using an overall lifestyle score based on WCRF/AICR recommendations for cancer prevention [213]. Two years following diagnosis, mean lifestyle score suggested that only marginal changes were made since time of diagnosis [213]. Specifically, survivors decreased their intake of sugary drinks (–45 g/day) and red and processed meat (–62 g/week) but made no changes to their fruit and vegetable, alcohol, or ultra-processed foods intake compared to time of diagnosis, suggesting that nutrition-focused support tools for patients were warranted [213]. Similarly, a group of 1458 patients with stage I-IV CRC reported several dietary changes, including decreased meat and increased fruit, vegetables, fibers, wholegrains and fish consumption [214]. Decreased meat intake (n=376) was more prevalent than increased fish consumption (n=342), although these dietary changes were not quantified in relation to total protein intake [214], and thus the effect of habitual dietary change on protein intake was unclear.

An American study of mixed cancer types used telephone interviews to assess dietary changes in patients (n=356) diagnosed with breast, prostate, or CRC within the 2 years prior to being surveyed and found that 40% of patients reported ≥1 dietary change within the prior year [215]. Patient characteristics such as younger age, >13 years of education, and a diagnosis >1 year prior to the interview all independently increased the likelihood of reported dietary change [215]. The most prevalent dietary change reported was increased intake of fruits and vegetables (n=272; 76.4%), followed by less red meat (n=69; 19.4%) and fat (n=77; 21.6%) intakes [215]. Within the year prior to the interview, 48% of patients started taking dietary supplements (i.e., vitamins, minerals, and/or herbals), a change that was more common in women (adjusted OR: 2.19; $p<0.001$) and patients <60 years of age (adjusted OR for 60–69 years: 0.42; $p<0.001$) [215]. An Italian study of patients (n=1257) with mixed cancer types who were receiving anti-cancer treatment found that 56% of patients reported making changes to intake from major food groups [216]. Changes to food and beverage intake included decreased red and processed meat, alcohol, and sugary drink intake, which are consistent with recommendations for cancer prevention [216, 217]. Notably, 61% of those surveyed reported decreased consumption of milk products since diagnosis [216]. Among the several types of cancers surveyed, those diagnosed with breast, prostate, or CRC were the most likely to alter their diet [216]. A Dutch study showed that people with mixed cancer types (n=239) reported decreased meat intake and increased intake of plant-based foods following a cancer diagnosis [193]. A study of the NutriNet-Santé cohort (n=696) of mixed cancer types found that post-diagnosis changes included decreased vegetable, dairy, meat, soy, and alcohol consumption which cumulatively resulted in significantly lower total protein intake (-17.4±12.5 g/day; $p<0.0001$), compared with pre-diagnosis [218]. Although some of these changes are beneficial to overall health (i.e., decreased alcohol consumption), a diet containing exclusively (i.e., vegan diet) or predominantly (i.e., vegetarian diet) plant-based foods during cancer treatment is concerning due primarily to the importance of animal-based protein for skeletal muscle health.

Amongst studies reviewed, changes to protein intake were frequently observed. Cases where protein intake increased post-diagnosis represented dietary choices in line with oncology nutrition guidelines [20, 219]. In contrast, if appropriate substitutions were not made for decreased consumption of specific proteins (i.e., meats, milk products), protein intake could

decrease, which would not align with oncology nutrition guidelines [20, 216]. These guidelines were developed for healthcare providers who are caring for patients receiving active cancer treatment and are not tantamount to guidelines for cancer prevention [220]. For example, red and processed meat are more commonly considered to be associated with CRC development although these foods may be associated with improved survival in patients with active cancer [221]. A prospective cohort study of 992 patients with stage III CRC found that low intake of red and processed meat post-diagnosis was associated with an increased risk of death (HR quartile 1 vs quartile 4: 1.72; 95% CI: 1.15-2.58) [221]. Changes to dietary choices that do not align with oncology nutrition guidelines may be based on misunderstandings of the relationship between specific foods or nutrients and health conditions (e.g., cancer).

2.6.2 The Effect of Nutrition Knowledge on Dietary Choices

Nutrition knowledge and information are major determinants of dietary choices and overall nutrient intake [205]. This area of research is both new and complex as nutrition knowledge is mediated by multiple factors, including age, sex, health literacy, cultural influences, socioeconomic status, and physical environment [205, 222]. Research on nutrition knowledge and dietary choices has been largely limited to general and athletic populations. A systematic review of the relationship between nutrition knowledge and dietary intake across all populations demonstrated a dearth of research in this area which precluded a meta-analysis of results and found no studies that investigated nutrition knowledge among patients with cancer [205].

The diagnosis of cancer may be a ‘teachable moment’ to make positive health behavior changes and presents an opportunity for healthcare professionals to provide nutrition-related health promotion education. Appraising the relationship between nutrition knowledge and dietary choices in individuals with cancer is essential to capitalize on the ‘teachable moment’ that often accompanies a diagnosis of cancer and subsequent treatment [189]. It is possible that the motivation to adopt a healthier lifestyle post-diagnosis may enhance the effect of nutrition knowledge on dietary choices as patients are inundated with conflicting nutrition information from mass media, particularly online [195, 205].

2.6.3 Information Needs of Patients with Cancer

It is important for patients across the cancer continuum to have access to credible, trustworthy, and user-friendly sources of nutrition information to guide dietary choices. To fulfill information needs, patients with cancer gravitate towards the internet but feel that more information should be available through their treating institution [216, 223, 224]. An Italian study surveyed patients with cancer and found that 92% (n=1146) would prefer to receive more nutrition-related advice from their medical team during cancer treatment [216]. In Ireland, 39% of cancer survivors (n=1073) saw a registered dietitian and 57% of those who did not see a registered dietitian wanted access to credible nutrition support, suggesting that their information needs were unmet [224]. In the absence of adequate information, patients may be more likely to seek unregulated or incorrect sources of information that may not provide credible recommendations. Given that a cancer diagnosis appears to be a teachable moment for patients, nutrition education that empowers patients to better detect credible sources of information could be integrated into care plans [225].

Patients with cancer are susceptible to nutrition misinformation [192, 210], leading to barriers to adhering to nutrition interventions and sub-optimal dietary choices, collectively contributing negatively to overall nutritional status [213, 216, 226]. Credible sources of nutrition information are diluted in the abundance of misinformation available on the internet, making it challenging for patients with cancer to determine which sources of information should guide dietary choices [191, 195, 210]. While internet search engines and social media platforms can offer reliable sources of information, people engage more with cancer-related misinformation than credible sources [192, 227].

Despite the dubious credibility of internet-based nutrition information, patients seeking material related to cancer often consult the internet before their physician [196]. Many patients experience an overall sense of lack of available nutrition information from their cancer care providers [223]. For many patients, access to a registered dietitian/nutritionist in the oncology setting is merely possible once a state of malnutrition is reached or significant nutritional risk is identified [228]. In some settings, nutritional assessment is only incorporated into oncologic care if requested by the patient [229]. In turn, many patients rely on their own online and social media-based research [223]. For many, the internet and social media platforms are ubiquitous

sources of information that are often used to inform health decisions [226, 230]. Although the internet, including social media platforms, is likely the primary source of nutrition information for patients, the effect of this type of information acquisition on dietary choices remains widely unknown.

2.6.4 Relevance of Nutrition-Related Decision Making to Clinical Practice

Regardless of the type of malignancy, cancer appears to be a motivating reason for many patients to alter their dietary choices. Dietary recommendations for cancer treatment may differ from recommendations for preventions and reported changes do not appear to be in alignment with recommendations. Most reported changes align with recommendations for cancer prevention but are implemented post-diagnosis. At the time of diagnosis, during treatment, and post-treatment are opportunistic times for patients to gain knowledge of nutrition and implement positive dietary changes. In the era of mass media, increasing availability of nutrition misinformation poses a challenge to accessing trustworthy sources. Informed dietary choices improve nutritional status and positively affect overall health; however, little is known about the determinants of dietary choices and patterns in patients with a recent diagnosis of CRC. Characterizing determinants of dietary choices in patients with cancer can inform effective nutritional interventions. This has the potential to personalize recommendations in the context of current intake and nutrition goals throughout cancer survivorship, ultimately contributing towards maintaining or improving health, quality of life, and clinical outcomes. This is especially relevant in addition to consideration for the impact of cancer or cancer treatments on REE or TEE through changes in body composition, physical activity, tumor burden, or systemic inflammation that may therefore indirectly affect dietary choices.

2.7 Conclusion

It is important for patients and clinicians to look beyond the disease itself and recognize the importance of nutrition for preventing and treating a common condition among CRC patients—loss of MM. Therapies to optimize muscle health in cancer are likely to fail without adequate nutritional provision, especially energy and protein intake. Thus, the overarching purpose of this research was to optimize muscle health in cancer using a targeted nutritional intervention. We sought to characterize energy expenditure, assess different doses of protein on

muscle health, and understand the determinants of dietary intake in patients with a recent diagnosis of CRC undergoing chemotherapy.

Table 2.1. Considerations for choosing an indirect calorimetry device.

Device	Measures	Calibration (frequency; time required)	Time for Warm Up	Time for REE Measurement	Device Cost[1]	Cost per Test[2]
Devices measuring O_2 and CO_2						
Vmax® Encore	VO_2 VCO_2	Daily ~20 min	60 min	20-30 min	$$$	**
Q-NRG™	VO_2 VCO_2	Monthly ~10 min	20 min for calibrations	10-15 min	$$	***
		Pre-test (automatic) 1 min	5 min for REE test			
Devices measuring O_2						
MedGem®	VO_2	Pre-test 30 seconds	~1 min	5-10 min	$	**
FitMate GS	VO_2	Pre-test (automatic) ~1 min	N/A	15 min	$	*

[1]$: < $20,000; $$: $20,000-$50,000; $$$: >$50,000. [2]*: < $10; **: $10-$20; ***: >$20.
Abbreviations: REE: resting energy expenditure; min: minutes; VO_2: volume of oxygen; VCO_2: volume of carbon dioxide. Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature Springer eBook. Ford KL, Oliveira CLP, Ramage SM, Prado CM. Protocols for the Use of Indirect Calorimetry in Clinical Research. In: Betim Cazarin CB, editor. Basic Protocols in Foods and Nutrition. New York, NY: Springer US; 2022. p. 265-91. [70]. COPYRIGHT (2022).

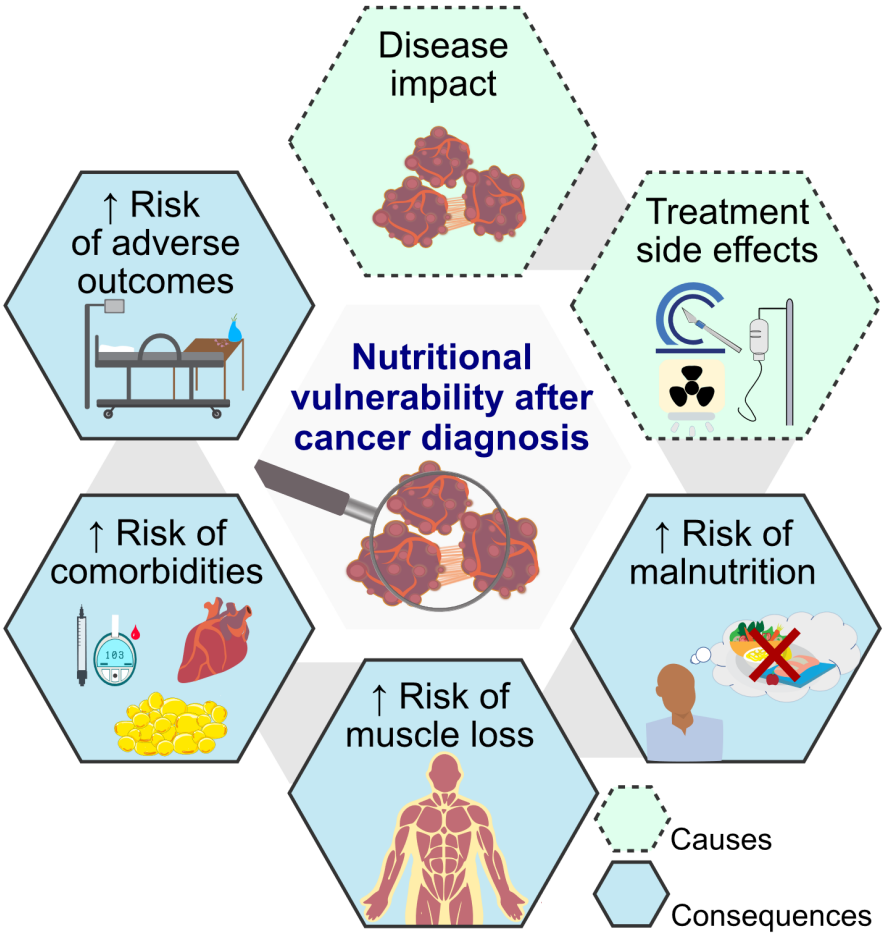

Figure 2.1. Causes and consequences of nutritional vulnerability after a cancer diagnosis. Optimal nutrition is critical to prevent or halt malnutrition and muscle loss, and to mitigate risk of adverse outcomes. This figure is included in a manuscript published in *Nutrition*; Ford KL, Orsso CE, Kiss N, Johnson SB, Purcell SA, Gagnon A, Laviano A, Prado CM. Dietary choices following a cancer diagnosis: A narrative review. Nutrition. 2022. Online ahead of print. DOI: 10.1016/j.nut.2022.111838 [231].

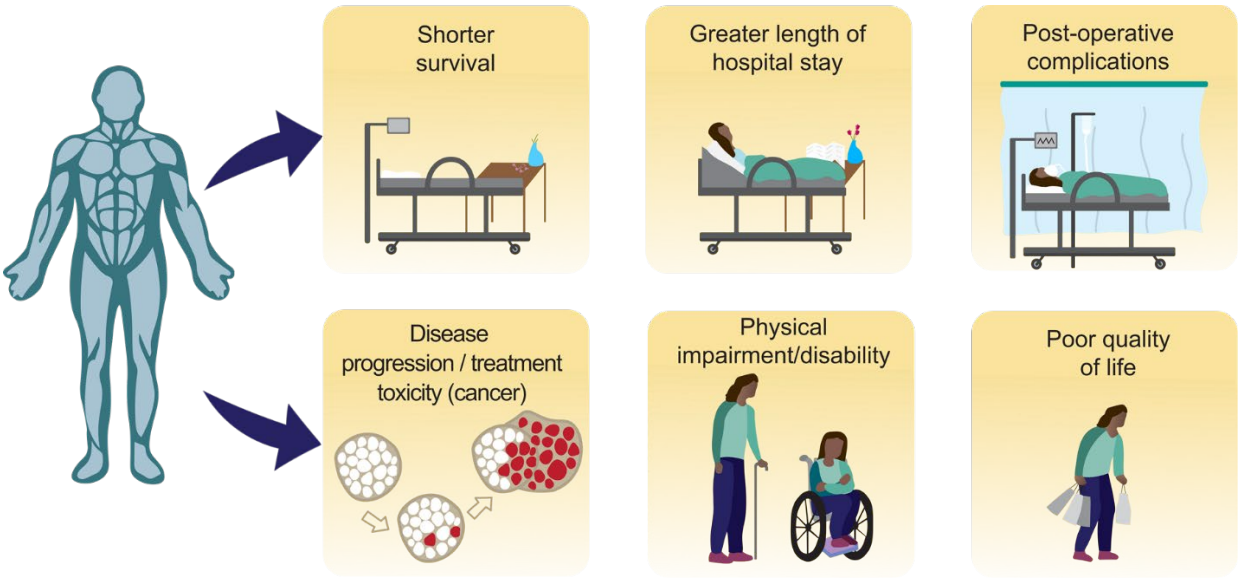

Figure 2.2. A graphical representation of consequences of low muscle mass in patients with cancer. This figure was adapted from a paper published in Clinical Nutrition. Prado CM, Landi F, Chew STH, Atherton PJ, Molinger J, Ruck T, Gonzalez MC. Advances in Muscle Health and Nutrition: A Toolkit for Healthcare Professionals. Clin Nutr. 2022;41:2244-2263. [15]

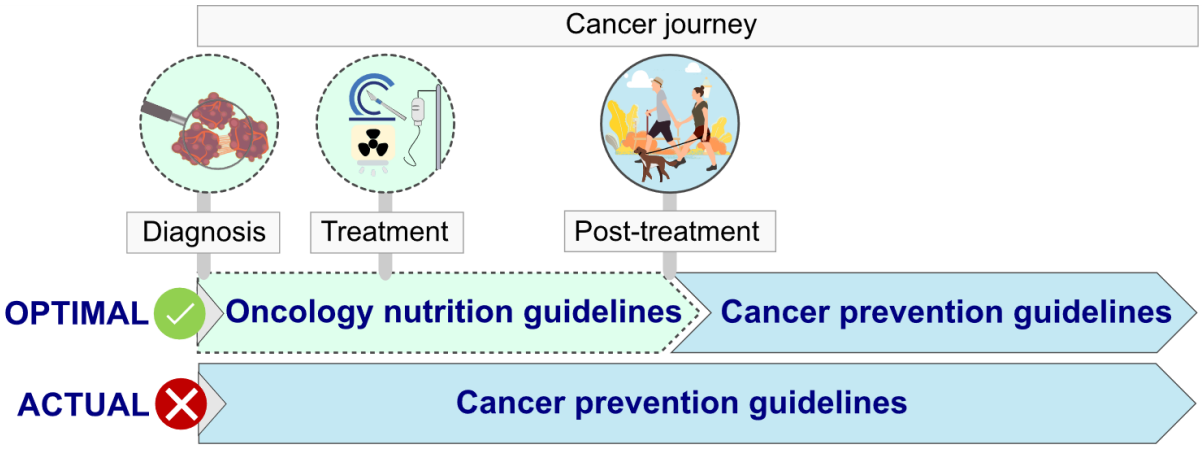

Figure 2.3. Discrepancies between optimal (i.e., recommended) dietary changes during active cancer and actual changes reported by patients post-cancer diagnosis. This figure is included in a manuscript published in *Nutrition*; Ford KL, Orsso CE, Kiss N, Johnson SB, Purcell SA, Gagnon A, Laviano A, Prado CM. Dietary choices following a cancer diagnosis: A narrative review. Nutrition. 2022. Online ahead of print. DOI: 10.1016/j.nut.2022.111838 [231].

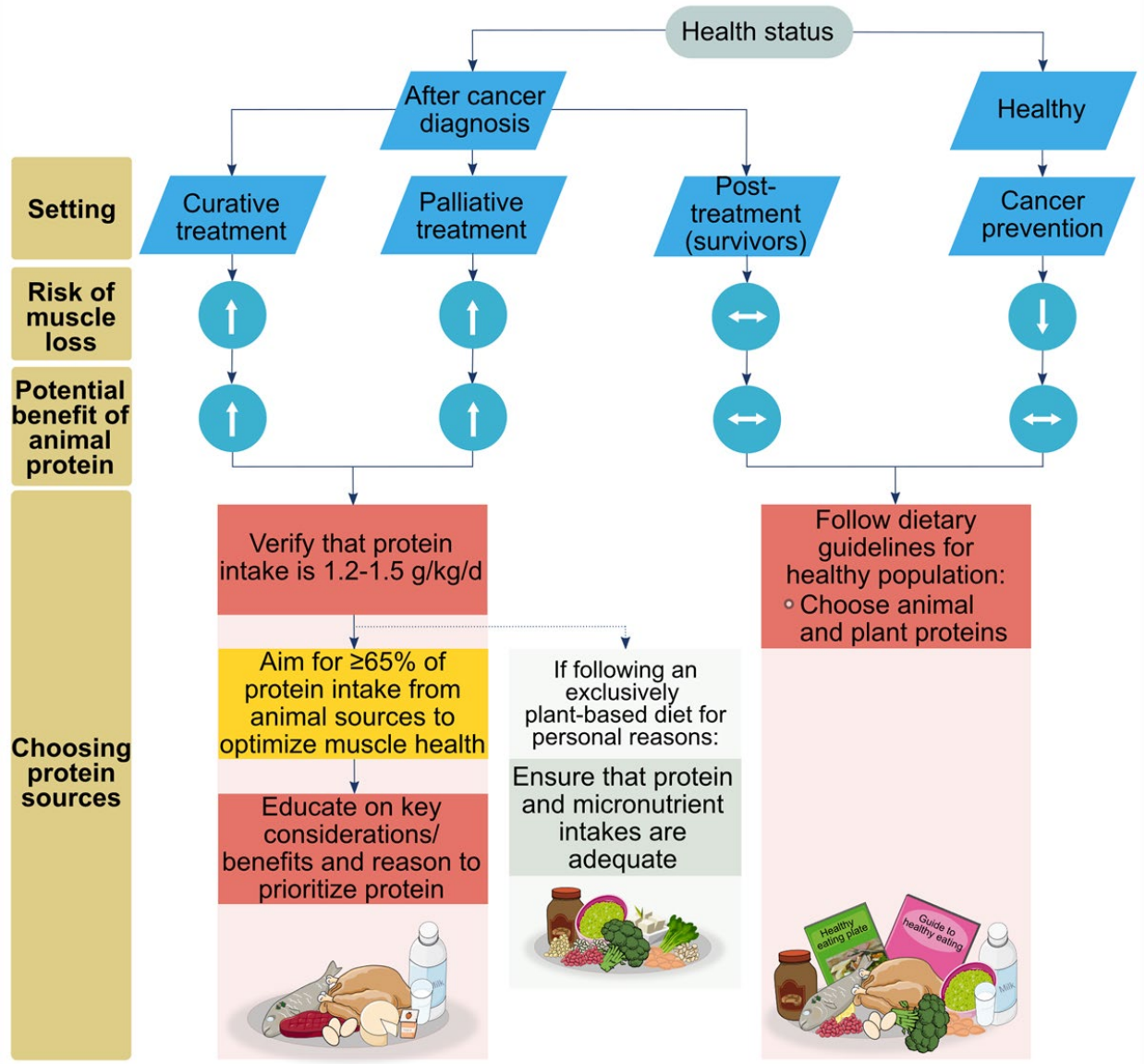

Figure 2.4. Flowchart of important nutrition-related considerations based on health status. Legend: ↑: increased; ↓: decreased; ↔: neutral; animal proteins: beef, pork, chicken, fish, eggs, milk, cheese, etc.; plant proteins: beans, lentils, soy, nuts, etc. Images retrieved from smart.servier.com. This figure was previously published under a Creative Commons licence (CC BY 4.0) as Ford KL, Arends J, Atherton PJ, Engelen MPKJ, Gonçalves TJM, Laviano A, et al. The importance of protein sources to support muscle anabolism in cancer: An expert group opinion. Clin Nutr. 2022;41:192-201 [220]. No changes were made to the original figure.

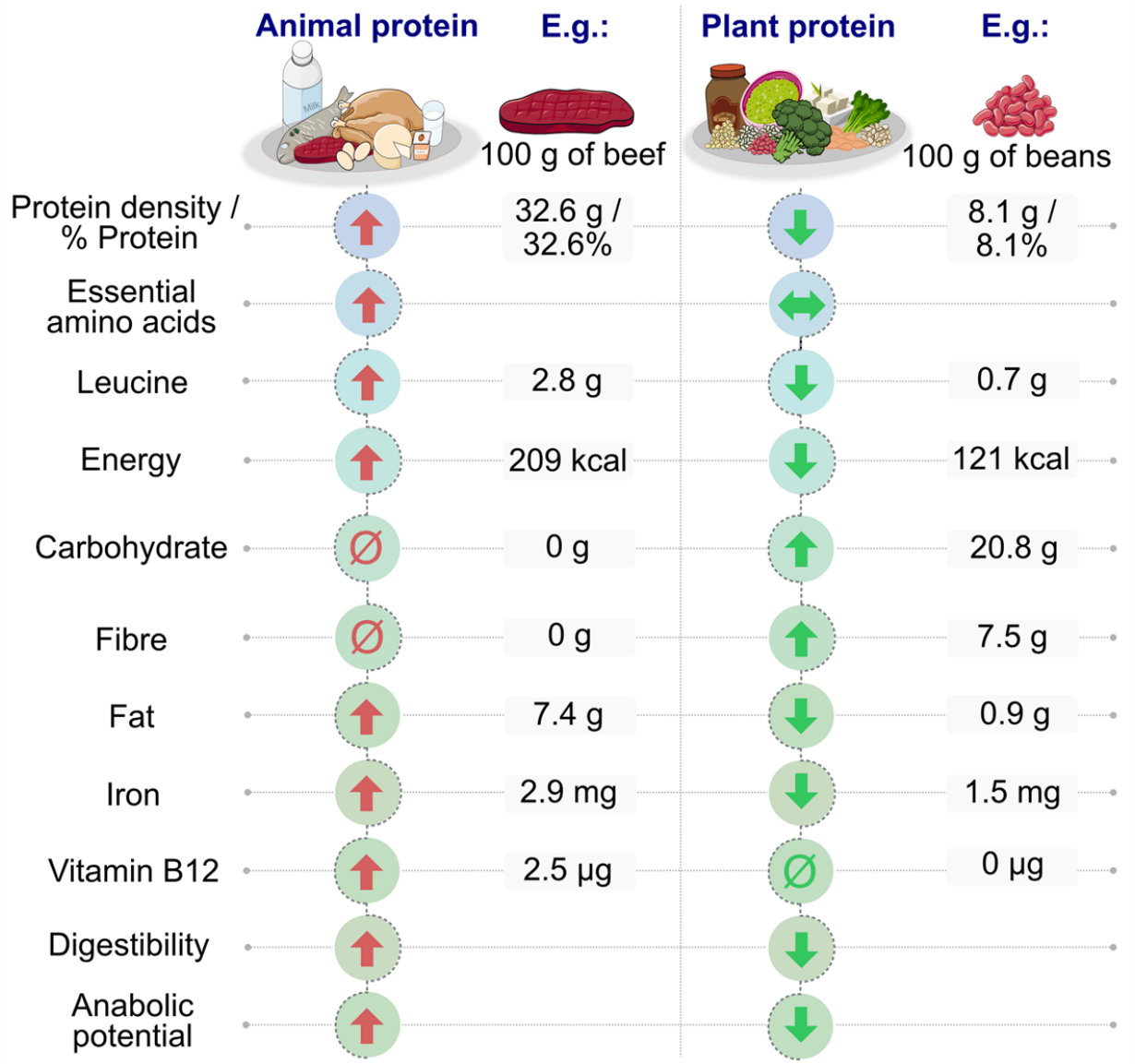

Figure 2.5. Visual comparison of select nutritional differences between animal and plant proteins highlighted with food examples. Animal proteins include beef, pork, chicken, fish, eggs, milk, cheese, etc. Plant proteins include beans, lentils, soy, nuts, etc. Images retrieved from smart.servier.com. Canadian Nutrient File food codes: beef – 6112; beans – 7085. This figure was previously published under a Creative Commons licence (CC BY 4.0) as Ford KL, Arends J, Atherton PJ, Engelen MPKJ, Gonçalves TJM, Laviano A, et al. The importance of protein sources to support muscle anabolism in cancer: An expert group opinion. Clin Nutr. 2022;41:192-201 [220]. No changes were made to the original figure.

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Chapter 3 Study Protocol

3.1 Preface

This chapter presents the protocol for the main randomized controlled trial that was the basis of this thesis: the Protein Recommendation to Increase Muscle (PRIMe) trial. The trial protocol has been published in Clinical Nutrition ESPEN (Ford KL, Sawyer MB, Trottier CF, Ghosh S, Deutz NEP, Sierco M, Porter Starr KN, Bales CW, Roitman Disi I, Prado CM. 2021;41:175-185). As the author of this article, I retain the right to include it in a thesis or dissertation, provided it is not published commercially. Permission is not required from the publisher (Elsevier). Within this article, I was responsible for writing the first draft of the manuscript; co-authors critically reviewed the intellectual content of the manuscript.

3.2 Abstract

Background: Severe muscle mass (MM) loss is a defining feature of cancer observed across all types and stages of disease and is an independent predictor of poor clinical outcomes including higher incidences of chemotherapy toxicity and decreased survival. Protein is essential to build MM, yet the optimal amount for preventing or treating muscle loss in patients with cancer remains undefined.

Methods: The Protein Recommendation to Increase Muscle (PRIMe) study is a single-center, two-armed, parallel, randomized, controlled pilot trial that assesses the feasibility of utilizing a diet containing 2 g/kg/day of protein to positively impact clinical outcomes in people undergoing chemotherapy to treat colorectal cancer (CRC). Forty patients with newly diagnosed stage II-IV CRC who are scheduled to receive chemotherapy will be included. Participants are randomly assigned to a diet containing 2 g/kg/day or 1 g/kg/day of protein for 12 weeks. The 2 g/kg/day and 1 g/kg/day diet groups receive nutrition recommendations to achieve 2.0 grams of protein per kilogram of body weight per day (g/kg/day) and 1.0 g/kg/day, respectively. These values refer to the upper and lower recommended range of protein intake for people with cancer. Energy recommendations are based on measured energy expenditure. Assessments are completed within 2 weeks of starting chemotherapy (baseline), at week 6, and at week 12. Changes to skeletal MM, physical function, anthropometrics, body composition, muscle strength, physical activity, energy metabolism, metabolic markers, nutritional status, quality of life, readiness to change and psychosocial determinants of behavioural change are assessed between the 2 g/kg/day and 1 g/kg/day groups. Feasibility of the nutritional intervention is assessed by change in MM as a surrogate marker.

Conclusions: This evidence-based study investigates the feasibility of increasing protein intake following a diagnosis of cancer on clinical outcomes during treatment for CRC. This study will inform larger trials assessing the impact of increasing protein intake in cancer to determine their importance and integration into standard clinical care for people with cancer.

3.3 Introduction

Malnutrition is prevalent among people with cancer. Unfortunately, limited improvements to this problem have been observed over the past several decades [1]. Few cases of cancer-related malnutrition present visually in the form of low body mass index (<18.5 $kg \cdot m^{-2}$) [1]. A more common but hidden condition is loss of muscle mass (MM), which is widespread across cancer types and stages at the time of diagnosis [2-7]. A review of the literature found prevalence of low MM to vary significantly among tumor topography, ranging from 5% in cancers of the respiratory tract to 89% in advanced pancreatic cancers [2, 8, 9]. Low MM in cancer is more pervasive than in healthy older adults aged 60-70 years [10], and is a defining feature of malnutrition in cancer, occurring with or without losses of fat mass [11].

Metabolic alterations (e.g., systemic inflammation, hypercatabolism) induced by cancer and anti-cancer treatments have compounding effects on muscle catabolism [2, 3, 12, 13]. In addition to the high prevalence of low MM at the time of cancer diagnosis, these patients are at risk for losing a significant amount of MM during chemotherapy [14, 15]. Low MM in cancer patients is a concern due to its association with diverse negative health outcomes including decreased physical function and mobility, higher incidences of chemotherapy toxicity and surgical complications, increased length of hospital stay, and decreased survival [2, 16-22] Fortunately, awareness of malnutrition in cancer has been heightened in recent years, implications of MM loss are being recognized, and maintenance of MM is emerging as an important health outcome in this population [7, 8, 19, 23-26].

While loss of MM is a hallmark of cancer, muscle anabolism remains possible despite the detrimental influences of age and physical deconditioning. An observational longitudinal study of patients with mixed cancer types found that 15% exhibited spontaneous increases in MM earlier in the disease trajectory [27]. Importantly, as reviewed by Engelen *et al*., anabolic potential is normal but driven by the amount and quality of nutrients (with the exception of refractory cachexia) [28]. Thus, targeted therapies are warranted to mitigate the impact of low MM in cancer [26].

Amino acids are essential for muscle health and a primary stimulator of muscle protein synthesis [29, 30]. Negative changes in MM are accentuated when protein consumption is

insufficient to support anabolism; thus, an adequate supply of exogenous protein and energy is required [10, 26, 31, 32]. The link between protein intake and MM is such that other anabolic promoters may not succeed without sufficient protein intake, which is known to be variable in people with cancer [26, 33]. The literature depicts a wide range of protein intake levels in this population, ranging from 0.2–2.7 grams of protein per kilogram of bodyweight per day (g/kg/day) [34, 35]. One study suggested that 35% of people living with cancer did not meet the minimum protein recommendation of 1.0 g/kg/day [35]. International oncology nutrition guidelines recommend 1.0-1.5 g/kg/day but specify 1.2 g/kg/day as a target. These standards are higher than those for healthy adults (0.8 g/kg/day) but nonetheless do not account for MM loss caused by cancer and its treatment [36-39].

Poor nutritional practices are commonly linked to cancers of the gastrointestinal tract, including colorectal cancer (CRC) [40, 41]. Colorectal cancer was the third most common cancer diagnosis and the second most common cause of cancer-related mortality worldwide in 2018 [42]. In North America, CRC is ranked fourth in terms of new cases but is the second most common cause of cancer-related death [42]. Although the prevalence of low MM varies across tumor groups, cancers of the gastrointestinal tract are associated with a high risk of malnutrition [43]. Thus, we developed the Protein Recommendation to Increase Muscle (PRIMe) study to inform the feasibility of a 12-week diet containing 2.0 g/kg/day versus 1.0 g/kg/day of protein, the extent to which nutrition therapy can halt MM loss during treatment, and the corresponding impacts on patient outcomes in this population [36]. A diet containing 2 g/kg/day protein is safe for people with normal kidney function and the 1 g/kg/day diet attains the minimum standard of care in oncology nutrition guidelines [34, 36, 44, 45]. This study is the first of its kind and will provide insight into the feasibility of conducting future large-scale studies exploring the impact of a higher protein intake on preventing loss of MM in cancer.

3.3.1 Study Objectives

The primary objective of the PRIMe study is to inform the feasibility of utilizing a diet containing 2 g/kg/day protein diet to halt MM loss during cancer treatment. The secondary objective is to assess potential effects of a diet containing 2 g/kg/day compared to 1 g/kg/day of protein on maintaining physical function over the course of cancer treatment. Exploratory objectives are to assess the feasibility of a diet containing 2 g/kg/day protein during cancer

treatment and compare effects of a diet containing 2 g/kg/day versus 1 g/kg/day of protein on anthropometrics, body composition, muscle strength, physical activity, energy metabolism, metabolic markers, nutritional status, quality of life (QoL), readiness to change and psychosocial determinants of behavioural change.

3.4 Methods/design

3.4.1 Trial design

The PRIMe study is a single-center, two-arm, randomized, controlled pilot trial that is currently recruiting participants [46]. This study takes place at the Human Nutrition Research Unit (HNRU) at the University of Alberta in Edmonton, Alberta, Canada. Patients are recruited at the Cross Cancer Institute, which provides cancer care to the largest catchment area in Alberta, Canada. A visual depiction of participant flow through the study is provided in **Figure 3.1**. Participation in this study takes place over the period of 12 weeks with outcome assessments conducted at 0, 6, and 12 weeks as shown in The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Figure for the PRIMe study (**Figure 3.2**).

3.4.2 Eligibility criteria

Ambulatory men and women between the ages of 18-85 years with a recent diagnosis of CRC (stage II-IV) who are able to provide written informed consent in English are eligible to participate in the PRIMe study if they are able to complete all baseline study assessments within 2 weeks of starting chemotherapy. Those with stage I disease are not eligible as these patients are considered cured after tumour resection [47]. Additionally, eligible participants have an estimated life expectancy of ≥1 year. Participants must have adequate hepatic and renal function and women of childbearing potential must agree to use an effective form of contraception for the duration of the study. Reasons for exclusion include: (1) acute inflammation (assessed by neutrophil/lymphocyte ratio >5 [48]), (2) ongoing (non-treatment related) nutritional impact symptoms, (3) severe dietary restrictions, (4) a medical condition that impacts ability to increase muscle (e.g. cachexia [49]), (5) a pacemaker *in situ*, (6) active treatment for another cancer site, (7) body weight >450 lbs, (8) uncontrolled diabetes, (9) or a recent diagnosis of thyroid disease.

3.4.3 Recruitment

Patients attending their initial medical oncology consultation appointment are screened

for eligibility by clinic nurses. A study coordinator obtains final eligibility confirmation from the treating medical oncologist before approaching the potential participant. The study coordinator follows up with interested individuals by telephone to schedule their screening/orientation study visit at the HNRU. Once a participant has provided written informed consent, their medical record is checked for final eligibility. We developed an educational video to assist with recruitment; the video can be shown to participants live or through a link sent by email. The video addresses the importance of low MM and how nutrition can help [50].

3.4.4 Randomization and blinding

After baseline assessments are complete, participants are randomly assigned to a diet containing 2 g/kg/day or 1 g/kg/day of protein in a 1:1 allocation ratio using block randomization. The random allocation sequence is concealed by blocked cells in an Excel spreadsheet that was created by a member of the study team who does not have any interaction with the study participants or any role in study arm allocation. A research coordinator consecutively unveils blocks for each new participant to be randomized.

Due to the nature of the intervention, neither the study team nor the participants are blinded to group allocation. The registered dietitian and members of the study team must know the group allocation to create individualized nutritional plans for participants and monitor adherence throughout the study. Being as the intervention is based on body weight and participants are asked to achieve a specified protein intake, it is possible that participants know which study arm they have been allocated to. The main outcome measure is assessed and quantified by technicians not associated with the PRIMe study who are blinded to group allocation. Secondary and exploratory outcomes are assessed by research personnel who are trained to follow a strict study protocol to avoid measurement bias.

3.4.5 Nutrition intervention

Participants complete a readiness to change questionnaire and a 1-hour resting energy expenditure (REE) test at their screening/orientation visit. Participants are provided a paper-based 3-day food record and a food scale to record their dietary intake prior to their baseline visit. Resting energy expenditure is measured at orientation to provide the registered dietitian with information needed to create a eucaloric (promote energy balance) diet plan unique to that

participant, using Food Processor Nutrition Analysis Software (version 11.0.124, ESHA Research, Salem, OR, USA). Specifically, REE is multiplied by a physical activity factor and a coefficient of 1.075 that represents the metabolizable energy content of the diet to obtain estimated energy expenditure [51].

Within 2 weeks of starting chemotherapy, but at least 3 days after chemotherapy infusion, participants return to the HNRU to complete all baseline outcome measures prior to study randomization. Once completed, the registered dietitian meets the participant to provide medical nutrition therapy. This involves a complete dietary assessment and providing nutrition counselling on the study diet unique to that participant. The unique study diet is based on the participants' energy expenditure and study arm allocation (2 g/kg/day or 1 g/kg/day diet based on body weight). Participants assigned to the diet containing 1 g/kg/day of protein receive instructions from the registered dietitian to achieve protein intake in line with the minimum standard of care (1.0 g/kg/day) while others are assigned to the diet containing 2 g/kg/day of protein [36]. Prescribed diets are translated into a daily meal pattern that are individualized and adapted for the participant's typical dietary pattern and preferences based on their reported usual intake, mimicking an approach described elsewhere [32]. An example of 3 meals and 2 snacks for a 53 kg person randomized to the diet group containing 2 g/kg/day of protein is depicted in **Figure 3.3**. The meal pattern specifies the number of 'choices' from each food group that is recommended per day. Participants are provided with an adapted version of the *Choose Your Foods for Weight Management* book developed by the Academy of Nutrition and Dietetics [52]. The book contains a list of foods and their respective serving size that represents a 'choice'. Items are stratified by food groups and provide an estimated breakdown for the macronutrient content of 1 'choice'. For example, a 'choice' from the protein group contains 7 grams of protein while one 'choice' from the milk group contains 8 grams of protein [52]. The reference amount of protein from each group counts towards total protein intake. To increase accuracy of estimated intake, participants are encouraged to use the food scale provided to them at the beginning of the study to weigh their food portions. Participants are strongly encouraged to weigh meat, poultry, fish, and seafood products as portion sizes are often difficult to estimate based on volume. Changes to individual nutritional plans can be made by the dietitian as needed. Examples of reasons for change could include significant change in body weight or energy expenditure (the

latter captured at week 6). Changes made to the intervention would not include a change in study arm allocation.

Analogous to how pre-intervention protein intake is evaluated, participants' ability to achieve their recommended level during the intervention is assessed by 3-day food records completed prior to week 6 and week 12 study visits. For those that are struggling to attain their recommended intake or anticipating protein intake to be challenging, an oral whey powder supplement made from high-quality whey protein is provided for the duration of the study. In this case, participants are encouraged to intake most of their allotted protein from whole foods and only use the protein powder provided to supplement their diet. Additional approaches to overcoming dietary challenges include information/resources on symptom management, high-protein recipes, and/or availability of pre-cooked frozen meat products.

Regardless of study group allocation, a member of the research team contacts participants by telephone on a weekly basis throughout the study to address any questions about the study diet, assess adherence (level of protein intake by 24-hour recall), inquire about any potential chemotherapy-related nutrition-impact symptoms, and monitor self-reported body weight. An in-person follow-up visit with the study team, including the registered dietitian, occurs at weeks 6 and 12 for a final round of outcome assessments.

To improve study adherence, the research team contacts participants by telephone on a weekly basis throughout the study. The midpoint study visit (week 6) is also expected to improve adherence to the study intervention as it provides the opportunity for in-person interaction with the study team and sustain motivation for dietary changes [53]. Participants are encouraged to reach out to the study team with any questions throughout the study.

During the 12-week intervention, participants are required to take a daily multivitamin that is provided to them (natural product number [NPN]: 80050882 or 80024313). They are also asked to avoid intentional weight changes and maintain baseline levels of physical activity if possible, in attempt to avoid cofounders. All other forms of concomitant standard of cancer care are permitted throughout the PRIMe study.

Although highly unlikely due to our inclusion criteria, nutritional care of the participants is transferred to oncology dietitians as part of standard of care if serious nutritional impact

symptoms occur, including substantial weight loss. The study registered dietitian uses clinical judgement to assess which participants require transfer of care at study completion.

3.4.6 Outcomes

As previously mentioned, participant flow is depicted in **Figure 3.1** and a detailed list of study outcome assessments and timeline is found in **Figure 3.2**. Outcome measures are assessed at baseline, week 6, and week 12.

3.4.6.1 Primary outcome

The feasibility of a diet containing 2 g/kg/day compared to 1 g/kg/day of protein to halt MM loss is assessed by change in absolute MM as measured by appendicular skeletal muscle (ASM in kg) from baseline to week 12, as described below. We will also explore changes in ASM as a percent change from baseline to week 12.

3.4.6.2 Secondary outcome

The ability of a diet containing 2 g/kg/day compared to 1 g/kg/day of protein to maintain physical function is assessed by Short Physical Performance Battery (SPPB) test score. Change in integral test score is assessed from baseline to week 12.

3.4.6.3 Exploratory outcomes

Feasibility of a diet containing 2 g/kg/day protein during cancer treatment is assessed by change in ASM as a surrogate marker of increased protein intake and study attrition rate. The ability of a diet containing 2 g/kg/day compared to 1 g/kg/day of protein to effect anthropometrics, body composition, muscle strength, physical activity, energy metabolism, metabolic markers, nutritional status, QoL, readiness to change and psychosocial determinants of behavioural change from baseline to week 12 is assessed as described in the section below.

3.4.7 Data collection and management

3.4.7.1 Anthropometry, muscle mass, and body composition

Anthropometric measurements including weight, height, and waist and calf circumferences are assessed. These measurements are taken with participants wearing thin, light clothing or a hospital gown. Mean weight is measured to the nearest 0.1 kg by taking 3 repeated

measures per assessment using a calibrated digital scale (Health o meter® Professional Remote Display, Sunbeam Products Inc., Fla., USA). Height is measured to the nearest 0.1 cm using a 235 Heightronic Digital Stadiometer (Quick Medical, Issaquah, Wash., USA). Waist and calf circumference are measured to the nearest 0.1 cm three and two times, respectively, using a measuring tape and mean value is recorded.

Appendicular skeletal MM is assessed by DXA using a General Electric Lunar Prodigy High Speed Digital Fan Beam Densiometer with encore 9.20 software (General Electric Company, Madison, WI, USA). Dual-energy X-ray absorptiometry is a safe and non-invasive measure of body composition that has minimal radiation exposure and provides compartmentalized and whole-body data on fat, lean, and bone content of the body.

Additional tools to evaluate body composition are used for future exploratory analysis of multicompartment modelling and validation of tools against more sophisticated measure in this population. Bioelectrical impedance analysis (BIA) is measured using a portable device (BODYSTAT® QuaScan 4000, BODYSTAT [Isle of Man] Ltd., Douglas, Isle of Man, British Isles) that can be used in the clinical setting to measure total body water, phase angle and impedance ratio [54]. Air-displacement plethysmography (ADP) (BOD POD Gold Standard Body Composition Tracking System, COSMED USA, Inc., Concord, CA, USA) is used to measure body volume and hence, density. When available, computed tomography (CT) scans originally used for diagnostic purposes are accessed from the patient's medical record for analyses of muscle radiodensity—the extent of lipid infiltration within the muscle [55, 56]. We expect these images to be available at baseline.

3.4.7.2 Physical function, muscle strength, and physical activity

Physical function is assessed by the SPPB test, a validated measurement that includes a sit-to-stand test (5 repetitions), balance testing (3 variations: feet side-by-side, semi-tandem, and tandem), and a timed 2.44 meter walking test, as described elsewhere [57]. Each activity can score up to 4 points, for a total of 12 points. Clinically, the SPPB is used as a measure to assess physical performance, with validated cut-points established [58].

Handgrip strength is a validated and commonly used measure of muscle strength [7]. Change in muscle strength is assessed using a Jamar® Hydraulic Hand Dynamometer (Sammons

Preston Rolyan, Bolingbrook, IL, USA). The highest score from 3 consecutive measures of strength in the non-dominant hand is used.

Free-living physical activity levels are measured for 7 consecutive days following baseline-week 12 study visits by an ActiCal accelerometer (Philips Respironics, Murrysville, PA, USA) worn on the hip. Participants are asked to keep a written log throughout the 7 days, indicating use of the accelerometer and times they wake up and go to bed. Daily step count and time spent in sedentary, light, or moderate/vigorous levels of physical activity are assessed. The International Physical Activity Questionnaire (IPAQ)—Short Form is a measure of self-reported physical activity that is used to complement the accelerometer data [59]. The IPAQ inquires about time spent sitting and time spent doing physical activity (walking, moderate-intensity activities, and vigorous-intensity activities) over the past 7 consecutive days [60]. A continuous total physical activity score is obtained, expressed in metabolic equivalencies of tasks minutes per week, and used to categorize self-reported physical activity as low, moderate, or high [60].

3.4.7.3 Energy metabolism

Energy metabolism is assessed by indirect calorimetry. The volume of oxygen (VO_2) and carbon dioxide (VCO_2) is measured using an open-circuit whole-body calorimetry unit (WBCU) using the Oxymat 6 O_2 analyzer (Siemens AG, Munich, Germany) and the Advance Optima AO2000 Series CO_2 analyzer (ABB Automation GmbH, Frankfurt, Germany). Participants complete a 1-hour REE test in the WBCU. Differences in VCO_2 and VO_2 concentrations of air are calculated every minute during the WBCU test by the Advance Optima AO2000 Series CO_2 analyzer (ABB Automation GmbH, Frankfurt, Germany) and the Oxymat 6 O_2 analyzer (Siemens AG, Munich, Germany). This information is transferred from the gas analyzers to a computer using the National Instruments NI USB-6221 device (National Instruments Corporation, Austin, Tex., USA) and PMCSS Software version 1.8 (Pennington Metabolic Chamber Software Suite, Pennington Biomedical Research Center, La., USA). Pre-WBCU testing preparation includes fasting for 10 hours and refraining from physical activity for 24 hours. Water, medication, and minimal physical activity (e.g., morning activities of daily living and commuting to the research unit) are allowed prior to study visit. Once in the WBCU, participants are instructed to lie on their back and rest for 1 hour without significant movement or falling asleep.

Total energy expenditure (TEE) is assessed in a sub-group of the study population due to the increased time-commitment from participants. At baseline and week 12, participants are offered the opportunity to complete an optional 24-hour WBCU stay to measure TEE in addition to REE. Preparation for TEE measurement is the same as for REE. A standard schedule is followed for all participants who choose to complete a 24-hour WBCU stay. Since fatigue is often associated with cancer treatment, participants can nap during their stay if they feel this is representative of their typical daily activities. Scheduled physical activity is not conducted while inside the WBCU, however the participants are able to move freely within the unit. A standardized menu (3 meals, 2 snacks) is prepared on-site in the HNRU metabolic kitchen based on their estimated energy requirements (eucaloric diet). Appetite sensations are completed immediately before a meal or snack and thirty minutes after finished eating using a validated 100-mm vertical visual analogue scale to assess sensations of hunger, satiety, and desire to eat [61]. Urine is collected throughout the 24-hour WBCU stay. Participants are asked to collect their urine in a sterile plastic jug throughout the 24-hour stay and keep the jug refrigerated in the WBCU when not in use. Urine collected is analyzed for urinary nitrogen (N) to assess N balance. Total urine volume is measured then aliquoted and banked in a -80°C freezer at the HNRU for future analysis. Twenty-four hour urinary N will be assessed by chemiluminescence using a Total Organic Carbon Analyzer High-Sensitivity model (TOC-L_{CPH}) with an ASI-L autosampler and TNM-L Total Nitrogen unit (Shimadzu Corporation, Nakagyo-ku, Kyoto, Japan).

3.4.7.4 Metabolic markers

Approximately 25 mL of blood is sampled from participants by venipuncture after a 10-hour overnight fast. The sample is collected into BD Vacutainer® tubes (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) containing spray-coated silica and a polymer gel for serum separation or K_2-ethylenediaminetetraacetic acid (K_2EDTA) for plasma separation. A protease inhibitor 4-(2-aminoethyl)benzenesulfonyl fluoride hydrochloride (Sigma-Aldrich, Oakville, ON, Canada) is added to the K_2EDTA tubes and all samples are centrifuged at a relative centrifugal force of 1176 times gravity (x g) for 10 minutes. Samples are aliquoted, stored at -80°C, and banked for future analysis. Hydrochloric acid (1 N, 100 µL) is added to the ghrelin aliquot prior to freezing. Plasma samples will be analyzed for ghrelin (active) using enzyme-linked immunosorbent assay (ELISA) kits from EMD Millipore Co. (Billerica, Mass., USA).

Serum samples will be analyzed for leptin, insulin-like growth factor 1, adiponectin, interleukin 6, and C-reactive protein.

3.4.7.5 Nutritional status

Dietary intake is assessed by 3-day food records that include 2 weekdays and 1 weekend day. Blank records are provided, and participants are asked to record the details of the food/beverages (brand name, preparation method, etc.), time, place, and weight of what was consumed. Information on supplement and meal replacement use is also captured in the dietary records as participants are encouraged to include recipes, packaging, and labels to increase the accuracy of their dietary record. Food records are reviewed by the study team for missing information, and clarifications are discussed with participants as needed. Dietary intake is also monitored on a weekly basis by 24-hour recall that is administered over the phone by a trained member of the study team using the multiple-pass method [62]. Ten 24-hour recalls are collected throughout the study. Weekly assessment of protein intake allows the researchers to tailor their nutrition advice based on each participant's ability to meet the protein quantity prescribed to them. All dietary data is entered into Food Processor Nutrition Analysis Software (version 11.0.124, ESHA Research, Salem, OR, USA), checked by a different member of the study team and then analyzed for total caloric and macronutrient content.

The Patient-Generated Subjective Global Assessment (PG-SGA) Short Form© is commonly used to assess nutritional status in the clinical and nutritional trial intervention settings [63]. In completing the PG-SGA, participants report weight change over the past 1 and 6 months; changes to food intake over the past month; nutritional impact symptoms; and functional capacity over the past month. The PG-SGA is then scored and associated with a nutritional stage (well nourished; moderately, or suspected of being, malnourished; or severely malnourished) whereby a lower score indicates a better nutritional status [63].

3.4.7.6 Quality of Life

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30, version 3) is used to assess health-related QoL in cancer [64]. Scales are used to measure function, symptoms, and global health status/QoL where a high score indicates a greater response to the measure [65]. Additionally, the Functional

Assessment of Anorexia/Cachexia Treatment (FAACT) is used to measure challenges related to anorexia and cachexia [66]. A total score and subscale scores for anorexia/cachexia and physical, social/family, emotional and functional well-being are calculated as described elsewhere [67]. Quality of life can also be affected by taste and smell, which are often altered in cancer [68]. A validated questionnaire is used to assess self-reported changes to taste and smell and a chemosensory complaint score is calculated [68, 69].

3.4.7.7 Psychosocial Determinants of Behavioral Change

As the intervention (in both study arms) involves dietary change from the participant, their readiness to make behavioral change is assessed using a questionnaire adapted from Marcus *et al*. prior to the intervention [70]. Resulting scores from the questionnaire are associated with 1 of 4 stages of change (precontemplation, contemplation, action, or maintenance) [70]. Determinants of behavioral change is an optional assessment conducted through a semi-structured interview that explores gendered experiences of nutritional preferences, perceived association between diet and disease, and adherence to the study diet. Interviews are recorded and transcribed verbatim. Coding is done by hand and analyzed using thematic analysis by two members of the research team [71]. Data analysis is ongoing and data collection from the semi-structured interviews will cease once data saturation is attained.

3.4.7.8 Feasibility and safety

Feasibility of the nutritional intervention is assessed based on attrition rates and change in ASM as a surrogate marker of increased protein intake. The use of a clinical outcome in addition to traditional markers of feasibility allows for evaluation of the potential effectiveness of the intervention and provides insight into the suitability of MM as a surrogate outcome in a larger trial design. Safety is monitored by renal function using the same parameters adopted by patient's medical oncologists in which an estimated glomerular filtration rate >60 mL/minute is considered as normal. Participants are also asked to report their weight during the weekly phone calls for close monitoring of significant weight changes that require immediate intervention. Safety is also assessed by monitoring adverse events and documenting them as they are presented.

3.4.8 Data management

Study data is managed using Research Electronic Data Capture (REDCap®) electronic data capture tools hosted at the University of Alberta [72, 73]. REDCap® is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources [72, 73]. All data is stored in a secure location for 5 years. All manually entered data will be checked by a different member of the research team for accuracy. Results of this study will be disseminated to researchers, health professionals, and the public using peer-reviewed manuscripts and poster and/or oral presentations at national and international nutrition and cancer conferences or meetings.

3.4.9 Sample size

As this is a pilot study, a sample size calculation was not performed [74]. Instead, for a medium (0.5) effect size, 90% power, and two-sided 5% significance, a sample size of 16 per arm was chosen [75]. To account for an estimated 20% attrition rate, we are recruiting n=20 per arm for a total sample size of 40. The effect size and estimates obtained from this pilot study will be used to design future studies and conduct further statistical testing.

3.4.10 Statistical methods

Statistical analysis will be conducted using IBM SPSS® Statistics version 25 (IBM Corp. Released 2017. IBM Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Analysis of primary and secondary outcome variables will be assessed using the intention-to-treat principal meaning that data will be assessed based on study arm randomization, regardless of adherence to the intervention. Due to the nature of this study (pilot) all outcome variables (including primary and secondary) will also be investigated using the per-protocol method of analysis meaning that data will be analyzed based on the intervention received (level of protein intake) rather than study arm allocation. All participants with complete data on primary and secondary outcomes at baseline and week 12 will be included in the analysis. Where data on a variable is missing in over 5% of cases, multiple imputation will be used. Sensitivity analysis

will be conducted between complete data and incomplete data to minimize bias.

Descriptive univariate statistics will be performed on all variables. Counts and percentages, means and standard deviations, or medians and inner quartile ranges will be used, as appropriate. All data comparisons will be carried out with an alpha-level of 5% but caution will be used when interpreting analysis as this study was not powered for drawing statistical inference on the outcomes assessed but rather, inform the feasibility of the study intervention and a larger scale trial. Data will be examined for outliers and distribution. Normality will be assessed through graphical visualization and Shapiro-Wilk tests. Non-normally distributed data will be transformed (e.g., logarithm, square root, etc.), and if data normalization is not possible, non-parametric tests will be used for analysis. Comparisons between individuals in the diet groups containing 2 g/kg/day and 1 g/kg/day of protein will be performed using the Student's t-test or the Mann–Whitney U test. Chi-squared test will be used to compare frequencies of categorical and ordinal outcome variables. We will use statistical modelling (regression analysis and generalized estimating equations) to investigate the relationship between secondary variables (e.g., tumour topography, stage, sex, and age) and changes in MM. Change over time will be explored using generalized estimating equations, a statistical technique that accounts for between-subject and within-subject correlation that is seen in repeated measures studies. Confounders (e.g., age, sex) known to affect the outcome variable will be included if collinearity is not present after verification by multiple linear regression at each time point is assessed.

Subgroup analysis of participants lost to follow up will take place to assess baseline characteristics in comparison to those who completed the trial to assess whether lost to follow up occurred at random. Total energy expenditure, urinary nitrogen, and appetite assessments will be assessed cross sectionally at baseline and separately as change over time for tests completed at both baseline and week 12.

In addition to a frequentist approach to analysis, Bayesian estimation will be used to explore evidence for intervention success as primary and secondary outcome data is gathered [76, 77]. The Bayesian method allows for model parameters to be estimated in addition to testing the hypotheses of intervention effect on our primary and secondary outcomes by utilizing prior information (evidence and/or expert belief) [76-78].

Lastly, multicompartment modelling will be explored based on the simultaneous collection of various body compartment data. Bone mineral mass is collected by DXA, total body water by BIA, body density by ADP, and body mass by scale [79]; data which will be utilized to foster the construction of a 4-compartment model to improve assessment of the impact of the intervention on body composition.

3.5 Discussion

Loss of MM is prevalent across different types and stages of cancer at the time of diagnosis and is accentuated with cancer treatment [2-7, 13, 25]. Uni- and multi-modal therapies from various sectors of health research (e.g., exercise, pharmaceutical, and nutrition) have been investigated in the context of MM loss and cancer but significant advances in this field remain necessary [1, 26]. In addition to nutrition, muscle anabolic potential can be enhanced by a combination of therapies in a multi-modal approach (e.g., exercise, anti-inflammatory therapy, optimal oncological management, etc. [26]). Exploring the synergistic effect of different concurrent therapies on muscle anabolism is needed. Despite scepticism, various nutritional therapies alone can positively impact the nutritional status of people with cancer and present as a promising ally in the fight again muscle depletion [26]. Protein is a fundamental component of muscle and thus, exogenous protein presents as a viable therapy to halt MM loss in cancer and must first be characterized in isolation before exploring the effects of a multi-modal approach.

Exploring the feasibility of utilizing a diet containing 2 g/kg/day protein to positively impact clinical outcomes in people undergoing chemotherapy to treat CRC allows for a deeper understanding of the willingness and ability of people in this circumstance to consume a diet containing 2 g/kg/day protein and the resulting effect that this has on MM, physical function, and other clinically important outcomes. These findings can be used to guide a phase III clinical trial to investigate the effectiveness of dietary protein as a nutritional intervention to halt MM loss in various types of cancer, in addition to CRC. Further, oncology nutrition guidelines are based on body weight and do not consider the quantity of target tissue—muscle [26, 54]. The new era of nutritional interventions should consider nutrition as a therapy with the goal of individualized recommendations to halt MM loss in cancer. To our knowledge, this is the first study to use a whole-body calorimetry unit to assess total energy expenditure in cancer. Our exploration of multicompartment modelling could lead to more accurate predictive equations in the future for

people with cancer. Ultimately, this cumulative work can help guide future oncology nutrition guidelines and begin to have a positive impact on the detrimental effects of muscle depletion in cancer.

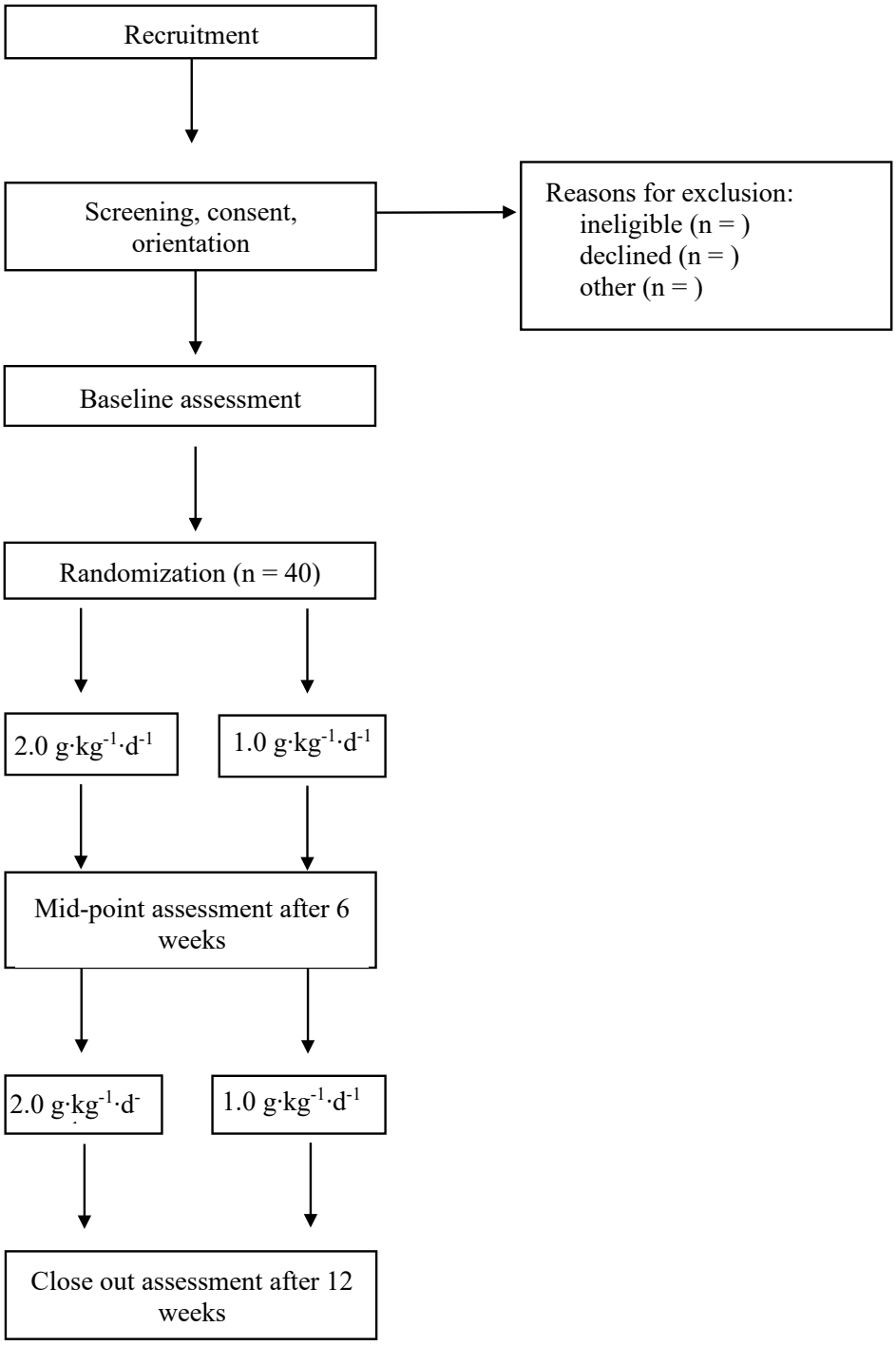

Figure 3.1. Diagram of participant flow through the Protein Recommendation to Increase Muscle (PRIMe) study. Abbreciations: $g \cdot kg^{-1} \cdot d^{-1}$ grams of protein per kilogram of body weight per day.

	STUDY PERIOD						
	Enrollment	**Pre-allocation**	**Allocation**	**Post-allocation**			**Close-out**
TIMEPOINT	***Week -2 or Week -1***	***Baseline***	**Week 0**	***Week 1***	***Week 6***	***Week 12***	***Week 12***
ENROLLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation			X				
INTERVENTIONS:							
1.0 g/kg/day				←	—	→	
2.0 g/kg/day				←	—	→	
ASSESSMENTS:							
Primary outcome: Muscle mass		X			X		X
Secondary outcome: Physical function		X			X		X
Exploratory outcomes: Anthropometry, body composition, muscle strength, physical activity, energy metabolism, metabolic markers, nutritional status, quality of life, behavior change*	X (Energy metabolism only)	X			X		X
Feasibility and safety outcomes:	X	X		X	X	X	X

Figure 3.2. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Figure for Protein Recommendation to Increase Muscle (PRIMe) study. *Completed in a sub-set of participants.

Figure 3.3. Example of 1-day worth of food consumed by approximately a 53 kg person randomized to the 2.0 g/kg/day study arm. From top left to bottom right: breakfast, lunch, supper, morning snack, evening snack.

3.6 References

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Chapter 4 Total 24-hour Energy Expenditure Assessed by Calorimetry Chamber in Patients with Colorectal Cancer

4.1 Preface

The following chapter is a secondary analysis of baseline data from the randomized controlled pilot trial conducted for this thesis. The chapter is based on data from 31 patients with stage II-IV colorectal cancer (CRC) who were recruited from the Cross Cancer Institute in Edmonton, Canada and were participating in the Protein Recommendation to Increase Muscle (PRIMe) trial. This work aimed to characterize total energy expenditure (TEE) and resting energy expenditure (REE) by calorimetry chamber at baseline (prior to any trial intervention) and compare findings with energy intake recommendations for patients with cancer. This work also aimed to investigate predictors of TEE and REE. To our knowledge, this is the first study in >25 years to characterize TEE by calorimetry chamber in patients with cancer and the first ever to do so in patients with CRC.

A version of Chapter 4 is being prepared for submission to an academic journal. Select data from this chapter was accepted for poster presentation at the 44th European Society for Clinical Nutrition and Metabolism (ESPEN) Congress in Vienna, Austria (Sept 3-6, 2022). The corresponding abstract was accepted for publication in Clinical Nutrition ESPEN (Katherine L. Ford, Claude Pichard, Michael B. Sawyer, Claire F. Trottier, Ilana Roitman Disi, Sarah A. Purcell, Sunita Ghosh, Mario Siervo, Nicolaas E.P. Deutz, Carla M. Prado. 2022.). I was also very fortunate to be awarded a travel grant from the Congress to present this work in-person.

Data from the first 10 patients were collected by individuals other than me; I was responsible for data collection for the remaining 21 patients. I maintained ethics approval for this study and was responsible for data management. I contributed towards data analysis, interpretation, and chapter/manuscript preparation. Dr. Carla Prado formulated the research question, study design and implementation, and oversaw data analysis/interpretation and chapter/manuscript preparation; all other authors contributed to developing the study concept.

4.2 Abstract

Rationale: Total energy expenditure (TEE) determines energy requirements, but objective data on TEE in patients with cancer is limited. The study objective was to characterize TEE and resting energy expenditure (REE) by a calorimetry chamber and compare measured TEE and REE with energy intake recommendations and common predictive equations. Predictors of TEE and REE were also investigated.

Methods: Patients with stage II-IV colorectal cancer (CRC) who participated in a randomized controlled pilot trial (Protein Recommendation to Increase Muscle [PRIMe]) were included. Energy expenditure (EE) was assessed via a 24-hour stay in a calorimetry chamber within 2 weeks of starting chemotherapy and prior to receiving the trial intervention. Patients were provided an isocaloric diet. Total EE was calculated using the Weir equation accounting for urinary nitrogen and 1- hour REE by the abbreviated Weir equation. Total EE was compared to energy intake recommendations in cancer (25-30 kcal/kg body weight [BW]/day) and dietary reference intake (DRI) equation for healthy populations. Resting EE was compared to Mifflin-St. Jeor and Harris-Benedict equations. Body composition was assessed by dual-energy X-ray absorptiometry (DXA). Physical activity level (PAL) was assessed as TEE/REE. The International Physical Activity Questionnaire–Short Form (IPAQ–SF) captured self-reported usual activity over the previous week. Self-reported physical activity was categorized as inactive, moderately active, or highly active. Appendicular lean soft tissue (ALST) was used as an indicator of muscle mass. Data were reported as mean ± standard deviation. Generalized linear models, paired samples t-tests, or Bland-Altman analysis were applied.

Results: Thirty-one patients (56 ± 10 years; body mass index: 27.9 ± 5.5 kg/m^2; 67.7% male; 74.2% stages II/III disease, 71% colon cancer; 35.5% with an ostomy) were included. Total EE (2074 ± 337 kcal/day) did not differ from the lower bound of the recommended intake of 25 kcal/kg/day but was below the upper bound of 30 kcal/kg/day (-430 ± 322 kcal/day; $p<0.001$). Total EE was highly variable (21-32 kcal/kg/day) and 58.1% (n=18) of patients had a TEE outside of the recommended intake range. At the group level, REE was higher than predicted by the Mifflin-St. Jeor (145 ± 144 kcal/day; $p<0.001$) and Harris-Benedict (77 ± 147 kcal/day; $p=0.006$) equations. Individual variability was high for both equations although Mifflin-St. Jeor had the smallest limits of agreement (-138 to 428 kcal/day). Measured PAL was

1.19 ± 0.08 and suggested sedentary activity. When self-reported, inactivity was observed in 22.6% of patients (n=7). Neither assessment of activity varied by sex or tumor location. Appendicular LST, sex, rectal cancer, and presence of an ostomy were among predictors of TEE and REE. In models adjusted for sex, ALST and tumor location were independent predictors of TEE (both $p<0.05$), while ALST remained an independent predictor of REE when adjusted for sex and tumor location ($p<0.001$).

Conclusion: This was the largest study to date and the only in the past 25 years to assess 24-hour EE of patients with cancer using a calorimetry chamber. Patients with rectal cancer presented with lower TEE and REE compared to patients with colon cancer. Hypermetabolism and TEE outside of the recommended intake range (25-30 kcal/kg/day) were also observed and the latter was more prevalent in older patients. Total EE was highly variable and predicted by tumor location and body composition; REE was also higher than predicted on a group level. While the lower bound of energy recommendations was accurate, TEE fell outside of current recommendations for most patients. Taken together, these findings highlight the potential for nutritional optimization at the time of a CRC diagnosis. Future investigations of the predictors of TEE in both confined and free-living settings is warranted to better understand energy recommendations; these should include physical activity monitoring.

4.3 Introduction

Total energy expenditure (TEE) determines energy requirements, but objective data on TEE in patients with cancer is limited. Current oncology nutrition guidelines are based on the notion that patients with cancer have similar metabolic demands to healthy individuals; thus, energy intake recommendations parallel those for healthy adults [1]. The metabolic demands of cancer vary by type and stage of disease and can influence TEE and resting energy expenditure (REE), resulting in altered energy metabolism [2]. Systemic inflammation is commonly observed in cancer and is one factor that may directly or indirectly affect energy expenditure (EE), likely through skeletal muscle breakdown and the ubiquitin-proteasome pathways [3, 4]. Skeletal muscle is a storage site of glycogen and amino acids and is a regulator of energy metabolism, especially when other energy sources in the body are depleted [5].

Energy needs are often predicted in clinical settings, especially outpatient settings, but their accuracy in conditions such as cancer is highly variable [6]. Indirect calorimetry is a technique to measure oxygen (O_2) and/or carbon dioxide (CO_2) exchange to determine EE [7]. Longer tests (i.e., 24-hours) can determine TEE while tests of short duration estimate REE [8]. Both types of EE assessments can be completed in a calorimetry chamber under a controlled environment. Calorimetry chambers employ indirect calorimetry methods to a whole room, enabling the patient to move freely about the space and engage in activities of daily living over a prolonged period of time [9]. This controlled setting allows for quantification of nitrogen intake (e.g., via nutrient intake analysis) and losses (e.g., via 24-hour urinary nitrogen) and O_2 and CO_2 exchange. These data are then applied to Weir's equation to assess TEE [10]. The complexity and intricacies of calorimetry chambers are such that there are less than 45 centers globally that are known to house functioning chambers and their use in various clinical conditions is limited [9]. The last known assessment of TEE by calorimetry chamber in patients with cancer was conducted in patients (n=5) with unresectable small-cell lung cancer >25 years ago [11].

In view of the importance of understanding energy metabolism in cancer and the paucity of data describing TEE in these patients, the objective of this cross-sectional study was to characterize TEE and REE by calorimetry chamber in patients being treated for stage II-IV colorectal cancer (CRC). Secondary objectives were (1) to compare measured TEE (mTEE) by calorimetry chamber to energy intake recommendations in cancer and the dietary reference

intake (DRI) equation for healthy individuals; and (2) to compare measured REE (mREE) to commonly used predictive equations. We also sought to investigate predictors of TEE and REE. It was hypothesized that mTEE and mREE would not differ from energy recommendations, but that wide individual variability would be observed. Additionally, it was hypothesized that weight, sex, stage of disease, and muscle would independently predict TEE and REE.

4.4 Methods

4.4.1 Study Design and Patients

This secondary analysis was a cross-sectional study of a convenience sample of patients with newly diagnosed CRC participating in a randomized controlled pilot trial [12]. Clinical assessments were completed at the Human Nutrition Research Unit [13], Department of Agricultural, Food & Nutritional Science, University of Alberta (Edmonton, Alberta, Canada). Patients enrolled in the trial were invited to complete an optional 24-hour stay in a calorimetry chamber as part of this exploratory study. All assessments for were completed prior to patients being randomized and receiving the intervention in the larger trial. A $50 (CAD) gift card to a grocery store was offered as an honorarium to patients who completed a 24-hr calorimetry chamber assessment. Recruitment for the trial occurred between August 2016 and January 2022. Of the 50 patients who completed baseline assessments for the larger trial, 31 patients completed the optional 24-hour calorimetry chamber assessment and were included herein.

The randomized controlled pilot trial was registered at clinicaltrials.gov (NCT02788955) and the study protocol published [14], **Chapter 3**. Methods specific to this study were expanded upon herein. Inclusion/exclusion criteria did not differ from the larger trial [14]. Specifically, medications that affect energy metabolism or body composition (e.g., new dose of thyroid disorder medication) were among reason for exclusion. Patients were 18-85 years of age, had been diagnosed with stage II-IV CRC within the past 7 months, did not present with cancer cachexia, and had started or were scheduled to start chemotherapy within 14 days of completing study assessments. The study was approved by the Health Research Ethics Board of Alberta-Cancer Committee (HREBA.CC-15-0193) and complied with standards on the use of human participants in research. All patients provided written informed consent prior to any study assessments. The Room Indirect Calorimetry Operating and Reporting Standards, version 1.0 guided the reporting of this study [9].

4.4.2 Patient Characteristics

Demographic and clinical characteristics including patient age, sex, disease and treatment history were obtained from electronic health records. Stage of disease was determined by tumor, node, metastasis (TNM) staging [15]. A questionnaire was used to collect data on self-reported race and ethnicity. The International Physical Activity Questionnaire–Short Form (IPAQ–SF) captured self-reported physical activity over the previous week [16]. A continuous total physical activity score categorized physical activity as inactive, moderately active, or highly active [17].

4.4.3 Anthropometry and Body Composition Assessments

Prior to entering the calorimetry chamber, height was measured once to the nearest 0.1 cm using a 235 Heightronic Digital Stadiometer (Quick Medical, Issaquah, Wash., USA). Body weight (BW) was measured to the nearest 0.1 kg with patients wearing thin, light clothing. The average of 3 measurements taken on a calibrated digital scale (Health o meter® Professional Remote Display, Sunbeam Products Inc., Fla., USA) was used. Weight was re-assessed using the same scale immediately following the EE assessment in the calorimetry chamber to quantify 24-hour weight change. Initial mean BW (kg) was divided by height (m^2) to calculate body mass index (BMI) which was categorized per the Centers for Disease Control (underweight: <18.5 kg/m^2; normal range: 18.5–24.9 kg/m^2; overweight: 25.0–29.9 kg/m^2; obesity: ≥30.0 kg/m^2) [18].

Body composition was assessed by whole-body dual-energy X-ray absorptiometry (DXA; General Electric Lunar iDXA High Speed Digital Fan Beam Densitometer with Encore 13.60 software [General Electric Company, Madison, WI, USA]) within 12 days of 24-hour EE assessment. Estimates of lean soft tissue (LST), fat mass (FM), and bone mineral content were generated at the whole-body and regional levels. Fat-free mass (FFM) was calculated by summing LST and bone mineral content values. Appendicular LST (ALST) was calculated by summing LST of the limbs. Appendicular LST index (ALSTI) was determined by dividing ALST by height (m^2). Low muscle mass (MM) was defined as ALSTI <7.0 kg/m^2 for males and <5.5 kg/m^2 for females [19]. Overweight and obesity is prevalent among patients with CRC [20] and impacts the evaluation of low MM [21], thus low MM was also investigated using an approach that accounted for body size [22]. Appendicular LST was divided by BW (ALST/BW) then multiplied by 100% and low MM was defined as <28.27% for males and <23.47% for females [22, 23].

4.4.4 Energy Expenditure Assessments

4.4.4.1 Calorimetry Chamber

Energy expenditure was assessed by 24-hour stay in an indirect calorimetry chamber within 2 weeks of starting chemotherapy and prior to receiving the trial intervention. An open-circuit calorimetry chamber was used to measure volumes of O_2 (VO_2) and CO_2 (VCO_2) exchanged. An air conditioning system ran at 410 $feet^3$/minute to maintain a temperature range of 21–23°C and relative humidity <70%. The system also mixed air within the chamber at a rate of 11.6 meters $(m)^3$/minute thus the totality of air within the chamber circulated through the air conditioner every 2 minutes and 30 seconds. Fresh air was drawn passively from the buffer zone into the chamber through a fresh air inlet at 60 litres (L)/minute and mixed expired air was withdrawn from the chamber by a minispiral fan. The extraction of air facilitated by the minispiral fan resulted in a slightly negative constant pressure within the chamber. A sample gas cooler set to 1°C removed moisture (condensate) from the air before it was pumped at a flow rate of 1 L/minute into O_2 (Oxymat 6, Siemens AG, Munich, Germany) and CO_2 (Advance Optima AO2000 Series, ABB Automation GmbH, Frankfurt, Germany) differential analyzers. The O_2 and CO_2 analyzers captured gas volumes within the chamber and buffer zone every 1-minute throughout the assessment period. Calculated difference in VO_2 and VCO_2 concentrations between the calorimetry chamber and the buffer zone were transmitted from the gas analyzers to a desktop computer by the National Instruments NI USB-6221 device (National Instruments Corporation, Austin, Texas, USA) and displayed on the screen via Pennington Metabolic Chamber Software Suite version 1.8 (Pennington Biomedical Research Center, Louisiana, USA).

The CO_2 and O_2 analyzers were calibrated once per week by conducting a "zero test" (i.e., recording gas exchange rates of the fresh air in the buffer zone versus itself) and a span gas calibration (i.e., recording gas exchange rates of the span gas bottle versus the buffer zone). The calorimetry chamber was calibrated prior to each assessment (i.e., by-pass calibration) with pre-mixed gas (20% O_2; 1% CO_2; balanced with nitrogen) and a 24-hour propane burn test was conducted quarterly. The chamber used in this study and its analytical components were previously tested for reliability using a test re-test approach with 1 day between assessments. The coefficient of variation was 2.2% for TEE in n=10 healthy participants (Human Nutrition Research Unit, personal communications).

4.4.4.2 Pre-test Protocol

Patients were advised to refrain from smoking or using nicotine the morning of the assessments, from consuming any calories or caffeine for 10 hours prior to assessments, and from physical activity and alcohol consumption for 24 hours prior to study assessments [8]. Water, medication, and minimal activity (e.g., morning activities of daily living and commuting to the research unit) were allowed prior to study visit.

4.4.4.3 Total Energy Expenditure Assessment

The TEE assessment lasted for 23 hours and 15 minutes. The software algorithm required 30 minutes of measurements before calculations of EE begun thus 22 hours and 45 minutes of data were obtained within the assessment period. Data were extrapolated to a 24-hour period: the first 15 minutes of data were duplicated and added to the beginning of the data set and the first 60 minutes of data were duplicated and added to the end of the data set to obtain 24 hours of data. This standard approach has been used for all TEE assessment studies conducted in our calorimetry chamber [24, 25]. Volume of O_2 consumed and VCO_2 produced minute-by-minute during were summed and used to calculate TEE using the Weir equation accounting for urinary nitrogen [10]. Total EE was compared to energy intake recommendations in cancer (25–30 kcal/kg/day) [1] and the DRI equation for healthy individuals [26] as the latter is a method of predicted TEE (pTEE) that considers individual variables beyond BW (**Supplementary Table 4.1**). For the DRI equation, a physical activity coefficient of 1.0 (sedentary activity) was applied based on the average physical activity level (PAL; TEE:REE) of this cohort being sedentary (PAL: 1.19) [26].

The calorimetry chamber (**Supplementary Figure 4.1**) had a geometric volume of 28.74 m^3, which enabled free movement within the space. Patients followed a standardized schedule within the calorimetry chamber (**Supplementary Table 4.2**) that included resting in the supine position for 60 minutes to assess REE, consuming 3 meals and 2 snacks, 8 hours of sleep, and time for leisure sedentary activity. Patients were allowed to rest or sleep during the day (not indicated in the schedule) if needed for cancer-related fatigue. Rest time did not alter mealtimes or other activities; the patient was awoken if sleeping during a scheduled activity.

4.4.4.4 Resting Energy Expenditure Assessment

Patients were instructed to rest in the supine position, remain awake, and minimize movement for the first 60 minutes inside the calorimetry chamber to assess REE. Patients were monitored visually every 15 minutes and standard music was played at a low volume. The software does not register the first 30 minutes of data (as mentioned above), which also allows time for patients to acclimatize to the calorimetry chamber environment. Thus, the first 30 minutes of data captured by the software were used to calculate REE. Volume of O_2 and VCO_2 were summed and divided by 30 to obtain mean values in L/minute. These data were applied to the abbreviated Weir equation [10] to obtain an estimate of REE (kcal/day). Measured REE was compared with predicted REE (pREE) by equations including Mifflin-St. Jeor [27] and Harris-Benedict [28] (**Supplementary Table 4.1**). These equations were chosen based on their clinical use and relative accuracy in patients with cancer [6]. Probable abnormalities in energy metabolism (i.e., hypo- or hypermetabolism) were characterized per Boothby et al. criteria (hypometabolism: mREE/pREE <90%; hypermetabolism: mREE/pREE >110%; normometabolism: mREE/pREE between 90-110%) [29].

4.4.4.5 Dietary Intake During the 24-hour Calorimetry Chamber Assessment

Patients were provided a standardized isocaloric diet while in the calorimetry chamber. A low-fibre menu option was available for patients who required diet modification (i.e., due to presence of an ostomy), **Supplementary Table 4.3**. An example of a menu was provided in **Chapter 3**, **Figure 3.3** [14]. Menus were designed by a registered dietitian and macronutrient distribution for both menus (range 1600–3000 kcal) were approximately 50% carbohydrate, 30% fat, and 20% protein, **Supplementary Table 4.4**.

A REE assessment in the calorimetry chamber or by metabolic cart (Vmax® Encore [CareFusion, Yorba Linda, California, USA]) was conducted up to 2 weeks prior to the 24-hour assessment to predict daily caloric requirements. Resting EE was multiplied by an assumed activity factor of 1.2 (sedentary activity level) and a coefficient of 1.075 (to account for the thermic effect of food) to predict 24-hour energy requirements [26]. This data was needed to prepare an isocaloric menu for the 24-assessment. Resting EE data reported herein was assessed during the first 1-hour of the 24-hour assessment as described above. On the day of the 24-hour assessment, EE predictions were completed using calorimetry chamber data after 45 minutes,

3.25 hours, and 7.25 hours (**Supplementary Table 4.2**). Adjustments to the caloric content of the diet were made to the closest 100 kcal, as needed. Food was prepared in a metabolic kitchen and each item was weighed to the nearest 0.1 gram prior to being served. Water and herbal tea were provided ad-libitum. Any items not consumed were weighed prior to disposal. Dietary intake from the 24-hour assessment period was evaluated using The Food Processor® Nutrition and Fitness Software (version 11.7.217, ESHA Research, Salem, Oregon, USA).

4.4.4.6 Urine Analysis

Patients voided their bladder prior to entering the calorimetry chamber. Once inside the chamber, patients were provided sterile 3 L urine jugs and instructed to collect all voided urine throughout the 24-hour assessment. On day 2, patients were reminded to empty their bladder prior to exiting the calorimetry chamber. Urine collections were refrigerated in a specimen fridge within the calorimetry chamber throughout the assessment period. Total urine volume was measured using a 2000 milliliter (mL) graduated cylinder.

Urine samples (1 mL each) were pipetted into aliquot tubes, frozen, and stored in a -80°C freezer. For analysis, thawed urine samples were diluted with double deionized water by a dilution factor of 101 (0.3 mL of urine; 30 mL of dilutant). Diluted samples were combusted to nitric oxide and nitrogen dioxide, and then reacted with ozone to form nitrogen dioxide in an excited state. A chemiluminescence detector (high-temperature Shimadzu TOC-L CPH Model Total Organic Carbon Analyzer with an ASI-L autosampler and TNM-L unit [Shimadzu Corporation, Suzhuo, Jiangsu, China]) measured resultant photon emission. Total nitrogen content (milligram [mg]/L) of the samples was quantified by calibrating the total organic carbon analyzer with ammonium or nitrate salts. Total nitrogen excretion for the 24-hour period was derived using the below equation:

Total nitrogen excretion (g) = ((sample nitrogen (mg/L]) * dilution factor) * 24-hour urine volume (L)) / 1000

4.4.5 Statistical Analysis

Data analyses were conducted using IBM SPSS® Statistics version 28 (International Business Machines Corporation, Armonk, NY, USA) or GraphPad Prism version 9.3.1 for Windows (GraphPad Software, San Diego, California, USA). Data were reported as mean ±

standard deviation (SD) or median and 25^{th}, 75^{th} percentile in the case of non-normality. Normality was assessed by Shapiro-Wilk test. Significance for all tests was set at $p<0.05$.

Continuous dependent variables were compared by sex and tumor location (colon versus rectum) using independent samples t-test, Welch's t-test in the case of heterogeneity of variances, or Mann-Whitney U test in the case of non-normality. Dichotomous dependent variables were compared using Fisher's exact test. Generalized linear models used identity link function to form a linear relation between the dependent variable (TEE or REE, kcal/day) and predictors (factors: sex, tumor location; covariates: ALST or LST) in the adjusted models. Both ALST and LST were investigated to account for any presence of tumor when whole-body LST was considered, especially in patients with un-resected stage IV disease [30, 31]. In model 1 and 2, TEE was the dependent variable and ALST and LST, respectively, were entered as covariates. In model 3 and 4, REE was the dependent variable and ALST and LST, respectively were considered covariates. All models included sex and tumor location as predictors. Results of the unadjusted models for TEE and REE and for models adjusted for sex and tumor location were presented as beta coefficient (β), standard error (SE), 95% confidence interval (CI), and P value.

Measured and predicted EE values were compared using a paired-samples t-test. Wilcoxon Signed Rank test was used to compare paired samples in the case of non-normality. Bland-Altman plots were used to assess agreement between measured and predicted EE variables. Bias was determined as the difference between predicted and measured TEE and REE values and was reported with 95% CI to indicate group-level agreement between methods. Bias was also assessed as a percentage of mREE or mTEE to account for variability in individual EE. Individual-level agreement was assessed using limits of agreement (LOA; bias ± 1.96*SD); 95% CI for the upper and lower LOA were considered individually [32]. Bias ± 5% was assessed for group-level agreement between methods based on intra-individual variation in REE [33-35]. Proportional bias was evaluated as the correlation between the mean of both assessment methods (e.g., pREE and mREE) and bias to determine if bias changed with higher levels of EE.

Log-log regression models as described elsewhere [36-38] were used to account for differences in body size and/or composition when assessing REE and TEE. A linear regression analysis was used to determine the slope of the regression line that related log (REE or TEE) with log (LST). Lean soft tissue was raised to the power of the relevant slope to adjust for

differences in LST between patients. Resting EE or TEE values were expressed as kcal/kg LST^{slope} and plotted against LST by sex and by BMI (BMI <30 kg/m^2 versus BMI ≥30 kg/m^2) to illustrate variability in EE.

4.5 Results

4.5.1. Patient Characteristics

A total of 31 patients were included in the study; body composition data were missing for n=1 patient. Patient characteristics are presented in **Table 4.1**. Patient age was 56 ± 10 years. Most patients were White (n=22; 71%) and male (n=21; 67.7%). Group-level BMI was classified as overweight (27.9 ± 5.5 kg/m^2) and sex differences were not observed although BMI was lower in patients with rectal cancer (23.9 ± 4.2 kg/m^2) compared to those with colon cancer (29.5 ± 5.2; p=0.008). One patient (3.2%) had a BMI classified as underweight (<18.5 kg/m^2) but was not an outlier for EE or body composition data. Eight patients (25.8%) had a BMI within the normal range (18.5–24.9 kg/m^2), 10 patients (32.2%) presented with a BMI in the overweight category (25.0–29.9 kg/m^2), and 12 patients (38.7%) had a BMI in the obesity category (≥30 kg/m^2). Males presented with higher ALSTI (8.3 ± 1.4 kg/m^2) compared with females (6.6 ± 0.9 kg/m^2; p=0.002). No difference in ALSTI was observed between patients with colon versus rectal cancer. Low MM assessed by ALSTI was observed in 10% of males (n=2) and 10% of females (n=1). When assessed as ALST/BW, the prevalence of low MM was 40% of males (n=8) and 30% of females (n=3). Measured PAL was 1.19 ± 0.08 and suggested sedentary activity. When self-reported, inactivity was observed in 22.6% of patients (n=7). Neither assessment of activity varied by sex or tumor location.

Most patients (n=23; 74.2%) had stages II/III colon cancer and 35.5% of patients (n=11) presented with an ostomy. Single agent capecitabine was prescribed for n=6 patients (19.4%). All other patients were prescribed oxaliplatin-based therapies (e.g., capecitabine with oxaliplatin [CAPOX], 5-fluorouracil, leucovorin, and oxaliplatin [FOLFOX]) or irinotecan-based therapies (e.g., 5-fluorouracil, leucovorin, and irinotecan [FOLFIRI]). Chemotherapy was started a median of 9 days (25^{th}, 75^{th} percentile: 5, 13 days) prior to study assessments. Nine patients (29.0%), all with a diagnosis of rectal cancer, received radiotherapy a median of 144 days (25^{th}, 75^{th} percentile: 48, 181 days) prior to study assessments.

4.5.2 Total Energy Expenditure

Total EE (2074 ± 337 kcal/day) was highly variable (males: 2201 ± 328 kcal/day; females: 1809 ± 152 kcal/day, **Figure 4.1**) and differed by sex and tumor location although these differences were not observed for TEE/BW, **Table 4.1**. Patients with rectal cancer had lower TEE (mean difference: -279 kcal/day; SE difference: 125 kcal/day; p=0.010) although no difference was observed for TEE/BW. These data are illustrated by sex in **Figure 4.2 A-B**. No differences in TEE were observed by stage (II/III versus IV) of disease. Total EE did not differ from the lower bound of the recommended intake for patients with cancer (25 kcal/kg/day) for the group, by sex, or by tumor location, **Figure 4.1**. Measured TEE was below pTEE using 30 kcal/kg/day for the group (-430 ± 322 kcal/day; p<0.001), by sex (females: -346 ± 290 kcal/day; p=0.004 and males: -470 ± 336 kcal/day; p<0.001), and by tumor location (colon: -492 ± 320; p<0.001 and rectum: -278 ± 291; p=0.021).

Group-level difference (i.e., bias) between mTEE and pTEE (using 25-30 kcal/kg/day or DRI equation) was highly variable (range: -13 to -430 kcal/day). The lower end of recommended intake range (25 kcal/kg/day) provided the most accurate pTEE at the group level as it had the smallest bias (-13 kcal/day; 95% CI: -103 to 77 kcal/day; **Figure 4.3 A**). Total EE predicted by 30 kcal/kg/day was the least accurate (bias: -430 kcal/day; 95% CI: -548 to -312 kcal/day; **Figure 4.3 B**). Predicted TEE by DRI equation had a bias of -212 kcal/day (95% CI: -287 to -138; **Figure 4.3 C**) and large variability was observed for males (-283 ± 198; p<0.001), and in patients with colon (-164 ± 203; p=0.001) and rectal (-332 ± 159; p=0.008) cancer, **Figure 4.1**. Proportional bias was observed (i.e., bias differed at higher TEE) for pTEE by 25 kcal/kg/day (r = -0.587; p<0.001) and 30 kcal/kg/day (r = -0.751; p<0.001), but not for pTEE by DRI equation.

When considered on an individual patient level, accuracy was best for pTEE by DRI as it had the tightest LOA (lower LOA: -612 kcal/day; 95% CI: -771 to -509 kcal/day; upper LOA: 187 kcal/day; 95% CI: 85 to 346 kcal/day). The widest LOA (i.e., least accurate method at the individual level) was observed for pTEE by 30 kcal/kg/day (lower LOA: -1062 kcal/day; 95% CI: -1313 to -900 kcal/day; upper LOA: 201 kcal/day; 95% CI: 39 to 452 kcal/day). Total EE predicted by 25 kcal/kg/day had a lower LOA of -493 kcal/day (95% CI: -684 to -370 kcal/day) and an upper LOA of 468 kcal/day (95% CI: 344 to 659 kcal/day). More than half of patients (58.1%; n=18) had mTEE outside of the recommended intake range (25–30 kcal/kg/day) and

most (n=16, 51.6%) were below 25 kcal/kg/day. Patients with mTEE outside of 25-30 kcal/kg/day trended towards being older (59 versus 52 years; p=0.057) while no differences were observed by sex or tumor location. Variability between recommended energy intake (25-30 kcal/kg/day) and mTEE or mREE x 1.2 (average PAL) was observed, **Figure 4.4**. Energy needs assessed as mREE x 1.2 were underestimated by the lower bound of recommended energy intake by up to 444 kcal/day and overestimated by up to 520 kcal/day. The upper bound of recommended energy intake underestimated energy needs assessed as mREE x 1.2 by up to 112 kcal/day and overestimated needs by up to 1160 kcal/day. When estimated energy needs were compared with mTEE, energy requirements were underestimated by up to 378 kcal/day and overestimated by up to 1111 kcal/day.

4.5.3 Resting Energy Expenditure

Resting EE (1741 ± 275 kcal/day) differed by sex (males: 1847 ± 262 kcal/day; females: 1518 ± 138 kcal/day; p<0.001) and tumor location (rectum: 1602 ± 158; colon: 1798 ± 295; p=0.025) although no differences were observed for REE/BW, **Table 4.1**. Males with rectal cancer had lower mREE compared to males with colon cancer (mean difference: -307 kcal/day; SE: 103 kcal/day; p=0.008) while no difference was observed for REE/BW, **Figure 4.5 A-B**. Two females presented with rectal cancer, thus analyses between tumor locations for females were not conducted.

At the group level, difference (i.e., bias) between mREE and pREE by Harris-Benedict (77 ± 147 kcal/day; 95% CI: 23 to 131 kcal/day; p=0.006) and Mifflin-St. Jeor (145 ± 144 kcal/day; 95% CI: 92 to 198 kcal/day; p<0.001) equations was observed, **Figure 4.6**. When bias was considered as a percentage of mREE, pREE by Harris-Benedict equation was the most accurate at the group level (bias: 5% kcal; 95% CI: 2 to 8% kcal) followed by pREE by Mifflin-St. Jeor equation (bias: 8% kcal; 95% CI: 6 to 11% kcal), although the difference in bias between equations was negligible, **Figure 4.7 A-B**. Proportional bias was not observed (i.e., bias did not differ at higher REE) for pREE by Harris-Benedict or Mifflin-St. Jeor equations.

At the individual patient level, variability was observed for both equations although pREE by the Mifflin-St. Jeor equation was most accurate with the tightest LOA (lower LOA: -7% kcal; 95% CI: -14 to -3% kcal; upper LOA: 24% kcal; 95% CI: 20 to 31% kcal). Predicted REE by Harris-Benedict equation resulted in a lower LOA of -13% kcal (95% CI: -19 to -8%

kcal) and an upper LOA of 22% kcal (95% CI: 18 to 29% kcal). When individual level accuracy was considered as a percentage of mREE, pREE by Harris-Benedict equation was within ±5% for 41.9% of patients (n=13) whereas pREE by Mifflin-St. Jeor was within ±5% for 22.6% of patients (n=7), **Figure 4.7 A-B**. Probable energy metabolism abnormalities were present in 41.9% of patients (n=13) when assessed by Harris-Benedict and Mifflin-St. Jeor equations, although the type of abnormality varied. When assessed by Harris-Benedict equation, hypometabolism was observed in 6.5% of patients (n=2) and hypermetabolism in 35.5% of patients (n=11). For the Mifflin-St. Jeor equation, hypometabolism was not detected and hypermetabolism was observed in 41.9% of patients (n=13).

4.5.4 Predictors of Energy Expenditure

In unadjusted models, weight, BMI, FFM, FM, LST, ALST, ALSTI, sex, tumor location, and presence of an ostomy were predictors of TEE (all $p<0.05$), **Table 4.2**. The same variables predicted REE although tumor location trended towards significance ($p=0.054$). In model 1, ALST ($p<0.001$) and tumor location ($p=0.023$) independently predicted TEE when adjusted for sex. Appendicular LST independently predicted REE ($p<0.001$) when adjusted for sex and tumor location (model 3). Lean soft tissue independently predicted TEE (model 2; $p<0.0001$) and REE (model 4; $p<0.001$) when each model was adjusted for sex and tumor location, **Table 4.3**.

Log-log regression models of EE and LST showed variability by sex (**Figures 4.8 A-B**) and by presence of obesity (**Figures 4.8 C-D**) after accounting for variability in LST. The log-log regression model of TEE and LST produced a slope (β) of 0.693 (SE: 0.062; $p<0.001$) thus $TEE/LST^{0.7}$ was plotted against LST to illustrate variability in TEE among patients by sex (**Figure 4.8 A**) and by presence of obesity (**Figure 4.8 C**). The log-log regression model of REE and LST resulted in a slope (β) of 0.631 (SE: 0.081; $p<0.001$) thus $LST^{0.6}$ was considered to account for variability is LST among patients. Resting $EE/LST^{0.6}$ varied amongst patients with similar quantities of LST by sex (**Figure 4.8 B**) and by presence of obesity (**Figure 4.8 D**).

4.6 Discussion

This study was the largest in over 25 years to assess TEE by calorimetry chamber in patients with cancer and to our knowledge, was the first to evaluate TEE in patients with CRC using this technique. Our findings showed that in a cohort of patients with colon and rectal

cancer with no difference in prevalence of metastatic disease by tumor location, patients with rectal cancer presented with lower TEE and REE by up to ~300 kcal/day. Hypermetabolism (mREE/pREE >110%) and mTEE outside of the recommended intake range (25-30 kcal/kg/day) were also observed and the latter appeared more prevalent in older patients. Taken together, these findings support the argument that energy metabolism assessment and/or intervention are needed at the time of CRC diagnosis to optimize nutritional health. Further, patients with CRC should be considered as a heterogenous group when determining which patients could benefit most from registered dietitian support.

Patients with stage II–IV CRC are commonly treated with radiotherapy and/or chemotherapy. In contrast to most patients with colon cancer, those with rectal cancer typically undergo neoadjuvant chemoradiotherapy prior to surgery and adjuvant chemotherapy [39]. In turn, rectal cancer has been associated with increased risk for weight loss, metabolic derangements, decreased treatment tolerability, malnutrition, and subsequently poorer prognosis [40-42]. Nonetheless, patients with colon and rectal cancer are often considered as a homogeneous group (i.e., as patients with CRC [43]). We showed that patients with rectal cancer (all received prior chemoradiotherapy) had lower TEE, REE, BW, BMI, FM, and were more likely to have an ostomy compared to patients who were treated for colon cancer. Rectal cancer also independently predicted TEE and suggested that patients with rectal cancer had lower TEE by approximately 140 kcal/day compared with patients who had colon cancer when sex and MM (assessed as ALST) were also considered although as mentioned, the difference in absolute TEE was even greater (~300 kcal/day). Patients with rectal cancer could likely benefit from EE assessment and thorough nutritional assessment that ideally would include assessment of body composition, specially given the noted differences in EE between cancer types. It is possible that our findings related to EE and rectal cancer were due to the greater use of cytotoxic therapy, prolonged duration with the tumor in-situ (due to neoadjuvant treatment), and need for invasive surgery (e.g., tumor resection and or placement of an ostomy) in patients with rectal cancer [44]. Interestingly, our findings showed that presence of an ostomy resulted in lower TEE and REE compared to patients without an ostomy. Oncology patients with ostomies have been found to have low levels of physical activity [45] which can contribute to decreased TEE although no

difference between patients with and without ostomies was observed for PAL or self-reported activity level in our cohort (data not shown).

Plausible altered energy metabolism was observed in 42% of patients studied herein, the majority of whom presented with hypermetabolism (i.e., mREE/pREE >110%). These findings contribute to the growing body of literature that suggests altered metabolism is present across the spectrum of disease and is not limited to patients with cancer cachexia [36, 46, 47]. Boothby's criteria is commonly used to assess altered energy metabolism [29] although variability is induced given the heterogeneity in predictive equations and indirect calorimetry devices used across studies. In 21 patients with primarily stage I-III CRC, half presented with hypermetabolism when mREE was assessed by indirect calorimetry and pREE by Mifflin-St. Jeor equation [47]. A study of 179 older adults with a solid tumor and predominantly advanced disease assessed REE by indirect calorimetry and the Harris-Benedict equation and found that about half of patients were hypermetabolic [46]. Notably, multivariate analysis showed that hypermetabolism was an independent predictor of early limiting toxicity (adjusted OR: 2.44; 95% CI: 1.02 – 5.80; p=0.012) in those patients [46]. Overall, pREE does not appear to accurately capture mREE across the disease spectrum, as observed in patients within our study. Inaccurate pREE can have serious clinical implications given that inadequate energy intake can promote alterations to body composition (e.g., MM loss) [48] that could in turn increase risk for treatment toxicity [49].

The Mifflin-St. Jeor equation is recommended for use in patients with overweight and obesity when mREE is not available [50]. Mean BMI in our patient population was classified as overweight which may explain why the smallest LOA were observed using the Mifflin-St. Jeor equation, suggesting that it may be the most appropriate on an individual patient level. The absolute mean difference between mREE and pREE by this equation did not vary amongst patients with obesity versus those without (data not presented). Our findings were similar to others that reported smallest LOA for pREE by Mifflin-St. Jeor equation when compared with mREE by indirect calorimetry [6]. Variable metabolic profiles have been observed in cancer although these should be interpreted with caution given that predictive equations were validated in healthy populations and have less accuracy in patients with cancer [6]. Notwithstanding this limitation, metabolic status has been classified using predictive equations given their prevalence

of use in the clinical setting. Portable indirect calorimetry devices can also be used in the clinical setting to assess REE in patients with cancer given the high individual variability observed from predictive equations [6, 51, 52]. Our findings support the notion that mREE should be assessed in clinical settings to provide patient-specific nutrition recommendations that can account for altered energy metabolism and ultimately promote improved patient care and outcomes.

Our findings suggested that in a highly controlled and sedentary environment, TEE at the group level was accurately predicted by the lower bound of energy intake recommendations in cancer (25 kcal/kg/day) and by the DRI equation for females when an assumed activity factor was used, although high individual variability was observed. The upper end of the recommended energy intake (30 kcal/kg/day) did not predict TEE at the group level. Proportional bias was detected for weight-based equations (25-30 kcal/kg/day) whereby bias became increasingly negative (i.e., pTEE was progressively different from mTEE) at higher levels of TEE suggesting that difference between mTEE and pTEE was greater in patients with higher BW. These findings may be in-part explained by the variability in MM and EE observed in the general population and that MM is exceeded by adipose tissue beyond a BMI of ~35 kg/m^2 in men and 25 kg/m^2 in women [21]. Cumulatively, this further reinforces the importance of EE and body composition assessment in the clinical setting to promote individualized nutrition optimization.

Body composition and EE are interrelated and highly variable among individuals [21]. Fat free mass, which includes LST, is a well-established determinant of EE [53] and the impact of cancer-induced changes to body composition on EE have been explored [36, 54-56]. Changes to body composition can alter EE when the proportion of tissues within the body change, given the varying metabolic rate of body tissues [57]. Although it has been rarely done in oncology EE studies [58], it is important (and recommended) to account for varying body composition phenotypes when assessing and interpreting EE, as explained in detail by others, and this should not be done by using a simple ratio [36-38]. Thus, to account for varying body composition profiles, we employed log-log regression models to assess TEE and REE without the effect of body composition. We showed that variable TEE and REE resulted among patients with CRC who had similar quantities of LST. As an example, we showed that n=2 males who both presented without obesity and ~47kg of LST had mTEE that differed by 609 kcal/day and mREE

that differed by 621 kcal/day. These findings highlight the substantial variability among patients with similar characteristics and reiterate the importance of individualized nutrition assessment.

Our prior knowledge of TEE in cancer has been limited to patients with severe weight loss (e.g., cancer cachexia) [59], a high inflammatory status [11], or patients with early-stage CRC [47]. Results from these previous studies showed presence of hypermetabolism while TEE findings differed, suggesting that TEE varies among cancer types and stages [11, 47, 59]. Within our cohort, TEE and REE did not differ between patients with metastatic disease (stage IV) and those with local or locally advanced disease (stage II or III). Notably, we screened for severe weight loss, life expectancy, and inflammatory status thus patients with cancer cachexia or acute inflammation were not included in our study [60]. While a paucity of studies has assessed TEE in patients with cancer, another gold-standard technique has been used. Our laboratory has previously published a study of n=21 patients with mostly (n=20) stage II-III CRC and found that TEE assessed by doubly labeled water was 29.7 ± 6.3 kcal/kg/day [47]. These findings reported by Purcell et al were approximately 5.8 kcal/kg/day higher than results presented herein and could be in part attributed to the sedentary nature of the calorimetry chamber assessment. Purcell et al showed that PAL in free-living conditions was 1.43 ± 0.27 [47] whereas PAL during TEE assessment by calorimetry chamber in our cohort was lower (1.19 ± 0.08). Physical activity level in confined conditions was previously shown to be an indicator of free-living physical activity [61]. Findings from that study suggested that activity EE assessed by 24-hour stay in a calorimetry chamber represented 47 ± 13% of that evaluated in free-living conditions and explained 25% of total variance in free-living activity EE [61]. In our cohort, self-reported physical activity over the prior week did not predict TEE or REE when categorized as inactive, moderately active, or highly active. Others have shown that activity EE in patients with cancer was up to 50% lower compared with healthy controls [62, 63]. A study of n=629 patients with mixed tumor types found that 79% of patients reported decreased levels of physical activity post-diagnosis compared with pre-diagnosis [64], which supports a speculative hypothesis that mTEE by calorimetry chamber could be more representative in patients with cancer due to the greater likelihood of greater time spent in sedentary activity. Compared to TEE assessed by indirect calorimetry chamber, doubly labeled water captures a representative valuation of activity EE in free-living conditions although variables such as energy intake are much less controlled [65]. To

our knowledge, no study has assessed free-living TEE in patients with cancer compared with TEE assessed by whole-body calorimetry chamber to quantify observed difference in activity EE.

The findings discussed herein presented a unique approach to TEE assessment in patients with CRC. These results reflect the precision and accuracy of a calorimetry chamber for the assessment of TEE in a highly controlled environment [66]. A limitation to this study was that physical activity was not captured during the 24-hour assessment and therefore may not represent usual physical activity. Our measure of self-reported physical activity used an abbreviated form that has not been extensively validated in patients with cancer and in some groups, has shown to overestimate physical activity [67]. Future trials should also incorporate the use of heart rate sensors or accelerometers to quantify activity [9]. Despite this limitation, the calorimetry chamber is highly accurate and thus presented EE values that were representative of a structured sedentary day [66]. In addition, our decision to exclude patients with acute inflammation precluded an understanding of inflammation of EE in this population. Ultimately, our sample size and exploratory nature of the study precluded definitive findings but nonetheless presents preliminary data that is the first of its kind and can be used to determine required sample size for future studies of TEE in controlled environments.

In conclusion, this study used a classic approach to assess TEE but its application to patients with cancer was novel. Our findings support the need for improved access to individualized EE assessment in patients with newly diagnosed CRC to optimize nutritional status. We showed that TEE was highly variable and was predicted by body composition and tumor location, which suggests that a one-size-fits all approach to energy intake recommendations may not be appropriate. On a group level, mREE was higher than predicted but individual variability was wide which reinforces the need for predictive equations with greater accuracy in patients with cancer. While the lower bounds of energy recommendations may accurately predict TEE in sedentary individuals, TEE fell outside of current recommendations for most patients. Future investigations of the predictors of TEE in both confined and free-living settings is warranted to better understand energy recommendations.

Table 4.1. Characteristics of 31 patients with newly diagnosed colorectal cancer.

		Sex			Tumor Location		
Characteristic	**Total (n=31)**	**Males (n=21)**	**Females (n=10)**	**P value**	**Rectum (n=9)**	**Colon (n=22)**	**P value**
Age, years	56 ± 10	57 ± 9	53 ± 10	0.272	53 (47, 58)	60 (54, 63)	0.060
Sex[1], n (%)							0.259
Male	21 (67.7)				7 (77.8)	14 (63.6)	
Female	10 (32.3)				2 (22.2)	8 (36.4)	
Race/Ethnicity[1], n (%)				0.348			0.801
Filipino	2 (6.5)	2 (9.5)	0 (0.0)		1 (11.1)	1 (4.5)	
Indigenous Peoples	4 (12.9)	1 (4.8)	3 (30.0)		1 (11.1)	3 (13.6)	
Latin American	2 (6.5)	2 (9.5)	0 (0.0)		1 (11.1)	1 (4.5)	
South Asian	1 (3.2)	1 (4.8)	0 (0.0)		0 (0.0)	1 (4.5)	
White	22 (71.0)	15 (71.4)	7 (70.0)		6 (66.7)	16 (72.7)	
Tumor[1], n (%)				0.259			
Colon	22 (71.0)	14 (71.4)	8 (80.0)				
Rectum	9 (29.0)	7 (28.6)	2 (20.0)				
Disease stage[2], n (%)				0.309			0.280
II/III	23 (74.2)	15 (71.4)	8 (80.0)		6 (66.7)	17 (77.3)	
IV	8 (25.8)	6 (28.6)	2 (20.0)		3 (33.3)	5 (22.7)	
Chemotherapy[1], n (%)				0.968			0.091
Capecitabine	4 (12.9)	3 (14.3)	1 (10.0)		3 (33.3)	1 (4.5)	
CAPOX	11 (35.5)	8 (38.1)	3 (30.0)		2 (22.2)	9 (40.9)	
FOLFOX	10 (32.3)	6 (28.6)	4 (40.0)		2 (22.2)	8 (36.4)	
FOLFIRI	3 (9.7)	2 (9.5)	1 (10.0)		2 (22.2)	1 (4.5)	
FOLFIRI + BEVA	3 (9.7)	2 (9.5)	1 (10.0)		0 (0.0)	3 (13.6)	
Prior radiotherapy[1], n(%)				0.315			**<0.001**
Yes	9 (29.0)	7 (33.3)	3 (30.0)		9 (100.0)	0 (0.0)	
No	22 (71.0)	14 (66.7)	7 (70.0)		0 (0.0)	22 (100.0)	
(continued on next page)							

		Sex			Tumor Location		
Characteristic	**Total (n=31)**	**Males (n=21)**	**Females (n=10)**	**P value**	**Rectum (n=9)**	**Colon (n=22)**	**P value**
Ostomy[1], n (%)				0.288			**<0.001**
Yes	11 (35.5)	8 (38.1)	3 (30.0)		8 (88.9)	3 (13.6)	
No	20 (64.5)	13 (61.9)	7 (70.0)		1 (11.1)	19 (86.4)	
Body weight, kg	82.5 (71.5, 97.7)	87.6 (75.3, 103.8)	79.0 (58.0, 81.9)	**0.016**	71.8 ± 14.7	88.2 ± 18.8	**0.027**
24-hr weight change, kg	-0.23 ± 0.70	-0.11 ± 0.70	-0.47 ± 0.67	0.184	-0.14 ± 0.37	-0.26 ± 0.80	0.677
BMI, kg/m^2	27.9 ± 5.5	28.5 ± 5.6	26.6 ± 5.4	0.386	23.9 ± 4.2	29.5 ± 5.2	**0.008**
TEE[†], kcal/day	2074 ± 337	2201 ± 328	1809 ± 152	**<0.001**	1877 ± 200	2155 ± 351	**0.010**
TEE, kcal/kg	23.9 (23.2, 28.7)	25.2 ± 3.1	25.7 ± 3.5	0.706	25.6 (24.3, 29.5)	23.7 (22.8, 27.4)	0.113
REE[†], kcal/day	1741 ± 275	1847 ± 262	1518 ± 138	**<0.001**	1602 ± 158	1798 ± 295	**0.025**
REE, kcal/kg	21.3 ± 2.8	21.2 ± 2.6	21.6 ± 3.4	0.690	22.8 ± 3.2	20.7 ± 2.5	0.056
PAL (TEE:REE)	1.19 ± 0.08	1.19 ± 0.08	1.19 ± 0.06	0.997	1.17 ± 0.06	1.20 ± 0.08	0.318
IPAQ Category[1, 3], n (%)				0.297			0.341
Inactive	7 (22.6)	6 (28.6)	1 (10.0)		2 (22.2)	5 (22.7)	
Moderately Active	12 (38.7)	9 (42.9)	3 (30.0)		6 (66.7)	6 (27.3)	
Highly active	7 (22.6)	3 (14.3)	4 (40.0)		1 (11.1)	6 (27.3)	
Fat mass[4], kg	28.8 ± 11.1	30.5 (19.9, 36.0)	34.2 (16.9, 36.6)	0.880	22.0 ± 8.9	31.7 ± 10.9	**0.025**
Fat mass[4], %	34.0 ± 8.8	31.8 ± 8.1	38.3 ± 8.8	0.052	29.7 ± 7.6	35.8 ± 8.7	0.076
Fat-free mass[4], kg	53.7 ± 11.2	59.0 ± 10.0	43.2 ± 3.1	**<0.001**	49.9 (43.6, 55.9)	51.2 (44.7, 65.3)	0.32
Fat-free mass[4], %	66.0 ± 8.8	68.2 ± 8.1	61.7 ± 8.8	0.052	70.3 ± 7.6	64.2 ± 8.7	0.076
FM:FFM[4]	0.54 ± 0.20	0.48 ± 0.16	0.65 ± 0.22	**0.027**	0.44 ± 0.14	0.58 ± 0.20	0.055
ALST[4], kg	23.0 ± 5.9	25.6 ± 5.3	17.7 ± 1.8	**<0.001**	21.1 ± 3.7	23.8 ± 6.5	0.161
ALSTI[5], kg/m^2	7.7 ± 1.5	8.3 ± 1.4	6.6 ± 0.9	**0.002**	7.1 ± 1.0	8.0 ± 1.6	0.126
ALST/BW[6], %	27.9 ± 3.7	29.3 ± 2.9	25.1 ± 3.6	**0.002**	29.6 ± 2.3	27.2 ± 4.0	0.055
(continued on next page)							

		Sex			Tumor Location		
Characteristic	**Total (n=31)**	**Males (n=21)**	**Females (n=10)**	**P value**	**Rectum (n=9)**	**Colon (n=22)**	**P value**
Low muscle mass[1,4] n (%)							
by ALSTI[5]				0.999			0.999
Yes	3 (87.1)	2 (9.5)	1 (10.0)		1 (11.1)	2 (9.1)	
No	27 (9.7)	18 (85.7)	9 (90.0)		8 (88.9)	19 (86.4)	
by ALST/BW[6]				0.702			0.999
Yes	11 (35.5)	8 (38.1)	3 (30.0)		3 (33.3)	8 (36.4)	
No	19 (61.3)	12 (57.1)	7 (70.0)		6 (66.7)	13 (59.1)	

Data presented as mean ± standard deviation or median (25^{th}, 75^{th} percentiles) for non-normally distributed variables. Differences assessed using independent samples t-test or Mann-Whitney U due to non-normal distribution of one or more groups. Bolded values are significant at $p<0.05$. [†]Welch t-test used due to heterogeneity of variances. [1]Fisher's exact test applied (Chi square test assumption violated [expected <5]). [2]Stage of disease grouped as per tumor, node, metastasis (TNM) staging [12]. Briefly, stage II: disease is localized to primary tumor site; Stage III: disease involves the lymph node(s); Stage IV: disease has spread to distant organ(s). [3]n=26; self-reported physical activity data missing for n=5 patients. [4]n=30; 1 patient missing body composition data. [5]Low muscle mass (MM) was defined as appendicular lean soft tissue index (ALSTI) <7.0 kg/m^2 for males and <5.5 kg/m^2 for females. [6]Low MM was defined as ALST/BW <28.27 for males and <23.47 for females. ALST: appendicular lean soft tissue; ALSTI: appendicular lean soft tissue index; BMI: body mass index; BW: body weight; CAPOX: drug combination of capecitabine and oxaliplatin; FFM: fat-free mass; FM: fat mass; FOLFIRI: drug combination of leucovorin calcium, fluorouracil, and irinotecan hydrochloride; FOLFIRI + BEVA: drug combination of leucovorin calcium, fluorouracil, and irinotecan hydrochloride plus bevacizumab; FOLFOX: drug combination of Leucovorin calcium, fluorouracil, and oxaliplatin; kcal: kilocalories; PAL: physical activity level; REE: resting energy expenditure; RER: respiratory exchange ratio; TEE: total energy expenditure.

Table 4.2. Parameter estimates for predictors of total energy expenditure and resting energy expenditure in n=31 patients with colorectal cancer.

	TEE, kcal/day				REE, kcal/day			
Variables	***β***	**SE**	**95% CI**	**P value**	***β***	**SE**	**95% CI**	**P value**
Age, years	8.90	6.00	-2.86, 20.66	0.138	5.34	4.99	-4.43, 15.11	0.284
Weight, kg	15.44	1.55	12.41, 18.47	**<0.0001**	12.26	1.38	9.56, 14.96	**<0.0001**
BMI, kg/m^2	43.57	7.63	28.61, 58.54	**<0.001**	35.10	6.34	22.68, 47.53	**<0.001**
FFM[1], kg	27.05	2.19	22.75, 31.34	**<0.0001**	20.28	2.43	15.51, 25.05	**<0.001**
FFM[1], %	-5.23	6.87	-18.70, 8.23	0.446	-6.94	5.54	-17.81, 3.92	0.210
FM[1], kg	16.96	4.50	8.14, 25.78	**<0.001**	14.79	3.57	7.78, 21.80	**<0.001**
FM[1], %	5.23	6.87	-8.23, 18.70	0.446	6.94	5.55	-3.92, 17.81	0.210
FM:FFM[1]	149.48	307.91	-454.01, 752.96	0.627	212.10	250.53	-278.94, 703.14	0.397
LST[1], kg	28.37	2.30	23.85, 32.89	**<0.0001**	21.26	2.56	16.24, 26.27	**<0.001**
ALST[1], kg	50.47	4.76	41.14, 59.81	**<0.0001**	38.48	4.80	29.08, 47.89	**<0.001**
ALSTI[1], kg/m^2	196.68	20.02	157.44, 235.93	**<0.0001**	151.51	19.28	113.71, 189.30	**<0.001**
ALST/BW[1], %	12.68	16.20	-19.07, 44.43	0.434	4.59	13.39	-21.66, 30.85	0.732
PAL	992.54	775.55	-527.52, 2512.59	0.201	-623.18	641.02	-1879.56, 633.19	0.331
IPAQ Category[2]								
Inactive	0				0			
Moderately Active	-139.2	160.60	-453.90, 175.66	0.386	-92.14	126.02	-339.13, 154.85	0.535
Highly active	-117.6	180.50	-471.38, 236.18	0.515	-116.57	141.63	-394.16, 161.02	0.677
Sex								
Female	0				0			
Male	391.20	106.11	183.22, 599.18	**<0.001**	328.36	85.74	160.31, 496.42	**<0.001**
Tumor location								
Rectum	0				0			
Colon	278.53	121.14	41.10, 515.97	**0.021**	195.48	101.26	-2.99, 393.95	0.054
Disease stage								
II/III	0				0			
IV	76.66	135.26	-188.45, 341.77	0.571	113.43	109.29	-100.78, 327.65	0.299
(continued)								

	TEE, kcal/day				REE, kcal/day			
Variables	***β***	**SE**	**95% CI**	**P value**	***β***	**SE**	**95% CI**	**P value**
Ostomy								
No	0				0			
Yes	-283.68	113.42	-505.98, -61.37	**0.012**	-238.31	92.23	-419.07, -57.55	**0.010**

Bolded values are significant at p<0.05. [1]n=30; 1 patient missing dual-energy X-ray absorptiometry-derived data. [2]n=26; 5 patients missing self-reported physical activity data. 95% CI: 95% confidence interval; ALST: appendicular lean soft tissue; ALSTI: appendicular lean soft tissue index; *β*: regression coefficient; BMI: body mass index; BW: body weight; FFM: fat-free mass; FM: fat mass; kcal: kilocalories; LST: lean soft tissue; REE: resting energy expenditure; SE: standard error; TEE: total energy expenditure.

Table 4.3. Parameter estimates for adjusted predictors of total and resting energy expenditure in 30 patients with colorectal cancer

Variables	*β*	SE	95% CI	P value
TEE				
Model 1				
ALST, kg	46.72	6.35	34.27, 59.17	**<0.001**
Sex				
Female	0			
Male	25.59	76.72	-124.79, 175.96	0.739
Tumor location				
Rectum	0			
Colon	139.69	61.36	19.44, 259.95	**0.023**
Model 2				
LST, kg	28.42	3.26	22.03, 34.80	**<0.0001**
Sex				
Female	0			
Male	-36.17	71.56	-176.42, 104.08	0.613
Tumor location				
Rectum	0			
Colon	99.44	56.13	-10.56, 209.44	0.076
REE				
Model 3				
ALST, kg	32.89	6.67	19.81, 45.97	**<0.001**
Sex				
Female	0			
Male	71.24	80.59	-86.71, 229.20	0.377
Tumor location				
Rectum	0			
Colon	104.72	64.45	-21.59, 231.03	0.104
Model 4				
LST, kg	19.11	3.82	11.63, 26.59	**<0.001**
Sex				
Female	0			
Male	42.39	83.85	-121.96, 206.73	0.613
Tumor location				
Rectum	0			
Colon	83.67	65.77	-45.24, 212.57	0.203

Bolded values are significant at $p<0.05$. 95% CI: 95% confidence interval; ALST: appendicular lean soft tissue; *β*: regression coefficient; LST: lean soft tissue; REE: resting energy expenditure; SE: standard error; TEE: total energy expenditure. In model 1 and 2, TEE was the dependent variable and ALST and LST, respectively, were entered as covariates. In model 3 and 4, REE was the dependent variable and ALST and LST, respectively were considered covariates. All models included sex and tumor location as predictors.

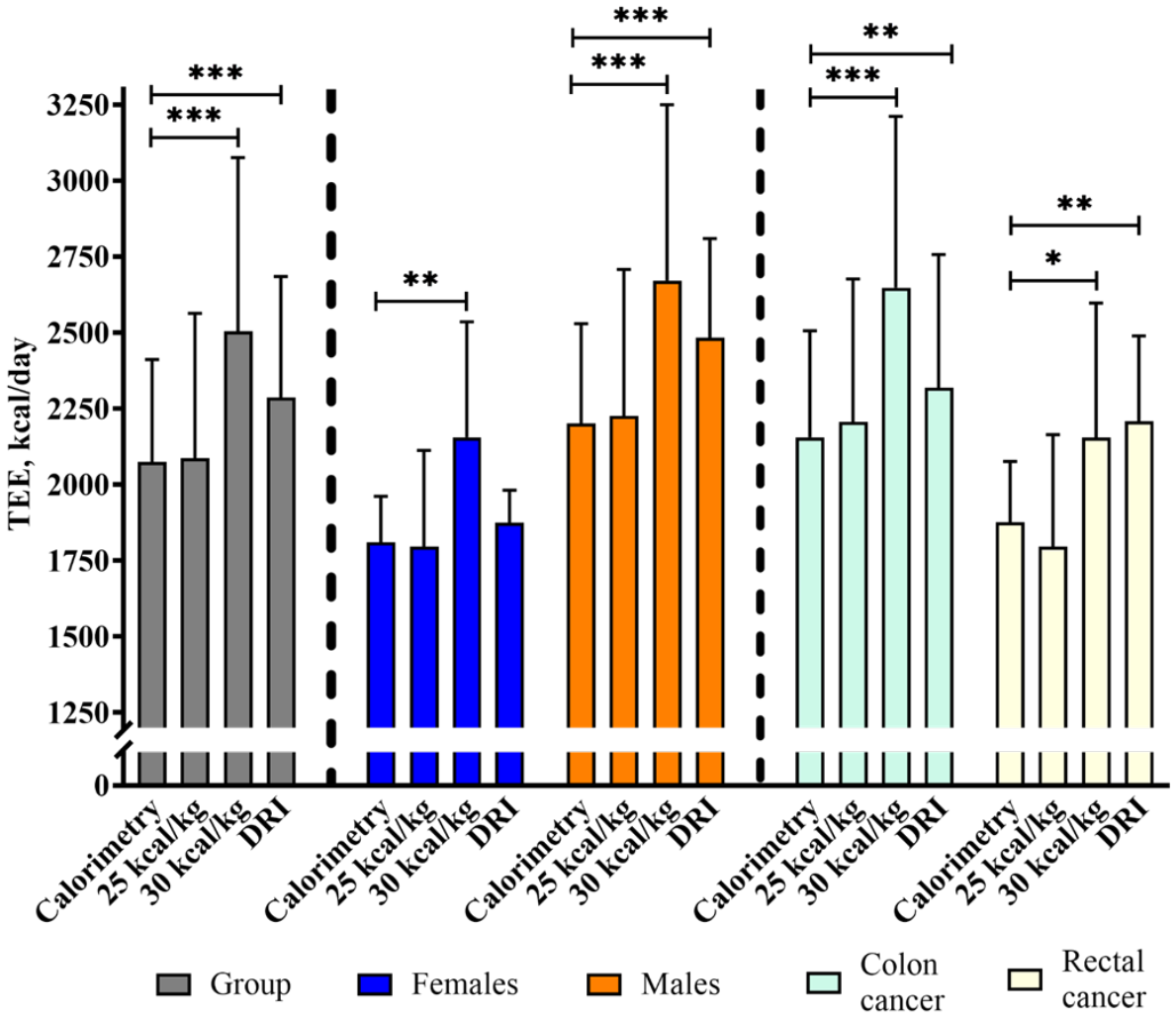

Figure 4.1. Total energy expenditure measured by 24-hour stay in a calorimetry chamber and compared with total energy expenditure predicted by the lower and upper bounds of the recommended intake in cancer (25-30 kcal/kg/day, respectively) and by dietary reference intake equation with an assumed activity factor of 1.0 (sedentary activity) in 31 patients with colorectal cancer. Results are presented for the group, by sex, and by tumor location. Mean difference between calorimetry and estimation method assessed by paired samples t-tests or Wilcoxon Signed Ranks Test in the case of non-normality. * $p<0.05$; ** $p<0.01$; *** $p<0.001$; kcal/kg: kcal per kg body weight per day; DRI: dietary reference intake; TEE: total energy expenditure.

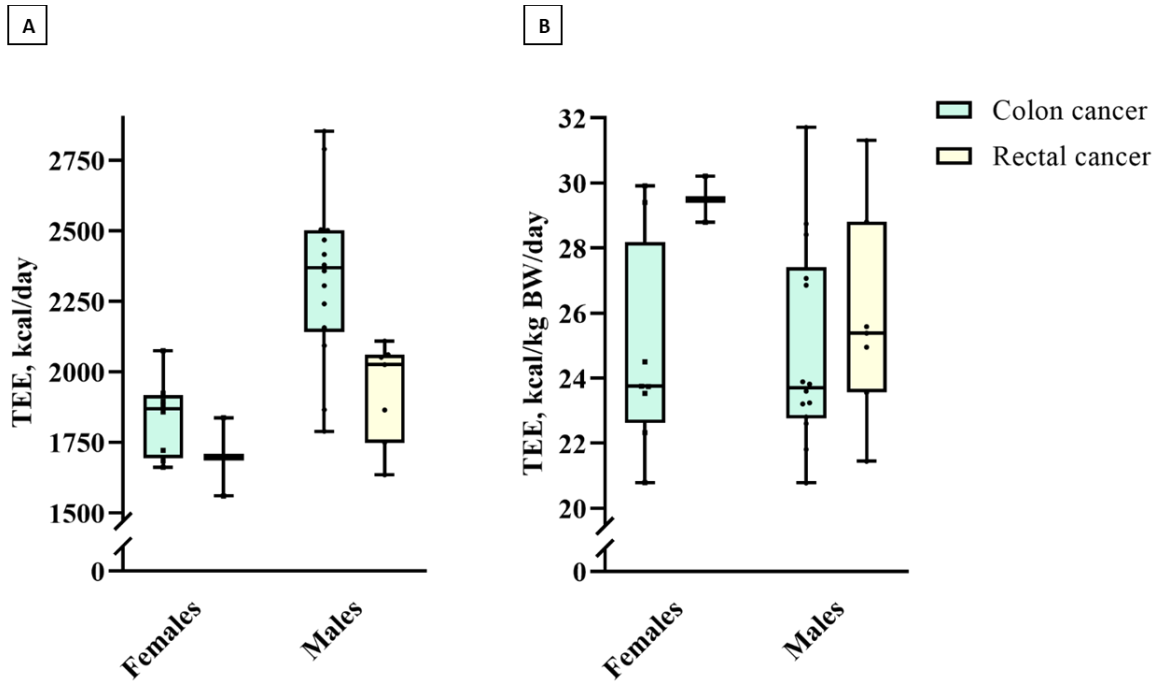

Figure 4.2 A-B. Total energy expenditure measured by indirect calorimetry chamber presented in kilocalories per day (A) and adjusted for body weight (B) in 31 patients with colorectal cancer. Patients with colon cancer (n=22; n=14 males and n=8 females) were compared with patients with rectal cancer (n=9; n=7males and n=2 females). Box plots present minimum and maximum values. Points represent individual patients. kcal: kilocalorie; kcal/kg BW/day: kcal per kilogram of body weight per day; TEE: total energy expenditure.

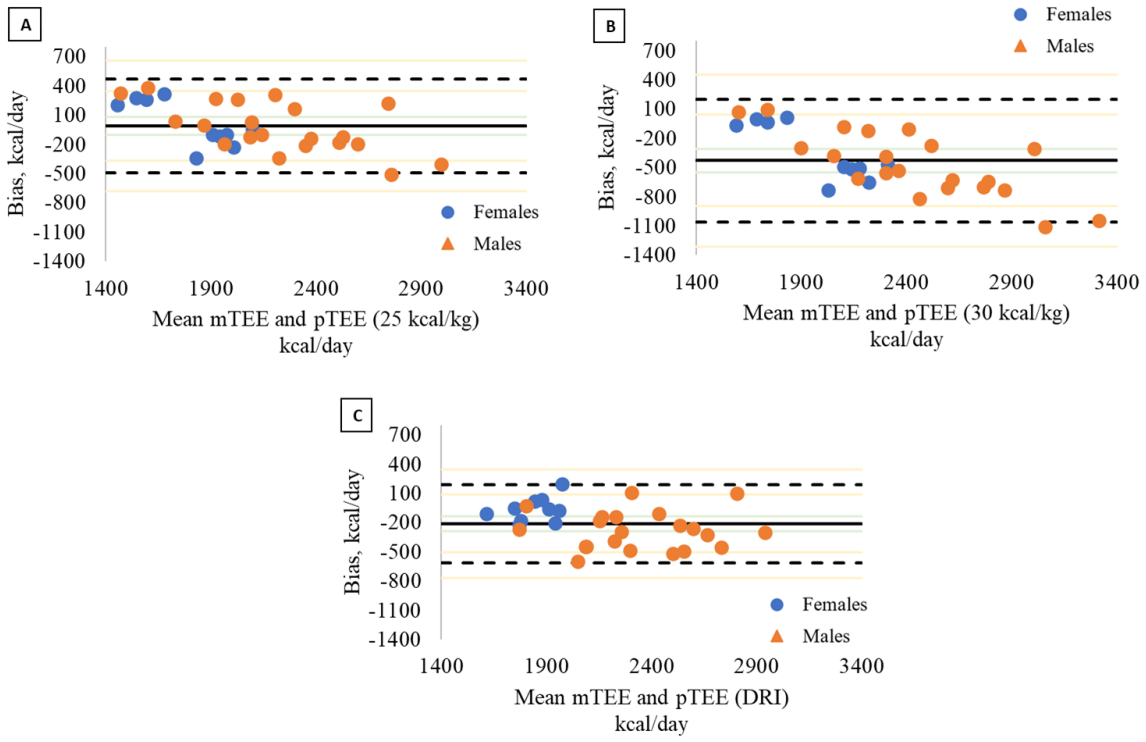

Figure 4.3 A-C. Bland-Altman plots of total energy expenditure measured by indirect calorimetry and predicted total energy expenditure by (A) the lower bound of energy intake recommendations in cancer (25 kcal/kg/day); (B) the upper bound of energy intake recommendations in cancer (30 kcal/kg/day); (C) Dietary Reference Intake equation with an assumed physical activity factor of 1.0 (sedentary activity level) in 31 patients with colorectal cancer. Solid black line represents the mean bias; solid green lines represent the 95% confidence intervals for the bias. Hashed lines represent the 95% limits of agreement (bias ± 1.96 x standard deviation); solid yellow lines represent the 95% confidence intervals for the limits of agreement. Blue circles represent female patients; orange triangles represent male patients. The difference between measured and predicted TEE was expressed as absolute kcal per day. kcal: kilocarlorie; mTEE: measured total energy expenditure; pTEE: predicted total energy expenditure; kcal/kg: kcal per kg body weight per day; DRI: dietary reference intake.

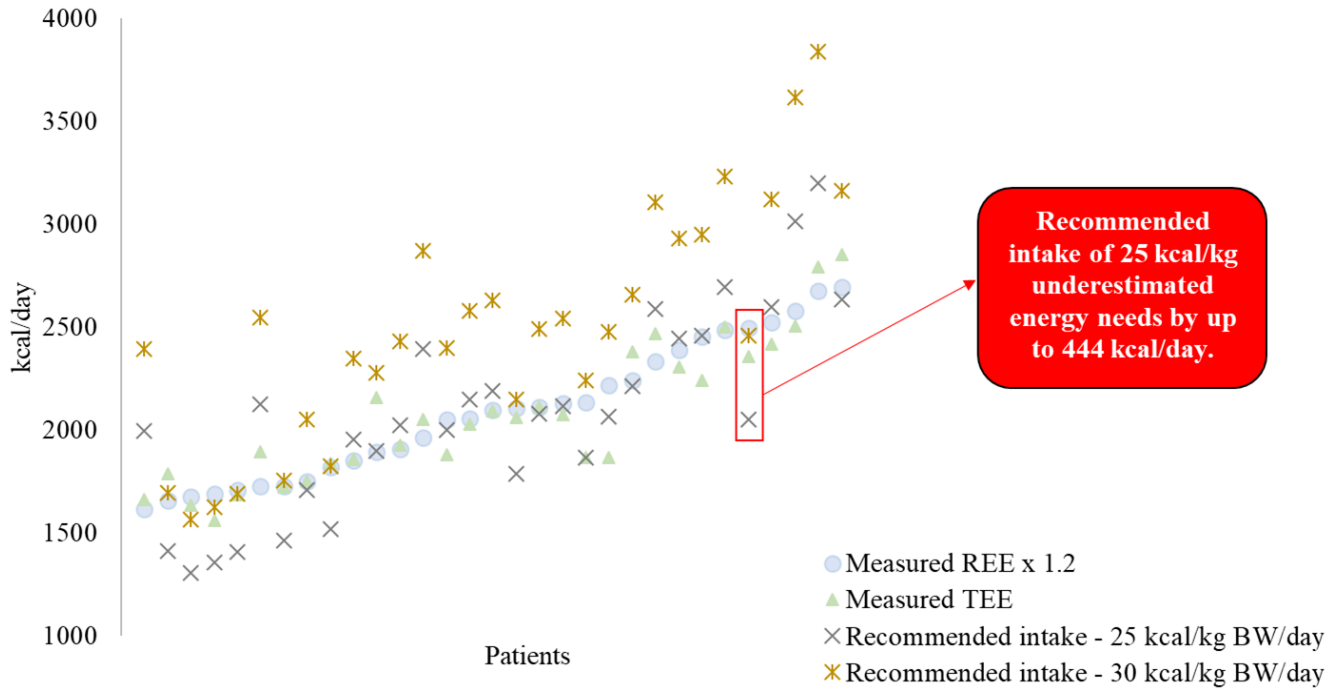

Figure 4.4. Measured and predicted energy expenditure of 31 patients with colorectal cancer. Each vertical series of quadruplicate points represents one patient. Resting Energy Expenditure was multiplied by 1.2 based on the average physical activity level of these patients. BW: body weight; kcal: kilocalories; REE: resting energy expenditure; TEE: total energy expenditure.

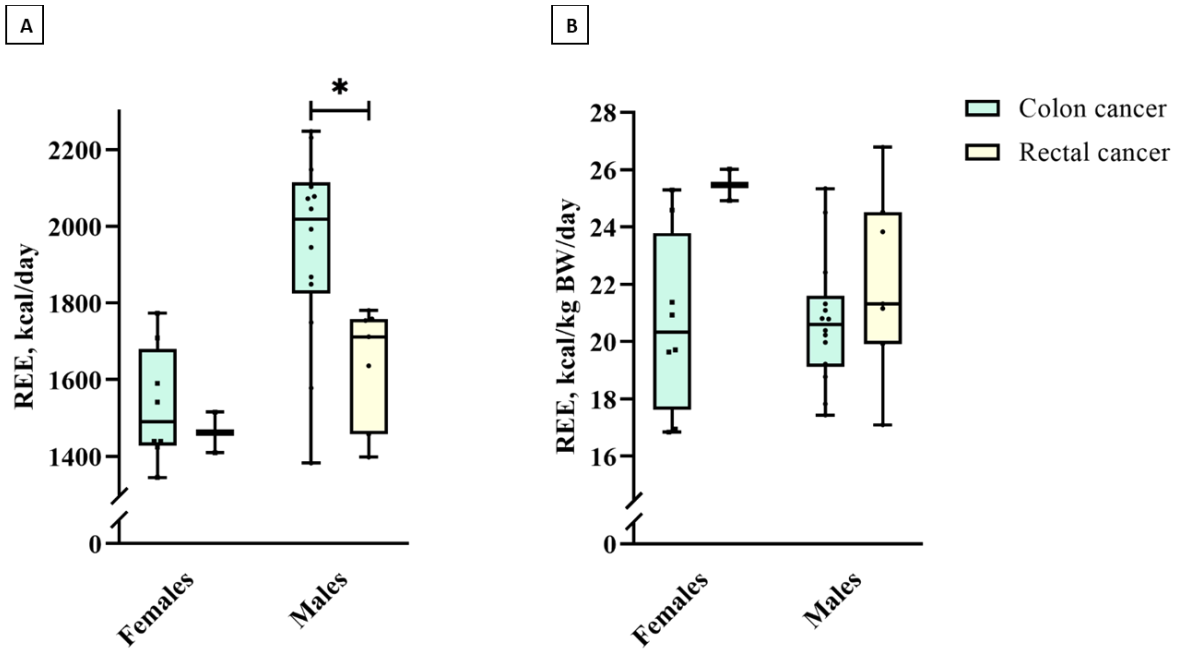

Figure 4.5 A-B. Resting energy expenditure measured by indirect calorimetry chamber presented in kilocalories per day (A) and adjusted for body weight (B) in 31 patients with colorectal cancer. Patients with colon cancer were compared to patients with rectal cancer by sex. Box plots present minimum and maximum values. Points represent individual patients. Males with colon and rectal cancer were compared using independent samples t-test. Analysis between females was not possible as n=2 females presented with rectal cancer. *p<0.01; kcal: kilocalorie; kcal/kg BW/day; kcal per kilogram of body weight/day; REE: resting energy expenditure.

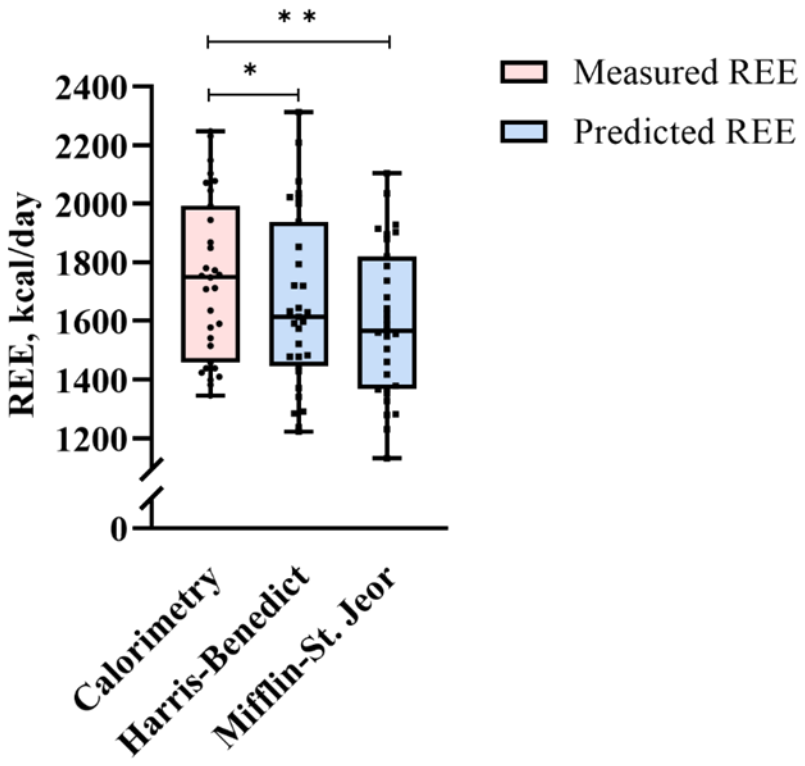

Figure 4.6. Resting energy expenditure measured by calorimetry chamber compared with commonly used predictive equations by paired samples t-test in 31 patients with colorectal cancer. Box plots present minimum and maximum values. Points represent individual patients. kcal: kilocalorie; REE: resting energy expenditure. *p<0.01; **p<0.001.

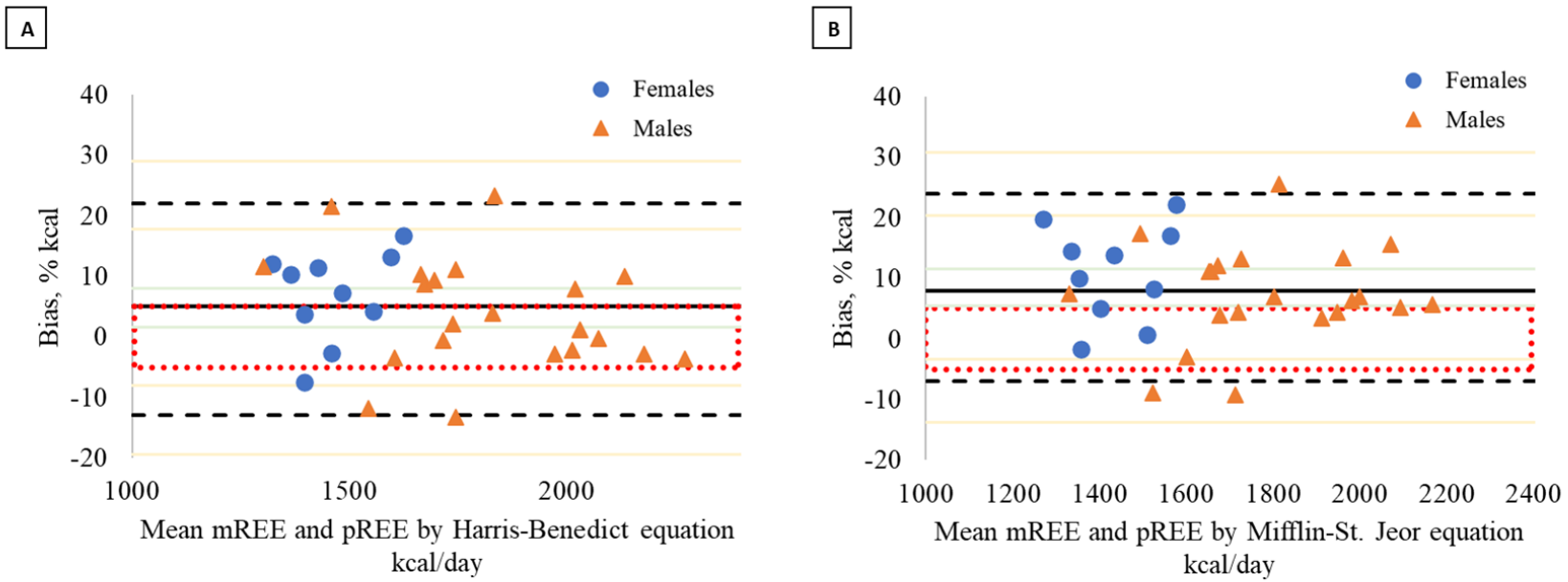

Figure 4.7 A-B. Bland-Altman plots of resting energy expenditure measured by indirect calorimetry and predicted resting energy expenditure by (A) Harris-Benedict and (B) Mifflin-St. Jeor equations in 31 patients with colorectal cancer. Solid black line represents the mean bias; solid green lines represent the 95% confidence intervals for the bias. Hashed lines represent the 95% limits of agreement (bias ± 1.96 x standard deviation); solid yellow lines represent the 95% confidence intervals for the limits of agreement. Red dotted box represents +/-5% of measured resting energy expenditure. Blue circles represent female patients; orange triangles represent male patients. The difference between measured and predicted REE was expressed as a percent of measured REE. kcal: kilocalorie; mREE: measured resting energy expenditure; pREE: predicted energy expenditure.

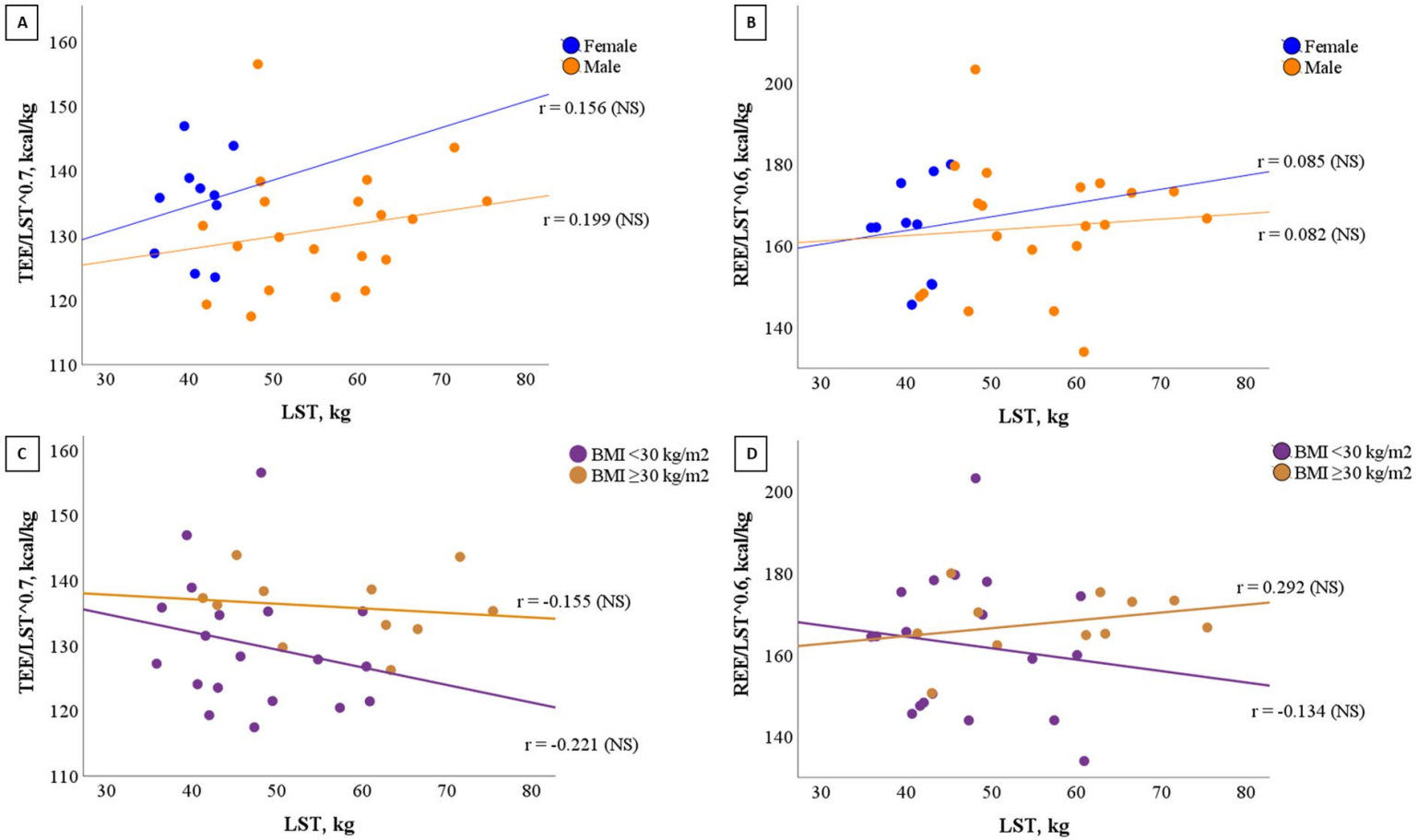

Figure 4.8 A-D. Relationship between total energy expenditure adjusted per kilogram of lean soft tissue raised to the power of 0.7 and lean soft tissue by sex (A) and by presence of obesity (C). Relationship between resting energy expenditure adjusted per kilogram of lean soft tissue raised to the power of 0.6 and lean soft tissue by sex (B) and by presence of obesity (D). As an example, these figures highlight that n=2 males who both presented without obesity and ~47kg of LST had measured total energy expenditure that differed by 609 kcal/day and measured resting energy expenditure that differed by 621 kcal/day. BMI: body mass index; kcal: kilocalorie; LST: lean soft tissue; NS: non-significance; REE: resting energy expenditure; TEE: total energy expenditure. N=30 patients with colorectal cancer.

Supplementary Table 4.1. Equations used to assess and predict total and resting energy expenditure

Equation	Formula
Total energy expenditure assessment	
Weir [10]	TEE (kcal/day) = (3.941 x VO_2 [L] + 1.106 x VCO_2 [L]) – (2.17 x urinary nitrogen [g/day])
Total energy expenditure prediction	
ESPEN Guidelines for Energy Intake [1]	Range (25–30 kcal/kg): EI (kcal/day) = 25 kcal x weight EI (kcal/day) = 30 kcal x weight
DRI Estimated Energy Requirements[1] [26]	Males: EER (kcal/day) = 662 – (9.53 x age) + PA x ([15.91 x weight] + [539.6 x height]) Females: EER (kcal/day) = 354 – (6.91 x age) + PA x ([9.36 x weight] + [726 x height])
Resting energy expenditure assessment	
Weir [10]	REE (kcal/day) = (3.941 x VO_2 [L/min] + 1.106 x VCO_2 [L/min]) x 1440 min/day
Resting energy expenditure prediction	
Mifflin-St. Jeor [27]	Males: REE (kcal/day) = (9.99 x weight) + (6.25 x height) – (4.92 x age) + 5 Females: REE (kcal/day) = (9.99 x weight) + (6.25 x height) – (4.92 x age) – 161
Harris-Benedict [28]	Males: REE (kcal/day) = 66.5 + (13.75 x weight) + (5.003 x height) – (6.755 x age) Females: REE (kcal/day) = 655 + (9.563 x weight) + (1.85 x height) – (4.676 x age)

Weight in kilograms; height in centimeters; age in years. [1]height in meters; PA: 1.0 (sedentary activity). DRI: dietary reference intake; EER: estimated energy requirements; ESPEN: European Society for Clinical Nutrition and Metabolism; EI: energy intake; g: grams; kcal: kilocalories; kg: kilogram; L: litre; min: minute; PA: physical activity coefficient; REE: resting energy expenditure; TEE: total energy expenditure; VCO_2: volume of carbon dioxide; VO_2: volume of oxygen.

Supplementary Table 4.2. Example of a Patient Schedule in the Calorimetry Chamber

Time	Task[1]
Day 1	
8:00 a.m.	24-hour energy expenditure assessment begins
8:00 – 9:00 a.m.	Resting energy expenditure
8:45 a.m.	Energy expenditure prediction using calorimetry chamber data
9:00 – 9:30 a.m.	Morning meal (asked to consume all food within thirty minutes)
9:30 a.m. – 12:00 p.m.	Leisure time (e.g., computer, television, reading)
11:15 a.m.	Energy expenditure prediction using calorimetry chamber data
12:00 – 12:30 p.m.	Mid-day meal (asked to consume all food within thirty minutes)
12:30 – 2:30 p.m.	Leisure time (e.g., computer, television, reading)*
2:30 – 3:00 p.m.	Afternoon snack (asked to consume all food within thirty minutes)
3:00 – 5:00 p.m.	Leisure time (e.g., computer, television, reading)
3:15 p.m.	Energy expenditure prediction using calorimetry chamber data
5:00 – 5:30 p.m.	Evening meal (asked to consume all food within thirty minutes)
5:30 – 8:00 p.m.	Leisure time (e.g., computer, television, reading)
8:00 – 8:30 p.m.	Evening snack (asked to consume all food within thirty minutes)
8:30 – 10:00 p.m.	Leisure time
10:00 p.m.	Sleep
Day 2	
6:00 a.m.	Wake-up call and reminder to void bladder
7:15 a.m.	Exit the calorimetry chamber

[1]A subset of patients completed a semi-structured interview over the phone during the 24-hour assessment. Results from that study are presented in **Chapter 4**.

Supplementary Table 4.3. Sample of regular and low-fibre menu items provided to patients during the 24-hour calorimetry chamber assessment

	Regular Menu	Low-fibre Menu
Morning meal	Eggs, scrambled Toast, whole wheat Peanut butter Juice, orange	Eggs, scrambled Toast, white Margarine Juice, apple
Mid-day meal	Turkey wrap • Tortilla, flour • Turkey, deli • Dressing, ranch • Cheese, cheddar • Lettuce, romaine • Tomato, diced Tomato soup Peaches, canned in juice[1] Yogurt, vanilla[1]	Turkey wrap • Tortilla, flour • Turkey, deli • Dressing, ranch • Cheese, cheddar Tomato soup Peaches, canned in juice[1] Yogurt, vanilla[1]
Afternoon snack	Apple Crackers, multigrain Cheese, mozzarella Yogurt, vanilla[1]	Applesauce Crackers, multigrain Cheese, mozzarella Yogurt, vanilla[1]
Evening meal	Chicken stir fry • Chicken breast • Celery • Carrot • Onion • Soy sauce • Ginger • Garlic Rice, brown Yogurt, vanilla[1]	Chicken stir fry • Chicken breast • Soy sauce • Ginger • Garlic Rice, white Yogurt, vanilla[1]
Evening snack	Almonds Milk[1] Cereal, Cheerios[1] Peaches, canned in juice[1]	Bread, white Margarine Jam, seedless Milk Peaches, canned in juice[1]

[1]use of these menu items varied depending on the caloric needs of the patient.

Supplementary Table 4.4. Macronutrient composition of a 2000 kilocalorie regular and low-fibre study diet

	Target	Regular Menu	Low-fibre Menu
Energy, kcal	2000	2020	1998
Carbohydrate			
Grams	250	247	258
% of energy	50	49	52
Fat			
Grams	67	66	62
% of energy	30	29	28
Protein			
Grams	100	111	101
% of energy	20	22	20

kcal: kilocalories.

Supplementary Figure 4.1. View inside of the calorimetry chamber located within the Human Nutrition Research Unit at the University of Alberta.

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Chapter 5 Assessing the Feasibility and Impact of Protein Intake on Muscle Mass and Physical Function in Patients with Colorectal Cancer: Findings from a Randomized Pilot Trial

5.1 Preface

The following chapter is based on data from 50 patients with stage II-IV colorectal cancer (CRC) who were recruited from the Cross Cancer Institute, Edmonton, Canada to participate in the Protein Recommendation to Increase Muscle (PRIMe) randomized controlled trial. This work aimed to explore the feasibility and potential effects of a diet containing 2 g/kg/day versus 1 g/kg/day protein on muscle mass (MM) and physical function. To our knowledge, this is the first randomized controlled trial investigating the potential impact of different levels of protein intake on MM in patients with CRC.

A version of **Chapter 5** is being prepared for submission to an academic journal. Select data from this chapter was accepted for poster presentation at the 44th European Society for Clinical Nutrition and Metabolism (ESPEN) Congress in Vienna, Austria (Sept 3-6, 2022). The corresponding abstract was accepted for publication in Clinical Nutrition ESPEN (Katherine L Ford, Michael B Sawyer, Sunita Ghosh, Claire F Trottier, Ilana Roitman Disi, Kathryn N Porter Starr, Connie W Bales, Mario Siervo, Nicolaas Deutz, Carla M Prado. 2022).

Data from the first 11 patients were collected by individuals other than me; I was responsible for recruitment and data collection for the remaining 39 patients. I maintained ethics approval for this study and was responsible for data management. A research coordinator also supported these activities. I was responsible for data analysis and interpretation and chapter/manuscript preparation. Dr. Carla M. Prado formulated the research question, study design and implementation, and oversaw data analysis/interpretation and chapter/manuscript preparation; all other authors contributed to conceptualizing the study.

5.2 Abstract

Rationale: Low muscle mass (MM) is prevalent in cancer and a predictor of negative clinical outcomes. Optimal nutrition, including adequate protein intake is essential to support muscle health, especially in catabolic conditions such as cancer. Protein is particularly important for muscle health but its requirements in cancer are not well characterized. The primary objective of this 12 week trial was to inform the feasibility of utilizing a diet containing 2 g/kg/day versus 1 g/kg/day protein to halt MM loss during cancer treatment. The secondary objective was to assess potential effects of a diet containing 2 g/kg/day versus 1 g/kg/day of protein on maintaining physical function. Exploratory objectives were to assess the feasibility sustaining a diet containing 2 g/kg/day protein and to compare the potential effects of a diet containing 2 g/kg/day versus 1 g/kg/day of protein on anthropometrics, body composition, physical activity, energy expenditure, nutritional status, and quality of life.

Methods: Patients with newly diagnosed stage II-IV colorectal cancer (CRC) were randomized to a diet containing 1.0 versus 2.0 g/kg/day of protein and were provided individualized nutrition counselling on how to adopt that level of protein intake for 12 weeks. Assessments were conducted at baseline, week 6, and week 12. Muscle mass was assessed by dual-energy X-ray absorptiometry (DXA). Appendicular lean soft tissue (ALST) index [ALSTI = ALST (kg) divided by height (m^2)], was used as an estimate of MM. Low MM was defined according to established cut-offs. Physical function was assessed by the Short Physical Performance Battery (SPPB) test. Nutritional status was assessed by the Patient-Generated Subjective Global Assessment (PG-SGA) Short Form©. Dietary intake was assessed by 3-day weighed food records. Data are mean ± standard deviation. Independent samples t-test was used to assess mean differences at timepoints. Generalized estimating equations were used to analyze the impact of study arm allocation (intention-to-treat analysis) or actual protein intake on outcome variables, accounting for repeated measures.

Results: Fifty patients (57 ± 11 years; body mass index: 27.3 ± 5.6 kg/m^2; 60% males; 78% colon; 64% stage III) were included at baseline. A diet containing 2 g/kg/day protein was not feasible (mean intake at week 12: 1.6 ± 0.5 g/kg/day) at a group level. At the individual level, 35.3% of patients (n=6) in the 2 g/kg/day diet group attained the target protein intake. This level of protein intake was observed in 8.7% of patients (n=2) in the 1 g/kg/day diet group. At week

12, difference between the 2 g/kg/day and 1 g/kg/day diet groups trended towards significance for MM (ALSTI 2 g/kg/day group: 8.2 ± 1.8 kg/m^2 and 1 g/kg/day group: 7.2 ± 1.2 kg/m^2; p=0.065) while differences were not observed for markers of physical function. At week 12, 58.8% of patients (n=10) in the 2 g/kg/day group maintained or gained MM compared with 43.5% of patients (n=10) in the 1 g/kg/day group. Prior to nutritional intervention, most (66%) patients reported protein intake <1.2 g/kg/day, the target amount for patients with cancer. When patients who completed the trial were considered, protein intake did not change in the 1 g/kg/day group but increased by 0.6 ± 0.4 g/kg/day (p<0.001) in the 2 g/kg/day group. At week 12, mean protein intake in the 2 g/kg/day group was 1.6 ± 0.5 g/kg/day compared to 1.2 ± 0.4 g/kg/day in the 1 g/kg/day group (p=0.012). Irrespective of diet group allocation, percent change in MM from baseline trended towards a positive association with protein intake, which suggested that an increase in protein intake of 1.0 g/kg/day could result in 1.6% increase in ALSTI (β: 1.57; 95% CI: -0.24, 3.39; p=0.090). A positive association between protein intake and SPPB score was observed (β: 0.37; 95% CI: 0.08, 0.67; p=0.014). Increased protein intake improved PG-SGA score (i.e., lower score; β: –2.71; 95% CI: –4.21, –1.20; p<0.001).

Conclusion: Our findings suggest that consuming a diet containing 2.0 g/kg/day of protein was not feasible for patients being treated for CRC although after 12 weeks of targeted nutrition intervention, difference in MM between patients assigned to a 2 g/kg/day or a 1 g/kg/day diet and receiving individualized nutrition counselling trended towards significance. Physical function was not different between diet groups. Mean difference in protein intake between groups at week 12 was 0.4 g/kg/day which may likely explain the lack of differences observed. Nonetheless, protein intake was above the minimum recommended intake in both groups and did not decrease over time. When protein intake was considered irrespective of diet group allocation, positive effects on overall nutrition status including MM and physical function were observed. This pilot trial highlights the challenge of consuming a diet containing 2 g/kg/day of protein but nonetheless showed the potential for nutrition intervention alone to halt MM loss in patients with cancer, suggesting that muscle anabolism is possible. Larger trials are needed to fully explore statistical significance and clinical relevance of interventions that improve protein intake.

5.3 Introduction

Cancer and anti-cancer treatment are known to negatively affect muscle mass (MM) [1], accelerating its loss [2] yet therapies to combat this prevalent condition are yet to be elucidated [3]. Low MM is prevalent in cancer and is associated with decreased physical function, poorer health-related quality of life, increased risk for treatment toxicity, delayed treatment, surgical complications, and shorter survival [4-12]. Muscle mass and physical function (i.e., performance) are commonly considered simultaneously in age- and disease-related muscle conditions [13, 14] and are endpoints of importance in oncology trials [15]. Colorectal cancer (CRC) is the third most diagnosed cancer globally, the second cause of cancer-related mortality [16], and low MM is observed in ~50% of patients with CRC [17] independent of body weight (BW) and weight loss [10]. Muscle loss negatively affects prognosis and is the primary nutritional problem in patients with cancer [3]. Without intervention, MM loss is observed in patients with early (mean change in skeletal muscle index over 1 year: -0.5%) [18] and advanced (-4% over 60 days to -6.1% over 90 days) [19, 20] CRC, and is predictive of survival. Early and continued optimization of nutritional status, including elevated protein requirements [21], is crucial to prevent and minimize negative health outcomes (e.g., muscle loss and decreased physical function) in patients with cancer [3, 22]. In turn, nutritional interventions to treat muscle-related conditions or abnormalities is the focus of several ongoing oncology trials [23].

Oncology nutrition guidelines recommend that protein intake should be at least 1.0 g/kg/day and up to 1.5 g/kg/day if possible [21]. These recommendations are higher than those for healthy populations (0.8 g/kg/day) [24] and are similar but higher than those for older (>65 years) adults (≥1.0–1.2 g/kg/day) [25]. Current oncology nutrition guidelines acknowledge the need for further research on protein intake in cancer and include a call for research investigating the effect of increased protein (1.0–2.0 g/kg/day) on clinical outcomes [21]. High protein oral nutritional supplements or intravenous amino acids have been shown to increase the anabolic potential of muscle in patients with cancer, regardless of disease stage [26, 27]. The use of oral nutritional supplements with dietary advice reduced MM loss and prevalence of low MM in patients at nutritional risk following CRC resection [28]. Despite skepticism, patients with cancer retain anabolic potential that is stimulated by protein [29]. A systematic review explored the impact of protein intake on MM in patients with a cancer that had a high risk of muscle loss and

found that MM maintenance during treatment was possible with protein intake >1.4 g/kg/day although patients who consumed less than 1.2 g/kg/day presented with muscle loss [30]. In light of these findings [30], current protein intake recommendations in cancer may not be sufficient to support MM maintenance. Pragmatic approaches are needed to evaluate the feasibility of higher protein (2.0 g/kg/day) diets and their ability to promote MM maintenance during cancer therapy [21].

In view of the evidence discussed above, the primary objective of this study was to inform the feasibility of utilizing a diet containing 2 g/kg/day versus 1 g/kg/day of protein for the first 12 weeks of chemotherapy to halt MM loss. The secondary objective was to assess potential effects of a 2 g/kg/day versus 1 g/kg/day protein diet on maintaining physical function. Exploratory objectives were to assess the feasibility of sustaining a 2 g/kg/day protein diet during cancer treatment and to compare the potential effects of a 2 g/kg/day versus 1 g/kg/day protein diet on anthropometrics, body composition, physical activity, energy expenditure, nutritional status, and quality of life.

5.4 Methods

5.4.1 Trial Design and Ethical Procedures

The Protein Recommendation to Increase Muscle (PRIMe) study was a single-center, two-arm, open-label, randomized, controlled pilot trial that took place between August 2016 and April 2022. The study protocol was published [31] (**Chapter 3**) and the trial was registered as NCT02788955 on ClinicalTrials.gov [32]. Clinical assessments of patients were completed at the Human Nutrition Research Unit [33], Department of Agricultural, Food & Nutritional Science, University of Alberta (Edmonton, Alberta, Canada). In response to the COVID-19 pandemic, recruitment was temporarily suspended from March until June 2020 due to public health restrictions. No patients were active on the trial when study assessments halted in March 2020 thus no patients were lost to follow up or dropped out of the study due to the COVID-19 pandemic. Trial assessments re-commenced in July 2020. No changes to the study protocol occurred; patients enrolled in the trial during the COVID-19 pandemic completed the same protocol as patients who were enrolled pre-pandemic. Trial reporting was guided by the Consolidated Standards of Reporting Trials (CONSORT) extension for randomized pilot and feasibility trials [34]. The study was approved by the Health research Ethics Board of Alberta-

Cancer Committee (HREBA.CC-15-0193) and complied with standards outlined in the Canadian Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans [35]. All patients provided written informed consent prior to any study assessments.

5.4.2 Study Protocol

Ambulatory men and women between the ages of 18-85 years with a recent diagnosis of stage II-IV CRC were recruited from the Cross Cancer Institute (Edmonton, Alberta, Canada). Patients were eligible to participate if they could complete all baseline study assessments within 2 weeks of starting chemotherapy and had adequate hepatic and renal function. Reasons for exclusion were acute inflammation (assessed by neutrophil/lymphocyte >5 [36]), ongoing (non-treatment related) nutrition-impact symptoms (e.g., anorexia), severe dietary restrictions (e.g., veganism), a medical condition that impacted ability to increase muscle (e.g., cachexia [14]), active treatment for another cancer site, body weight >450 lbs, women who were pregnant or lactating, a pacemaker *in situ*, insulin-dependant diabetes, or unstable thyroid disease.

Patients were screened for eligibility and a study coordinator obtained approval from the treating medical oncologist before potential patients were approached and offered study information. Interested patients were invited to the Human Nutrition Research Unit at the University of Alberta for a screening/orientation study visit. Final eligibility verification (adequate hepatic and renal function) was assessed through the electronic medical record of consented patients. Eligible patients completed a 3-day weighed food record to assess usual dietary intake and returned to the research unit to complete baseline study assessments within 2 weeks of starting chemotherapy.

In preparation for study visits, patients were advised to refrain from: smoking or using nicotine the morning of the assessments; consuming any calories or caffeine for 10 hours prior; and physical activity and alcohol consumption for 24 hours prior [37]. Water, medication, and minimal activity (e.g., morning activities of daily living and commuting to the research unit) were permitted prior to study visits. At the baseline visit, anthropometrics, dietary intake, body composition, physical function and activity, energy metabolism, nutritional status, and quality of life were evaluated. After baseline assessments were complete, patients were randomly assigned to the 1.0 versus 2.0 g/kg/day protein diets in a 1:1 allocation ratio using block randomization. A registered dietitian provided individualized nutrition counselling on how to adopt the specified

level of protein intake. A graphical illustration of the study protocol is provided in **Figure 5.1**. An overview of assessment techniques is provided below; detailed descriptions are presented in the published trial protocol (**Chapter 3**) [31].

5.4.3 Nutrition Intervention

A registered dietitian met with the patient at the baseline study visit to provide individualized nutrition counselling. This involved a complete dietary assessment and nutrition education. Patients assigned to the 1 g/kg/day diet received instructions from the registered dietitian to achieve protein intake in line with the minimum standard of care (1.0 g/kg/day) while those assigned to the 2 g/kg/day protein diet were instructed to follow such a diet [21]. Prescribed diets were translated into a daily meal pattern that was individualized and adapted for the patient's typical dietary intake and mimicked an approach described elsewhere [38]. The meal pattern specified the number of 'choices' from each food group that was recommended per day. Patients were provided an adapted version of the *Choose Your Foods for Weight Management* book developed by the Academy of Nutrition and Dietetics [39]. The book contained lists of foods and respective serving sizes that represented a 'choice'. For example, 1 'choice' from the protein group contained 7 g of protein and 1 'choice' from the milk group contained 8 g of protein [39]. The reference amount of protein from each group counted towards total protein intake. Patients were encouraged to use the food scale provided to weigh their food portions, especially meat, poultry, fish, and seafood products as portion sizes of these foods are difficult to estimate by volume. Patients were provided a multivitamin (natural product number: 80043120 or 80024313 [40], Supplementary Table 5.1) to consume daily during the 12-week intervention.

Patients were encouraged to meet their protein goal by adjustments to their regular diet but were provided a high-quality oral whey protein powder (Beneprotein® [Nestlé Health Science, Toronto, Ontario, Canada] or PC® Whey Protein Isolate [President's Choice, Brampton, Ontario, Canada], **Supplementary Table 5.2**) as needed to supplement intake, regardless of diet group allocation. A member of the research team contacted all patients who were active in the trial by telephone on a weekly basis throughout the study to address study-related questions, assess adherence to protein intake, inquire about any potential chemotherapy-related nutrition-impact symptoms, and monitor self-reported body weight. The registered dietitian followed-up

with patients at the week 6 visit and as needed throughout the study.

5.4.4 Outcomes

Outcomes assessments were conducted at baseline, week 6, and week 12 by trained research staff using standardized procedures. Muscle mass was a surrogate marker of feasibility and was considered the primary outcome. Physical function was the secondary outcome and anthropometrics, resting energy expenditure (REE), nutritional status, physical activity, and quality of life were exploratory outcomes.

5.4.4.1 Patient Characteristics and Anthropometrics

Electronic medical records were used to obtain patient characteristics including patient age, sex, and disease and treatment history. Stage of disease was determined by tumor, node, metastasis (TNM) staging [41]. A questionnaire was used to collect data on self-reported race and ethnicity, household income, and education level.

Anthropometric measurements including height, weight, and waist and calf circumferences (CC) were assessed. These measurements were taken with patients wearing thin, light clothing or a hospital gown. Height was measured to the nearest 0.1 cm using a 235 Heightronic Digital Stadiometer (Quick Medical, Issaquah, Wash., USA) at baseline. Mean BW was measured in triplicate to the nearest 0.1 kg using a calibrated digital scale (Health o meter® Professional Remote Display, Sunbeam Products Inc., Fla., USA). Body weight (kg) was divided by height (m^2) to calculate body mass index (BMI) which was categorized per the Centers for Disease Control (underweight: <18.5 kg/m^2; normal range: 18.5–24.9 kg/m^2; overweight: 25.0–29.9 kg/m^2; obesity: ≥30.0 kg/m^2) [42]. Waist circumference and right-sided CC were measured to the nearest 0.1 cm in triplicate and duplicate, respectively, using a measuring tape. Calf circumference was adjusted for patients with a BMI outside of the normal range as follows: BMI <18.5 kg/m^2: CC + 4 cm; BMI 25.0–29.9 kg/m^2: CC - 3 cm; BMI 30.0–39.9 kg/m^2: CC - 7 cm; BMI ≥40 kg/m^2: CC - 12 cm [43].

5.4.4.2 Body Composition

The feasibility of using a 2 g/kg/day versus 1 g/kg/day protein diet to halt MM loss was assessed by absolute change in MM from baseline to week 12 and by percent change from baseline. Body composition was assessed by dual-energy X-ray absorptiometry (DXA) using a

General Electric Lunar iDXA High Speed Digital Fan Beam Densiometer with Encore 13.60 software (General Electric Company, Madison, WI, USA). Whole-body and regional estimates of lean soft tissue (LST), fat mass (FM), and bone mineral content were derived from the DXA scan. Fat-free mass (FFM) was calculated by summing LST and bone mineral content values. Appendicular LST (ALST) was divided by patients' height (m^2) to derive an ALST index (ALSTI). This was used as an estimate of muscle status and subsequently our MM outcome; albeit different, both words will be used in this chapter (i.e., MM and LST). Low MM was defined as ALSTI <7.0 kg/m^2 for males and <5.5 kg/m^2 for females [13]. Overweight and obesity is prevalent among patients with CRC [44] thus we also investigated low MM with an approach that accounted for body size [45]. Appendicular LST was divided by BW then multiplied by 100% and low MM was defined as <28.27% for males and <23.47% for females [45, 46].

5.4.4.3 Physical Function and Activity

Physical function was assessed by the short physical performance battery (SPPB) test, a validated measurement that includes a sit-to-stand test, balance testing, and a timed 2.44 meter walking test [47]. Each activity can score up to 4 points, for a total of 12 points. Change in handgrip strength was assessed using a Jamar® Hydraulic Hand Dynamometer (Sammons Preston Rolyan, Bolingbrook, IL, USA). The highest score from a triplicate assessment in the non-dominant hand while standing was used. Handgrip strength was presented in absolute terms and adjusted by BW and by BMI [45, 48, 49].

The International Physical Activity Questionnaire–Short Form (IPAQ–SF) was used as a measure of self-reported physical activity [50]. A continuous total physical activity score was expressed in metabolic equivalencies of task (MET) in minutes per week, and used to categorize self-reported physical activity as inactive, moderately active, or highly active [51]. Total, walking, moderate, and vigorous MET-minutes/week were also obtained from the IPAQ-SF.

5.4.4.4 Energy Expenditure

Resting energy expenditure was assessed by calorimetry chamber at each study visit, as described in **Chapters 3–4** [31]. Briefly, the open-circuit calorimetry chamber was used to measure volumes of O_2 ($\dot{V}O_2$) and CO_2 ($\dot{V}CO_2$) exchanged. Temperature was maintained within a

range of 21–23 °C and relative humidity <70%. Fresh air was drawn passively into the chamber at 60 liters (L)/minute and mixed expired air was withdrawn from the chamber by a minispiral fan. Air was pumped at a flow rate of 1 L/minute into O_2 (Oxymat 6, Siemens AG, Munich, Germany) and CO_2 (Advance Optima AO2000 Series, ABB Automation GmbH, Frankfurt, Germany) differential analyzers. Calculated minute-by-minute difference in VO_2 and VCO_2 concentrations between the calorimetry chamber and the buffer zone were transmitted from the gas analyzers to a desktop computer by the National Instruments NI USB-6221 device (National Instruments Corporation, Austin, Texas, USA) and displayed on the screen via PMCSS Software version 1.8 (Pennington Metabolic Chamber Software Suite, Pennington Biomedical Research Center, Louisiana, USA). The CO_2 and O_2 analyzers were calibrated once per week. The calorimetry chamber was calibrated prior to each assessment with pre-mixed gas (20% O_2; 1% CO_2; balanced with nitrogen) and 24-hour propane burn tests were conducted quarterly.

To assess REE inside of the room calorimetry chamber, patients were instructed to rest in the supine position, remain awake, and minimize movement for 60 minutes. Patients were monitored visually every 15 minutes to ensure they remained awake and motionless in the supine position. The first 30 minutes of data are not registered by the software, and this allows time for patients to acclimatize to the calorimetry chamber environment. The subsequent 30 minutes of data were used to calculate REE. Volume of O_2 and VCO_2 were summed and divided by 30 to obtain mean values in L/minute. These data were applied to the abbreviated Weir equation [52] to obtain an estimate of REE expressed in kilocalories per day (kcal/day).

5.4.4.5 Nutritional Status and Intake

The Patient-Generated Subjective Global Assessment (PG-SGA) Short Form© was used to assess nutritional status [53]. This form collected patient-reported measures of weight, food intake, nutrition-impact symptoms, and activities/function [53] and is a validated nutrition screening tool in the outpatient oncology setting [54-56]. Total score for the PG-SGA ranged from 0–36 and higher scores indicated increased nutritional risk. Patients who score ≥4 are considered to be at nutritional risk and should receive nutritional intervention from a registered dietitian [53] while others have suggested that a score ≥3 [55] or ≥6 [56] is the optimal cut-off to distinguish malnourished from well-nourished patients. Herein, patients were considered at nutritional risk when PG-SGA score was ≥4.

The feasibility of consuming a 2 g/kg/day protein diet during cancer treatment was further assessed by changes to protein intake during the intervention. Protein intake was compared with the recommended intake for patients with cancer (minimum: 1.0 g/kg/day; optimal: 1.2-1.5 g/kg/day) [21] and the recommended dietary allowance (RDA; 0.8 g/kg/day) for healthy populations [24]. All dietary data from food records were entered into The Food Processor® Nutrition and Fitness Software (version 11.0.3 or version 11.7.217, ESHA Research, Salem, OR, USA) and assessed for nutrient composition. Protein and energy intakes per kg were compared with recommended intakes in cancer [21].

5.4.4.6 Quality of Life

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30, version 3) was used to assess health-related quality of life in cancer [57]. Scales to measure function, symptoms, and global health status/quality of life were included and a high score was indicative of a greater response to the measure [58]. The Functional Assessment of Anorexia/Cachexia Therapy (FAACT) was used to measure challenges related to anorexia and cachexia [59]. A total score and subscale scores for anorexia/cachexia and physical, social/family, emotional and functional well-being were calculated as described elsewhere [60].

5.4.5 Sample Size

Since this was a pilot study to assess feasibility of the nutritional intervention, a formal sample size calculation was not required or performed [34]. We enrolled n=25 per arm for a total sample size of 50. A post hoc power calculation of achieved effect was not calculated given its mathematical redundancy [61, 62]. Instead, effect size and estimates obtained from this pilot study can be used to design future studies.

5.4.6 Statistical Analysis

Data entries were verified for quality control using the double data-entry method. Statistical analyses were completed using IBM SPSS® Statistics version 28 (International Business Machines Corporation, Armonk, NY, USA) and GraphPad Prism version 9.3.1 for Windows (GraphPad Software, San Diego, California, USA). Variables were analyzed using the intention-to-treat principal meaning that data were assessed based on study arm randomization,

regardless of adherence to the intervention. Due to the nature of this pilot study, complete case analysis (i.e., only those who completed the study were considered) and analyses based on the intervention received (i.e., amount of protein consumed) were also conducted.

No formal hypothesis testing was conducted as this was a pilot trial designed to assess feasibility of a novel intervention and provide preliminary evidence that can be used to design a definitive trial [34, 63]. Data comparisons were carried out with an alpha-level of 5% but caution was used when interpreting analyses as this study was not powered for drawing statistical inference on the outcomes assessed but rather, was intended to inform the feasibility of the intervention and a larger scale trial. Thus, $0.05<p<0.10$ was noted as trending. Data are mean ± standard deviation or median and interquartile range (25^{th} percentile, 75^{th} percentile) for non-normality unless otherwise indicated. Normality was assessed by Shapiro-Wilk test.

Our intention to treat analysis explored change over time using generalized estimating equation (GEE) models, a statistical technique used to account for between-subject (i.e., patient ID) and within-subject (i.e., time) correlation among responses seen in repeated measures studies [64, 65]. Generalized estimating equation models are valid under the assumption of data missing completely at random [64, 65]. Our intention-to-treat analysis used an autoregressive model order 1 (AR–1) working correlation matrix to account for change in correlations with time and an identity link function to form a linear relation between the dependent variable (ALSTI) and the predictor (study arm allocation). Analyses that considered actual protein intake as a predictor were also conducted. Models to assess MM loss (versus MM maintenance or gain) used a binomial distribution and logit link function. Additionally, repeated measures analysis of covariance (ANCOVA) was used to assess outcomes while accounting for baseline value of the outcome as a covariate. Mean adjusted differences, 95% confidence intervals (CI), and eta-squared (η^2; a measure of effect size) were presented. Comparisons between the 2 g/kg/day and 1 g/kg/day diet arms were also explored using independent samples t-test or Mann–Whitney U test (for non-normally distributed data) to assess mean differences and Chi-squared test to compare frequencies of categorical and ordinal outcome variables at study timepoints (i.e., baseline, week 6, and week 12) and $p<0.025$ was used to account for multiple hypothesis testing.

5.5 Results

Patient flow through the trial is illustrated in **Figure 5.2**. Fifty patients completed baseline assessments, were randomized to the 2 g/kg/day diet (n=25) or the 1 g/kg/day diet (n=25) and were included in the intention-to-treat analysis. Lost to follow up was more prevalent in the 2 g/kg/day (32%; n=8) compared with the 1 g/kg/day (8%; n=2) group. Analyses specific to the week 6 timepoint included n=44 patients and those specific to the week 12 timepoint included n=40 patients. Lost to follow up occurred prior to week 6 assessments for most (60%; n=6) of the patients who did not complete the trial. Patient-reported reasons for discontinuing trial participation included feeling overwhelmed with managing a new cancer diagnosis or required time commitment.

5.5.1 Patient Characteristics

Baseline characteristics of patients by study group allocation are detailed in **Table 5.1**. Group differences at baseline were observed for the impact of diarrhea on quality of life; no other differences were noted. Patients were a mean age of 57 ± 11 years with a BMI of 27.3 ± 5.6 kg/m^2. Most patients were male (60%), had colon cancer (78%), and were diagnosed with stage II or III disease (74%). Initially, most (66%; n=33) patients reported protein intake <1.2 g/kg/day, the target amount for patients with cancer. Five patients (10%) had protein intake below the RDA (0.8 g/kg/day) while 20% of patients (n=10) were meeting the RDA but had not achieved the recommended intake for patients with cancer. Prior to dietary intervention, n=1 patient (2%) had protein intake >2.0 g/kg/day. The proportion of patients attaining various protein intake categories across study timepoints is illustrated in **Supplementary Figure 5.1**. Protein powder supplied by the study team was used by 29.5% of patients (n=13; n=10 2 g/kg/day group and n=3 1 g/kg/day group) at week 6 and 35% (n=14; n=11 2 g/kg/day group and n=3 1 g/kg/day group) at week 12.

At diagnosis, low MM assessed by ALSTI was observed in 20% of patients (n=10; n=6 males and n=4 females). When assessed as ALST/BW, the prevalence of low MM was 38% (n=19; n=9 males and n=10 females). At week 12, low MM assessed by ALSTI was observed in 12.5% of patients (n=5; n=4 males and n=1 females). When assessed as ALST/BW, the prevalence of low MM was 32.5% (n=13; n=7 males and n=6 females). Absolute values across study timepoints for anthropometrics and body composition, nutrition intake and status, and

energy expenditure are presented by study arm in **Table 5.2**, by sex in **Supplementary Table 5.3**, and by tumor location in **Supplementary Table 5.4**. Percent change from baseline to week 6 and baseline to week 12 for anthropometric measures are presented in **Figure 5.3 A-B**. Percent change in BW was greater in the 2 g/kg/day (1.6 ± 3.6%) compared with the 1 g/kg/day (-0.9 ± 3.1%; p=0.020) group at week 6 while no difference was observed at week 12 (2 g/kg/day group: 3.4 ± 5.6%; 1 g/kg/day group: 0.8 ± 5.1%; p=0.104). In turn, percent change in BMI since baseline was greater in the 2 g/kg/day (1.6 ± 3.7%) compared with the 1 g/kg/day (-0.9 ± 3.0%; p=0.019) group at week 6 while the difference between groups trended towards significance at week 12 (2 g/kg/day group: 3.4 ± 4.5%; 1 g/kg/day group: 0.7 ± 5.1%; p=0.096). Percent change from baseline to week 6 (2 g/kg/day group: 2.9 ± 5.0%; 1 g/kg/day group: -0.3 ± 4.2; p=0.027) and week 12 (2 g/kg/day group: 4.0 ± 6.0%; 1 g/kg/day group: 0.9 ± 3.9%; p=0.052) was greater in the 2 g/kg/day versus the 1 g/kg/day group for waist circumference. No difference between groups was observed for percent change in adjusted CC at either timepoint.

5.5.2 Protein and Energy Intakes

When patients were considered based on diet group allocation, a GEE model showed that being in the 2 g/kg/day diet group resulted in 0.25 g/kg/day greater protein intake compared with patients in the 1 g/kg/day group (β: 0.25; 95% CI: 0.04, 0.46; p=0.019) across timepoints. In the 2 g/kg/day group, the protein intake goal (2.0 g/kg/day) was achieved by 30% of patients (n=6) at week 6 and by 35.3% (n=6) at week 12 while 8.7% of patients (n=2) in the 1 g/kg/day group also consumed ≥2.0 g/kg/day of protein at week 12. Over the course of the study, protein intake did not change in the 1 g/kg/day group but increased by 0.6 ± 0.4 g/kg/day (p<0.001) in the 2 g/kg/day group when patients who completed the trial were considered. At week 12, mean protein intake in the 2 g/kg/day group was 1.6 ± 0.5 g/kg/day compared to 1.2 ± 0.4 g/kg/day in the 1 g/kg/day group (p=0.012), **Figure 5.4 A**. Protein intake by study arm and sex is illustrated in **Figure 5.4 B**. After adjusting for baseline protein intake as a covariate, protein intake in the 2 g/kg/day group (1.7 g/kg/day; 95% CI: 1.5, 1.9 g/kg/day) was higher than the 1 g/kg/day group (1.2 g/kg/day; 95% CI: 1.0, 1.4 g/kg/day; p<0.001) at week 12. Baseline protein intake accounted for 26% of variability in protein intake at week 12 (p<0.001; η^2=0.264). Difference in percent change in protein intake since baseline trended towards significance (2 g/kg/day group: 40.4 ± 44.8%; 1 g/kg/day group: 17.4 ± 36.9%; p=0.069) at week 6, **Figure 5.5 A.** At week 12, percent

change in protein intake since baseline was greater in the 2 g/kg/day compared with the 1 g/kg/day diet group (2 g/kg/day group: 54.5 ± 48.6%; 1 g/kg/day group: 10.2 ± 33.7%; p=0.002), **Figure 5.5 B.** Using a GEE model, no effect of study arm on energy intake was observed. In patients who completed the trial, percent change in energy intake since baseline (kcal/kg/day) trended towards being greater in the 2 g/kg/day compared with the 1 g/kg/day group at week 12 (2 g/kg/day group: 24 ± 27 kcal/kg/day; 1 g/kg/day group: 4 ± 34 kcal/kg/day; p=0.062).

5.5.3 Body Composition

When considered based on study arm allocation using a GEE model, the odds of MM loss (versus maintained or gained) appeared to be 54.1% lower for patients in the 2 g/kg/day group compared with the 1 g/kg/day group although this did not reach significance (odds ratio [OR]: 0.459; 95% CI: 0.163, 1.295; p=0.141). When further explored based on sex within each study arm, the odds of MM loss were 86.3% lower for females in the 2 g/kg/day group compared to females in the 1 g/kg/day group (OR: 0.137; 95% CI: 0.021, 0.897; p=0.038) whereas no association was observed for males between study groups (OR: 0.912; 95% CI: 0.254, 3.278; p=0.888). When all patients were considered at week 6, 43.2% (n=19) had maintained or gained MM (i.e., ALSTI). At week 12, 50% of patients (n=20) had maintained or gained MM. At week 12, difference in MM between study arms trended towards significance (ALSTI 2 g/kg/day group: 8.2 ± 1.8 kg/m^2; 1 g/kg/day group: 7.2 ± 1.2 kg/m^2; p=0.065), **Figure 5.6 A**. Sex differences within study groups are illustrated by timepoint in **Figure 5.6 B**. Males in the 2 g/kg/day group had higher MM compared to males in the 1 g/kg/day diet group at week 6 (ALSTI 2 g/kg/day group: 8.9 ± 1.8 kg/m^2; 1 g/kg/day group: 7.5 ± 1.0 kg/m^2; p=0.022) and week 12 (2 g/kg/day group: 9.2 ± 1.5 kg/m^2; 1 g/kg/day group: 7.6 ± 1.1 kg/m^2; p=0.007). No difference in MM between study arms for females was observed.

Change in MM from baseline to week 6 and week 12 were assessed on an absolute basis (**Figure 5.7 A-B**), as a percentage of change (**Figure 5.7 C-D**), and by sex (**Figure 5.8 A-D**) in patients who completed MM assessments at respective timepoints. Absolute change in MM did not differ between study arms at week 6 and 12. Change in MM as a percentage of baseline status at week 6 trended towards significance (2 g/kg/day group: 0.6% [-2.9%, 5.2%]; 1 g/kg/day group: -1.6% [-5.4%, 0.7%]; p=0.094) although no difference between groups was observed at week 12. Baseline MM accounted for 94% of variance in follow up measures of MM (p<0.001;

η^2=0.943). When adjusted for baseline MM, patients in the 2 g/kg/day diet group had a mean adjusted ALSTI of 7.6 kg/m^2 (95% CI: 7.4, 7.7 kg/m^2) compared with patients in the 1 g/kg/day group (adjusted mean: 7.3 kg/m^2; 95% CI: 7.2, 7.5 kg/m^2; p=0.084) at week 6. No difference in adjusted ALSTI between study arms was observed at week 12. Irrespective of study arm allocation, percent change in MM since baseline trended towards a positive association with actual protein intake and suggested that an increase of 1.0 g/kg/day protein may result in 1.6% increase in ALSTI (β: 1.572; 95% CI: -0.243, 3.387; p=0.090). Fat mass and FFM (both in kg and as % of total mass) were not predicted by study arm allocation or actual protein intake across timepoints when assessed by GEE model. At week 12, change in FM trended towards a difference between groups (2 g/kg/day group: 2.2 ± 2.6 kg; 1 g/kg/day group: 0.5 ± 2.8 kg; p=0.065) for patients who completed the trial.

5.5.4 Physical Function and Quality of Life

When considered based on study arm allocation using a GEE model, no difference between diet groups for the SPPB total test score or sub-component scores was observed. When each timepoint was considered individually, no difference in scores between groups were noted. Irrespective of study arm allocation, an increase in 1.0 g/kg/day protein resulted in an increase in SPPB test score of 0.4 points (β: 0.374; 95% CI: 0.077, 0.670; p=0.014). For the sit-to-stand component of the SPPB test, scores increased by 0.4 points for every 1.0 g/kg/day increase in protein intake (β: 0.337; 95% CI: 0.095, 0.578; p=0.006). No sex differences were observed for total or sub-components of the SPPB test. Using a GEE model, there was no difference in handgrip strength between study arms across timepoints. No difference in percent change since baseline for handgrip strength was observed between groups at week 6 and week 12, **Figure 5.5 A and B**. Similarly, no difference between study arms across timepoints were observed for absolute handgrip strength or when divided by BW or BMI.

A GEE model showed that being allocated to the 2 g/kg/day group was associated with an additional 503 moderate MET-minutes per week (β: 503; 95% CI: 46, 960; p=0.031). Findings trended towards increased total time of MET-minutes per week in the 2 g/kg/day group (β: 1118; 95% CI: -94, 2330; p=0.071). No significant associations between study arm allocation and walking or vigorous MET-minutes per week were observed. In patients who completed assessments at week 6 and week 12, no difference between the 2 g/kg/day and 1 g/kg/day diet

groups was observed for intensity of physical activity or for total MET-minutes per week at either timepoint.

Study group allocation was not associated with quality of life assessments using a GEE model. In patients who completed these assessments at all timepoints, no difference in total scores or change in scores since baseline were observed between study arms. Absolute values across study timepoints by group are presented for physical function, activity, and quality of life variables in **Table 5.3**.

5.5.5 Nutritional Status and Energy Expenditure

Prior to intervention, 58% of patients (n=29; n=13 2 g/kg/day group and n=16 1 g/kg/day group) presented with a PG-SGA score ≥4 which indicated nutritional risk. At week 12, 60% of patients (n=24; n=11 2 g/kg/day group and n=13 1 g/kg/day group) had a PG-SGA score ≥4. Using a GEE model, nutritional status assessed by PG-SGA total score and sub-scores was not impacted by study arm allocation although a 1.0 g/kg/day increase in protein intake resulted in improved PG-SGA score (i.e., lower score by 2.7 points), β: –2.708; 95% CI: –4.214, –1.203; p<0.001. Patients who lost MM during the study (i.e., did not maintain or gain MM) had worse PG-SGA score (i.e., higher score by 2.8 points), β: 2.816; 95% CI: 0.944, 4.688; p=0.003. Similar to the GEE model, no difference in scores was observed between diet groups at each timepoint (**Table 5.2)**.

Resting energy expenditure was not associated with study arm allocation using GEE models although patients who lost MM (versus maintained or gained) trended towards lower REE (β: -84; 95% CI: -171, 3; p=0.06). In patients who completed all study assessments, no difference between study arms was observed in REE percent change since baseline.

5.6 Discussion

The primary findings of this randomized controlled pilot trial were that a 2.0 g/kg/day diet for 12 weeks supported by individualized nutritional counselling from a registered dietitian was not achievable for patients being treated for CRC (mean intake at week 12 in 2 g/kg/day diet group: 1.6 g/kg/day). Notwithstanding the challenge of attaining a 2 g/kg/day diet, 35% of patients (n=6) assigned to the 2 g/kg/day group achieved the target intake level. Notably, 8.7% of patients (n=2) assigned to the 1 g/kg/day diet group also achieved 2 g/kg/day of protein intake at

week 12. After 12 weeks of targeted nutrition intervention, difference in MM between the 2 g/kg/day and 1 g/kg/day diet groups trended towards significance while differences were not observed for markers of physical function. Notably, 58.8% of patients (n=10) in the 2 g/kg/day group maintained or gained MM compared with 43.5% of patients (n=10) in the 1 g/kg/day group at week 12. We found that it was feasible for patients to increase dietary protein intake from pre-intervention intake levels and sustain increased intake although attaining 2.0 g/kg/day was challenging. When protein intake was considered, regardless of diet group allocation, increased protein consumption showed positive effects on MM maintenance and anabolism, physical function, and nutritional status.

To our knowledge, this was the first randomized controlled trial to assess the feasibility and potential impact of a 2 g/kg/day diet on MM and physical function in patients receiving chemotherapy for CRC. Preliminary findings from a study that investigated the impact of supplemental whey protein (13.5 g/day) versus a placebo control for 6 months on MM in patients being treated with chemotherapy for CRC showed promising impact of increased protein intake on FFM measured by bioelectrical impedance analysis [66]. The findings from our study further add to the body of literature on dietary interventions to treat low MM across cancer types [3] and responded to a call for research from the European Society for Clinical Nutrition and Metabolism [21]. Our study employed several pragmatic components to gain insight into the feasibility of implementing a targeted nutrition intervention for 12 weeks in an outpatient oncology setting. Although the 2 g/kg/day diet was not feasible, patients over- and under-consumed protein in comparison to their assigned protein intake goal (1.0 versus 2.0 g/kg/day), as suggested by a mean difference of 0.4 g/kg/day intake between groups. Although the observed difference in protein intake between groups is likely insufficient to surmount a physiological response over 12 weeks, our findings highlight the promising impact of targeted nutrition intervention on MM in patients with cancer. These findings add to the literature suggesting that increased protein intake has a positive effect on MM [30].

The nutritional support provided to patients in our trial extended beyond what is available in most outpatient oncology settings [67]. Nutritional intervention by registered dietitians or regulated nutrition professionals is needed to ensure patients receive evidence-based nutrition information to guide dietary decision-making [68, 69]. Protein intake in patients with cancer

varies; many patients do not meet the minimum recommended intake of 1.0 g/kg/day or the target of 1.2 g/kg/day [70-73] as further confirmed by our cohort at baseline. Prior to nutritional intervention, protein intake in our patient group met the minimum recommended amount for patients with cancer (i.e., 1.0 g/kg/day) but was below the target of 1.2 g/kg/day on a group level. Notwithstanding the mean intake in our cohort (1.1 g/kg/day), individual protein consumption was highly variable and 30% of patients did not attain the minimum recommended intake prior to intervention. These findings are similar to those previously reported in the literature although most studies have been conducted in patients with advanced cancers [71-73]. The threshold of protein intake to maintain MM in cancers associated with muscle loss has been suggested as 1.4 g/kg/day [30], which could imply that current protein recommendations in cancer may not be sufficient to support muscle health [21]. After 12 weeks of targeted nutrition intervention, we found that mean protein intake was 1.4 g/kg/day (irrespective of study arm allocation). Baseline protein intake accounted for ~25% of variation in observed protein intake at week 12, suggesting that dietary changes to protein intake were possible among patients with varied intake prior to targeted intervention. Over the course of the intervention, protein intake in the 2 g/kg/day diet group increased by 0.6 g/kg/day in patients who completed the trial. For a person weighing 80 kg, that represented an increase in protein intake of 48 g/day (e.g., ~6 oz or 171 g of meat), and 40% of a recommended target level for people with cancer (e.g., 1.5 g/kg/day). In response to a call for research investigating 2.0 g/kg/day protein intake [21], we showed that this level of intake was not feasible in patients being treated for CRC despite increased intake post-intervention. This finding is notable considering that our cohort had adequate functional status at baseline based on the inclusion criteria of the trial.

Our choice of the 1.0 g/kg/day diet group potentially impacted our findings as we felt ethically compelled to use the minimal recommended protein intake as the target for the active control arm (versus no intervention). This approach likely improved patient outcomes in the 1 g/kg/day arm but may have contaminated or lessened the observed difference between groups, as highlighted by a 0.4 g/kg/day difference in protein intake between groups (versus the intended 1.0 g/kg/day difference). In fact, we noted that n=2 patients in this group consumed ≥2.0 g/kg/day protein at week 12. Our choice to use an active control arm was further supported by

the low protein intake and prevalence of nutritional risk among patients at baseline which suggested nutritional intervention by a dietitian was warranted.

After 12 weeks of targeted nutrition intervention, MM assessed by ALSTI trended towards being different between groups at week 12 which could be explained by the exploratory nature of the study therefore without an a-priori power calculation. Nonetheless, the probable increase in MM with every 1.0 g/kg/day increase in protein intake is clinically relevant [3, 14, 21] and suggested that muscle anabolism in cancer is possible and was stimulated from diet alone. To put our findings into context, a person weighing 80 kg with an ALSTI of 7.26 kg/m^2 could potentially increase their ALSTI to 7.42 kg/m^2 by consuming an additional 80 g of protein per day (e.g., ~10 oz or 283 g of meat). Although this increase in ALSTI may seem negligible, it represents muscle anabolism in patients with cancer, is clinically significant [3, 21, 74], and could potentially reverse a diagnosis of low MM.

Patients with cancer often present with low MM at diagnosis, independent of cancer cachexia and/or metastatic disease [11, 75]. In our cohort, 26% of patients (n=13) had stage IV disease and none of these patients presented with low MM (per ALSTI) at baseline although when low MM was assessed by ALST/BW, 38% of patients (n=5) with metastatic disease were considered to have low MM. The difference in prevalence of low MM between cut-points highlights the importance of considering body size when classifying MM [45]. We showed that baseline MM accounted for 94% of the variance observed in follow up assessments of MM and further emphasizes the importance of MM in cancer. We also showed that despite mean protein intake above the minimum recommended intake in cancer for both diet groups, patients in the 2 g/kg/day group had decreased risk of muscle loss. Interestingly, sex-differences were observed between groups whereby females in the 2 g/kg/day group were 86% less likely to lose muscle compared to females in the 1 g/kg/day group but a similar observation was not present in males. These findings could be explained in part by sex-differences in rates of muscle loss (higher in males) [76] as prior work suggested that muscle protein synthesis rates do not differ between sexes with increased protein intake [77]. Prior research on the anabolic potential of skeletal muscle during cancer has been controversial; studies have indicated both anabolic resistance [27, 78] and retained anabolic potential [27, 29, 79, 80]. Our findings are particularly important given that nutritional status and interventions are not often a point of focus at the time of a cancer

diagnosis and that skepticism surrounding the importance of nutrition is prevalent in the clinical setting [3]. Notably, MM maintenance alone (without anabolism) is considered a positive health outcome in oncology [3, 21, 74]. Loss of MM during chemotherapy is predictive of negative health outcomes including poorer survival [20] and, when converted to a timeline that aligns with our study, can range from 0.12% over 12 weeks in patients with early stage disease [18] to 5.6% over 12 weeks in patients with advanced CRC [19, 20]. Preservation of MM is essential to avoid detrimental and rapid loss of muscle that requires significantly more time to rebuild [20, 81, 82]. This concept has been described using the analogy of a wildfire [22].

Our assessment of MM utilized DXA-derived measures (i.e., indirect measures), which may not be as sensitive compared with other body composition assessment techniques such as computed tomography. Dual-energy X-ray absorptiometry offers the ability to evaluate ALST by summing the LST found in the arms and the legs [83]. Appendicular LST is composed primarily of skeletal muscle, with the remainder of ALST accounted for by water and fibrotic and connective tissues [84]. Given that ALST accounts for >75% of whole-body muscle [85], it provides a surrogate marker to whole-body MM [86]. At the whole-body level, LST from DXA includes organ, fibrotic, and other tissues [84]. Thus, in cases of abnormal tissue presence (e.g., tumor) within the trunk of the body, it is especially important to consider ALST as a surrogate marker of whole-body MM. Dual energy X-ray absorptiometry has been more recently criticized as a poor marker of physical function and mobility limitations in older adults [87]. While DXA is an imperfect methodology, it is still widely used and recognized body composition technique [88]. Further analyses of computed tomography scans, and multicomponent models within our study are planned, and will provide insight into the accuracy of DXA within our population.

Given the limited access to DXA or other body composition assessment techniques in the clinical setting, body weight is commonly a focus of nutritional status although this measurement alone can mask clinically relevant changes to MM in patients with CRC [10]. We showed that patients in the 2 g/kg/day group had higher percent change from baseline to week 6 in BW, BMI, and waist circumference. Percent change in MM trended higher in the 2 g/kg/day group although no differences were observed for change in percent FM although difference in FM change between groups trended towards significance. These shifts in body composition require further investigation on a regional level and using multicomponent models but may suggest that patients

in the 2 g/kg/day group experienced an increase in visceral adipose tissue. As observed in CRC [44], a high prevalence of overweight and obesity was noted in our cohort. Current protein recommendations in healthy [24] and oncology populations [21] are adjusted by BW despite vide variability in MM across body types, including in patients with obesity [89]. Inroads have begun [90, 91] although further research is needed to determine the best approach for protein recommendations that support MM, thus protein doses in our study were based on BW.

Physical function was assessed by the SPPB test which also provides an indicator of low MM severity [13]. Established cut-off point for low performance by SPPB test in a healthy population is ≤8 points [13], which questions the clinical relevance of the change in score (0.4 points) that was observed with increased protein intake in our cohort. Our use of the SPPB should be considered when interpreting our findings as this assessment tool was originally created for use in patients >70 years [92] although it has been compared between younger and older patients with cancer and no differences were observed for test scores [93]. Patients in our cohort had adequate physical function that appeared to be positively impacted by increased protein intake. Handgrip strength did not differ between intervention groups. These findings are similar to other groups who investigated the impact of muscle building nutrients or agents on handgrip strength and found no difference between patients who consumed higher amounts of energy and protein following oncologic surgery [94], who received eicosapentaenoic acid supplementation [95], or who were treated with anamorelin [96]. With regards to physical activity, the 2 g/kg/day group had higher moderate MET-minutes per week although no other differences between groups were observed. The high variability in activity levels and MET-minutes per week aligns with findings in other cancer cohorts [97].

Quality of life was not impacted by diet group randomization although it should be noted that the impact of diarrhea on quality of life differed between intervention arms at baseline. Our findings are in contrast to others who have shown that hospitalized patients with cancer who received individualized nutrition support reported improvements in quality of life [98]. It is possible that the impact of nutritional intervention on quality of life is more apparent in patients who are malnourished or at high risk of malnutrition [99]. Regardless, quality of life remains an important consideration in nutritional care of oncology patients [100]. Nutritional status of patients has been shown to be an independent predictor of low MM in patients with CRC [101].

Herein, an increase in protein intake of 1.0 g/kg/day (e.g., 80 g protein for an 80 kg person) resulted in a 2.7 point improvement in nutritional status score assessed by the PG-SGA Short Form. This change in score is clinically relevant and could result in a patient no longer requiring specialized nutritional intervention (i.e., PG-SGA score ≥4) [53]. Concerning energy expenditure, we did not observe an impact of study arm allocation or protein intake on REE. In a separate cohort of patients with CRC, age, sex, weight, LST, and FM were found to be main contributors to REE [102] which varied minimally between diet groups.

Strengths of our study are the generalizability of our patient cohort to patients receiving chemotherapy for CRC. Our choice to include non-cachectic patients with metastatic disease who were receiving any type of chemotherapy likely captures the broad spectrum of CRC outpatients. Nutritional assessment and follow-up by a registered dietitian were provided for 12 weeks near start of chemotherapy and patients received details of their personalized nutrition intervention and were provided resources to support their learning. To increase the accuracy of the dietary assessment data, food scales and detailed food record instructions were provided to all patients. The pragmatic approach to the dietary intervention provided insight into the feasibility of implementing dietary change in this population. This strength in our study is coupled with the limitation that a lack of placebo-controlled and/or blinded approach may have induced contamination in our 1 g/kg/day group. It is important to consider that reaching statistical significance was never the intention of the trial, given the exploratory nature of the study design. Our approach highlighted the positive impact of nutrition alone on MM maintenance in cancer given that exercise was not included in our study design. This approach was taken to understand the impact of diet alone, as increased physical activity, especially resistance exercise, would increase nutritional needs. Nonetheless, we acknowledge that our approach could also be viewed as a study limitation since exercise is known to positively impact MM in cancer, regardless of type of exercise (e.g., resistance, aerobic) and thus may have increased anabolic response [103].

Our study was a feasibility pilot trial that can be used to design larger independent and definitive trials to assess the impact of protein intake on MM and physical function in cancer. A key consideration for future trials, that speaks to the feasibility of the interventional approach, is the fourfold higher dropout observed in the 2 g/kg/day group. Several other considerations are

needed when interpreting our results and/or considering larger trials. Firstly, loss of MM increases with age [104], regardless of disease presence. Age at time of diagnosis in patients with CRC is trending younger on a global scale [16], especially in North America [105], thus the impact of the disease on MM in younger adults with CRC is an area that warrants further investigation. Secondly, the prevalence of advanced disease stage at time of diagnosis is postulated to increase secondary to delayed screening and treatment caused by the COVID-19 pandemic [106] and should continue to be a consideration.

The findings from this trial will support the development of independent and/or larger definitive trials investigating a pragmatic approach to nutritional interventions that support MM maintenance (or anabolism) in patients receiving anti-cancer treatment. Importantly, we learned that despite our 2 g/kg/day diet not being feasible to consume, difference in MM between the 2 g/kg/day and 1 g/kg/day diet groups trended towards significance after 12 weeks of targeted nutrition intervention and positive outcomes were observed with increased protein intake, although variability was observed. Overall, our findings highlight the potential for nutritional intervention alone to halt muscle loss in cancer. Definitive and adequately powered well controlled randomized trials that include robust assessment techniques are needed to confirm our findings and to investigate the optimal protein dose to support muscle that is feasible for patients to consume while undergoing anti-cancer treatment.

Table 5.1. Baseline characteristics of 50 patients with colorectal cancer.

Characteristics	1 g/kg/d (n=25)	2 g/kg/d (n=25)	P value
Demographic and Clinical			
Age, years	57 ± 13	58 ± 9	0.840
Sex, n (%)			0.564
Female	9 (36)	11 (44)	
Male	16 (64)	14 (56)	
Race and ethnicity, n (%)[§]			0.369
White	20 (80)	19 (76)	
Indigenous Peoples	1 (4)	3 (12)	
Latin American	0 (0)	2 (8)	
Filipino	2 (8)	0 (0)	
Other	2 (8)	1 (4)	
Education level, n (%)[§]			0.574
Less than high school diploma	0 (0)	1 (4)	
Completed high school	8 (32)	4 (6)	
Completed trade school or college	9 (36)	9 (36)	
Completed undergraduate degree	5 (20)	8 (32)	
Completed post-graduate degree	3 (12)	3 (12)	
Household income, n (%)[§]			0.887
<$20,000	0 (0)	1 (4)	
$20,000–$39,999	2 (8)	3 (13)	
$40,000–$69,999	6 (25)	6 (26)	
$70,000–$99,999	4 (17)	2 (9)	
≥$100,000	12 (50)	11 (48)	
Tumor, n (%)			0.088
Colon	17 (68)	22 (88)	
Rectum	8 (32)	3 (12)	
Disease stage, n (%)			0.747
II/III	19 (76)	18 (72)	
IV	6 (24)	7 (28)	
Chemotherapy, n (%)[§]			0.158
Capecitabine	5 (20)	1 (4)	
Oxaliplatin-based therapy	14 (56)	20 (80)	
Irinotecan-based therapy	6 (24)	4 (16)	
Ostomy, n (%)			0.208
Yes	9 (36)	5 (20)	
No	16 (64)	20 (80)	
Anthropometrics			
Body weight, kg	77.3 ± 15.5	82.8 ± 20.1	0.284
Body mass index, kg/m^{2}[‡]	23.9 (22.1, 30.8)	28.6 (24.5, 32.8)	0.143
Waist circumference, cm			
Total	95.0 ± 15.1	96.8 ± 16.3	0.686
Female	92.0 ± 19.8	89.0 ± 12.4	0.684
Male	96.6 ± 12.2	102.9 ± 16.9	0.252

Characteristics	1 g/kg/d (n=25)	2 g/kg/d (n=25)	P value
Adjusted Calf circumference[1], cm			
Total‡	34.3 (32.3, 36.6)	33.7 (32.8, 34.9)	0.381
Female	33.2 ± 2.8	32.5 ± 2.7	0.582
Male‡	35.2 (33.9, 36.8)	33.8 (33.1, 35.1)	0.155
Body Composition			
Fat mass, kg			
Total	26.6 ± 10.3	29.5 ± 10.8	0.337
Female	30.6 ± 11.5	30.0 ± 9.9	0.902
Male	24.4 ± 9.2	29.1 ± 11.9	0.226
Fat mass, %			
Total	33.9 ± 9.1	35.1 ± 9.1	0.619
Female‡	41.0 (36.4, 46.8)	43.5 (31.2, 45.8)	0.941
Male	29.5 ± 7.0	31.0 ± 7.6	0.557
LST, kg			
Total‡	48.5 (41.8, 54.8)	46.0 (41.0, 60.6)	0.808
Female	38.7 ± 5.5	40.2 ± 4.4	0.516
Male	53.1 ± 6.7	58.5 ± 1.9	0.149
BMC, kg			
Total‡	2.7 (2.2, 3.1)	2.6 (2.4, 3.3)	0.560
Female	2.2 ± 0.4	2.4 ± 0.3	0.178
Male†	3.0 ± 0.4	3.2 ± 0.6	0.226
Fat-free mass, kg			
Total‡	51.2 (44.1, 57.7)	48.5 (43.3, 63.9)	0.793
Female	40.9 ± 5.8	42.6 ± 4.6	0.481
Male†	56.1 ± 7.1	61.7 ± 12.4	0.151
Fat-free mass, %			
Total	66.1 ± 9.1	64.9 ± 9.1	0.619
Female‡	59.0 (53.2, 63.6)	56.5 (54.2, 68.8)	0.941
Male	70.5 ± 7.0	69.0 ± 7.6	0.557
ALST, kg			
Total‡	22.1 (17.8, 24.0)	20.3 (17.2, 27.3)	0.869
Female	17.0 ± 2.7	17.3 ± 2.4	0.767
Male	24.0 ± 3.9	26.7 ± 6.5	0.168
ALSTI, kg/m^2			
Total	7.3 ± 1.2	7.7 ± 1.8	0.262
Female	6.5 ± 1.0	6.6 ± 1.0	0.819
Male	7.7 ± 1.1	8.6 ± 1.8	0.079
ALST/BW, %			
Total	27.91 ± 4.15	27.16 ± 4.01	0.521
Female‡	23.68 (21.67, 27.46)	23.05 (22.09, 25.51)	0.941
Male	30.05 ± 2.74	29.58 ± 2.71	0.645
(continued on next page)			

Characteristics	1 g/kg/d (n=25)	2 g/kg/d (n=25)	P value
Low muscle mass, n (%)	6 (24)	4 (16)	0.480
by ALSTI[2]	19 (76)	21 (84)	
Yes			
No	8 (32)	11 (44)	0.382
by ALST/BW[3]	17 (68)	14 (56)	
Yes			
No			
Physical Function and Activity			
Short physical performance battery test score[4, ‡], 0–12	11.0 (10.5, 12.0)	11.0 (9.5, 12.0)	0.632
Physical activity level[1, §], n (%)			0.420
Inactive	9 (39)	4 (20)	
Moderately Active	9 (39)	11 (55)	
Highly active	5 (22)	5 (25)	
Physical activity, MET-min per week[1, ‡]	1386 (269, 2499)	1752 (924, 2986)	0.141
Handgrip strength, kg			
Total	31.8 ± 11.2	31.1 ± 11.1	0.835
Female	21.7 ± 2.5	21.7 ± 4.1	0.997
Male	37.4 ± 10.2	38.5 ± 8.9	0.765
Energy Expenditure			
REE, kcal	1642 ± 251	1695 ± 337	0.534
REE, kcal/kg	21.6 ± 2.4	20.9 ± 3.1	0.399
Nutritional Intake and Status			
Energy intake, kcal[†]	2116 ± 755	2178 ± 500	0.736
Energy intake, kcal/kg[‡]	26 (22, 35)	26 (21, 33)	0.648
Protein intake, g	85.0 ± 33.2	92.4 ± 22.9	0.365
Protein intake, g/kg[‡]	1.0 (0.9, 1.3)	1.1 (1.0, 1.4)	0.577
Protein intake, g/kg ALST[‡]	3.8 (3.1, 4.6)	4.3 (3.3, 4.7)	0.299
Patient generated Subjective Global Assessment Short Form score[5, ‡], 0–36	4.0 (2.5, 6.5)	4.0 (1.5, 7.5)	0.598
Quality of Life			
EORTC QLQ-C30 score[6, ‡], 0–100			
Global health status	75 (67, 83)	67 (50, 83)	0.214
Functioning			
Physical functioning	100 (87, 100)	93 (74, 100)	0.127
Role functioning	100 (67, 100)	67 (67, 100)	0.107
Emotional functioning	83 (75, 100)	83 (75, 92)	0.464
Cognitive functioning	100 (67, 100)	83 (75, 100)	0.868
Social functioning	83 (67, 92)	67 (67, 83)	0.163
Symptoms			
Fatigue	33 (22, 44)	33 (22, 39)	0.912
Nausea and vomiting	0 (0, 17)	17 (0, 17)	0.949

Characteristics	1 g/kg/d (n=25)	2 g/kg/d (n=25)	P value
Pain	17 (0, 33)	0 (0, 25)	0.558
Dyspnoea	0 (0, 33)	0 (0, 33)	0.297
Insomnia	33 (17, 33)	33 (17, 67)	0.616
Appetite loss	0 (0, 33)	0 (0, 33)	0.930
Constipation	0 (0, 17)	0 (0, 33)	0.273
Diarrhea	0 (0, 33)	33 (0, 33)	**0.009**
Financial difficulties	0 (0, 0)	0 (0, 33)	0.071
Functional Assessment of Anorexia/Cachexia Therapy score			
Total[7], 0–156	120.5 ± 15.3	119.2 ± 18.6	0.783
Anorexia/Cachexia, 0–48‡	40.0 (35.5, 43)	39.0 (34.0, 42)	0.496
Physical well-being, 0–28‡	24.0 (19.5, 26.9)	23.0 (20.5, 25.0)	0.350
Social well-being, 0–28	21.9 ± 4.5	23.3 ± 3.6	0.236
Emotional well-being, 0–24‡	19.0 (16.5, 22.0)	19.0 (17.0, 22.0)	0.682
Functional well-being, 0–28	18.6 ±4.0	17.5 ± 5.1	0.188

Data are presented as mean ± standard deviation if normally distributed or as median (25^{th} percentile, 75^{th} percentile) in cases of non-normality. Bolded font indicates significant difference between groups assessed at $P<0.05$. Independent samples t-test were used to assess the mean difference between groups for continuous variables and the Chi square test was used for difference between categorical variables. [1]1 g/kg/day group n=23; 2 g/kg/day group n=20; calf circumference adjusted as follows: BMI <18.5 kg/m^2: CC + 4 cm; BMI 25.0–29.9 kg/m^2: CC – 3 cm; BMI 30.0–39.9 kg/m^2: CC – 7 cm; BMI ≥40 kg/m^2: CC – 12 cm [43]. [2]Low muscle mass was defined as ALSTI <7.0 kg/m^2 for males and <5.5 kg/m^2 for females. [3]Low muscle mass was defined as ALST/BW <28.27 for males and <23.47 for females. [4]Lower scores indicate decreased physical function. [5]Higher scores indicate increased risk for malnutrition. [6]Higher scores for the global health status and functioning scales represent a high level of the global health status and functioning. Higher score for the symptom scales represents a high level of that symptom or problem. [7]Higher scores indicate better quality of life. †Welch t-test used due to heterogeneity of variances. ‡Mann-Whitney U due to non-normal distribution of one or more groups. §Fisher's exact test applied (Chi-square assumption violated). ALST: appendicular lean soft tissue; ALSTI: appendicular lean soft tissue index; BMC: bone mineral content; BW: body weight; d: day; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; kcal: kilocalorie; LST: lean soft tissue; MET: metabolic equivalencies of task; VCO_2: volume of carbon dioxide; VO_2: volume of oxygen.

Table 5.2. Anthropometrics, body composition, nutritional intake and status, and energy expenditure across study time points by intervention group.

	Pooled Baseline (n=50)	Week 6			Week 12		
		1 g/kg/d (n = 24)	2 g/kg/d (n = 20)	P value	1 g/kg/d (n = 23)	2 g/kg/d (n = 17)	P value
Anthropometrics and Body Composition							
Weight, kg	80.0 ± 18.0	76.2 ± 15.7	84.8 ± 21.9	0.136	77.8 ± 15.5	90.1 ± 21.8	0.044
BMI, kg/m^2	27.0 (22.8, 31.2)	23.5 (22.0, 30.0)	27.9 (23.1, 32.6)	0.122‡	24.3 (22.2, 30.2)	30.1 (25.9, 34.5)	**0.024**‡
WC, cm	95.9 ± 15.6	93.6 ± 13.5	98.6 ± 17.3	0.287	95.0 ± 13.3	101.9 ± 18.1	0.172
Adjusted CC[1], cm	33.9 (32.6, 35.2)	34.6 (32.8, 36.5)	34.4 (33.3, 35.1)	0.693‡	34.9 ± 2.6	34.5 ± 2.7	0.671
ALSTI, kg/m^2	7.4 ± 1.5	7.1 ± 1.2	7.9 ± 1.9	0.114†	7.2 ± 1.2	8.1 ± 1.8	0.065
Fat mass, %	34.5 ± 9.0	33.9 ± 8.8	34.6 ± 9.1	0.796	33.7 ± 8.1	36.9 ± 7.8	0.222
Low MM, n (%)							
ALSTI				0.150§			0.061§
Yes	10 (20)	7 (29.2)	2 (10.0)		5 (21.7)	0 (0)	
No	40 (80)	17 (70.8)	18 (90.0)		18 (78.3)	17 (100)	
ALST/BW				0.647			0.314
Yes	19 (38)	8 (33.3)	8 (40.0)		6 (26.1)	7 (41.2)	
No	31 (62)	16 (66.7)	12 (60.0)		17 (73.9)	10 (58.8)	
MM Change, n (%)				0.149			0.337
Maintained or gained		8 (33.3)	11 (55.0)		10 (43.5)	10 (58.8)	
Lost		16 (66.7)	9 (45.0)		13 (56.5)	7 (41.2)	
Nutritional Intake and Status							
Energy intake, kcal	2147 ± 635	1812 (1553, 2663)	2321 (1784, 2632)	0.294‡	2217 ± 803	2594 ± 674	0.125

(Continued)

	Pooled Baseline (n=50)	Week 6			Week 12		
		1 g/kg/d (n = 24)	2 g/kg/d (n = 20)	P value	1 g/kg/d (n = 23)	2 g/kg/d (n = 17)	P value
Energy intake, kcal/kg	26 (22, 33)	28.4 ± 9.0	28.1 ± 10.0	0.938	28.6 ± 9.4	29.8 ± 8.3	0.663
Protein intake, g	88.7 ± 28.5	92.4 ± 26.6	129.0 ± 43.3	**0.001**	96.0 ± 40.5	140.9 ± 43.3	**0.002**
Protein intake, g/kg	1.0 (0.9, 1.4)	1.2 ± 0.3	1.6 ± 0.6	**0.024**	1.2 ± 0.4	1.6 ± 0.5	**0.012**
PG-SGA$_{SF}$ score[2], 0–36	4 (2, 7)	5 (1, 9)	3 (1, 7)	0.498‡	6 (1, 11)	5 (2, 8)	0.829‡
Energy Expenditure							
REE, kcal/day	1668 ± 295	1578 ± 233	1683 ± 401	0.282	1667 ± 201	1798 ± 401	0.180
REE, kcal/kg	21.2 ± 2.8	21.1 ± 2.5	20.2 ± 3.2	0.336	21.9 ± 3.0	20.2 ± 2.7	0.082

Data are presented as mean ± standard deviation if normally distributed or as median (25th percentile, 75th percentile) in cases of non-normality. Bolded font indicates significant difference between groups assessed at P<0.025. Independent samples t-test were used to assess the mean difference between groups for continuous variables and the Chi square test was used for difference between categorical variables. †Welch t-test used due to heterogeneity of variances. ‡Mann-Whitney U due to non-normal distribution of one or more groups. §Fisher's exact test applied (Chi-square assumption violated). [1]calf circumference adjusted as follows: BMI <18.5 kg/m^2: CC + 4 cm; BMI 25.0–29.9 kg/m^2: CC – 3 cm; BMI 30.0–39.9 kg/m^2: CC – 7 cm; BMI ≥40 kg/m^2: CC – 12 cm [43].; [2]Higher scores indicate increased risk for malnutrition. BMI: body mass index; CC: calf circumference; d:day; PG-SGA$_{SF}$: Patient Generated Subjective Global Assessment Short Form; WC: waist circumference.

Table 5.3. Physical function and activity and quality of life across study time points by intervention group.

	Pooled Baseline (n=50)	Week 6			Week 12		
		1 g/kg/d (n = 24)	2 g/kg/d (n = 20)	P Value	1 g/kg/d (n = 23)	2 g/kg/d(n = 17)	P value
Physical Function and Activity							
SPPB test score[1]							
Total score	11 (10, 12)	11 (10, 12)	12 (10, 12)	0.780‡	12 (11, 12)	11 (11, 12)	0.745‡
Sit-to-stand	3 (3, 4)	4 (3, 4)	4 (2, 4)	0.905‡	4 (3, 4)	4 (3, 4)	0.914‡
Balance	4 (4, 4)	4 (4, 4)	4 (4, 4)	0.369‡	4 (4, 4)	4 (4, 4)	0.725‡
Gait speed	4 (3, 4)	4 (4, 4)	4 (4, 4)	0.585‡	4 (4, 4)	4 (4, 4)	0.999‡
Handgrip strength, kg	29.0(22.0, 40.5)	31.5 ± 11.3	33.6 ± 11.5	0.536	31.4 ± 12.0	33.7 ± 11.4	0.542
Adjusted for BW	0.42(0.30, 0.48)	0.42 ± 0.13	0.40 ± 0.11	0.711	0.40 ± 0.12	0.38 ± 0.11	0.653
Adjusted for BMI	1.18 ± 0.40	1.25 ± 0.45	1.20 ± 0.40	0.733	1.21 ± 0.45	1.14 ± 0.40	0.620
Physical activity, MET-min per week[2]							
Total	1386 (487, 2686)	1280 (560, 2559)	2200 (396, 3600)	0.191‡	1230 (552, 1918)	2175 (874, 4232)	0.128‡
Walking	842 (235, 1386)	982 (223, 1435)	792 (185, 2194)	0.593‡	792 (419, 1386)	693 (346, 1287)	0.730‡
Moderate	120 (0, 480)	0 (0, 180)	300 (0, 1440)	0.135‡	80 (0, 375)	360 (140, 960)	**0.018**‡
Vigorous	0 (0, 560)	0 (0, 300)	0 (0, 1440)	0.551‡	0 (0, 260)	160 (0, 1260)	0.265‡
Self-reported PAL[2],n(%)				0.758§			0.399§
Inactive	13 (30.2)	7 (31.8)	6 (37.5)		6 (30.0)	3 (21.4)	
Moderately Active	20 (46.5)	11 (50.0)	6 (37.5)		11 (55.0)	6 (42.8)	
Highly active	10 (23.3)	4 (18.2)	4 (25.0)		3 (15.0)	5 (35.7)	
Quality of Life							
QLQ-C30 score[3], 0–100							
Global health status	67 (56, 83)	67 (52, 83)	67 (58, 81)	0.649‡	75 (67, 83)	67 (50, 79)	0.134‡
Functioning							
Physical	93 (80, 100)	93 (87, 100)	93 (75, 100)	0.769‡	93 (80, 100)	93 (77, 100)	0.789‡
Role	67 (67, 100)	83 (67, 100)	67 (67, 96)	0.174‡	83 (67, 100)	67 (67, 75)	0.173‡
Emotional	83 (75, 100)	92 (83, 100)	88 (75, 100)	0.298‡	92 (83, 100)	100 (79, 100)	0.808‡

	Pooled Baseline (n=50)	Week 6			Week 12		
		1 g/kg/d (n = 24)	2 g/kg/d (n = 20)	P Value	1 g/kg/d (n = 23)	2 g/kg/d(n = 17)	P value
Cognitive	83 (67, 100)	100(83,100)	100 (67, 100)	0.608‡	83 (83, 100)	83 (67, 100)	0.516‡
Social	67 (67, 83)	83 (67, 100)	75 (67, 83)	0.216‡	83 (67, 100)	83 (67, 91)	0.999‡
Symptoms							
Fatigue	33 (22, 44)	33 (22, 33)	33 (22, 56)	0.527‡	33 (22, 44)	33 (22, 50)	0.464‡
Nausea/vomiting	8.5 (0, 17)	0 (0, 17)	17 (4, 17)	0.104‡	0 (0, 17)	17 (0, 17)	0.705‡
Pain	17 (0, 33)	0 (0, 17)	0 (0, 17)	0.956‡	0 (0, 33)	0 (0, 17)	0.914‡
Dyspnoea	0 (0, 33)	0 (0, 33)	0 (0, 33)	0.933‡	0 (0, 33)	0 (0, 33)	0.201‡
Insomnia	33 (25, 33)	33 (0, 33)	33 (8, 33)	0.069‡	33 (0, 33)	33 (0, 67)	0.290‡
Appetite loss	0 (0, 33)	0 (0, 33)	33 (0, 33)	0.380‡	0 (0, 33)	33 (0, 33)	0.329‡
Constipation	0 (0, 33)	0 (0, 33)	0 (0, 25)	0.704‡	0 (0, 33)	0 (0, 33)	0.808‡
Diarrhea	16.5 (0, 33)	0 (0, 25)	33 (0, 33)	0.027‡	0 (0, 33)	0 (0, 33)	0.432‡
Financial	0 (0, 33)	0 (0, 0)	0 (0, 33)	0.025‡	0 (0, 0)	0 (0, 33)	0.685‡
FAACT score							
Total[4], 0–156	120 ± 17	121 ± 18	121 ± 19	0.945	123 ± 18	119 ± 17	0.441
Anorexia, 0–48	39 (35, 42)	40 (36, 43)	42 (36, 46)	0.943‡	40 ± 6	37 ± 5	0.148
Physical, 0–28	24 (20, 26)	22 (18, 26)	23 (20, 26)	0.943‡	24 (17, 25)	24 (19, 25)	0.914‡
Social, 0–28	23 (20, 26)	24 (18, 27)	22 (19, 25)	0.571‡	24 (21, 26)	21 (19, 25)	0.957‡
Emotional, 0–24	19 (17, 22)	19 (18, 23)	20 (19, 23)	0.576‡	21 (18, 24)	20 (18, 23)	0.871‡
Functional, 0–28	18 ± 5	18 ± 6	19 ± 4	0.988	19 ± 5	18 ± 5	0.435

Data are presented as mean ± standard deviation if normally distributed or as median (25th percentile, 75th percentile) in cases of non-normality. Bolded font indicates significant difference between groups assessed at P<0.025. Independent samples t-test were used to assess the mean difference between groups for continuous variables and the Chi square test was used for difference between categorical variables. †Welch t-test used due to heterogeneity of variances. ‡Mann-Whitney U due to non-normal distribution. §Fisher's exact test applied (Chi-square assumption violated). [1]Lower scores indicate decreased physical function. [2]1 g/kg/day group n=23; 2 g/kg/day group n=20. [3]Higher scores for the global health status and functioning scales represent a high level of the global health status and functioning. Higher score for the symptom scales represent a high level of that symptom or problem. [4]Higher scores indicate better quality of life. BMI: body mass index; BW: body weight; d: day; MET: metabolic equivalencies of tasks; QLQ-C30: quality of life questionnaire; FAACT: Functional Assessment of Anorexia/Cachexia Treatment; SPPB: Short Physical Performance Battery.

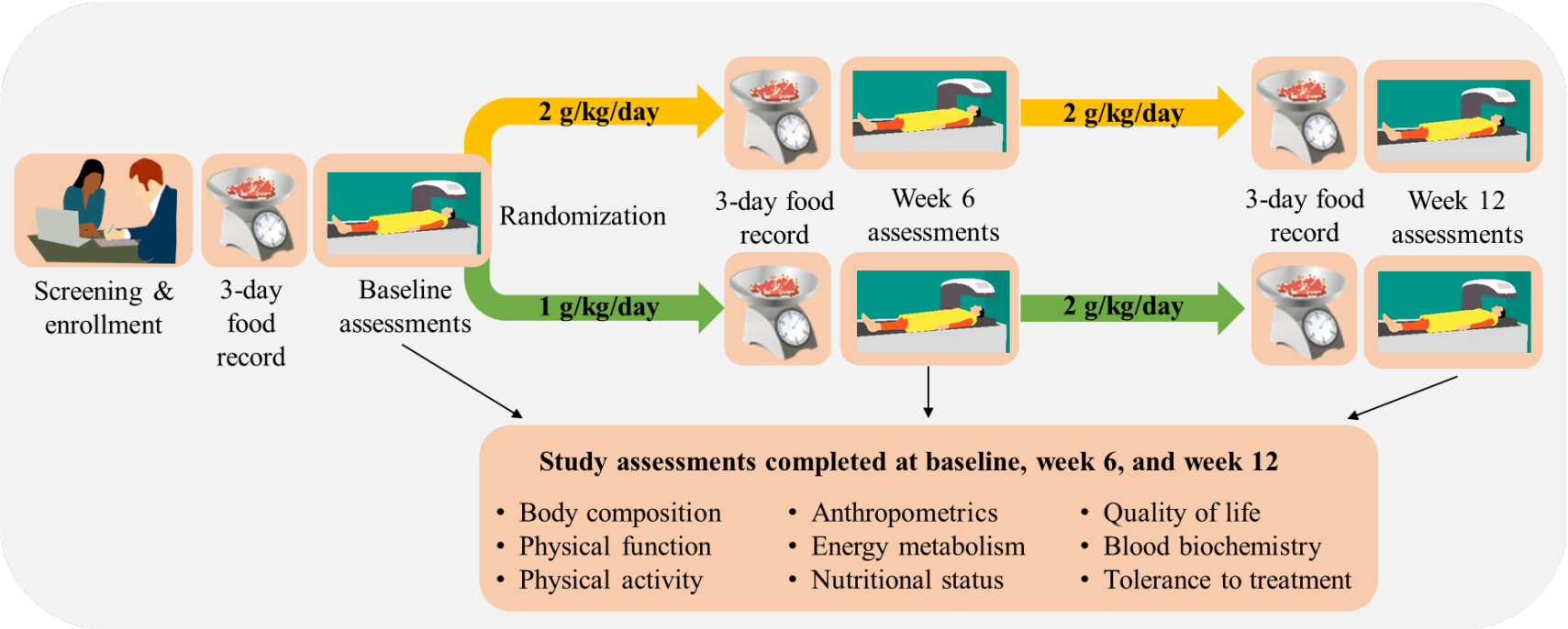


Figure 5.1. Graphical illustration of the Protein Recommendation to Increase Muscle (PRIMe) study protocol. .

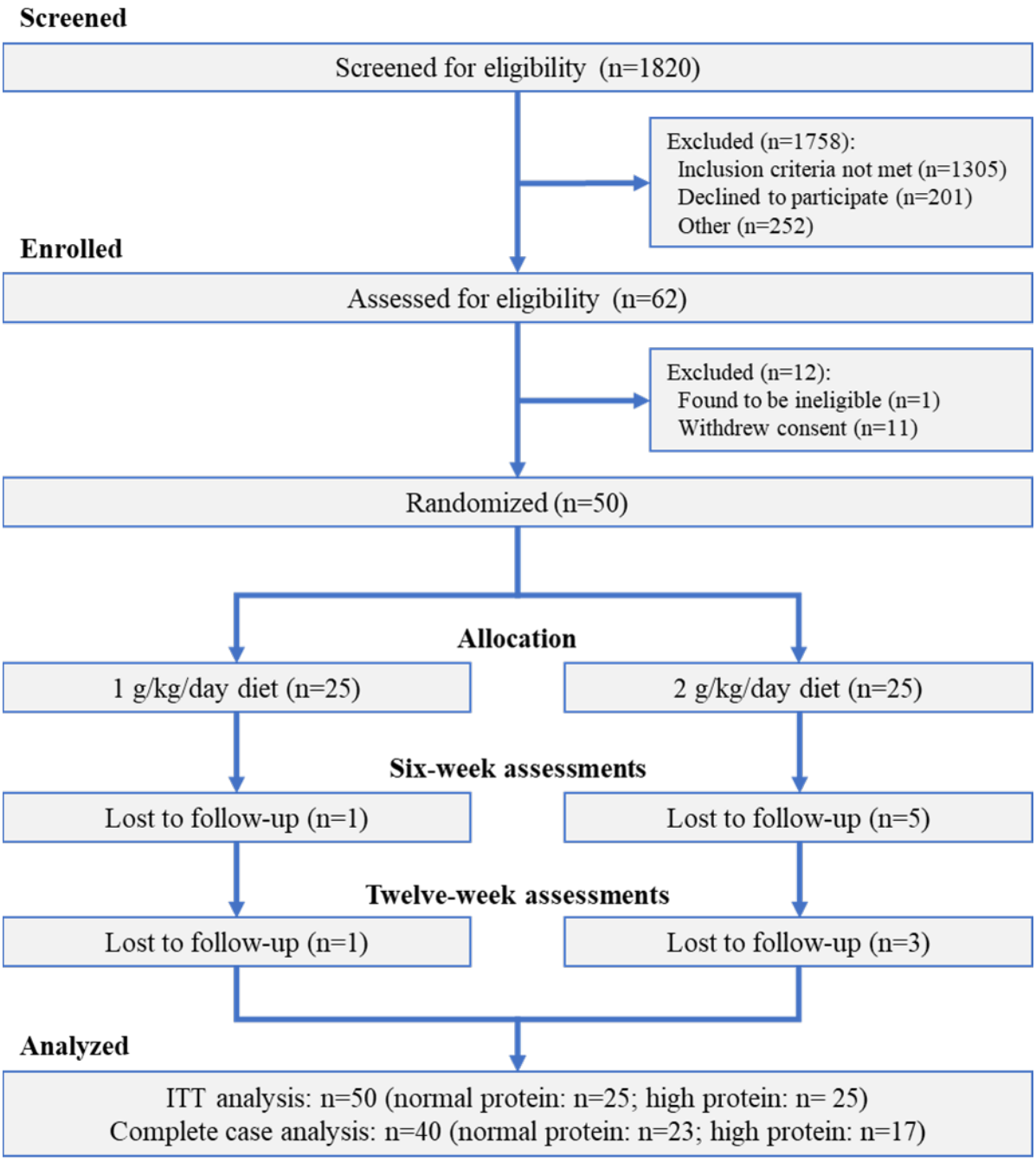


Figure 5.2. Patient flow through the trial. ITT: intention to treat.

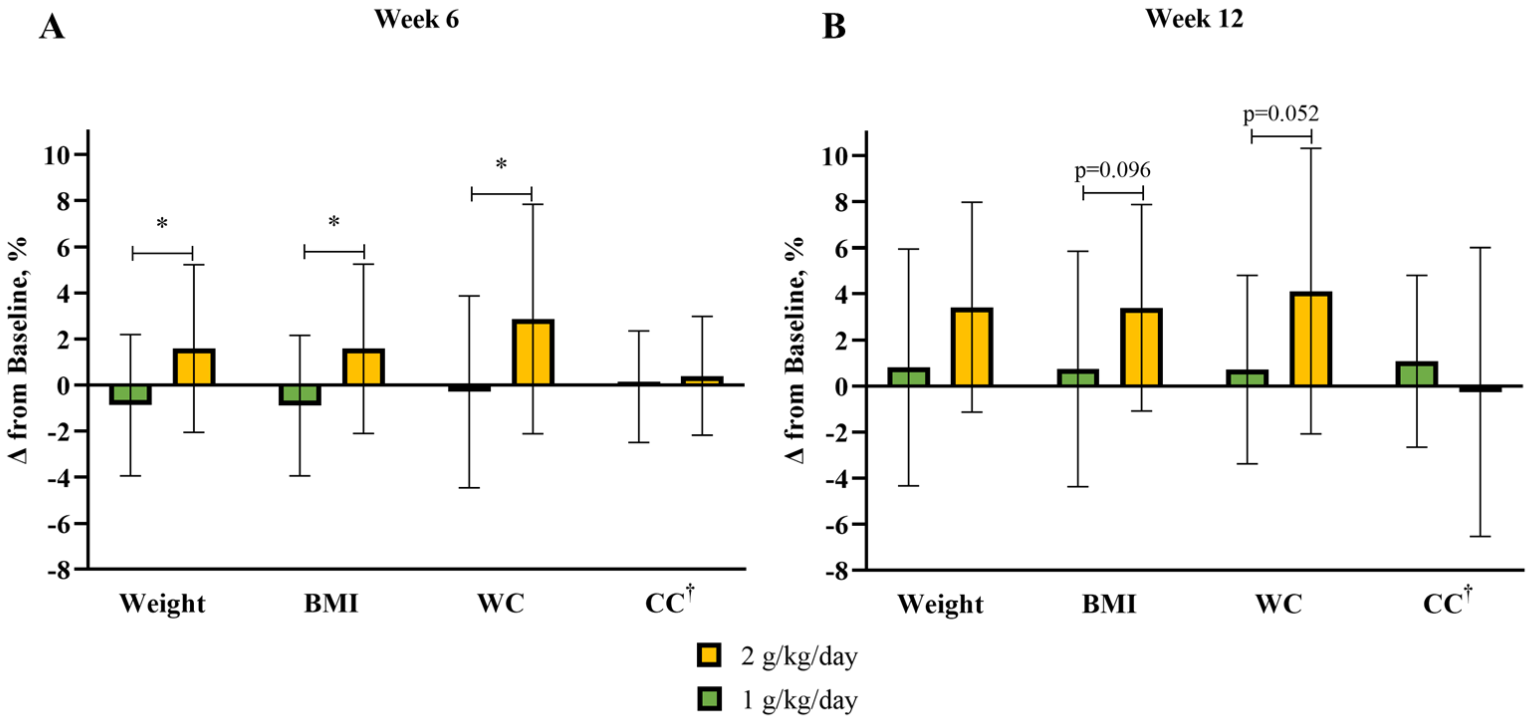


Figure 5.3 A-B. Percent change from baseline for weight, body mass index, and waist and adjusted calf circumferences at six (A) and twelve (B) weeks for weight, body mass index, waist and calf circumferences. Boxes represent the mean; error bars represent the standard deviation. Independent samples t-test was used to compare groups for each variable at each time point. *$p<0.05$; $0.05<p<0.10$ are indicated. All patients who completed the illustrated assessments are included. Six weeks: n=44 (1 g/kg/day diet group: n=24; 2 g/kg/day diet group: n=20); Twelve weeks: n=40 (1 g/kg/day diet group : n=23; 2 g/kg/day diet group : n=17). †Six weeks: n=38 (1 g/kg/day diet group : n=22; 2 g/kg/day diet group : n=16); Twelve weeks: n=34 (1 g/kg/day diet group : n=212 g/kg/day diet group: n=13); calf circumference adjusted as follows: BMI <18.5 kg/m^2: CC + 4 cm; BMI 25.0–29.9 kg/m^2: CC – 3 cm; BMI 30.0–39.9 kg/m^2: CC – 7 cm; BMI ≥40 kg/m^2: CC – 12 cm [43]. Δ: change; BMI: body mass index; WC: waist circumference; CC: calf circumference.

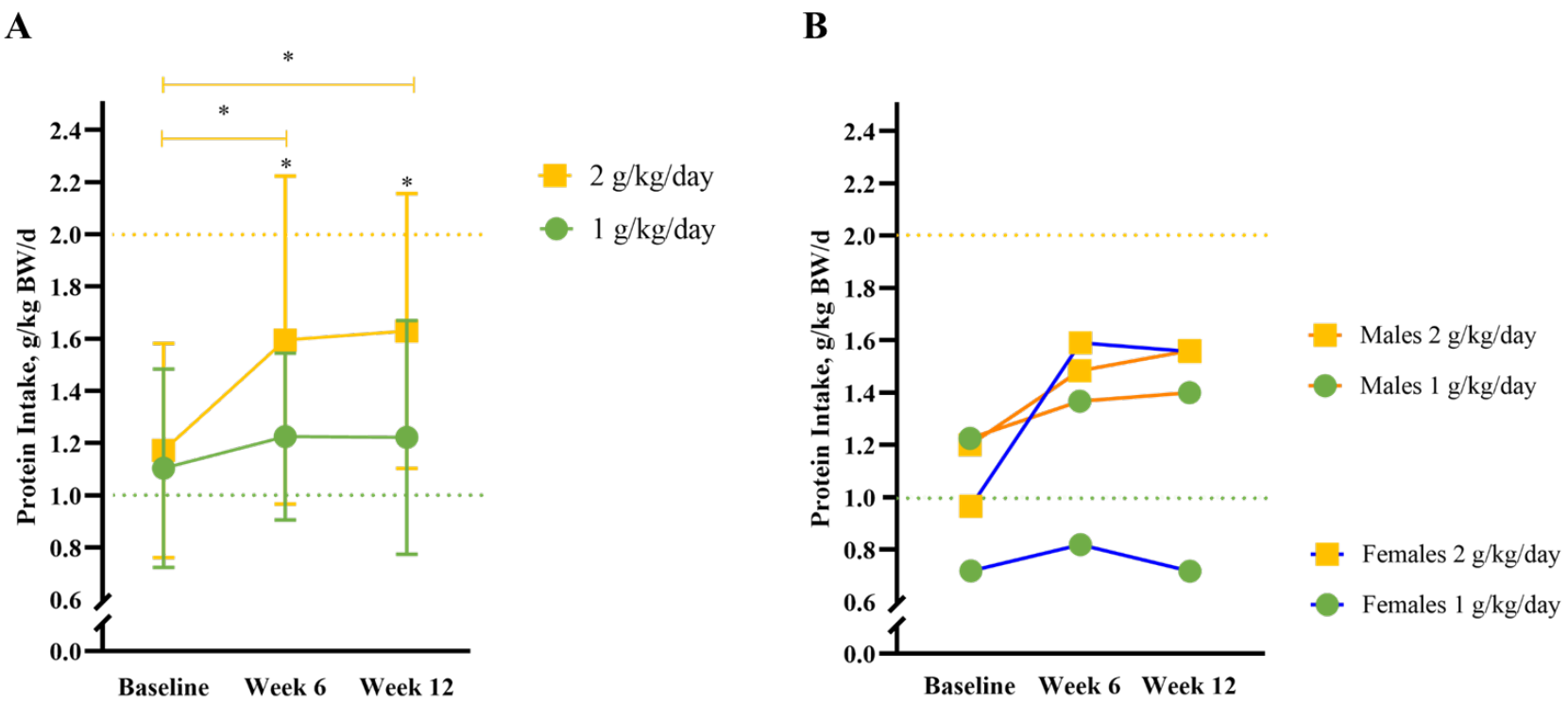


Figure 5.4 A-B. Protein intake by study arm and time point (A) and by study arm, time point, and sex (B). Data are presented as mean and standard deviation. Green circles represent the 1 g/kg/day protein diet group; yellow squares represent the 2 g/kg/day protein diet group. The dotted lines represent the target protein intake per study group. Differences between study arms at each time point were assessed by independent samples t-test or Mann-Whitney U for non-normality; *$p<0.05$. Difference between time points by study arm was assessed by paired samples t-test or Wilcoxin test for non-normality; *$p<0.05$. g/kg/d: grams of protein per kilogram of body weight per day. Baseline: n=50 (1 g/kg/day diet group: n=25; 2 g/kg/day diet group: n=25); Six weeks: n=44 (1 g/kg/day diet group: n=24; 2 g/kg/day diet group: n=20); Twelve weeks: n=40 (1 g/kg/day diet group: n=23; 2 g/kg/day diet group: n=17).

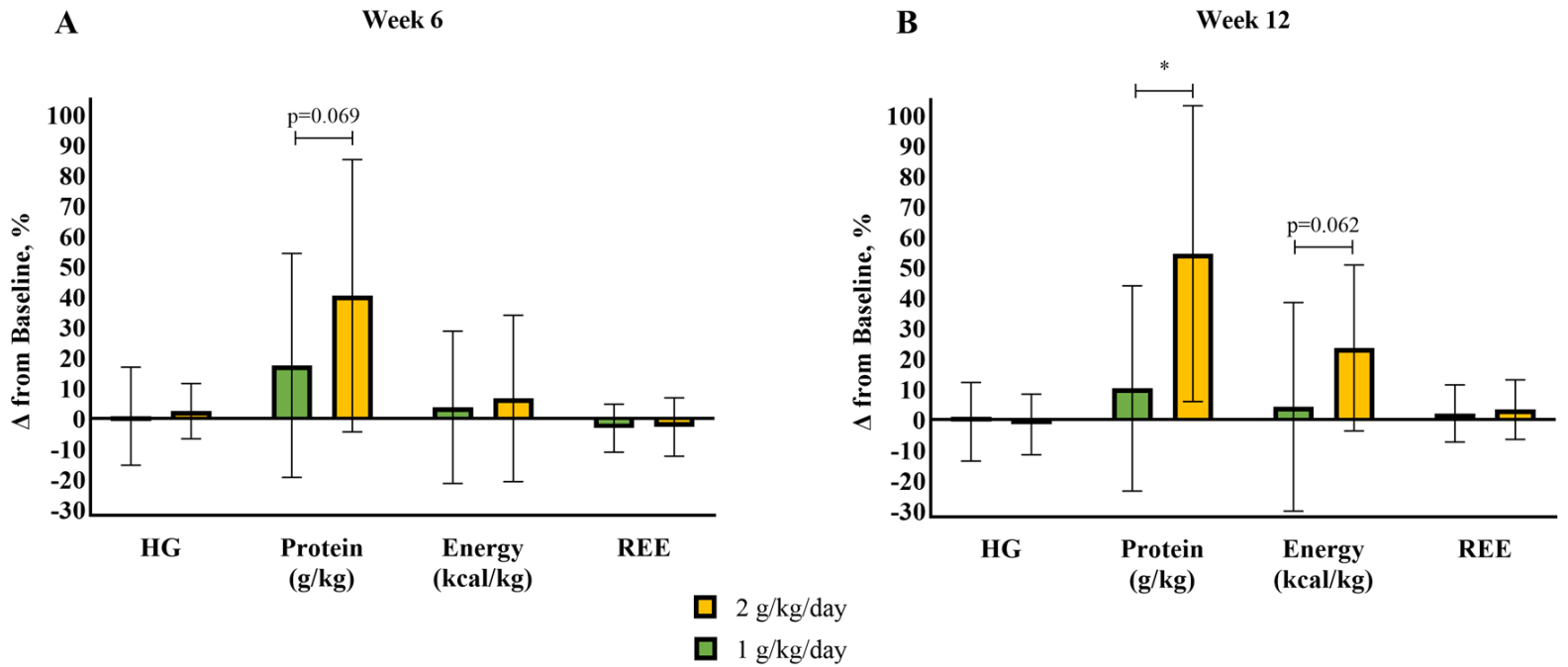


Figure 5.5 A-B. Percent change from baseline for handgrip, protein and energy intake, and resting energy expenditure at six (A) and twelve (B) weeks for handgrip strength, protein intake adjusted for body weight, energy intake adjusted for body weight, and resting energy expenditure. Boxes represent the mean; error bars represent the standard deviation. Independent samples t-test was used to compare groups for each variable at each time point. *$p<0.05$; $0.05<p<0.10$ are indicated. All patients who completed the illustrated assessments are included. Six weeks: n=44 (1 g/kg/day diet group: n=24; 2 g/kg/day diet group: n=20); Twelve weeks: n=40 (1 g/kg/day diet group: n=23; 2 g/kg/day diet group: n=17). Δ: change; HG: handgrip strength; g/kg: grams per kilogram [body weight]; kcal/kg: kilocalories per kilogram [body weight]; REE: resting energy expenditure.

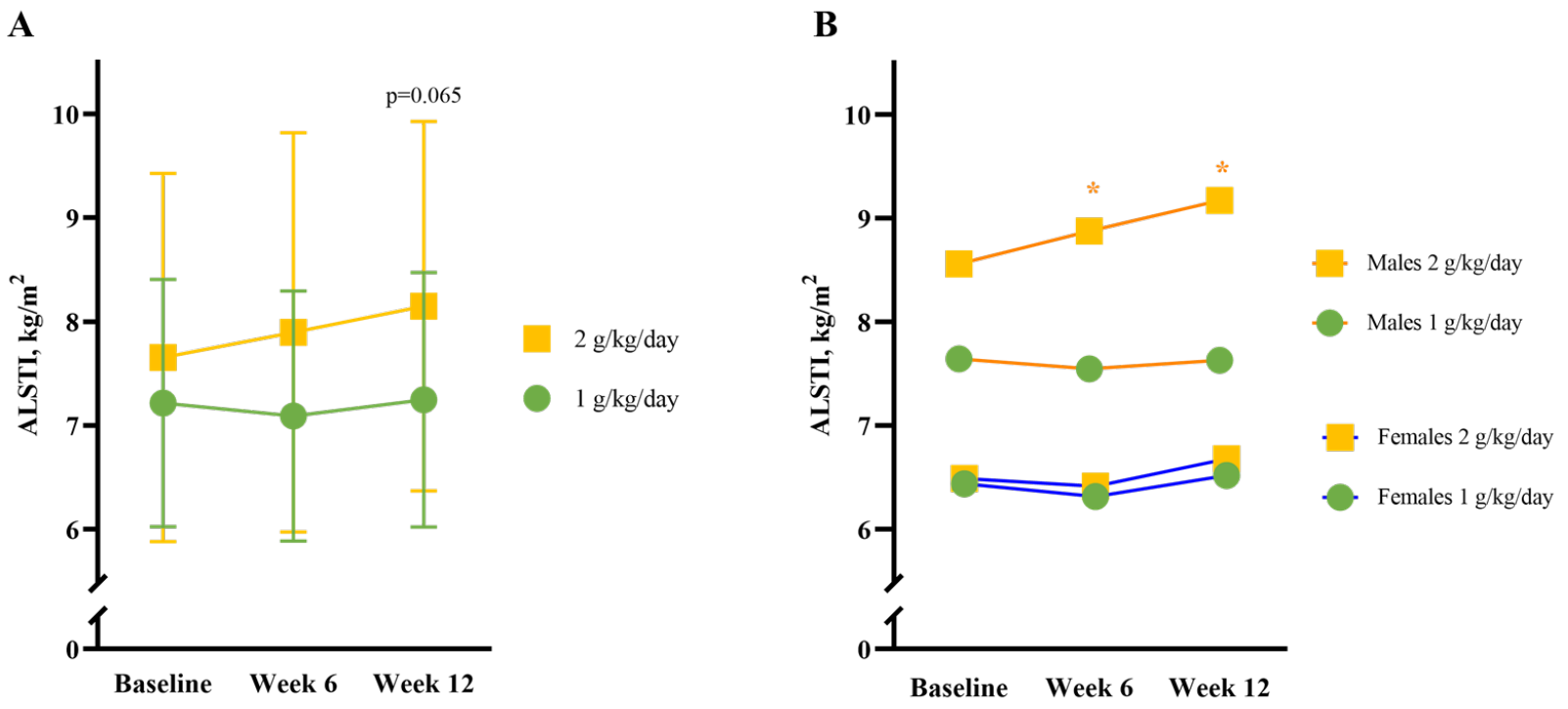


Figure 5.6 A-B. Appendicular lean soft tissue index by study arm and time point (A) and by study arm and time point with data illustrated by sex (B). Data points are mean; error bars represent standard deviation. Green circles represent the 1 g/kg/day protein diet group; yellow squares represent the 2 g/kg/day protein diet group. Differences between study arms at each time point were assessed by independent samples t-test. Difference within study arm between time points was assessed by paired samples t-test. *p<0.05; ALSTI: appendicular lean soft tissue index. Baseline: n=50 (1 g/kg/day diet group: n=25; 2 g/kg/day diet group: n=25); Six weeks: n=44 (1 g/kg/day diet group: n=24; 2 g/kg/day diet group: n=20); Twelve weeks: n=40 (1 g/kg/day diet group: n=23; 2 g/kg/day diet group: n=17).

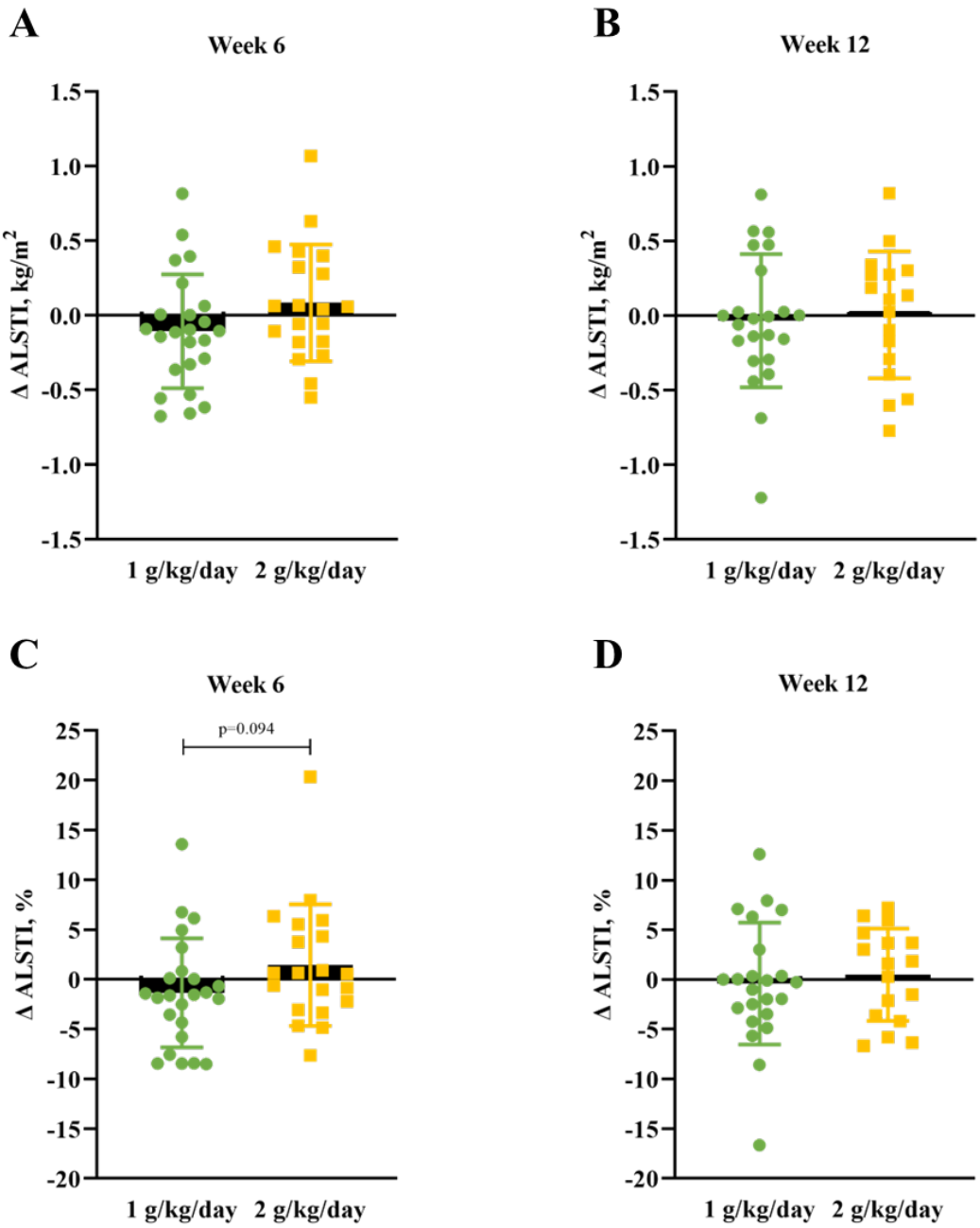


Figure 5.7 A-D. Absolute change in appendicular lean soft tissue index from baseline to six weeks (A) and baseline to twelve weeks (B). Percent change from baseline in appendicular lean soft tissue index at six weeks (C) and at twelve weeks (D). Each data point represents a patient. Black bars represent the group mean; error bars represent standard deviation. Differences between study were assessed by independent samples t-test or Mann-Whitney U test in the case of non-normality. ALSTI: appendicular lean soft tissue index. Six weeks: n=44 (1 g/kg/day diet group: n=24; 2 g/kg/day diet group: n=20); Twelve weeks: n=40 (1 g/kg/day diet group: n=23; 2 g/kg/day diet group: n=17).

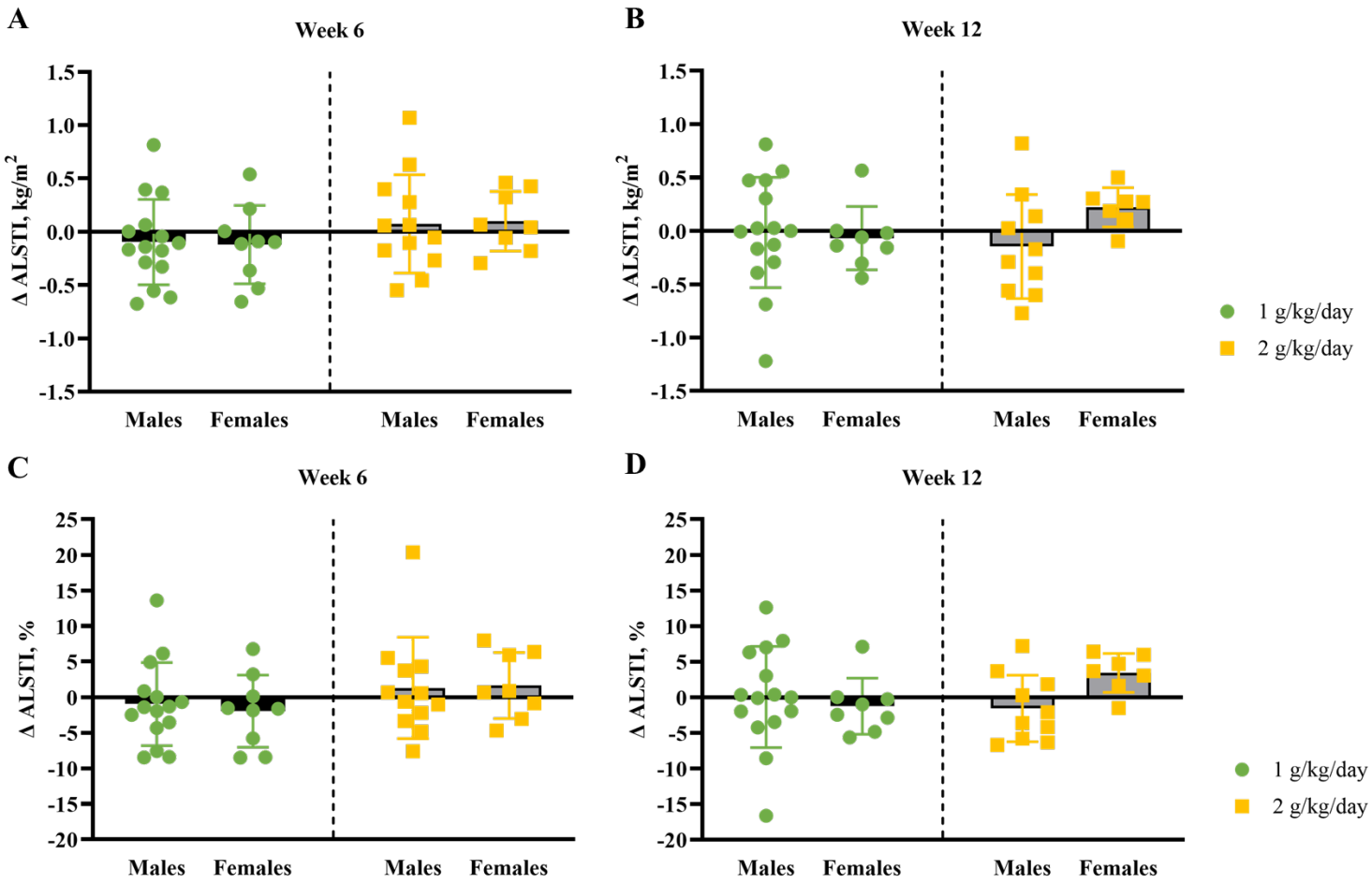


Figure 5.8 A-D. Absolute change in appendicular lean soft tissue index by study arm and sex from baseline to six weeks (A) and baseline to twelve weeks (B). Percent change from baseline in appendicular lean soft tissue index at six weeks (C) and at twelve weeks (D). Each data point represents a patient. Black bars represent the group mean; error bars represent standard deviation. ALSTI: appendicular lean soft tissue index. Six weeks: n=44 (1 g/kg/day diet group: n=24; 2 g/kg/day diet group: n=20); Twelve weeks: n=40 (1 g/kg/day diet group: n=23; 2 g/kg/day diet group: n=17).

Supplementary Table 5.1. Composition of multivitamins provided to patients with colorectal cancer in the Protein Recommendation to Increase Muscle (PRIMe) study.

	Centrum Men 50+ Complete Multivitamin	**Nature's Bounty Multivitamin Adult Gummies**
NPN	80043120	80024313
Dose, capsules/day	1	2
Medical ingredients per dose:		
Beta-carotene	1800 mcg (3000 IU)	
Biotin	54 mcg	300 mcg
Folate	300 mcg	400 mcg
Niacinamide	16 mg	10 mg
Pantothenic acid	12.5 mg	5 mg
Vitamin A	225 mcg (750 IU)	750 mcg RAE (2500 IU)
Vitamin B_1	4.2 mg	
Vitamin B_2	4.6 mg	
Vitamin B_6	10 mg	2 mg
Vitamin B_{12}	45 mcg	6 mcg
Vitamin C	180 mg	60 mg
Vitamin D	20 mcg (800 IU)	20 mcg (800 IU)
Vitamin E	22.5 mg (50 IU)	6.8 mg AT (15 IU)
Vitamin K1	25 mcg	
Calcium	250 mg	
Choline		40 mcg
Chromium	100 mcg	
Copper	0.5 mg	
Iodine	150 mcg	
Inositol		60 mcg
Iron	2 mg	
Lutein	600 mcg	
Lycopene	600 mcg	
Magnesium	125 mg	
Manganese	3 mg	
Molybdenum	50 mcg	
Selenium	55 mcg	
Zinc	11 mg	5 mg

IU: international units; mcg: microgram; mg: milligram; NPN: natural product number; RAE: retinol activity equivalents.

Supplementary Table 5.2. Composition of whey protein powder provided to select patients in the Protein Recommendation to Increase Muscle (PRIMe) study.

	Beneprotein®		**PC Natural Source Whey Protein Isolate Unflavoured Protein Drink Mix**	
Serving size per	7 g		30 g	
Nutritional Information	Amount	% Daily Value	Amount	% Daily Value
Calories	25		110	
Fat, g	0	0%	0.2	1%
Saturated fat, g			0	0%
Trans Fat, g			0	0%
Cholesterol, mg			0	
Sodium, mg	15	1%	50	2%
Potassium, mg	35	2%	0	0%
Carbohydrate, g	0	0%	2	1%
Sugars, g			1	
Dietary Fibre, g			1	4%
Protein, g	6		25	
Calcium		2%		10%
Iron				2%

g: gram; mg: milligram.

Supplementary Table 5.3. Anthropometrics, body composition, nutritional intake and status, and energy expenditure across study time points by sex.

	Pooled Baseline (n=50)	Females		Males	
		Week 6 (n = 17)	Week 12 (n = 15)	Week 6 (n = 27)	Week 12 (n = 25)
Anthropometrics and Body Composition					
Weight, kg	79.9 (67.8, 87.8)	65.8 (57.1, 81.7)	75.3 (57.9, 85.1)	79.6 (72.7, 98.9)	83.4 (74.6, 103.6)
BMI, kg/m^2	27.0 (22.8, 31.2)	23.5 (22.1, 31.9)	28.6 (22.4, 32.6)	26.9 (22.7, 30.8)	27.1 (23.2, 31.6)
WC, cm	97.4 (83.2, 105.3)	83.8 (76.9, 99.2)	94.7 (76.5, 103.3)	95.7 (86.6, 108.2)	97.1 (91.9, 109.1)
Adjusted CC[1], cm	33.9 (32.6, 35.2)	33.4 (31.2, 34.5)	34.5 (31.2, 36.7)	34.8 (33.7, 36.1)	35.1 (33.2, 36.6)
ALSTI, kg/m^2	7.3 (6.3, 8.1)	6.1 (5.7, 7.0)	6.3 (6.0, 7.3)	7.8 (6.8, 8.9)	8.0 (7.3, 9.0)
Fat mass, %	34.9 (27.4, 42.4)	42.4 (34.5, 46.7)	41.6 (36.6, 47.4)	29.5 (26.0, 36.5)	29.8 (26.5, 37.1)
Low MM, n (%)					
ALSTI					
Yes	10 (20)	2 (11.8)	1 (6.7)	7 (25.9)	4 (16.0)
No	40 (80)	15 (88.2)	14 (93.3)	20 (74.1)	21 (84.0)
ALST/BW					
Yes	19 (38)	9 (52.9)	6 (40.0)	7 (25.9)	7 (28.0)
No	31 (62)	8 (47.1)	9 (60.0)	20 (74.1)	18 (72.0)
ALSTI Change, n (%)					
Maintained or gained		8 (47.1)	8 (53.3)	11 (40.7)	12 (48.0)
Lost		9 (52.9)	7 (46.7)	16 (59.3)	13 (52.0)
Nutritional Intake and Status					
Energy intake, kcal	2061 (1685, 2478)	1783 (1431, 2181)	1666 (1506, 2365)	2491 (1752, 2769)	2614 (2124, 3193)
Energy intake, kcal/kg	26 (22, 33)	27 (18, 32)	27 (22, 29)	28 (22, 35)	31 (23, 37)
Protein intake, g	88 (67, 108)	80 (64, 119)	85 (58, 134)	106 (90, 144)	117 (96, 164)
Protein intake, g/kg	1.0 (0.9, 1.4)	1.2 (0.9, 1.5)	1.2 (0.7, 1.6)	1.4 (1.2, 1.8)	1.3 (1.0, 1.9)
PG-SGA$_{SF}$ score[2], 0–36	4 (2, 7)	6 (2, 9)	6 (2, 12)	2 (1, 7)	6 (1, 7)

(continued)

	Pooled Baseline (n=50)	Females		Males	
		Week 6 (n = 17)	Week 12 (n = 15)	Week 6 (n = 27)	Week 12 (n = 25)
Energy Expenditure					
REE, kcal/day	1663 (1441, 1874)	1447 (1234, 1559)	1536 (1446, 1691)	1682 (1590, 1938)	1859 (1631, 1983)
REE, kcal/kg	21.1 (19.8, 23.2)	19.8 (17.6, 23.3)	22.0 (19.0, 23.6)	20.9 (19.6, 22.6)	21.1 (18.8, 23.2)

Data are presented as median (25^{th} percentile, 75^{th} percentile) or as n (%) for count data. [1]calf circumference adjusted as follows: BMI <18.5 kg/m^2: CC + 4 cm; BMI 25.0–29.9 kg/m^2: CC – 3 cm; BMI 30.0–39.9 kg/m^2: CC – 7 cm; BMI ≥40 kg/m^2: CC – 12 cm [43].; [2]Higher scores indicate increased risk for malnutrition. PG-SGA$_{SF}$: Patient Generated Subjective Global Assessment Short Form; WC: waist circumference.

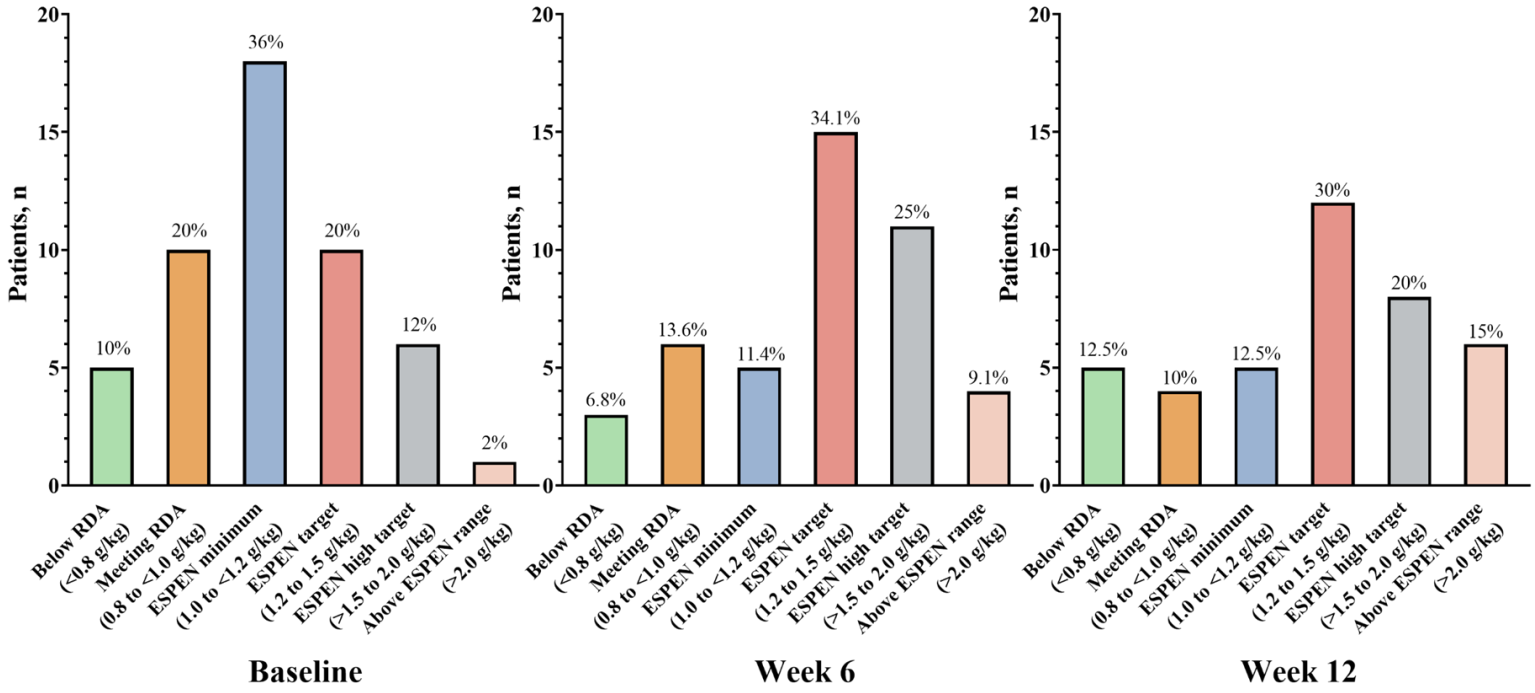
Supplementary Table 5.4. Anthropometrics, body composition, nutritional intake and status, and energy expenditure across study time points by tumor location.

	Pooled Baseline (n=50)	Rectal Cancer		Colon Cancer	
		Week 6 (n = 11)	Week 12 (n = 10)	Week 6 (n = 33)	Week 12 (n = 30)
Anthropometrics and Body Composition					
Weight, kg	79.9 (67.8, 87.8)	70.5 (56.6, 78.8)	74.6 (63.0, 83.7)	80.3 (66.6, 98.7)	82.3 (70.0, 99.6)
BMI, kg/m^2	27.0 (22.8, 31.2)	22.7 (21.5, 27.6)	24.4 (22.3, 28.8)	27.6 (22.5, 32.4)	28.8 (22.7, 32.9)
WC, cm	97.4 (83.2, 105.3)	86.6 (75.0, 100.4)	91.3 (77.9, 104.3)	95.9 (83.8, 108.4)	96.3 (88.6, 109.9)
Adjusted CC[1], cm	33.9 (32.6, 35.2)	34.5 (34.1, 36.2)	35.3 (33.0, 37.1)	34.3 (32.5, 35.6)	34.7 (32.5, 36.2)
ALSTI, kg/m^2	7.3 (6.3, 8.1)	7.0 (5.8, 7.7)	7.3 (6.1, 7.7)	7.0 (6.4, 8.8)	7.7 (6.5, 8.8)
Fat mass, %	34.9 (27.4, 42.4)	31.9 (26.0, 35.1)	35.2 (28.9, 38.0)	36.7 (27.5, 43.9)	36.4 (28.0, 42.6)
Low MM, n (%)					
ALSTI					
Yes	10 (20)	2 (18.2)	0 (0.0)	7 (21.2)	5 (16.7)
No	40 (80)	9 (81.2)	10 (100.0)	26 (78.8)	25 (83.3)
ALST/BW					
Yes	19 (38)	3 (27.3)	3 (30.0)	13 (39.4)	10 (33.3)
No	31 (62)	8 (72.7)	7 (70.0)	20 (60.6)	20 (66.7)
ALSTI Change, n (%)					
Maintained or gained		4 (36.4)	6 (60.0)	15 (45.5)	14 (46.7)
Lost		7 (63.6)	4 (40.0)	18 (54.5)	16 (53.3)
Nutritional Intake and Status					
Energy intake, kcal	2061 (1685, 2478)	2300 (1783, 2590)	2333 (1714, 2977)	2072 (1561, 2758)	2311 (1760, 3013)
Energy intake, kcal/kg	26 (22, 33)	33 (26, 34)	30 (24, 39)	27 (18, 32)	29 (21, 33)
Protein intake, g	88 (67, 108)	94 (81, 143)	100 (72, 155)	100 (77, 135)	114 (82, 153)
Protein intake, g/kg	1.0 (0.9, 1.4)	1.4 (1.2, 1.8)	1.3 (1.0, 2.2)	1.3 (0.9, 1.6)	1.3 (0.9, 1.8)
PG-SGA$_{SF}$ score[1], 0–36	4 (2, 7)	2 (1, 6)	1 (1, 8)	5 (1, 8)	6 (2, 10)

(continued)

	Pooled Baseline (n=50)	Rectal Cancer		Colon Cancer	
		Week 6 (n = 11)	Week 12 (n = 10)	Week 6 (n = 33)	Week 12 (n = 30)
Energy Expenditure					
REE, kcal/day	1663 (1441, 1874)	1562 (1352, 1673)	1584 (1473, 1751)	1636 (1441, 1886)	1732 (1529, 1940)
REE, kcal/kg	21.1 (19.8, 23.2)	21.2 (20.2, 23.5)	22.3 (19.2, 25.3)	20.6 (18.6, 22.6)	21.4 (18.6, 23.0)

Data are presented as median (25^{th} percentile, 75^{th} percentile) or as n (%) for count data. [1]calf circumference adjusted as follows: BMI <18.5 kg/m^2: CC + 4 cm; BMI 25.0–29.9 kg/m^2: CC – 3 cm; BMI 30.0–39.9 kg/m^2: CC – 7 cm; BMI ≥40 kg/m^2: CC – 12 cm [43].; [2]Higher scores indicate increased risk for malnutrition. PG-SGA$_{SF}$: Patient Generated Subjective Global Assessment Short Form; WC: waist circumference.



Supplementary Figure 5.1. Protein intake across study timepoints in patients with newly diagnosed colorectal cancer. ESPEN: European Society for Clinical Nutrition and Metabolism; g/kg: grams of protein per kilogram of body weight per day; RDA: recommended dietary allowance. Baseline n=50; Week 6 n=44; Week 12 n=40.

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Chapter 6 Drivers of Dietary Choice Following a Diagnosis of Colorectal Cancer: A Qualitative Study

6.1 Preface

The following chapter is a secondary analysis of baseline data from the randomized controlled trial conducted for this thesis. The chapter is based on data from 29 patients with stage II-IV colorectal cancer (CRC) who were recruited from the Cross Cancer Institute in Edmonton, Canada and were participating in the Protein Recommendation to Increase Muscle (PRIMe) trial. This work aimed to understand if and why dietary changes were made by patients and learn about their food-related beliefs when starting chemotherapy following a CRC diagnosis. We also sought to understand if patients made dietary changes that had the potential to impact muscle health.

This chapter was published in the Journal of the Academy of Nutrition and Dietetics (Ford KL, Trottier CF, Wismer WV, Sawyer MB, Siervo M, Deutz NEP, Prado CM, Vallianatos H. Drivers of Dietary Choice Following a Diagnosis of Colorectal Cancer: A Qualitative Study. Online ahead of print. DOI: 10.1016/j.jand.2022.08.128). Within this article, I was responsible for data analysis and writing the first draft of the manuscript; co-authors critically reviewed the intellectual content of the manuscript.

6.2 Abstract

Background: Dietary changes often accompany management of a cancer diagnosis but how and why patients with colorectal cancer (CRC) make dietary decisions requires further investigation.

Objective: To understand if and why dietary changes were made by patients and learn about their food-related beliefs when starting chemotherapy following a CRC diagnosis. We also sought to understand if patients made dietary changes that had the potential to impact muscle health.

Design: A qualitative semi-structured interview study was conducted at baseline as a secondary analysis among a subset of patients with stages II-IV CRC enrolled in a randomized controlled trial. Twenty-nine patients participated in the interview. Data was collected at the University of Alberta (Edmonton, Alberta, Canada) from 2016-2019 prior to any trial intervention. Audio-recorded interviews were transcribed verbatim then coded inductively by two research team members. Qualitative content analysis was applied to capture emergent themes.

Results: Patients reported varied degrees of dietary change that stemmed from internal and external influences. Four main themes emerged to describe patients' dietary decisions after a CRC diagnosis: (1) Medical Influences: eating to live; (2) Health Beliefs: connecting lived experiences with new realities; (3) Static Diets: no changes post-diagnosis; and (4) Navigating External Influences: confluence of personal agency and social constraints.

Conclusion: The extent to which patients altered their dietary choices depended on perspectives and beliefs. These included the degree to which dietary decisions provided some agency (i.e., feeling of control) for dealing with physical ramifications of cancer treatment, individuals' personal understandings of healthy foods, and the role of diet in managing their new physical reality post–diagnosis. This information provides registered dietitian nutritionists and healthcare providers with insight into dietary intentions of select patients being treated for CRC. These findings can guide future research focused on effective strategies for streamlined nutritional support that aligns with patient needs.

6.3 Introduction

Cancer is the leading cause of premature death in the Western World [1]. In 2020, colorectal cancer (CRC) was the second cause of cancer-related deaths and the third most diagnosed cancer globally [2]. As a gastrointestinal cancer, linkages between diet and CRC (e.g., association between dietary intake and risk of disease [3]) are recognized. Lifestyle modifications including dietary changes are often initiated after a cancer diagnosis [4].

People with cancer value the importance of optimal health and view nutrition as a key contributor [5, 6]. An Italian study found that patients with cancer (n=1257) were attentive to nutrition throughout their treatment, and more than half made positive dietary changes [6]. Patients are motivated and seek nutrition information to guide food choices [4, 7]. Common sources of nutrition information include physicians, family/friends, and mass media [7, 8]. Notably, about one third of social media articles on cancer contain misinformation [9]. Patients thus receive conflicting information and have misconceptions regarding optimal nutrition [10].

Self-guided dietary changes may not align with oncology nutrition guidelines [11]. For example, patients with cancer report decreasing or eliminating meat and/or dairy products. This change can result in decreased protein intake which is contrary to oncology nutrition guidelines that suggest increased protein intake during cancer treatment [11]. Decreasing or eliminating intake of animal products results in decreased protein quantity and quality as animal-based foods are sources of high-quality proteins and are important for people with cancer, especially for muscle health [11, 12]. A systematic review of post-diagnosis dietary intake and cancer outcomes found that certain dietary patterns (i.e., Western diet) are associated with disease progression and recurrence but that specific food categories (i.e., meat, dairy products) were not associated with disease progression and should not be eliminated [13].

Dietary changes that occur after a cancer diagnosis are not well-characterized, especially among patients with CRC [14]. Most research on dietary change has been described quantitatively; to our knowledge, there is a paucity of qualitative analyses that describe the impact of cancer on food intake from the patients' perspective and further explore the phenomena affecting post-diagnosis dietary choices [15-17]. To date, most of the literature in this area has focused specifically on the impact of chemosensory alterations on food behaviour [18]. Thus, this study sought to learn about patients' food-related beliefs following a CRC

diagnosis and ultimately understand if dietary changes were made by patients and their reasons for altering, or not, their diet.

6.4 Methods

6.4.1 Study Design and Ethics

This qualitative study took place from 2016-2019 and was a secondary baseline analysis among a subset of patients participating in a randomized controlled trial at the University of Alberta (Edmonton, Alberta, Canada) [19]. The primary objective of the trial was to inform the feasibility of utilizing a diet containing 2 g/kg/day versus 1 g/kg/day of protein to halt muscle mass loss in patients being treated for CRC [20], **Chapter 5**. The trial protocol is described elsewhere [20], **Chapter 3**. No incentive was provided for patients who completed the semi-structured interview. A trained member of the study team obtained written informed consent from patients. The study was approved by the Health Research Ethics Board of Alberta-Cancer Committee (HREBA.CC-15-0193) and complied with standards on the use of human participants in research. Reporting was guided by Consolidated Criteria for Reporting Qualitative Research (COREQ): a 32-item checklist for interviews and focus groups [21].

6.4.2. Participants

Inclusion/exclusion criteria are detailed in the trial protocol [20]. Briefly, patients were 18-85 years of age, were diagnosed with stages II-IV CRC within the past seven months, did not have cancer cachexia, and had started or were scheduled to start adjuvant chemotherapy within 14 days of completing the semi-structured interview. Some patients had surgery (typically 6-8 weeks prior) to remove the tumor and/or place an ostomy.

6.4.3 Demographic and Clinical Characteristics

Patient age and sex were obtained from electronic health records. A questionnaire was used to collect data on self-reported race and ethnicity, annual household income, and highest level of education completed. Body weight and height were measured during trial participation and body mass index was calculated. Clinical characteristics including type and stage of disease and presence of an ostomy were obtained from electronic health records. Quantitative data are presented as mean ± standard deviation.

6.4.4 Qualitative Data Collection

The first 36 patients to complete baseline assessments in the trial were invited to participate in a semi-structured interview. At that point, 29 interviews had been completed and data saturation was reached, thus participants were no longer offered the opportunity to complete the interview, which was not required for participation in the trial. The trial from which patients were invited purposefully included patients with a range of demographic and clinical characteristics (e.g., age, sex, disease location and stage, presence of an ostomy) that are commonly observed in patients undergoing adjuvant treatment. Interviews were completed at the baseline study visit, prior to randomization and receiving any intervention (i.e., nutrition counselling) in the trial. Five patients received nutrition counselling (mostly related to an ostomy) at the cancer center prior to the interview although codes that emerged from their data did not differ from the larger patient cohort; thus, their data was considered in the analysis.

Interviews followed a semi-structured guide (**Figure 6.1**) and took place in a private room at the University of Alberta where only the patient and interviewer were present. The interview guide was developed by study team members whereby open-ended questions and optional probing questions were informed by a review of the literature and clinical experience pertaining to food choice and nutrition-impact symptoms in the oncologic setting. An expert in qualitative research and an expert in dietary intake in chronic disease reviewed the interview guide. The interview guide was then pilot tested with the first two patients, whose data were included in the analysis since no major changes were subsequently made to the interview guide.

The first two interviews were conducted by an experienced qualitative researcher (H.V.) who trained another female member of the team (C.T.; present for all interviews) to conduct the remaining interviews. Training included readings [22] and observing the experienced researcher during the first two interviews. Patient interaction was limited to recruitment, scheduling of visits, and baseline study assessments that occurred during the same encounter as the interview. Using the same team member for these tasks ensured consistency in data collection methods.

Patients were informed that the audio-recorded interview would take approximately 45 minutes, and the interviewer would be taking notes. Interviews lasted until the patient had the opportunity to respond to all questions and offer any relevant thoughts that had not yet been captured. Audio files were transcribed verbatim by third-party services. Transcribed files were

verified for accuracy by a member of the research team and personal field notes added to the end of each transcript. Patients were not offered the opportunity to review the transcripts nor to provide feedback on data analysis.

6.4.5 Qualitative Data Analysis

Qualitative content analysis is a systematic method for analyzing and interpreting data in a way that enables one to describe the meaning of the data [23]. Qualitative content analysis was employed concurrently to data collection. To enable an in-depth description of the semi-structured interview data, a data-driven coding frame was built inductively [23]. Two members of the study team independently conducted line-by-line manual open coding at the word- and sentence-level to identify relevant concepts. Codes emerged inductively and formed a master coding frame based on congruent findings. Selective coding was used to structure concepts and group open codes into key categories [23]. From this process, themes emerged inductively from the data. This approach has been described by Hsieh and Shannon (2005) as conventional content analysis; an approach that enables researchers to describe a phenomenon [24]. To ensure rigor and reliability of our coding frame, the first five transcripts were double coded to discover and discuss differences. Minimal differences emerged thus the master coding frame was used for constant comparison with new data (coding additional transcripts), as they became available. Theoretical saturation occurred after approximately 72% of transcripts were analyzed although all coded transcripts were included to ensure that perspectives of all patients contributed to informing emergent themes. Once theoretical saturation was achieved, no additional participants from the trial were invited to participate. Data were managed using Excel (Microsoft Corp, Redmond, WA) and are presented as themes. The team member who conducted the interviews reviewed the analysis to ensure the themes matched their understanding of the interviews and field notes.

6.5 Results

Twenty-nine patients completed an interview at baseline and are included. Mean patient age was 57 ± 10 years and mean weight was 80.4 ±18.5kg. Most were White (65.5%) males (62.1%) with stage [28] III (58.6%) colon (82.8%) cancer. Patient characteristics are shown in **Table 6.1.** Drivers of dietary choices post-diagnosis were informed by four main emergent

themes (**Figure 6.2**): (1) medical influences; (2) health beliefs; (3) static diets; and (4) navigating external influences.

6.5.1 Medical Influences: Eating to Live

Medical procedures, treatments, side effects, and interaction with health professionals emerged as a major influence of dietary decisions following a CRC diagnosis. Patients described their food intake as being influenced by medical procedures and treatments that forced dietary change (e.g., prescribed a low fiber diet post-operatively). In other words, the pleasure of food had become a less influential driver of dietary choice than prior to diagnosis for many patients and dietary decisions pivoted to focus on meeting nutritional needs. Participants described changes to their gastrointestinal tract and ability to digest foods as limiting factors that forced them to alter their typical intake. For example, "*I used to eat a lot of fried foods. Now [since diagnosis] it's like, I can't eat fried foods. I do, but it gives me gas and indigestion*" (Patient 108).

Following ostomy surgery, patients received varying dietary advice; some surgeons recommended a low fiber diet for six weeks while other patients were told to resume their regular diet in moderation and as tolerated. Patient 123 described how they handled receiving conflicting dietary advice from their medical team: "*the nurse gave me a little bit of conflicting advice when I was first discharged from the hospital, she thought I should be on a low fiber diet initially. But the surgeon said just eat what you want in moderation and small quantity, so that's what I did.*"

Patients described the post-surgery dietary changes as limiting: "*I can't eat a lot of foods right now. No seeds. No nuts. No roughage. Can't eat lettuce*" (Patient 108). Other challenges that emerged following ostomy surgery were the inability to digest certain foods. Patient 109 described what they experienced when consuming cooked vegetables:

> "*I notice that as it comes out [from the ostomy], it still looks the same…broccoli still looks like broccoli to me. Carrots, unless it's really finely mushed, still looks like carrots to me. Obviously, corn is always going to look like corn, but a lot of those vegetables like spinach and even lettuce, when it comes out, it doesn't look like it's being digested at all.*"

Patients with an ostomy routinely described their output as containing undigested food: "*I have craved a little bit of fresh vegetables – raw vegetables – so I'm starting to introduce them a little bit, but I notice that a lot of them go through my body, my body doesn't digest them*" (Patient 124). The health impact of dietary changes resulting from an altered gastrointestinal tract and/or ostomy were concerning for patients. Patient 117 summarized their discontent with the dietary changes that they had to make, saying:

> "*It sucks because I used to eat brown rice and wild rice and things like that, and I have to eat white rice… I never used to eat white pasta. I stayed away from bad carbs, but now I have to add them in. I never used to drink Gatorade, but because of my output, I have to now, so I don't get dehydrated and everything and the salts. I never used to use salt. Now I have to use a little bit of it…I would never touch white bread before. Now I have to have it… raw vegetables used to be my snack, and now I can't have them.*"

In addition to physical changes to the gastrointestinal tract that resulted in food intolerances, nutrition-impact symptoms commonly observed with anti-cancer therapies, such as sensitivity to cold, forced patients to make dietary changes: "*I have to drink lots of water and drinking warm water is – I struggle, I can't*" (Patient 122). Patient 114 described the feeling of cold-sensitivity and corresponding impact on food intake as:

> "*I'm addicted to milk, but that's something I cut down on quite a bit now because of the side effects of the IV chemo…cold liquids make my throat strain up. And the first day, it was almost painful. So now you're faced with warming up your milk because I can drink it only when it's warm, and warm milk tastes disgusting…We switched to chocolate milk, because I don't mind hot chocolate.*"

Diarrhea is a known side-effect of chemotherapy agents (e.g., capecitabine, 5-fluorouracil) used to treat CRC. Some patients felt forced to alter their diet to control diarrhea. Patient 110 described their attempt at regulating diarrhea through food intake: "*I got really bad diarrhea then … I had to lower the fat content just to make my digestive system happier, so you do what you have to.*" Similarly, patients with an ostomy described modifying their diet based on the consistency of their output: "…*trying to manage … how to thicken it up, so I'd have a lot of peanut butter and banana sandwiches, things like that*" (Patient 117). Dairy was commonly avoided due to digestion and absorption challenges and diarrhea. Patient 121 described the

impact that avoiding dairy had on themself and their family: "*I didn't have milk for most of the summer. Milk, ice-cream. The family would all go for ice-cream cones, and I would get a water.*"

Another approach to managing diarrhea that included dietary change was varying the volume of fluid and food that a person consumed: "…*adjusting how much I drank, how much I ate, to limit the amount of diarrhea that I had…*" (Patient 125). Overall, patients attempted to remedy several symptoms through diet. For example, Patient 114 explained: "*I actually found out that my nausea would go away if I would start eating*". In addition to altering meal timing and frequency to manage gastrointestinal symptoms, this strategy was employed to remedy the feeling of early satiety.

The concept of eating for strength also emerged through a lack of appetite and the need to actively cue oneself to eat: "… *after surgery, you have no appetite or don't feel like eating, but I would force myself to eat just so I'd get stronger*" (Patient 104). Patient 116 described this concept simply as: "*I don't even feel hungry, but I eat*". Patient 114 described the shift in their mindset as "*I've generally been kind of casual with my eating habits, but when you get to health issues, you focus a little bit more on that kind of stuff*".

Another medical reason that motivated dietary change was an altered immune system induced by anti-cancer treatment. For example, Patient 115 avoided some favorite foods during chemotherapy: "…*over the last few years, I actually got interested in eating sushi and sashimi. I like that quite a bit, although currently I can't have it…I'm on the chemo and because of the possibility of a lowered immune system, can't have anything raw*". Foods commonly avoided due to food safety concerns included raw fish: "*Japanese foods, that's the best. But only for cooking, not the raw sushi. That's what I ate before, but no more. Everything has to cook*" (Patient 102).

6.5.2 Health Beliefs: Connecting Lived Experiences with New Realities

Personal health beliefs emerged as a driver of food choice and dietary change. This theme examined patients' health beliefs and their interpretations of dietary guidelines based on lived experiences. Patients described reducing or eliminating red and/or processed meat post-diagnosis because of their perceived relationship between these foods and health: "*Totally contrary to 6 months ago…before I started watching it [food choices] and knowing my diagnosis, it was a lot of stuff like pepperoni, sausage, smokies, hot dogs, just grabbed that stuff and munch on it. We*

don't even buy it anymore" (Patient 115). Patient 113 simply stated: "*I have eliminated a lot of red meat. I read that red meat could be a possibility of cancer.*" Reduced intake of red meat primarily affected the evening meal while elimination of processed meat changed food choices at breakfast and lunch. Red meat at supper was often replaced with chicken, turkey, pork, or fish while processed meat at lunch was replaced with salads or leftover non-processed meat from the evening before. In addition to decreasing meat intake, patients also altered their food preparation methods in fear of health implications: "*we've not been doing much barbequing since my diagnosis. We've kind of stayed away from any super-heated red meat*" (Patient 115).

Patients iterated a link between red meat consumption and colon cancer and talked about the challenge of drastic dietary changes such as eliminating red meat from the diet: "*…somewhere I read that especially for colon cancer that red meat doesn't really help. And I did [eliminate red meat] till I got hungry enough for a hamburger, and then I had the hamburger because that's hard to do…*" (Patient 110). Patients struggled to balance their personal health beliefs with enjoyment of food. Patient 116 said: "*I know it wasn't healthy to eat too much [meat], but I find out that I cannot resist. I still am eating [meat], but not as much as I used to, because every dish it has to have meat for me. I love meat*".

Sugar consumption was a concern and efforts were made to reduce added and total sugar intake after diagnosis. Sugar-sweetened carbonated beverages were often eliminated. Ginger ale was an exception; most patients added ginger ale to their diet after surgery or at the start of anti-cancer treatment to help with digestive issues. The disconnect between the desire to eliminate added sugar but use ginger ale to aid with digestion was exemplified by Patient 121: "*In the last month I've had a couple of ginger ale for sure. It feels almost like not bad*".

Quantity of food was often described as volume of intake or portion sizes. Patients expressed a desire to decrease the quantity of food consumed. When asked about any dietary changes made post-diagnosis, Patient 127 said: "*I restrict a lot of what I'm eating now. Trying to decrease amounts…not necessarily specific foods, just amounts*". Reasons for decreasing food intake were not consistent; some related it to their weight (i.e., many felt a need to lose weight, as a step towards optimizing health), others to a feeling of fullness, or to their ability to digest large quantities of food.

A pattern of replacing frozen or canned foods with fresh options emerged, especially in relation to meat, fish, and produce: "*just trying to stay away from processed foods. More vegetables, more fruit, right, eating lots more fruit*" (Patient 126). Some patients were also advised by a dietitian at the cancer center to increase protein intake and reported increasing their fish intake and focusing on protein when choosing foods. Patient 115 explained how they replaced highly processed meat with a meal-replacement cereal to make healthier food choices:

> "*My favorite was Schneiders Pepperettes. Whenever they went on sale, I'd binge buy them. I'd buy 3 packages, and I'd eat unhealthy because it was convenient, because I had it, and I liked the taste of it, and it was my go-to munchie. Now I'd sooner take a bowl of Vector cereal with milk for the protein rather than having – I don't miss that stuff anymore, knowing that I shouldn't have it.*"

Overall, health improvement was the driving motivation for chosen diet change (i.e., changes to food choice that were not required due to a surgically altered gastrointestinal tract). Patient 115 explained: "*Every once in a while, I do crave those salty, greasy snacks, but I just realize that it's not good for me, so I guess I miss it a little bit, but not enough that I'm going to go out and buy any*".

6.5.3 Static Diets: No Changes Post-diagnosis

Within this theme, drivers of dietary choice emerged as: (1) a perception that diet prior to cancer was healthy and that no further changes were needed to support healthy eating practices post-diagnosis; and (2) prior health challenges resulted in sustained dietary changes which remained appropriate post-diagnosis. Approximately one quarter of patients in this study described experiences that contributed to the formation of the static diet theme, one of whom intersected with the theme on medical influences related to the presence of an ostomy.

When asked if they had eliminated or changed any foods in their diet, answers included: "*Nothing's changed*" (Patient 105); "*Absolutely nothing*" (Patient 111); "*I'm eating everything that I've eaten before*" (Patient 120); and "*I find that the variety is all there, so I know that I'm getting a good mix of things. I don't think I need to change too much in my diet*" (Patient 109). For some patients, diet had not been a focus since their diagnosis: "*I never thought about that. I guess it's possible, but not in any way that I've noticed*" (Patient 119).

Changes to food choices were based on lived experiences for some patients who talked about specific foods that were commonly associated with past health conditions (i.e., prior to this cancer diagnosis). Meat is a source of high-quality protein but was frequently avoided due to comorbidities. Patient 107 explained: "… *I don't think I've had a hamburger probably once in the last 2 years. Not because I don't like them, just primarily because after my stroke, I just quit doing that altogether*" and Patient 109 said: "*because of my previous condition with gout, I don't like to actually eat too much beef. We cook it all the time, but I don't usually eat it*". Patient 103 described the impact that a different gastrointestinal condition had on their eating practices: "*Well with my Crohn's, I found beef really bothered me, so that kept me away from it, and I guess that's just kind of kept me away from it. But not that I wouldn't enjoy a slice of roast beef, but it's certainly nothing I would choose very often*". Patient 112 said: "*We try not to eat pork because of my arthritis. It's not good for arthritis*."

6.5.4 Navigating External Influences: Confluence of Personal Agency and Social Constraints

Patients had varied capacities to control their environments and navigate their cancer journey. Nevertheless, patients actively interpreted knowledge and subsequently enacted dietary recommendations to varying degrees. This thematic category highlights patients' agency (i.e., feeling of control) in practicing dietary behaviors that they believe promote an optimal response to cancer.

Patients showed their agency as they interpreted the scientific literature and related findings to their personal situation. They relied on information from sought-out online sources (e.g., websites, social media, etc.) to sought-out or unsolicited advice from health care providers, colleagues, and friends and family: "*I've been told [about red meat] by my coworkers when we have lunch together, we talk sometimes, and then when I had before the surgery and I got colonoscopy, doctors advised me just to cut red meat. It's not healthy. It was always, but I didn't enforce that*" (Patient 116).

Patients' interpretation of the literature was based on their own values and understandings. Patient 114 commented:

"*Nuts…That is one thing I've added to my diet that I usually haven't eaten a lot of…Specifically almonds. I saw a special on nutrition...British research determined that the almond is the most nutritious food in the world…I don't know what factors they look at, but apparently, it's the most nutritious. So I figured I might as well add it to my diet*".

They expressed having to navigate the interweaving landscape of health care provider advice and their own personal learnings to effect heath beliefs and ultimately health behavior change: "*after the stomach [surgery] one of the recommendations from the nurse, they say don't eat that one [food] because it's too much seeds. I say – but I want to go back to that, because that's one of the big things for me, especially in the breakfast. Normally I prepare my smoothies*" (Patient 128).

The importance of verifying advice, regardless of the reputability of the source, was also expressed by some patients. When asked where they heard about nutrition information pertaining to cooking practices for meat, Patient 115 explained:

"*From friends and from research on the Internet…Actually, first got the hint of it when I talked to [dietitian's name redacted] for the first time at the cancer center and when I was first starting on my original chemo. I had a consultation with her, and we talked quite a bit about charring meat, barbequing, and that it's – they know now that that's not necessarily a good thing, so that was where I initially got the bug in my ear and then did more research on it on my own.*"

For others, physical activity was a major influencer of health and personal agency: "*before, I didn't worry so much about nutrition because I know I was getting enough, but it was for a different purpose. It was to maintain all that exercising I was doing*" (Patient 110). Regardless of the external influence, patients with prior experience managing their nutrition focused on dietary practices that dovetailed with their past ways of eating post-diagnosis.

6.6 Discussion

This study adds to the paucity of global qualitative research on dietary decision making of patients with cancer near time of diagnosis and beyond. Data from semi-structured patient interviews suggested that medical influences, health beliefs, and navigating external influences were drivers of dietary choices. Additionally, static diets emerged for patients who felt their

dietary behaviors already exhibited healthy eating patterns. Making sense of dietary advice was also of high importance to patients and was easier for those whose dietary health beliefs and practices merged with dietary recommendations.

The findings presented herein fit within the large body of literature that describes factors affecting eating behaviors [26, 27] including individual determinants (e.g., medical influences, health beliefs, and prior dietary changes resulting in static diets post-diagnosis) and environmental influences (e.g., social and physical environments). Our findings align with the Information-Motivation-Behavioral Skills Model, a highly generalizable model used across health behavioral domains (including nutrition) that seeks, in-part, to understand health behaviors [28]. This model postulates that health-related information, personal/social motivation, and behavioral skills are core determinants of behavior engagement [28].

The theme of *Medical Influences: eating to live* emerged from interviews with study patients. Many discussed symptoms/side effects of medical conditions or treatments and how these forced dietary change that shifted the notion of eating from pleasure to health. These findings were similar to those from a group in the United Kingdom (UK) who used principles of phenomenology to guide their qualitative thematic analysis of people's relationships with food and CRC [17]. They also found that symptoms from the medical attributes of cancer were major drivers of dietary change for participants [17]. Similar to the findings presented herein, other studies found that participants self-managed symptoms of nausea [15] and ostomy output through self-guided dietary modifications [17].

Contrary to the current findings, the UK team discovered that participants with stages I-IV CRC used weight as measure of overall recovery post-operatively [17]. Weight was a topic of discussion in our cohort but not in the context of recovery from surgery or cancer. Instead, patients' discussion of weight contributed to the theme of *Health Beliefs: connecting lived experiences with new realities* but was not a focus at this point in their cancer journey. In line with the findings from the present study, a qualitative study of post-diagnosis dietary decision-making in Chinese cancer survivors found that personal belief guided dietary decisions [15].

Given the unique nutritional impact of cancer, surgical and oncologic nutrition guidelines are used by practitioners to promote optimal nutrition during the perioperative and anti-cancer therapy periods, respectively [11, 29]. High-quality (i.e., animal-based) proteins are an important

dietary component during cancer treatment [11] due to their superior anabolic properties and role in muscle mass maintenance [12, 30]. Dietary behaviors that decrease animal-protein (e.g., meat, dairy) intake during cancer do not align with oncology nutrition guidelines [11]. Resulting protein intake may not be sufficient to preclude muscle depletion, one of the primary nutritional problems these patients experience [12].

Patients herein equated dietary guidelines for cancer prevention with appropriate intake during cancer treatment which adds to the literature suggesting that nutritional recommendations throughout the cancer journey may be unclear to patients and families [5, 31]. As discussed elsewhere [12], nutrition goals and guidelines for optimal intake vary across the cancer continuum whereby nutrition recommendations for cancer prevention do not necessarily parallel recommendations during active cancer treatment. For example, red meat is likely associated with colon cancer incidence but inversely related to mortality from the disease [32]. Increased protein intake is a protective mechanism against mortality in older adults [33] who make up the majority of cancer cases. Given that patients have variable protein intake that is often below recommendations [34-37], dietary patterns should likely shift following a CRC diagnosis to better align with oncology nutrition guidelines, especially if protein was not previously emphasized as a key nutrient in the diet [11]. A shift in dietary patterns was not observed in this study where a main theme emerged as '*Static Diets: no changes post-diagnosis'*.

The theme *Navigating External Influences: confluence of personal agency and social constraints* encompassed the idea that patients experienced confluence between personal agency and social constraints which led to dietary change. Similar to these findings, participants in the UK study expressed personal feelings and emotions as stronger influencers of dietary decisions than any objective dietary advice received [17]. Culture and family influence were external influencers of dietary decisions in the Chinese cohort [15]. This contrasts with the findings from this study where culture and family were discussed but did not emerge as major drivers of dietary change. This difference may be due to time since diagnosis (i.e., patients in this study were much closer to diagnosis). Consequently, the medical aspect of their cancer was prioritized. Cultural or other personal factors influencing dietary choices may emerge once patients' comfort with managing medical side effects has stabilized. Overall, a loss of food enjoyment emerged in the themes which has been observed across various other cancer types and described as "eating

without satisfaction" [16], "impact on social functioning" [38], and "trial and error to find tolerable foods" [39]. Beyond nutritional considerations, food is an important aspect of quality of life in patients with cancer [40]. Despite the importance of nutrition, it is often a lower priority for oncologists due to time constraints and lack of clear nutritional guidelines [41].

6.6.1. Strengths and Limitations

This qualitative study compliments previous quantitative research discussed. The format of the in-person one-on-one semi-structured interviews, including the presence of the same researcher for all interviews and their ability to note patients' facial expression and body language in field notes were strengths of this study. Notably, the sex-split observed is indicative of prevalence differences seen in CRC [2]. This study captured the perspectives of a group of nutrition-focused patients being treated for stages II-IV CRC. Nonetheless, patients' interest in nutrition captured herein does not necessarily represent all persons receiving adjuvant treatment for CRC. Furthermore, a demographically diverse sample was enrolled which may have enhanced the generalizability of findings to a wider group of patients with CRC but is not generalizable to all given the inclusion/exclusion criteria of the larger trial. A limitation of this study is that patients were not offered the opportunity to review transcripts of their interview or review the analysis to ensure their words were interpreted as they were intended.

6.7 Conclusion

A qualitative approach provides the opportunity to understand, from a patient perspective, dietary decisions following a CRC diagnosis and provides preliminary insight into the influencers and practical components of dietary change in select patients being treated for CRC. Patients' perspectives and beliefs determined the extent to which dietary choices were altered post-diagnosis. These included the degree to which dietary decisions provided some agency for dealing with physical ramifications of cancer treatment, individuals' personal understandings of healthy foods, and the role of diet in managing their new physical reality post–diagnosis. From a clinical perspective, this type of research can provide insight into relevant dietary trends, fallacies, and motivations for dietary change experienced by a group of patients with CRC receiving adjuvant therapy. Findings presented herein are hypothesis-generating and can be useful for tailoring future quantitative studies on effective strategies to optimize nutritional needs in patients with CRC.

Table 6.1. Aggregated patient characteristics of n=29 adults with colorectal cancer participating in a semi-structured interview on experiences with dietary decisions.

Patient characteristic	
Age, years (mean ± SD)	57 ± 10
Sex, n (%)	
Female	11 (37.9)
Male	18 (62.1)
BMI Category*, n (%)	
Underweight	1 (3.5)
Normal Range	9 (31.0)
Overweight	8 (27.6)
Obesity	11 (37.9)
Tumor Location, n (%)	
Colon	24 (82.8)
Rectum	5 (17.2)
Stage of Disease, n (%)	
II/III	21 (72.4)
IV	8 (27.6)
Ostomy, n (%)	
Yes	8 (27.6)
No	21 (72.4)
Race and Ethnicity, n (%)	
Black	1 (3.4)
Filipino	2 (6.9)
Indigenous	4 (13.8)
Latin American	2 (6.9)
South Asian	1 (3.4)
White	19 (65.5)
Household Income‡, n (%)	
< $20,000	1 (3.5)
$20,000–$39,999	3 (10.4)
$40,000–$69,999	8 (27.6)
$70,000–$99,999	5 (17.2)
≥ $100,000	9 (31.0)
Prefer not to answer	3 (10.3)
Highest Level of Education Completed, n (%)	
High school	8 (27.6)
College diploma	10 (34.5)
University undergraduate degree	8 (27.6)
University post-graduate degree	3 (10.3)

SD: standard deviation; BMI: body mass index. *BMI categories defined as per the Centers for Disease Control [24]; Underweight: <18.5 kg/m^2; Normal range: 18.5-24.9 kg/m^2; Overweight: 25.0-29.9 kg/m^2; Obesity: >30.0 kg/m^2. ‡Annual household income before taxes and deductions in Canadian dollars.

1.	Could you share with me some of your favorite foods? (How do you prepare your favorite foods?) (When do you eat your favorite foods?)
2.	How has being diagnosed with cancer changed the way you eat?
2a.	What foods have you added to your diet since your diagnosis? (Why did you add these foods?)
2b.	What foods have you eliminated from your diet? (Why did you eliminate these foods?) (What do you miss most about these foods?)
2c.	What foods do you think are most important for people living with colorectal cancer to eat?
3.	What do you enjoy about your current diet?
3a.	How does this enjoyment compare to before you were diagnosed with cancer?
3b.	What aspects of eating do you enjoy more since your diagnosis?
4.	What diet guidelines did you use before being diagnosed with cancer? (Why did you follow these?)
4a.	Do you follow any specific guidelines now? (How did you go about selecting guidelines to follow?)

Figure 6.1. Semi-structured interview guide questions for adults receiving treatment for colorectal cancer. Probing questions were used as needed and are indicated in parentheses.

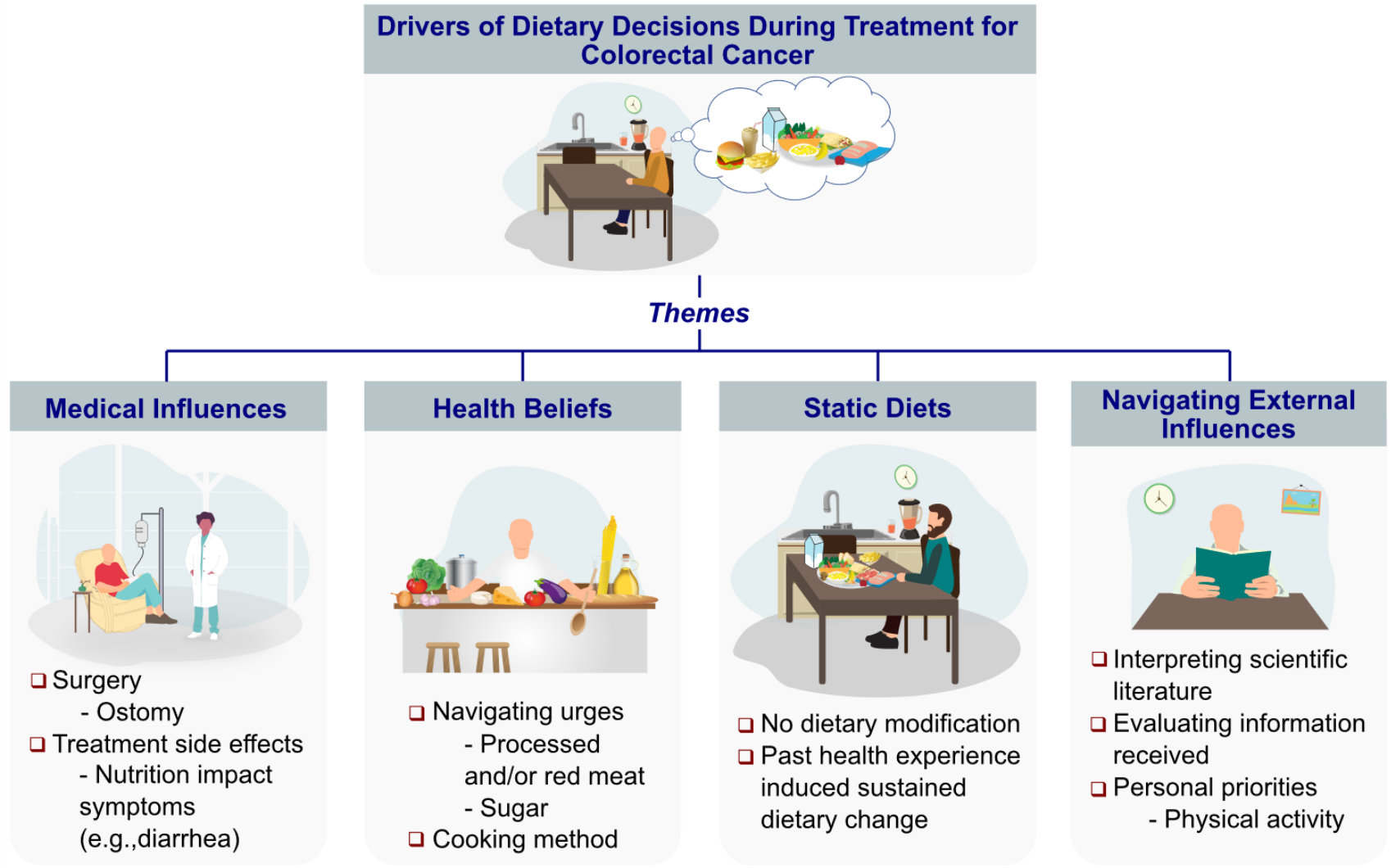

Figure 6.2. Categories and main themes emerging as drivers of dietary choices in adults receiving treatment for colorectal cancer.

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Chapter 7 Discussion and Conclusions

7.1 Introduction

Cancer is the leading cause of premature death in the Western World [1]. Loss of muscle mass (MM) is a prevalent condition observed in the oncology setting and is associated with negative clinical outcomes regardless of disease stage [2-13]. It is increasingly apparent that muscle loss is the primary nutritional problem experienced by oncology patients [14]. Optimizing nutritional status through targeted nutrition intervention (e.g., energy and protein intakes) is essential for muscle health yet patients may underestimate the severity of nutrition-related conditions [15] and not consider the importance of nutrition when making dietary choices. Thus, the overarching aim of this thesis was to characterize total energy expenditure (TEE) and resting energy expenditure (REE), assess the feasibility of increased protein consumption and potential effect of a diet containing 2 g/kg/day versus 1 g/kg/day of protein on MM and physical function, and gain an understanding of what drives dietary decision-making and ultimately dietary intake related to muscle health in patients being treated for colorectal cancer (CRC). The main randomized controlled trial that is the basis of this thesis responds to a call for research investigating different doses of protein [16] and thus was a pilot trial to assess feasibility of the interventions (diets containing 2 g/kg/day versus 1 g/kg/day of protein) in patients with a new diagnosis of CRC. Although definitive conclusions are not possible from the nature of this trial, we completed unique work that in some cases (e.g., **Chapter 4**) was the first of its kind in patients with CRC. Furthermore, **Chapter 5** describes a novel dietary approach to combat muscle loss in cancer that to our knowledge, was also the first of its kind in this patient population. **Chapter 6** adds to the paucity of research that has explored patients' food-related beliefs at the time of a cancer diagnosis.

The work presented herein involved data collection that spanned >5 years, required 12 weeks of significant dedication and diligence from patients, and necessitated a considerable number of hours of preparation by the study team. In total, 196 study visits were completed, including 47 TEE assessments that in and of themselves lasted 24-hours each. Approximately 1,650 hours were spent in new-patient medical oncology clinics recruiting patients for the trial. The culmination of these findings contributes to the body of literature in oncology nutrition and

provides an important knowledge base for future trials. A summary of the main thesis findings is illustrated in **Figure 7.1**.

In **Chapter 4**, it was hypothesized that measured TEE and REE would not differ from energy intake recommendations, but that wide individual variability would be observed. We also hypothesized that body weight (BW), sex, stage of disease, and muscle (i.e., lean soft tissue [LST]) would independently predict TEE and REE. We showed that TEE was highly variable and predicted by tumor location and body composition; REE was also higher than predicted on a group level. While energy needs estimated by the lower bounds of energy recommendations (25 kcal/kg/day) may be accurate under sedentary conditions, TEE fell outside of current energy recommendations for most patients. To our knowledge, this was the largest study of its kind and the only in > 25 years to assess 24-hour TEE of patients with cancer using a calorimetry chamber.

In **Chapter 5**, no formal hypothesis testing was conducted as this was a pilot trial designed to assess feasibility of a novel intervention and provide preliminary evidence that can be used to design a definitive trial [17, 18]. To our knowledge, this was the first trial to assess the feasibility and potential impact of a 2.0 g/kg/day versus a 1.0 g/kg/day diet on MM and physical function in patients being treated with chemotherapy for a new diagnosis of CRC. We found that consuming 2.0 g/kg/day of protein was not feasible for patients although 12 weeks of targeted nutrition intervention suggested differences in MM between diet groups may be possible. Diet allocation did not impact markers of physical function. Nonetheless, it was feasible for patients to increase their protein intake from pre-intervention intake levels and sustain increased intake during the first ~12 weeks of chemotherapy. When protein intake was considered irrespective of study arm allocation, increased intake showed positive effects on MM maintenance, physical function, and overall nutritional status.

In **Chapter 6**, we aimed to understand if and why dietary changes were made by patients who were within 2 weeks of starting chemotherapy. We also wanted to learn about patients' beliefs pertaining to food intake following a diagnosis of CRC. We used one-on-one semi-structured interviews and applied qualitative content analysis to the data obtained from n=29 patients with CRC to capture emergent themes. This study was hypothesis generating and findings can be used to design future quantitative studies. We found that patients reported varied

degrees of dietary change that stemmed from internal and external influences. Four main themes emerged to describe patients' dietary decisions after being diagnosed with CRC: (1) Medical influences: eating to live; (2) Health beliefs: connecting lived experiences with new realities; (3) Static diets: no changes post-diagnosis; and (4) Navigating external influences: confluence of personal agency and social constraints. The extent that patients altered their dietary choices post-diagnosis depended on personal perspectives and beliefs. These included the degree to which dietary decisions provided some agency (i.e., feeling of control) for dealing with physical ramifications of cancer treatment, patients' personal understandings of healthy foods, and the role of diet in managing their new physical reality during cancer treatment.

Considered in totality, this thesis contributes towards advancing the field of oncology nutrition by outlining findings derived from robust assessments of TEE, REE, feasibility of a targeted nutrition intervention, and drivers of dietary decision making. Notably, **Chapter 5** details findings that respond in-part to a call for research from the European Society for Clinical Nutrition and Metabolism to investigate the "effect on clinical outcome of increased supply (1–2 g/kg/day)" [16]. Our novel work was hypothesis generating and generated findings that can be used as a springboard for designing independent and definitive trials. Select key findings from **Chapters 4, 5, and 6** are discussed in the context of the broader literature below. Strengths and limitations of our approaches as well as the clinical implications are then presented followed by suggestions for future research and overall conclusions.

7.2 Total Energy Expenditure in Patients with Colorectal Cancer

Total energy expenditure guides energy intake recommendations but is impractical to assess in the clinical setting and is resource-intensive to properly evaluate in a research setting. Current oncology nutrition guidelines acknowledge a paucity of evidence pertaining to TEE in patients with cancer [16]. In practice, energy needs of patients with cancer are considered similar to those of healthy adults and are estimated using a factor of 25–30 kcal/kg/day when TEE or REE assessment is not possible [16]. These recommendations were guided by studies of TEE in patients with advanced pancreatic cancer [19] and small cell lung cancer [20] that suggested patients with cancer had lower measured TEE compared with values predicted for healthy adults [16]. Interestingly, pancreatic and lung cancers have the highest prevalence of low MM (56% and 70%, respectively) [21] which may contribute to the altered energy metabolism profile of

these patients. The decrease in TEE compared with healthy adults may also be attributed to a reduction in physical activity, given the observed increase in REE in this population [16].

Doubly labeled water is an objective and accurate technique to estimate carbon dioxide (CO_2) production and TEE in free-living conditions with an estimated error of up to 8% [22, 23]. Compared with TEE assessed by indirect calorimetry chamber (error varies by chamber), doubly labeled water yields a representative valuation of TEE in free-living conditions, although drawbacks of this technique include the inability to explore components of TEE (e.g., REE, activity energy expenditure [EE]) and accurately capture total energy intake [23]. Recently, our understanding of TEE in cancer expanded thanks to work by our laboratory. Doubly labeled water was used to assess TEE in patients with newly diagnosed CRC [24]. Under free-living conditions, TEE was not predicted by the lower end of energy recommendations in cancer (25 kcal/kg/day) and error between measured and predicted EE was related to BW, body composition, and physical activity level (PAL) [24]. In contrast, findings presented in **Chapter 4** suggest that TEE assessed by calorimetry chamber is predicted by the lower end of the recommended intake range. Cohorts of patients in these two studies from our laboratory had similar proportions of females and patients with rectal cancer although the cohort presented herein included more patients with stage IV disease. Notwithstanding the varying prevalence of metastatic disease, the difference in mean TEE between findings was 399 kcal/day. The energy cost of 399 kcal of activity is estimated as 1-hour and 22 minutes of walking for pleasure (metabolic equivalent of tasks [MET]: 3.5 METs/hour) by a person weighing 83.5 kg (mean weight of our patients) [25]. Differences between findings may be in-part attributed to patient characteristics (e.g., disease stage) and/or physical activity EE. Evidence exists to suggest that the latter may not be a major contributor to observed differences between cohorts as others have shown that PAL in confined conditions is indicative of free-living physical activity [26]. Self-reported activity level of our patients was categorized as moderate or highly active by 61% near the start of chemotherapy although objective measures are warranted given that patients may over-report PAL [27] and it may decrease over the course of cancer treatment [28, 29].

A key finding of our study was that patients with rectal cancer (all with prior chemoradiotherapy) had lower TEE, REE, BW, body mass index (BMI), fat mass (FM), and were more likely to have an ostomy compared to patients with colon cancer. Rectal cancer

independently predicted TEE which was ~140 kcal/day lower compared to patients with colon cancer when adjusted for sex and MM (as appendicular lean soft tissue [ALST]) although absolute difference in TEE was ~300 kcal/day. These findings may be explained by the prolonged use of cytotoxic therapy and duration with the tumor in-situ (due to neoadjuvant treatment), and the need for invasive surgery (e.g., tumor resection and/or placement of an ostomy) in patients with rectal cancer [30]. We also showed that patients with an ostomy had lower TEE and REE compared to patients without. Oncology patients with ostomies have lower PAL [31] which can contribute to decreased TEE although no difference between patients with and without ostomies was observed for PAL or self-reported activity level in our cohort (data not shown).

Overall, the broader literature on TEE in patients with cancer does not extent much beyond the initial studies [19, 20] used to support the oncology nutrition guidelines [16]. Weight-based recommendations (i.e., 25-30 kcal/kg/day) are known to overestimate TEE in patients with obesity [16], likely due to the increased level of adiposity and variable MM observed with this condition [32]. This is an important consideration when interpreting findings presented in **Chapter 4**, as 38.7% of patients presented with obesity. Although its use in the oncology literature is rare, we used a log-log regression to account for the variability in body composition among patients. To illustrate the impact of varying body types on EE, we showed that n=2 males who both presented without obesity and ~47kg of LST had measured TEE that differed by 609 kcal/day and measured REE that differed by 621 kcal/day. These findings highlight the substantial variability among patients with similar characteristics and reiterate the importance of individualized EE assessment in the oncology setting, suggesting that a one-size-fits-all weight-based ratio for estimating energy needs in cancer is not appropriate. Considering all literature on TEE in cancer, we are confident that the highly controlled setting and technical preciseness of a calorimetry chamber offers novel data on TEE in patients with CRC despite the sedentary nature of this assessment technique.

7.3 The Feasibility of Increased Protein Intake to Impact Muscle Health in Colorectal Cancer

The importance of MM as a prognostic indicator in the oncology setting is evident in the literature [33-47]. Targeted nutrition interventions to support muscle health in cancer are the

focus of several ongoing trials [48] although many gaps and opportunities remain [14]. We found that a diet containing 2.0 g/kg/day of protein supported by individualized nutritional counselling from a registered dietitian was not feasible for patients newly diagnosed with CRC during the first ~12 weeks of chemotherapy. On an individual level, about one-third of patients in the 2 g/kg/day group achieved the target intake level at week 12, suggesting that this level of protein consumption was possible albeit challenging. Importantly, the trial suggested the potential for positive effects on MM from diet alone after 12 weeks of targeted nutrition intervention. Overall, it was feasible for patients to increase dietary protein intake from pre-intervention levels and sustain increased intake. When considered irrespective of diet group, increased protein consumption showed positive effects on MM maintenance and anabolism, physical function, and nutritional status.

Low MM is prevalent in patients with cancer regardless of disease stage and BW [10, 49, 50] and is a predictor of treatment toxicity, disease progression, and survival [9, 12, 39, 43, 51-53]. Prevalence of low MM at baseline was 20% when assessed by ALST index (ALSTI) cut points [54] and 38% when assessed by ALST/BW [55, 56]. Our findings are lower than previously reported in patients with CRC (~46% present with low MM) although this figure varies slightly based on chosen cut points disease prognosis (e.g., curative versus non-curative) [49]. Our planned secondary analysis of body composition using opportunistically acquired computed tomography images from patient medical records will assess prevalence of low MM compared with our findings from dual-energy X-ray absorptiometry (DXA).

In the clinical setting where body composition assessment is not routinely available, BW is commonly used as a marker of health status [57]. It has long been postulated that a measure of BW alone is insufficient to detect marked alterations to nutritional or metabolic status in patients with malignant disease [58]. In contemporary society, it has been further shown that BW stability can mask clinically significant shifts in body composition, including loss of MM [8]. Findings from our study indicate that patients who completed the trial, when considered as a group (i.e., regardless of study arm allocation), increased BW and FM over 12 weeks while ALSTI did not change (data not presented). These findings highlight the importance of body composition assessment in the oncology setting. Although weight change will not describe changes to body composition, it remains a simple assessment that can alert health care providers to drastic

changes in a patient's health status (e.g., >15% weight loss) and is a phenotypic criterion included in a diagnosis of malnutrition [57, 59, 60].

Protein is the most researched nutrient to combat muscle loss across populations [48, 61] yet defined recommendations to preserve MM in cancer remain to be elucidated. Current oncology nutrition guidelines suggest a minimum of 1.0 g/kg/day of protein intake but advise a target intake of 1.2–1.5 g/kg/day [16]. These guidelines propose that protein intake up to 2.0 g/kg/day may be required [16], especially in patients with systemic inflammation and/or high PAL [62]. In healthy older adults, protein intake 2 times the recommended daily allowance (i.e., 1.6 g/kg/day) positively impacted ALST [63]. Given the pro-catabolic nature of cancer induced by the presence of the tumor [64, 65], chemotherapy [66], and the immune response [67], it is postulated that patients may have elevated protein needs compared with healthy adults of the same age-group although as shown herein, this level of intake may not be feasible for patients with cancer. In times where exogenous protein intake is insufficient, skeletal muscle is broken down to supply amino acids to tissues [68]. The findings presented in **Chapter 5** suggest that it is possible for protein intake to be increased during chemotherapy to support metabolic demands, although achieving 2.0 g/kg/day is not trivial, as highlighted by mean intake (2 g/kg/day group: 1.6 g/kg/day) and perhaps by the fourfold greater attrition rate in this group. Not discounting the challenges faced, our findings parallel others who have shown that protein intake can be increased, regardless of disease stage [69-72].

The association between protein intake and MM is evident, yet the anabolic potential of patients with cancer remains a contentious area in the literature [73-80]. Others have suggested that when it comes to MM maintenance in pro-catabolic conditions, the focus should be on stimulating anabolism rather than alleviating catabolism [81]. Our findings support the notion that patients being treated for cancer retain anabolic potential. Results from our trial provide insight for the design and implementation of a robust definitive trial that can support future oncology nutrition guidelines given that a nutrition prescription to address cancer-related muscle loss remains to be defined [82]. To our knowledge, the trial presented in **Chapter 5** is the first to assess 2 doses of protein intake on MM in patients with CRC cancer. A similar study to ours empowered women with breast cancer to positively alter dietary intake (e.g., increased protein, fruits and vegetables, whole grain intakes) [83]. This single-arm pre-post study in non-metastatic

breast cancer patients receiving chemotherapy found that protein intake of 1.2–1.5 g/kg adjusted ideal BW/day for 6 months was sufficient to sustain ALSTI despite BW and FM loss [83]. Overall, studies that assessed the impact of nutritional interventions and/or nutrition counselling showed positive effects on patient outcomes in patients with cancer [70, 84-86]. Studies specific to CRC and MM have used nutritional supplements (e.g., oral nutritional supplements, protein powder) as the primary method for improving dietary intake [87]. Regardless of method used to increase protein intake, our findings align with the broader oncology literature [88, 89] and in healthy populations [90, 91], suggesting that increased protein intake is associated with MM retention.

7.4 Drivers of Dietary Choice in Cancer

The impact of cancer on dietary intake is an essential consideration for health care providers since optimized nutrition status plays an important role in cancer-related outcomes including muscle health [16, 92-95]. For many patients, receiving a diagnosis of cancer is a motivator for positive lifestyle alterations, including dietary changes [96]. Findings presented in **Chapter 6** summarize factors influencing dietary change in patients with CRC. Further, the trial presented in **Chapter 5** highlights patients' dedication to making dietary changes to promote positive effects on muscle health, physical function, and overall nutrition status. In line with findings presented within this thesis, patients and their families seek information to inform dietary choices [96, 97] but may be challenged with the abundant availability of conflicting and erroneous cancer-related information, particularly from online and social media sources [98, 99]. Knowledge translation materials and patient education resources could improve availability of reliable nutrition information available to patients and their families.

Dietary changes that occur after a cancer diagnosis are not well-characterized, especially among patients with CRC [100]. Self-guided dietary changes to food intake may not align with oncology nutrition guidelines [16], as highlighted by patients who explained that dietary changes (e.g., decreased animal protein consumption) were in response to medical or external influences and personal health beliefs. Dietary changes that result in decreased protein intake do not align with oncology nutrition guidelines, which recommend increased protein intake during cancer treatment [16]. These changes can cause a depletion of amino acid reserves and compound the negative impact to skeletal muscle observed in patients with cancer [101, 102]. In an opinion

paper written in collaboration with international experts, we suggest that nutrition goals for cancer treatment do not necessarily parallel those for cancer prevention or post-treatment [103]. Interestingly, our inspiration to write this paper was based on feedback received from oncology dietitians that suggested a gap in knowledge between protein related guidelines for cancer prevention and for cancer treatment. If this gap in knowledge existed in practicing healthcare providers, there was likely a lack of understanding from patients, as we corroborated with findings presented in **Chapter 6**. These findings add to other literature suggesting that patients and their families are unsure of appropriate nutritional strategies in cancer [104, 105].

General changes to dietary intake are captured in most nutrition screening tools [106-110] although the resulting impact on nutritional status may not be adequately predicted. Our findings in **Chapter 5** briefly highlight changes to nutritional intake as assessed by a nutrition screening tool (the Patient-Generated Subjective Global Assessment) and dietary changes were further explored in detail in a sub-set of patients in **Chapter 6**. Overall, post-diagnosis dietary decisions were driven in-part by a feeling of control over the physical ramifications (e.g., nutrition-impact symptoms) of cancer treatment. Support from registered nutrition professionals is important as literature suggests that many patients alter their diet in attempt to cure the cancer or alleviate symptoms [111] but may not consider the impact of dietary choices on muscle health. The prevalence of malnutrition (and low MM) and associated negative clinical outcomes is evident in the literature although as highlighted in **Chapter** 6, this information is not translated to patients and they underestimate the manifestation of these conditions [15].

7.5 Limitations

The findings presented in this thesis stemmed from a novel trial that used sophisticated assessment techniques although they should be interpreted in consideration of noteworthy limitations. Those specific to each study are presented in **Chapters 4-6**. Most importantly, findings from **Chapters 4** and **5** are not powered to draw statistical inferences as the main trial was a feasibility and pilot study. Nonetheless, fundings presented in **Chapters 4** and **5** are first-of-their-kind data and provided important information for designing and implementing independent definitive trials.

The technique (calorimetry chamber) used to assess TEE in **Chapter 4** is highly controlled and precise. For context, the calorimetry chamber used in this thesis is the only

function one in Canada and is situated in one of approximately 45 laboratories world-wide that house a calorimetry chamber [112]. Total EE assessed by the calorimetry chamber provides an accurate assessment of EE in patients consuming an isocaloric diet during a day of sedentary activity. A limitation to acknowledge in our study was that physical activity was not assessed within the chamber in an effort to reduce patient burden. For patients who are highly active (22% of patients based on self-reported data), it is possible that TEE during the assessment period yielded an underestimation of non-resting components of EE compared with free-living conditions. Additionally, the diet provided to patients during their 24-hour stay was standardized and the total energy and macronutrient intake may not represent patients' usual intake.

Our use of dual-energy X-ray absorptiometry (DXA) to measure ALST is a limitation as it is not a direct assessment of MM. Nonetheless, ALST is largely composed of fat-free skeletal muscle and is highly correlated with total body MM [113]. Body composition varies by sex with females having increased proportions of FM compared with males. Differences in cut-points for consideration of low MM are presented by sex [54-56]. A limitation of the study presented in **Chapter 5** is the lack of sex-stratification within study arm randomization. To explore potential impacts of protein intake on MM by sex, exploratory data was presented that suggested study arm allocation may have influenced MM differently based on sex, although this warrants further investigation. Additionally, physical activity was self-reported but may not have been accurately captured. A more robust measure of physical activity or the inclusion of a physical activity component in future trials should be explored. Lastly, adherence to individually prescribed diets was a challenge for patients and warrants consideration when interpreting the intention to treat analyses presented in **Chapter 5**.

The sampling strategy utilized in **Chapter 6** enabled us to capture the perspectives of a group of nutrition-focused patients being treated for stages II-IV CRC. Nonetheless, patients' interest in nutrition captured herein does not necessarily represent all persons receiving adjuvant treatment for CRC. The use of maximum variation sampling strategy likely increased the generalizability of findings to a wider group of patients with CRC but is not applicable to all patients given the inclusion/exclusion criteria of the larger trial. It should also be mentioned that patients were participating in a larger trial and the baseline interview was a secondary analysis,

thus, patients approached to partake in the interview included only patients who had consented to participating in the larger trial.

7.6 Implications for Clinical Practice

Findings from this research show that altered energy metabolism, low MM, and self-guided dietary changes are prevalent in patients with CRC near time of diagnosis. In the clinical setting, EE, body composition and overall nutritional status are often assessed by BW alone but this approach will not capture all detrimental changes [8]. Nutrition is not often considered a priority in the clinical oncology setting even though anti-cancer treatments may not be efficacious without optimized nutritional status. For example, it has been shown that patients with low MM have increased risk of treatment toxicity and subsequent treatment delays [12, 13, 51, 114]. In the outpatient setting, sufficient registered dietitian time is not available to see all patients who are prescribed chemotherapy [115]. Baseline findings presented herein provide evidence that increased support is needed for patients prior to starting chemotherapy, even if they do not present with overt weight loss or physical decompensation. Our approach of individualized nutrition education and weekly follow up is not feasible on a large-scale outpatient front but group nutrition education sessions that focus on the importance of protein and how to increase protein intake may benefit patients.

7.7 Directions for Future Research

Body composition and EE are highly variable in patients with cancer and thus are poorly estimated by prediction equations, resulting in sub-optimal protein and energy intake [24, 116, 117]. Improved ability to assess energy requirements in the oncology setting can be accomplished using bedside techniques (e.g., portable indirect calorimetry) although much groundwork is needed before this approach can be integrated into the clinical setting. To improve ability to individually assess TEE of outpatients, a future trial should compare TEE measured by calorimetry chamber (taking into consideration usual physical activity) with doubly labelled water assessment. A second comparison could be made with measured REE using a clinically-accessibly technique (e.g., Q-NRG) and an individualized physical activity coefficient. Another consideration to improve the translation of research findings into feasible approaches for clinical practice relates to the length of trial interventions. The trial presented in **Chapter 5** occurred for 12 weeks near the start of chemotherapy. Most patients with high-risk stage II or stage III disease

are treated with chemotherapy for approximately 6 months (24 weeks) while patients with stage IV are treated indefinitely. Nutrition-impact symptoms from chemotherapy compound over time, with severity of symptoms worsening with each round of treatment [118, 119]. Thus, the feasibility of increased protein intake in later treatment cycles warrants further investigation.

In **Chapter 5**, protein recommendations were provided to patients based on actual BW. Planned secondary analyses will explore the association between protein intake adjusted by LST and trial outcomes. Additionally, future trials should consider investigating the feasibility and impact of dietary protein intake adjusted by LST rather than BW, as also suggested by others [120, 121]. Our trial focused on total daily protein intake and promoted distribution of intake throughout the day although per meal intake guidelines were not provided to patients due to the increased patient burden and more pragmatic nature of our intervention. Our robust assessment techniques including the use of food scales and detailed 3-day food records will allow us to explore, in a secondary analysis, our findings considering protein intake per meal. Based on our experiences, taking a standardized approach to supplementing protein intake with protein powder may be more feasible for patients. For example, providing nutrition education on how to increase protein intake from diet first and then adding a standardized dose (e.g., 15 g protein from whey powder) to each meal. Importantly, the length of this trial (>5 years) and the difference in attrition rate observed between groups (fourfold greater in the 2 g/kg/day group) are essential considerations when designing future trials. Lastly, in muscle wasting conditions, MM maintenance is likely best achieved through a combination of resistance exercise and adequate nutrition support [81]. The optimal exercise and nutrition prescription to address cancer-related muscle loss remains to be determined [82] and presents a promising intervention that requires further investigation.

7.8 Conclusion

The major findings of this thesis were that patients with newly diagnosed CRC presented with altered EE that varied by tumor location and was not accurately predicted by energy recommendations. When provided a targeted nutrition intervention and supported with nutrition counselling, it was not feasible for patients to consume a diet containing 2.0 g/kg/day although a high protein diet suggested positive effects on MM over 12 weeks. When protein intake was considered irrespective of diet group allocation, increased protein intake positively affected MM,

physical function, and overall nutritional status. These are important considerations, especially given that patients expressed post-diagnosis self-guided dietary changes prior to targeted nutritional intervention by a registered dietitian. attempt dietary changes that are guided by individual perspectives and beliefs. The research presented in this thesis highlights the potential for targeted nutrition intervention alone to positively influence muscle health in patients with cancer. We present data that can be used as a first step towards designing and implementing definitive trials to assess the effects of increased protein intake on MM, with the ultimate goal of improving patient care.

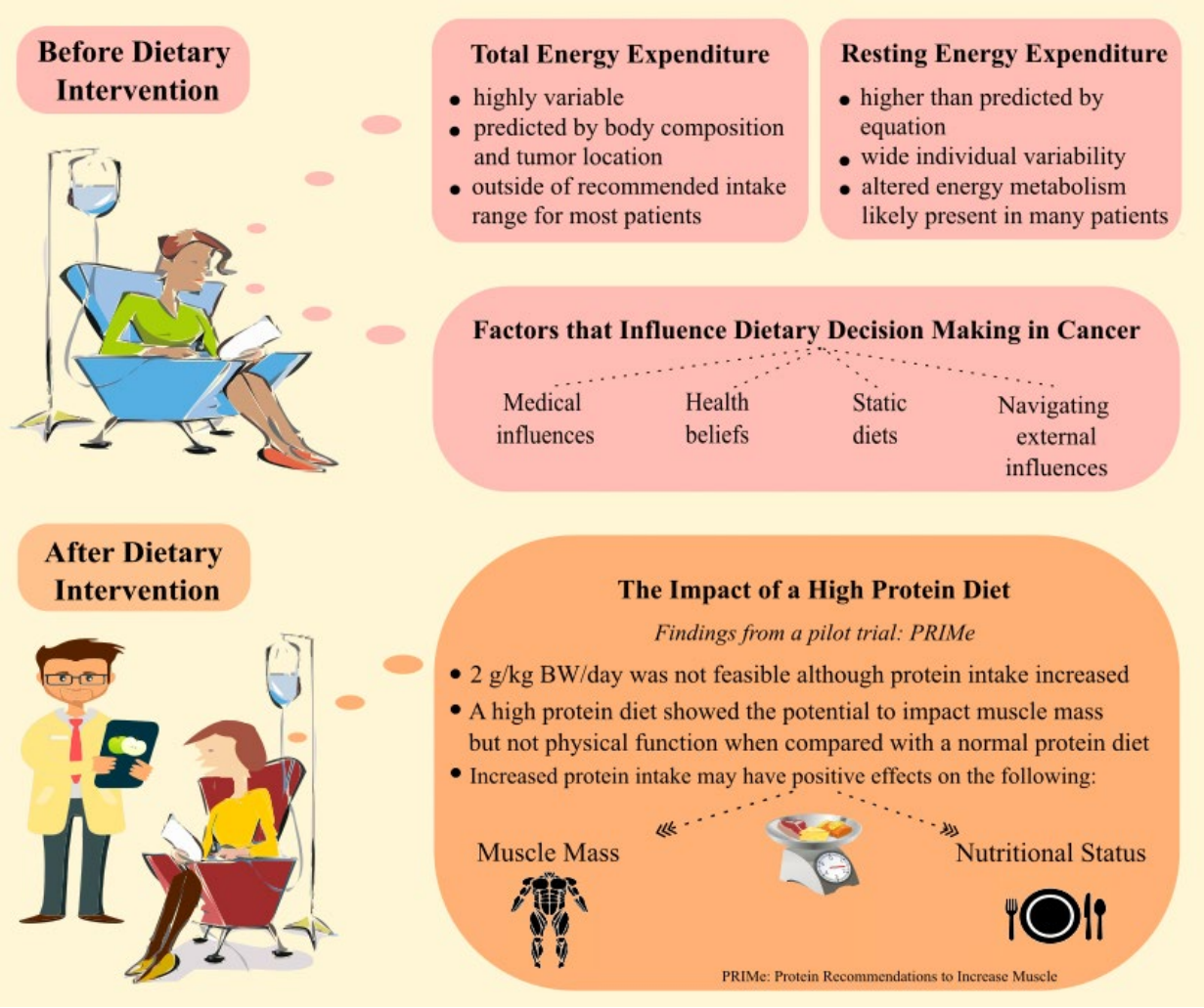

Figure 7.1. Summary of main thesis findings. g/kg BW/day: grams of protein per kilogram of body weight per day.

7.9 References

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Appendix 1 Protocols for the Use of Indirect Calorimetry in Clinical Research

This appendix is a published book chapter and reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature Springer eBook. Ford KL, Oliveira CLP, Ramage SM, Prado CM. Protocols for the Use of Indirect Calorimetry in Clinical Research. In: Betim Cazarin CB, editor. Basic Protocols in Foods and Nutrition. New York, NY: Springer US; 2022. p. 265-91. Copyright (2022). I was responsible for the review and analysis of the literature and writing the first draft. All co-authors provided critical contributions and reviewed the manuscript for intellectual content.

Abstract

Resting energy expenditure (REE) is the largest energy expenditure component and is defined as the body's amount of energy required to maintain vital functions at rest while awake, in a fasting state, and in a thermoneutral environment. Several equations to predict REE have been developed over the years, but indirect calorimetry measurement provides the most accurate value. However, for the REE measurement to be accurate, some requirements apply. In this chapter, the protocols for measuring REE in healthy adults by a selection of four indirect calorimetry devices are described: Vmax® Encore; Q-NRG™ Metabolic Monitor; MedGem®; and FitMate GS.

Keywords

Indirect calorimetry; Resting energy expenditure; Resting metabolic rate; Protocol; Clinical Trial; Energy expenditure; Resting energy metabolism; Calorie needs; Energy needs.

Introduction

Human energy needs are assessed by measuring an individual's energy expenditure (EE) by calorimetric and non-calorimetric methods [1, 2]. Indirect calorimetry (IC) is an evidence-based calorimetric method that measures the products of respiration: oxygen (O_2) and carbon dioxide (CO_2). Using the volume of O_2 and CO_2 ($\dot{V}O_2$ and $\dot{V}CO_2$, respectively), the amount of energy released in the combustion of substrates (metabolism) is estimated [3]. Several energy metabolism components can be assessed using IC, such as total energy expenditure (TEE) and its major physiological components (i.e., resting energy expenditure [REE], thermic effect of food [TEF], and activity thermogenesis [AT]). However, this is limited to the availability of a whole-body IC.

More commonly assessed is REE, the largest TEE component, contributing approximately 60-70%, depending on an individual's physical activity levels [4]. This energy metabolism component is defined as the amount of energy required to maintain vital bodily functions while at rest, awake, in a post-absorptive state, and a thermoneutral environment [5]. Assessment under such conditions ensures that the TEF and AT are not accounted for, providing an accurate REE assessment [6]. Although the terms REE and basal energy expenditure (BEE) are commonly used interchangeably, these energy metabolism components are not synonymous. The difference between REE and BEE relies mainly on how they are measured, and, for this reason, BEE is usually ~10% lower than REE, with the difference representing the energy expended during arousal [1, 7, 8]. Protocols required to measure BEE are beyond this chapter's scope and fully described elsewhere [9]. The focus of this chapter is on the most commonly used protocols to assess REE via IC.

Indirect calorimetry has been used for centuries and is based on the known amounts of heat generated per liter of O_2, and CO_2 consumed and produced when macronutrients are oxidized [1, 10, 11]. Because the oxidation of different macronutrients results in distinct $\dot{V}O_2$ and $\dot{V}CO_2$, IC estimates substrate oxidation rates, caloric equivalents for macronutrients, and EE [10, 11]. Several scientists have dedicated their work to develop equations for the estimation of EE based on measurements of O_2 and CO_2 [12, 13]. One of the most commonly used equations to estimate REE using IC is the abbreviated Weir equation [12]:

$$\text{REE (kcal/day)} = (3.941 \times \dot{V}O_2\,[\text{L}] + 1.106 \times \dot{V}CO_2\,[\text{L}]) \times 1440 \text{ minutes/day}$$

IC obtains volumes of O_2 and CO_2 through total collection (rigid or flexible system), open-circuit (ventilated or expiratory collection), confinement (respiratory chamber), or closed-circuit systems [1]. Open-circuit calorimeters are a common type of IC devices used to measure REE in both clinical and research settings and include metabolic carts (with a facemask, mouthpiece, or canopy hood to capture gas exchanges) or whole-body calorimetry units, the latter of which, albeit its accuracy and preciseness, will not be discussed in this chapter due to rarity and impracticality in the clinical setting [7, 14]. Techniques and devices commonly used to measure fractional expired oxygen (F_EO_2) and carbon dioxide (F_ECO_2) will be discussed, including the Vmax® Encore and Q-NRG™ Metabolic Monitor. These devices are also compatible with a facemask, although the ventilated hood systems will be discussed. Systems that calculate REE by measuring only F_EO_2 and estimating F_ECO_2 include the FitMate GS (ventilated hood system) and the MedGem® (a mouthpiece/nose clip device) [15-17]. The FitMate GS uses a combination of F_EO_2 and an assumed Respiratory Quotient (RQ), the ratio of CO_2 produced to O_2 consumed, of 0.85 to estimate F_ECO_2 [12, 18, 19]. The MedGem® uses an abbreviated version of the Weir equation that includes a constant RQ of 0.85 [15]. Overall, considerations for choosing an IC device for the research and/or clinical settings will be dependent on the researcher's needs. Below, various considerations are outlined by the device. A summary of time and cost considerations are shown in **Table 2.1 (Chapter 2)**.

Vmax® Encore Metabolic Cart

Several brands of metabolic carts are available in the marketplace; the Vmax® is one of the most accurate and has been used as a reference method to assess the accuracy of other IC devices [20-22]. The Vmax® requires the most time and expertise to perform an REE test. For a trained user, the calibration process will take between 20-30 minutes and must be completed at the start of every testing day. The time to complete a test will vary from 20-30 minutes, depending on how long it takes a participant to achieve a steady-state of breathing. Lastly, this device requires that the user select the data points for EE calculations, whereas the other devices discussed herein automatically provide EE information. Overall, this device is highly accurate, but access to trained personnel and time should be considered.

Q-NRG™

The Q-NRG™ is the newest device of those discussed herein and is the most practical for use in the clinical setting due to its high accuracy, rapid measurement time, usability, size, and affordability [23-25]. However, this device utilizes many disposable components, which increases the cost per test and must be considered for ongoing equipment operation compared to devices with a higher initial investment but are less costly per test (**Table 1**). However, considering the current COVID pandemic, the use of disposables greatly minimizes the risk of contamination, placing less responsibility on the technician for ensuring complete sanitization between participants/patients.

In-vitro studies of the Q-NRG™ found accurate concentrations of O_2 and CO_2 (within 2%) [24] and within 1% for $\dot{V}O_2$, $\dot{V}CO_2$, and EE [25]. A study of fifteen healthy adults found that the Q-NRG™ had very good inter-unit precision (coefficient of variation <3% for $\dot{V}O_2$, and $\dot{V}CO_2$) and accuracy (mean difference ± SD (%) between Q-NRG™ and mass spectrometry analysis: 1.61 ± 1.41% for $\dot{V}O_2$, and -1.53 ± 2.50% for $\dot{V}CO_2$) [25]. Additional studies to assess the accuracy and preciseness of the Q-NRG™ device in various population groups are ongoing [26-28].

MedGem®

The MedGem® offers practicality and convenience for measuring REE in the clinical setting due to its size, portability, and the short time required for testing. Compared to the other devices discussed, the MedGem® uses a mouthpiece and a nose clip instead of a ventilated canopy hood; a setup that may prove more acceptable to participants, depending on their comfort. Compared to a metabolic cart, participants are likely to achieve a steady-state of breathing more rapidly when their EE is assessed by the MedGem® [29]. Additionally, this device measures $\dot{V}O_2$ and estimates $\dot{V}CO_2$ based on an assumed respiratory quotient (RQ) of 0.85 rather than measuring both $\dot{V}O_2$ and $\dot{V}CO_2$ [15, 29].

Studies that assessed the accuracy and precision of the MedGem® had returned varying results, including overestimating, underestimating, or validly predicting REE compared to other devices [29]. A systematic review by Hipskind *et al.* concluded that the MedGem® was an accurate portable IC device used in a healthy population, but the acceptability for its use in

hospitalized and/or nutritionally-compromised groups requires further research [29]. Most studies reviewed by Hipskind *et al.* that compared the MedGem® to a metabolic cart in healthy adults found that the MedGem® either overestimated or found no significant difference in REE compared to a metabolic cart. All but one study reviewed found that the MedGem® returned ≤200 kcal/day difference compared to a metabolic cart; the authors suggested that the significant differences observed did not necessarily equate to clinically relevant differences [29-33].

FitMate GS

Portable IC devices are used in clinical practice in place of predictive equations if they prove accurate and precise EE measures [19, 29]. The FitMate GS is a portable unit that would be practical for the clinical setting, although validation studies conducted in healthy adults across the BMI spectrum returned conflicting results. A study including sixty healthy adults compared REE measured by the FitMate GS (1668 ± 344 kcal/day) and the Douglas Bag (1662 ± 340 kcal/day) and found no statistically significant difference (p=0.579) between devices, concluding that the FitMate GS was a precise and accurate device for REE measurement in healthy adults [17]. Another group compared the FitMate GS to Quark CPET (COSMED) in thirty adults and found the FitMate GS to be highly precise and accurate (mean REE 1779±480 and 1785±409, respectively; p=0.55)) [34]. Recently, Purcell *et al.* compared the FitMate GS to whole-body IC in seventy-seven adults and found good precision (intra-class correlation coefficient: 0.80; 95% CI: 0.70-0.87) upon repeated measures but poor accuracy (1680 ± 420 and 1916 ± 461 kcal/day, respectively; p<0.001) [19]. The device underestimated REE by 240 kcal/day on a group level [19]. Overall, the FitMate GS presents a viable portable IC device, but REE should be interpreted with caution given the heterogeneous results from validations studies.

Regardless of the IC device, to obtain an accurate and precise REE measure, steady-state breathing (metabolic equilibrium) must be achieved. Steady-state occurs when $\dot{V}O_2$ and $\dot{V}CO_2$ remain stable (<10% variation) for five consecutive minutes [8, 35]. Several other factors that also impact EE must be considered, and thus, specific protocols should be followed [36]. The most commonly followed requirements for REE assessment are summarized in **Figure 1**. Specific techniques that are device-specific will be discussed in the following sections.

Materials

Metabolic Cart Vmax® Encore

The protocol for the Metabolic Cart Vmax® Encore described in the following section utilizes the below-listed materials:

1. Vmax® Module
2. Desktop computer with Vmax® software
3. 3L syringe for flow sensor calibration
4. Two compressed gas cylinders for external gas calibration.
    - Recommended gas mixes:
        i. 4% CO_2, 16% O_2, Balance N_2
        ii. 26% O_2, Balance N_2
5. Ventilated hood with veil
6. Disposable hose

Q-NRG™ Metabolic Monitor

The protocol for the Q-NRG™ described in the following section utilizes the below-listed materials:

1. Q-NRG™ main unit
2. Laptop computer with OMNIA software
3. Canopy mode kit that includes a canopy hood and hose.
    - The items are reusable and require cleaning between each test.
4. Canopy veils and antibacterial filters.
    - These items are single-use and must be disposed of after each test.
5. 3L syringe for flow sensor calibration
6. Compressed gas cylinder and pressure regulator for flowmeter calibration.
    - Recommended gas mixture: 16% O_2, 5% CO_2, Balance N_2

MedGem®

The protocol for the MedGem® described in the following section utilizes the below-mentioned materials:

1. MedGem® device and power supply cord
2. Disposable mouthpieces and nose clips

FitMate GS

The protocol for the FitMate GS described in the following section utilizes the below-mentioned materials:

1. FitMate GS device
2. Canopy hood with veil
3. Canopy blower and unit with a connected sampling line

Methods

Pre-test Protocol

Indirect calorimetry, regardless of the device used, requires preparation on behalf of the person being tested, herein referred to as the participant, to ensure that steady-state breathing is achieved (**Figure 1**). In brief, prior to measuring REE by IC, individuals should be instructed to fast for at least 7 hours, refrain from moderate to vigorous physical activity for 12-48 hours, avoid caffeine for 4 hours, and nicotine for 2.5 hours [36]. Water and essential medication can be consumed, but no calories should be ingested. The participant should minimize daily living activities and physical activity before the measurement by driving or taking public transit to the testing facility and using the elevator instead of the stairs (if applicable). The testing environment should be at an ambient room temperature (22-25°C/72-77°F) and quiet [36]. The individual should rest, in the supine position, for 20-30 minutes prior to beginning the IC measurement [36, 37]. It is important that the individual abstain from sitting, standing, reading, listening to music, and/or fidgeting during this period to increase energy expenditure [36, 38-40]. The resting component of the protocol is crucial to ensure accurate measurement and decrease the influence of any activity that occurred leading up to the test [36]. Notably, an IC measurement can be done at any time of the day, given that the above conditions are met [36, 41, 42].

When the participant arrives for their measurement, verification that they followed the pre-test protocols is needed. Ask the participant to lay in a supine position (**Figure 2**) and rest quietly, without fidgeting, for 20-30 minutes. During the resting and testing period, the participant should be free from distractions, including any noises, music, reading, cell phone, etc.

Indirect calorimetry devices require information about the participant described in the device-specific sections below; it is important to acquire this information before having the participant begin the resting period.

Vmax® Encore Metabolic Cart

The following methods are based on manufacturer recommendations, training, and the authors' combined clinical experience [43].

Calibration

The flow sensor must be calibrated at the start of every testing day. We recommend powering on the device 1 hour prior to starting the calibration process. The calibration takes approximately 20 minutes to complete and should be completed before the participant arrives. To complete the calibration:

1. Select the VMAX icon from the desktop.
2. Remove the flow sensor from the Vmax® device (silver box) and attach the open end, not the mesh end, to the 3 L syringe (**Figure 3**).
3. On the computer, click on '1. Flow Sensor Calibration' in the Vmax® application.
4. Click 'F1. Calibration' to begin.
5. Follow the prompts on the screen to zero the mass flow sensor. To do this, the following is needed:
    a. Pump the syringe by pulling the black handle on the 3 L syringe all the way out and then pushing it all the way back into the syringe. Repeat this process twice, and then press the space bar on the keyboard to zero the machine.
    b. Wait for the countdown on the screen and wait for the green bar to reach the dialogue box's end.
    c. A screen with yellow bars will pop up automatically. The yellow bars will turn to green bars once the calibration has passed.
6. Manually calibrate the flow sensor using the 3 L syringe:
    a. Pump the syringe (as instructed in step 5a above) to complete one full circle within each pair of yellow bands on the computer screen. Start with the inner-most bands and work outwards.

- The first 1.5 pumps of the syringe do not register.
- Pump the syringe slowly at first and then increase speed to work from the inner-most bands towards the outer bands on the screen. Watch the screen while pumping the 3 L syringe and adjust the pumping speed based on the bands on the screen.

b. A green bar will appear on the right side of each band when each circle is completed.

c. The time allotted to complete this screen is 5 minutes and 15 strokes on the syringe. Once completed, the calibration verification screen will pop up.

7. To verify the flow sensor calibration:
    a. Perform 5 full syringe pumps to draw circles between the different bands on the graph that is on the screen.
        - The circles can either all be the same size or of varying sizes that match the circles made in the yellow bands in step 6a.
    b. Once the calibration has been accepted, 'F2 Verify Calibration' will appear in a grey box at the bottom left of the screen in small a black print.
        - If the calibration was not accepted, a dialogue box would appear and prompt a recalibration. Measurement should not be conducted until the calibration has been accepted.
    c. Detach the flow sensor from the 3 L syringe and plug the flow sensor back into the silver box (Vmax® device).
    d. Attach the blue hose from the ventilated hood to the flow sensor (**Figure 3c**).
        - The end of the hose attached to the ventilated hood should be attached at the chin position (not at the forehead position), as shown in **Figure 4**.
    e. Press 'F3' to save and exit back to the main menu.
8. The external gas calibration is an optional quality assurance measure that may be performed before the participant arrives to ensure the O_2 and CO_2 analyzers are working properly. We recommend that this step be performed once per testing day. To perform an external gas calibration:

a. Remove the flow sensor from the silver box and attach the open end, not the mesh end, to the 3L syringe.
b. Unplug the sample line from the flow sensor and plug it into the calibration port on the silver unit's front, as shown in **Figures 3d** and **5**.
c. Open both gas tanks by turning the top rectangular knob counterclockwise 2-3 half turns.
d. Select "Calibrate O_2 CO_2" from the toolbar on the computer screen.
e. Press "F1" to begin the calibration.
    - If the first calibration attempt fails, repeat the calibration by starting at step 8d. A successful calibration is indicated by a green box in the bottom right-hand corner of the screen that says "PASS".
f. Press "F3" to store calibration.
g. Close both gas tanks by turning the top rectangular knob clockwise until tightened.
    - This step is very important, or else the gas tanks will continue to release their contents.
h. Remove the sample line from the calibration port of the Vmax® device and re-insert the line into the flow sensor (**Figures 5** and **3d**).

Participant preparation

1. Measure the participant's height (centimeters) and weight (kilograms). Date of birth and biological sex are also required.
2. Ask the participant to lay down and rest in the supine position for 20-30 minutes.
3. Before starting the test, inform the participant of the following:
    a. You must not fall asleep.
    b. You can use a blanket if they are cold, but this should be put on prior to the resting period to minimize movement.
    c. The ventilated hood used for the measurement is not airtight, although it may feel stuffy at first. If this feeling persists, the participant can notify the person conducting the test.

d. The participant can take the hood off at any time if it becomes uncomfortable, but this will stop the test.
e. The sound of the pump will be audible while under the hood.
f. Notify the researcher immediately if any medical concerns arise during the test (headache, shortness of breath, etc.).

Device Preparation

1. In the Vmax® application on the computer, click on '2. New Study'.
2. Enter the ID, date of birth, sex, height, and weight of the participant.
3. Press 'F3' to save and exit to the main menu.
4. Open both gas tanks by turning the top rectangular knob counterclockwise 2-3 half turns.
5. On the main menu of the computer application, click '4. Exercise/Metabolic Test'.
6. Use the default settings and press 'F1. Start Test'.
7. Press 'F1. Analyzer Calibration' to begin calibrating the O_2 and CO_2.
8. A green box will appear in the bottom right-hand corner of the screen when the calibration is complete.
    - Repeat steps 5 through 7 listed above if the calibration fails. Do not continue until the operator and the participant are ready to start the test.

Running a REE Test

1. On the computer, press 'F3' to store and exit the gas calibration screen.
2. Click on 'New Study'.
    - Double-click on the computer screen if the testing screen does not appear immediately.
3. A dialogue box will appear; follow the prompts.
4. Turn on the flow pump on the Vmax® device. The flow pump is switched on by pressing the black switch at the device's bottom center, where there is a fan symbol, as shown in **Figure 3e**.
5. Place the ventilated hood over the participant's head, with the blue tube at the participant's chin, as shown in **Figure 4**. Smooth out and press down on the plastic

draping around the participant's head to ensure that it is laying as flat as possible on the bed.

- This step is crucial to prevent air leaks which will affect the measurement.

6. Press the space bar on the keyboard.
7. Press 'F8' to start the test and then set the starting pump flow rate:
    - Use the default 30 L/min for adult females and pediatrics.
    - Use 40 L/min for adult males.
8. Monitor the following during the test:
    - F_ECO_2 should be between 0.60-0.80%. The most accurate measurement occurs between 0.75-0.80%.
        1. Wait for 7-8 minutes or until the participant is in a steady state of breathing before adjusting the flow rate.
        2. If necessary, adjust the flow rate by 2-3 units at a time and wait 2-3 minutes between adjustments.
            - If the F_ECO_2 value is high, increase the pump flow rate to remove CO_2.
            - If the F_ECO_2 value is low, decrease the pump flow rate to remove less CO_2.
    - Steady State
        1. A green box will appear in the bottom right-hand corner that says "Steady State" when the participant is in a steady state of breathing.
        2. Manual annotation of the data points (time intervals) where the participant is in a steady state of breathing is needed. Approximately 15 minutes of data in a steady-state are needed.
            - Typically, it takes about 7 minutes for a person to enter a steady state. It is normal for a person to move in and out of a steady-state during a test.
9. Stop the test once the participant has been in a steady-state for at least 15 minutes. To stop the test:

- Click ‘Exit/Pause’ on the toolbar at the top of the screen and select ‘Y/Exit/Pause.’
- Remove the ventilated hood from the participant and turn off the flow pump (**Figure 3e**).
- Press space the bar on the keyboard to continue (there is no need to enter any comments) and then press ‘F3’ to save the test results. A data analysis screen will appear.
- Turn off gas tanks by turning the rectangular top clockwise until sealed tightly.

10. The participant has now finished the test.
11. On the computer, select the steady-state interval(s) for data analysis:
    - Steady-state data points will be colored black.
        1. Select ‘1SS’ and then mark the first steady-state interval by clicking and dragging the mouse to shade over the desired steady state intervals that occur consecutively.
        2. Click on the ‘2SS’ tab and then repeat step 11.1.
        3. Repeat step 11.2 for a 3rd and 4th set steady-state intervals, if necessary.
        4. If only 1 to 3 steady-state intervals were used, click on the ‘SS4’ tab and ensure the box ‘SS4=average SS1-3’ is checked.
        5. Press ‘F3’ to store.
12. Ensure that the flow pump is turned off and that the gas tanks are closed.

Q-NRG™ Metabolic Monitor

The following methods are based on manufacturer recommendations, training, and the authors’ combined clinical experience [44].

Calibration

The gas analyzers must be calibrated monthly. To calibrate the device:

1. Make sure the device has warmed up for 20 minutes (i.e., device has been powered on for 20 minutes).
2. Connect the output of the calibration cylinder to the calibration gas port on the back of the device.

3. Adjust gas output pressure to 5-6 bar (70-90 psi).
4. On the device screen, tap on ‘Calibration’ then select ‘Gas Analyzers (Cylinder)’ and lastly, choose ‘Canopy-Face Mask Mode’. Start the calibration procedure by following the on-screen instructions. Calibration will be performed automatically.
5. To calibrate the gas analyzer to room air:
    a. Make sure the device has been warmed up for 20 minutes.
    b. On the device touch screen, tap on ‘Calibration’ then select ‘Gas Analyzer (Room Air)’ and lastly, select ‘Canopy/Face Mask Mode’.
    c. Start the calibration procedure by following the on-screen instructions. The calibration will be performed automatically.
6. To calibrate the blower/internal flowmeter:
    a. Connect the calibration syringe to the canopy inlet port on the screen-side of the device using the blower calibration adapter.
    b. On the device touch screen, tap on ‘Calibration’ then select ‘Flowmeters’ and lastly, select ‘Blower’.
    c. Start the calibration procedure by following the on-screen prompts.
    d. Perform the required number of syringe strokes, paying particular attention to cover the whole motion range in 8-12 seconds.

Participant preparation

1. Measure the participant’s height (centimeters) and weight (kilograms). Date of birth and biological sex are also required.
2. Ask the participant to lay down and rest in the supine position for 20-30 minutes.
3. Before starting the the test, inform the participant of the following:
    a. They must not fall asleep.
    b. They can use a blanket if they are cold, but this should be put on prior to the resting period to minimize movement.
    c. The ventilated hood used for the measurement is not airtight, although it may feel stuffy at first. If this feeling persists, it can notify the person conducting the test.
    d. The participant can take the hood off at any time if they become uncomfortable, but this will stop the test.

e. The sound of the pump will be audible while under the hood.
f. Notify the researcher immediately if any medical concerns arise during test (headache, shortness of breath, etc.).

Device Preparation

1. Power on the device by pressing and holding the On/Off button for two seconds. Wait for 5 minutes before starting the measurements.
2. Set up the canopy by placing the single-use veil over the canopy hood according to the instructions printed on the veil packaging.
3. Connect the canopy hose and the antibacterial filter to the canopy hood, as shown in **Figure 6**.
    - It is important to note that the canopy hose and antibacterial filter are connected at the forehead position and not at the canopy hood's chin position.
4. Connect the canopy hose to the "Canopy" port of the Q-NRG™ device, located on the front of the device in the bottom right-hand corner.
5. Select or add a new participant:
    - To enter new participant data:
        i. Tap 'New test' and then 'New patient'.
        ii. Enter the participant's last/first name, date of birth (DOB), sex, weight, and height.
            - To ensure confidentiality, we recommend entering the participant ID instead of the person's last name and using a "-" or another symbol for their first name.
            - The device requires the participant's sex (listed as gender in the machine). This information is used to calculate predicted values for REE; thus, we recommend that the person's biological sex be entered instead of their gender identity.
    - To select an existing participant from the device:
        i. Tap 'New test' and then 'Search patient'.
        ii. Select the appropriate participant and tap 'Ok' to confirm the selection.
        iii. Edit the person's information, if necessary, then tap 'Ok' to confirm.

Running a REE Test

1. To start the test, tap 'Canopy' to start and activate the internal blower.
    - The blower must be running before placing the canopy over the participant's head.
2. Carefully place the canopy hood and veil over the participant's head, avoiding air leaks around the veil and bed's surface (**Figure 6**).
    - This step is crucial to prevent air leaks which can cause underestimation of $\dot{V}O_2$ and $\dot{V}CO_2$.
3. The automatic calibration will begin and takes about one minute to complete. Once the calibration is complete, press the 'Start' button on the screen.
4. Measurements will begin appearing on the device screen after about 90 seconds.
5. Tap 'Start recording' to record data immediately. Alternatively, the device will automatically start storing data after two minutes of testing.
6. Adjust the dilution flow to achieve a CO_2 % (F_ECO_2) of 0.5-1.5%.
    - Note that measured values taken immediately after dilution flow changes are not reliable.
7. To stop the test, remove the canopy from the participant and tap 'Stop Recording' on the device screen.
8. Dispose of the non-reusable items (canopy veil and antibacterial filter).
9. The device screen will display REE, RQ, $\dot{V}O_2$, $\dot{V}CO_2$, among others. We recommend noting the variables of interest.
10. To export the data from the device:
    - Insert a USB flash drive into the USB port on the device's left-hand side.
    - On the screen, select 'Utility/export test' and tap 'CSV to USB' or 'PDF to USB'. Once the data has been successfully exported, the device will display the message 'Test successfully exported'.
    - Insert the USB flash drive into a computer and access the PDF data file exported from the device. Alternatively, data can be reviewed through a connected computer using the OMNIA software program, which provides additional editing capabilities, for example, customizing data points for inclusion in test results.

MedGem®

The following methods are based on manufacturer recommendations, training, and the authors' combined clinical experience [15].

Participant preparation

1. Weigh the participant.
2. Ensure that the participant has been resting quietly for at least 15 min prior to initiating the test.
3. Obtain a new mouthpiece and instruct the participant how to put the mouthpiece in their mouth, with their teeth behind the mouthpiece's ridge and their lips sealed over it.

Device Preparation

1. Plug the MedGem® (**Figure 7**) power supply into a wall outlet and connect to the device.
    - The device will beep once, and the indicator light will turn from red to green to amber once the device is warmed up.
    - The device must remain attached to a power supply until the test and data extraction are completed.
2. Offer a pillow to the participant, which can be placed under their dominant arm for support while holding the device throughout the test. Have the participant place the nose clip on their nose and blow air to ensure that no air can escape through their nostrils.
3. Wash or sanitize hands and then don medical gloves and attach the mouthpiece firmly to the device. Alternatively, the participant can attach the mouthpiece to the device to minimize any contamination. The larger end of the mouthpiece base should be facing downwards.
4. Calibrate the MedGem® by pressing the start (amber-colored) button located on top of device. The MedGem® must be on a solid, flat surface during calibration. Once the indicator light turns from amber to flashing green, the calibration is complete. The self-calibration process takes approximately 30 seconds.

Running a REE Test

1. Once the indicator light is flashing green, hand the device to the participant and encourage them to relax while ensuring that their mouth remains sealed around the mouthpiece.
    - The test must be started within one minute of the indicator light begins to flash green.
2. The measurement will begin automatically when the participant begins breathing into the device as shown by the indicator light turning to solid green.
3. After 5-10 minutes, the test will stop automatically and alert by beeping once. The indicator light will turn from green to amber to indicate completion of the test.
    - The time to complete a test will vary by participants as the time required to reach a steady-state of breathing varies widely among individuals.
    - The person's $\dot{V}O_2$ will appear on the screen, followed by the REE displayed in kcal/day. This information is available on the device until a new test begins.
4. Dispose of the mouthpiece and nose clip.
    - If completing repeating measures on the same participant, a new mouthpiece is recommended for each measurement to ensure accuracy.

FitMate GS

The following methods are based on manufacturer recommendations, training, and the authors' combined clinical experience [16].

Calibration

The FitMate GS (**Figure 8**) will automatically calibrate the analyzer at the start of every test.

Participant preparation

1. Have the participant lay down and rest for 20-30 minutes.
2. Do not place the canopy hood on the participant until prompted to do so.
3. Before starting the test, inform the participant of the following:
    a. You must not fall asleep.
    b. You can use a blanket if they are cold, but this should be put on prior to the resting period to minimize movement.

c. The ventilated hood used for the measurement is not airtight, although it may feel stuffy at first. If this feeling persists, you can notify the person conducting the test.
d. The participant can take the hood off at any time if they become uncomfortable, but this will stop the test.
e. The sound of the pump will be audible while under the hood.
f. Notify the researcher immediately if any medical concerns arise during the test (headache, shortness of breath, etc.).
g. The flow selector may be adjusted throughout the test. This piece of equipment is attached to the canopy hood.

Device Preparation

1. Insert the electrical cord into the external power connector and plug it into an outlet. Insert the green connector tube from the blower and unit into the flow connector on the back of the FitMate GS device. Connect the canopy blower to the hood connector and ensure a secure connection between them.
    - If the blower is not pressed far enough into the canopy hood, an alarm will sound when you start the test. If this occurs, verify that the canopy blower is connected properly.
2. Insert the sampling line from the device into the sampling connector on the hood.
3. Press the on/off button for up to 4 seconds to turn the unit on.
    - The unit should only be turned on during a test. An alarm will sound if turned on when a test is not running.
4. Select '3.Options' then '3.RMR' and 'Canopy'. The following default settings are what we recommend using during a test but can be changed if necessary:
    - Initial time interval to discard before the data acquisition: 5 minutes
    - The average time interval for the RMR test: 10 minutes
    - Automatic print at the end of the test: yes
    - Print of the RMR graph: no
    - Automatic detection of the start/end of the test: no
    - Test mode: Canopy

5. Preparing the measurement for a new versus existing participant will vary as indicated below:
    - To enter a new participant:
        i. From the main menu, select '1.New'.
        ii. Update 'ID' to participant ID or make a note of the automatically-generated FitMate GS ID for your records.
            - We recommend entering the participant ID and using a "-" or another symbol for their first and last name for research purposes.
        iii. Enter DOB, sex, height (cm), and weight (kg). Press OK
            - The device requires you to indicate the participant's sex. This information is used to calculate predicted values for REE; thus, we recommend that the person's biological sex be entered instead of their gender identity, as shown on the screen.
    - To select an existing participant:
        i. Select '2.View/Search' on the main menu.
        ii. Scroll through the list of subjects to find the relevant participant ID. Select 'OK'.
6. Adjust the flow selector to line up the participant's weight with the canopy blower's red dot.

Running a REE Test

1. Select '1.Resting Metabolic Rate' from the menu and follow the prompts on the warning messages.
    - If you are testing an existing participant, a warning message may appear asking for a new session to start. Press OK.
    - When the canopy is turned on after being prompted, the unit will beep a few times. When the green led on the front of the unit turns on, the test can be started. If the green led does not go on, do not proceed with the test.
    - Do not place the canopy hood over the participant's head until the blower has been turned on.

2. Once the green led is on, place the canopy hood over the participant's head. The canopy blower must be placed near the top of the participant's head.
    - It is important to flatten the veil on the bed to prevent air leaks which will affect the measurement.
3. The equipment will automatically calibrate the analyzer.
4. Press '1.Start' to start the test, or the test will automatically begin after one minute.
    - F_EO_2 should be between 19.50 -20.25%. Adjust the flow selector on the canopy blower as needed by rotating the selector counterclockwise if the F_EO_2 is too low and clockwise if the F_EO_2 is too high. Wait 30-45 seconds after adjustments to observe the effect before adjusting further. Continue to observe the F_EO_2 values throughout the test and adjust the flow selector as needed.
5. When the test is over, the device will prompt the removal of the hood from the participant and turn off the canopy unit. Once these steps have been completed, press 'OK'.
6. The test results will be displayed on the screen and printed by the device automatically.
7. Hold the on/off button to power off the device. Disassemble, sanitize, and store.

Notes

Predictive equations

Indirect calorimetry offers a precise prediction of REE in the clinical setting but creates challenges due to the accessibility of equipment, cost, time, and required skills associated with performing IC measurements. Predictive equations offer clinicians the ability to predict EE on an individual level during the nutritional assessment, albeit with sub-optimal accuracy and preciseness. The most common and clinically relevant predictive equations include those by Harris and Benedict [45], Mifflin-St Jeor [46], Owen [47, 48], and the World Health Organization/Food and Agriculture Organization/United Nations University [49, 50]. In healthy adults, Mifflin-St Jeor is the most precise equation and has been shown to predict REE within 10% of the measured value [46, 49]. In older adults, the Mifflin-St Jeor equation has the least bias (-0.3%) while the Harris-Benedict equation has the highest precision (~70%), suggesting that the former is best for group-level while the latter is best suited for individual-level predictions of REE [46, 51]. Predictive equations are formulated from regressing data on a group level and thus induce error (of which is often clinically relevant) when utilized on an individual

basis [49]. To diminish error when predicting EE, especially on an individual level, IC should be applied using an evidence-based protocol [49]. Portable IC devices that provide a precise EE measure across health conditions are needed in the clinical setting.

Use of RQ to Detect Measurement Error

RQ's physiological range reported across the fed and fasting state is 0.67 to 1.30, while an expected fasting RQ is 0.68 to 0.90 [36]. If the RQ is between 0.91 and 1.30, a problem may have occurred, and the measurement should be repeated [36]. Problems could include an error in calibration, an air leak in the IC system, participant hyper- or hypoventilation, or a pre-test protocol deviation such as insufficient fasting time, caffeine intake, or exercise [36]. If problems persist despite secure device connection points and the absence of protocol deviation, technical support for the equipment should be sought.

COVID-19 considerations

An indirect calorimetry is an important tool used to guide the early nutritional management that is critical for the therapeutic care of patients with various conditions, including the new coronavirus disease 2019 (COVID-19) [52-54]. A recent report of prospective IC measurements throughout the course of intensive care unit (ICU) admission for COVID-19 revealed increasing measured REE (hypermetabolism) and increased variability in measured REE after one and three weeks of ICU admission [54]. Although controversial, IC can be safely performed in patients with COVID-19 and thus, can continue to be used safely for people not exhibiting the virus if proper protocols are followed [53] with enhanced cleaning procedures and the use of disposables. For example, if measuring REE by Q-NRG™, all device components that contact the person undergoing a measurement can be purchased in disposable format (i.e., one-time-use), including the flow meter, sampling lines, FiO_2 adapter, and filter. Additionally, single-use veils for the canopy hood can also be purchased. Upon completion of a measurement, the canopy, flowmeter (if not using a disposable option), Q-NRG™, and the canopy hose can all be disinfected with high-efficiency cleaners while the disposables can be discarded. These safety measures can be translated to the research setting.

Factors that affect EE

Several factors affect EE and its major physiological compartments, such as genetics, age, sex, menstrual cycle, body composition, physical activity, diet composition, health status, medications, and environmental stimuli [55]. Generally, REE is higher in men than in women even after adjusting for confounding variables such as age, body composition, and activity levels [56, 57]. Another important factor that affects EE is the menstrual cycle. Webb [58] demonstrated that TEE was 8% higher in the luteal phase compared to the follicular phase. Similarly to TEE, a recent meta-analysis including three hundred eighteen women also found REE to be higher during the luteal phase compared to the follicular phase of the menstrual cycle [59]. External factors such as diet composition are also able to affect EE. In fact, the energy expended to digest, absorb, process, and store dietary protein is 25-30% of the energy content of the meal, followed by carbohydrates (6-8%) and fat (2-3%) [60]. The RQ is a highly sensitive value that is also affected by diet composition. An RQ value <0.67 or >1.30 is physiologically unlikely in a fasted and rested state; thus, RQ can be used as an indicator of pre-test protocol adherence [36]. If an RQ value is outside of the anticipated fasting range (0.68-0.90) and cannot be explained by a pre-test protocol deviation, then the possibility of an air leak should be considered [36, 61]. In addition to diet composition, medications can affect EE by affecting respiration or heart rate, leading to increased or decreased EE. Anti-asthmatic drugs such as salbutamol have been found to increase $\dot{V}O_2$, $\dot{V}CO_2$, and RQ [62]. Conversely, β-blockers have been shown to decrease EE related to their activity, decreasing skeletal muscle sympathetic nerve activity and resting heart rate [63, 64]. Additionally, anti-seizure drugs [65], antidepressants [66, 67], antipsychotics [68], corticosteroids [69], and stimulant medications for attention-deficit/hyperactivity disorder [70] have been found to decrease EE. Therefore, if IC is being used in a research design that includes repeated measures, the above-mentioned factors and strict adherence to pre-test protocols should be verified to ensure that captured change is truly representative of the change in EE and that the effect of measurement error is minimized. Depending on the research question and study design, these medications should be considered when defining clinical studies' exclusion criteria measuring EE.

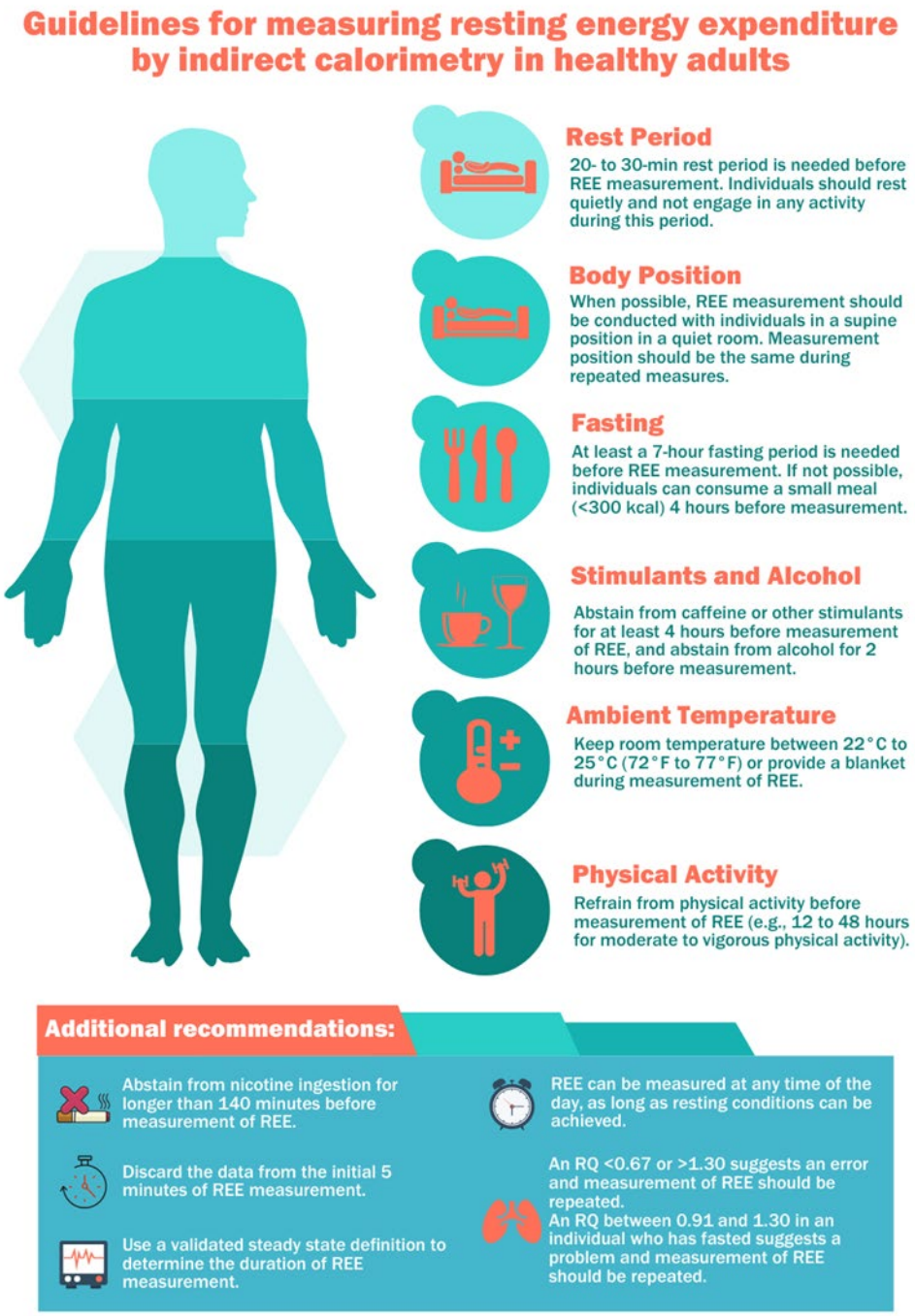

Figure 1. Guidelines for measuring resting energy expenditure by indirect calorimetry in healthy adults. Abbreviations: min: minutes; REE: resting energy expenditure; RQ: respiratory quotient.

Figure 2. Participant resting in the supine position during a ventilated hood indirect calorimetry measurement.

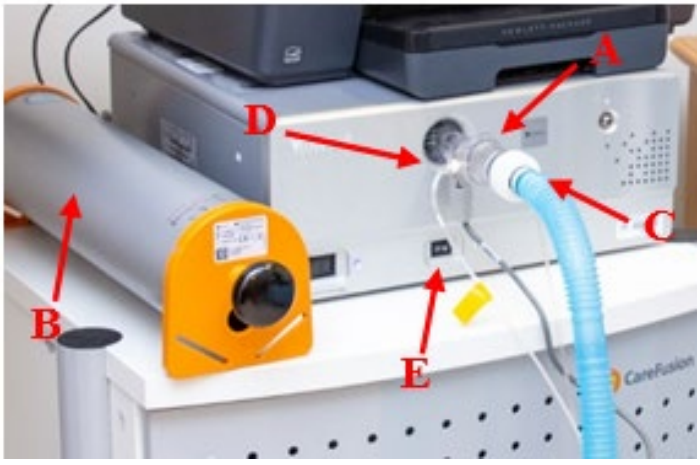

Figure 3. Components of the Vmax. Arrows point to a specific component of the device, as defined by the letters: Vmax flow sensor (A); 3-liter syringe (B); blue hose attached to flow sensor (C); sample line connected to flow sensor (D); flow pump switch (E).

Figure 4. The blue hose is attached to the ventilated hood at the chin position.

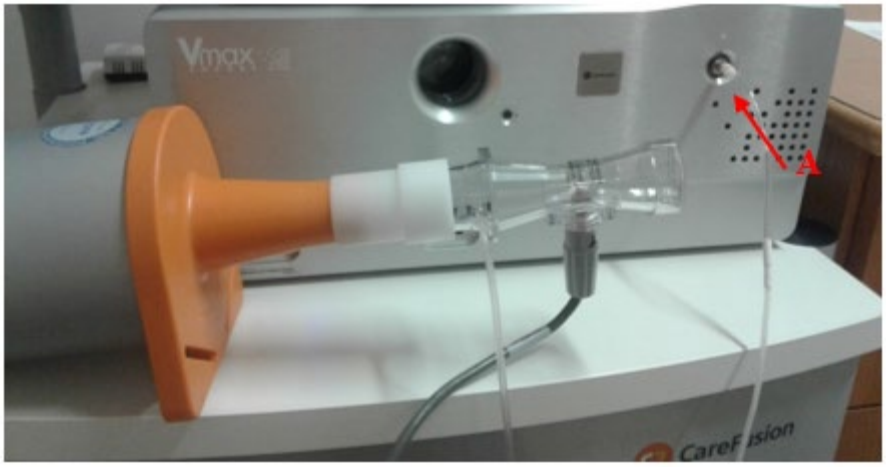

Figure 5. Vmax sample line is now connected to the calibration port (A) as shown by the arrow indicating the connection point.

Figure 6. Q-NRG™ canopy hood.

Figure 7. MedGem® device.

Figure 8. FitMate GS with a canopy hood option.

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Appendix 2 Analysis of Skeletal Muscle Mass from Pre-existing Computed Tomography (CT) Scans

This appendix has been accepted for publication as a book chapter (Ford KL, da Silva BR, Limon-Miro AT, Prado CM. Analysis of Skeletal Muscle Mass from Pre-existing Computed Tomography (CT) Scans. Atherton PJ and Wilkinson DJ (Eds.), Neuromuscular Assessments of Form and Function. New York: Springer Nature). Within this book chapter, I was responsible for writing the first draft; co-authors critically reviewed the intellectual content of the manuscript.

Abstract

Computerized tomography (CT) is a gold standard imaging technique for assessing body composition at the tissue-organ level, particularly for the quantitative and qualitative analyses of skeletal muscle. A single slice measurement at the third lumbar vertebra has a strong correlation with whole body values. Thus, regional skeletal muscle cross-sectional area can be used as such or extrapolated using predictive equations to estimate whole-body skeletal muscle mass. CT images also allow for the assessment of skeletal muscle "quality", reflective of myosteatosis (i.e., fat infiltration into muscle). Several software packages and protocols for assessing body composition via CT image are available. In this chapter, the protocol for analyzing a CT image at the third lumbar vertebra using sliceOmatic (Tomovision, Magog, Canada) software will be described.

Keywords

Computerized tomography; Skeletal muscle; Body composition; Adipose tissue; Protocol; Muscle assessment; Muscle attenuation; Intermuscular adipose tissue; Myosteatosis

Introduction

Computerized tomography (CT) is a nuclear medicine imaging technique that produces a reconstructed image of a specific section of the body based on the measurement of repeated radiologic projections at different positions and angles [1]. The varying attenuations from the X-ray beams as they pass through the body are reconstructed to form a gray-scale two-dimensional image of a 'slice' of the body [1]. The cross-sectional image is composed by pixels of different attenuation values that can be used to further explore quantity and "quality" of the tissues included in that particular body section (adipose, skeletal muscle, bone, visceral organs, and brain) [2]. The resulting CT images are the gold standard for body composition assessment at the tissue-organ level, particularly for the quantitative analysis of skeletal muscle and adipose tissue areas [2-5]. Though, CT is regularly used for screening and monitoring certain health conditions (e.g., cancer, liver and pulmonary diseases) rather than for body composition assessment [6].

Body/tissue composition is assessed by quantifying those represented within given CT image(s). The tissues are identified based on their attenuation which is represented through pixels (typically 1 mm x 1 mm) in the image by a numerical value known as a CT number which is expressed in Hounsfield units (HU) [1, 2, 4]. Specific HU ranges represent the different types of tissues and are typically represented by unique colours (e.g., skeletal muscle: red) as shown in **Figure 1.** Hounsfield units are primarily determined based on tissue density in relation to air (least dense) and water (most dense) at standard temperature and pressure with air being equal to -1,000 HU and water equal to 0 HU [4]. Tissues with a lower HU will appear darker on the image while denser tissues (higher HU) will appear grey or white. Notably, HU ranges for tissues are not consistent throughout the literature and may vary based on the protocol used [7]. In addition to quantity of muscle tissue (a focus of this chapter), CT images can also assess the integrity (quality) of skeletal muscle. The varying attenuation (represented by HU) allows for the distinction between skeletal muscle and intermuscular adipose tissue (IMAT), with lower attenuation indicating increased intermuscular lipid accumulation [2, 4, 8]. The IMAT identified on CT imaging encompasses intramyocellular and extramyocellular lipid content; exclusive identification of intramyocellular lipids is possible through a muscle biopsy or magnetic resonance imaging with a magnetic resonance spectroscopy technique applied [4, 9].

For body composition assessment, the cross-sectional area (cm^2) of skeletal muscle at the third lumbar (L3) vertebra correlates best with whole-body skeletal muscle and adipose tissues [4, 7, 10, 11]. Selecting the area of interest (herein, the L3 image) is known as landmarking and is the first step in CT image analysis for body composition assessment. The skeletal muscle index can be determined using skeletal muscle area standardized by height, assessed at the level of the L3 vertebra [12]. Alternative landmarks and approaches have been used for the analysis of body composition using CT images such as the mid-thigh cross-sectional area, thoracic, cervical, single muscle approaches (e.g., psoas), and the superior mesenteric artery level (**Figure 2**) [7, 12-15]. Moreover, agreement between sex-specific L3 cut-offs for low muscle mass and those derived from the tenth thoracic vertebra to the fifth lumbar vertebra have been confirmed in healthy kidney donors [14]; and, it has been suggested that when the L3 image is unavailable, the following images should be considered in order of: L2, L4, L5, L1, T12, T11, and T10 [14]. Various publications have reported limitations to these alternative landmarks when compared to the L3 vertebra reference including a low proportion of total trunk muscles per scan, measurements with a high level of error, and discrepancies among observers [7, 13, 16, 17]. For these reasons, alternative anatomical landmarks have not been recommended by any guideline or expert group for skeletal muscle mass assessment [16]. Although software-specific standards for body composition analysis by CT scans exist, assessing the L3 vertebra using the Edmonton Protocol [18] is one of the most common approach within the literature and will be discussed. All information contained herein was used with permission of Voronoi Health Analytics (Coquitlam, Canada) and TomoVision, a division of Virtual Magic, Inc. (Magog, Canada).

Body composition assessment by CT is perhaps most appropriate in patient populations (e.g., aortic valve replacement, cancer, critically ill, respiratory failure, trauma) where pre-existing scans are available in the medical record [2, 19-24]. When used under these conditions, CT scans are widely available at minimal cost [5]. Indeed, it is noteworthy that the high dose of ionizing radiation required for a CT scan curbs the use of this body composition assessment technique in prospective studies when requiring repeated measures of healthy individuals [2, 4]. Exposure to ionizing radiation depends on the type of CT scan and is 31 milli Sieverts (mSv) for a CT scan of the abdomen and pelvis [25]. Instead, studies can exploit scheduled re-assessments when patients are expected to receive a follow-up CT image for clinical reasons within the

course of their disease trajectory [26]. Altogether, given the widespread opportunity for those without CT scanning facilities to access pre-existing clinical images for repurposing to the study of skeletal muscle related readouts, this chapter will focus upon post-image acquisition analyses of CT scans.

Various software and protocols are available for body composition analysis using CT imaging; this chapter will focus on the Edmonton Protocol, housed within the sliceOmatic (TomoVision, version 5.0) software. Computed tomography image analysis involves the following three steps and will be reviewed in detail in the methods section: 1) landmarking to isolate a L3 CT image; 2) CT image analysis using the sliceOmatic region growing/painting mode; 3) Retrieving region growing analysis output from the CT images.

Best practices for CT image analysis include training to meet precision standards against an experienced trained observer (training for the analysis of images of varying quality); using a single observer in any study (person analyzing the images should remain consistent throughout the study); monitoring data quality; and consulting with a radiologist for questionable images.

Materials

1. A computer with sliceOmatic (TomoVision, version 5.0) software. A paid subscription is required to save images.
2. A trained technician with basic knowledge of radiology and anatomy to landmark and segment the images.
3. Access to CT images of interest.

Methods

The following methods are based on the software manufacturer recommendations, training, and the authors' combined experience [18]. Some sections are worded per user manual, used with permission as mentioned above.

CT Image Analysis

In accordance with institutional ethics board approval and local health authority processes, obtain CT images from medical records of interest. Using the Alberta Protocol shortcut to access the sliceOmatic (TomoVision, version 5.0) software, read and landmark

obtained CT. When image of interest (e.g., L3) are obtained, drag and drop the specific DICOM (Digital Imaging and Communications in Medicine) files into sliceOmatic. TAG images should not be imported in this step as this can cause the software to close unexpectedly. Alternatively, navigate the files on the left-hand side of the window to select the study folder. Select the images of interest by clicking the folder name, the icon, or using "Shift" and click to select multiple images or files. Selected files will be outlined in green. Click and move the slider under the preview window to scroll through the image files. Once satisfied with selected images, click "Read "x" image files" to view images in the software and click "Exit". The previous steps may be repeated to analyse additional images later.

Landmarking

Landmarking is the process of selecting the anatomical location of interest for analysis; in this case the third lumbar vertebra. Once images are imported, sliceOmatic will display two image windows. The program is best used when maximized to fit the computer screen size. Click on the image window on the right so that it is outlined in green. Under "Tools", select "Colour Scheme" and then select "Frame Selection" under the subheadings "All Modes" and "Tool 2D". Under "Mode", select "Region Growing". Navigate the "Frame Selection" display on the right-hand side of the screen and click on any axial frame. Select the left-hand image window to transfer the green selection border and re-navigate to the "Frame Selection" display to select any scout, sagittal, or coronal image frame displaying the L3 vertebra. Place the cursor over the L3 vertebra in the left window and press the "." button to displays the closest axial version of the scout image. The axial slice that is closest to the position of the cursor on the scout image will populate. To view alternate axial images, use the "Page Up" and/or "Page Down" keys. Ensure that the image in the right screen is that of interest as this image that will be segmented for body composition analysis. When only axial images are available, navigate "Frame Selection" in the right-hand column and click "One" to increase the size of the viewing window. Press the space bar to view the axial images and select the one displaying the L3 vertebra as described below.

To select the L3 image from a full-body (or larger) series, hover the mouse over "Frame scale" on the right-hand side of the screen and use the scroller on the mouse to move through the images. Lumbar vertebrae are distinct from thoracic vertebrae because the former does not have rib attachments while the latter do. Example images of thoracic and lumbar vertebrae are shown

in **Figure 3**. Scroll down through the images to identify the thoracic vertebrae which have a rib attachment and posterior transverse processes. Scroll past the thoracic vertebrae to identify the first lumbar (L1) vertebra; the first image without rib attachment and with horizontal transverse processes. Using the transverse processes, count down through the images until an image displaying the L3 vertebra is obtained. Typically, three to five slices (images) per vertebra, occasionally up to eleven slices, are available. Notably, each time the transverse process disappears and reappears, a different (and lower) vertebra is being viewed. If the iliac crest (top of the pelvis) or short transverse processes are visible, the L4 or L5 vertebra is being viewed and the L3 was passed (**Figure 3, part D**). In approximately 10% of the population an L6 vertebra is visible. Once the L3 vertebra has been identified, select the image within the L3 vertebra frames that best displays even and thickest transverse processes on either side of the spine, as shown in **Figure 4**. The middle image within the series of L3 vertebra frames is generally most acceptable. To identify the image, the middle of the L3 is tagged with a dot of colour. Once satisfied that the most appropriate L3 vertebra frame has been selected, click "File", "Save Tag". Under "Mode", select "DB File Management" and select "All/Close Selected/Update DB". Repeat the above-described processes for each subject folder.

Manual Segmentation

Once the image of interest (L3) is identified, the image is ready for analysis. Segmentation is the process of tagging a grey-scale image to produce a colour-coded image representing skeletal muscle, IMAT, visceral adipose tissue (VAT), and subcutaneous adipose tissue (SAT), as shown in **Figure 1**. These tissues are identified based on defined lower and upper threshold limits of HU. The HU limits and TAG colour can be manually adjusted in the "Region Growing" mode although the colours associated with each tissue (**Figure 1**) are those most used. An image must be loaded into sliceOmatic before manually adjusting the HU limits by clicking the TAG colour of choice and setting the appropriate HU ranges (both lower and upper). This process is continued for each tissue that needs identifying. Once the TAG colours have been selected with desired HU ranges applied, the process of colouring the image can begin. Traditionally, tissues are tagged in the following order to ensure accuracy: skeletal muscle, IMAT, VAT, and SAT.

The most accurate method of identifying skeletal muscle is through the "Paint" sub-mode. To 'paint' an image, select the brush size (the larger the better) and TAG colour based on the tissue that will be evaluated. Left click and drag the mouse to move the paintbrush over the appropriate areas of the image to manually identify the desired tissue. For example, select TAG 1 (red colour) to evaluate skeletal muscle. Note that fascia bundles that connect muscle should not be analysed as skeletal muscle, as shown in **Figure 5, part A**. The lumbar artery and fascia under the spinalis muscle are not considered part of the muscle area and should not be coloured. Muscle wasting near the end of muscles is also not coloured. Contrarily, abdominal muscles are coloured, although it is important to note the ligaments and the linea alba as these are not coloured. Next, evaluate the IMAT by selecting TAG 2 (green colour) and dragging the paintbrush (left click and hold on the mouse) over the uncoloured areas within the skeletal muscle. The empty spaces between the iliocostalis lumborum muscle, longissimus lumbalis muscle, and fascia are all coloured as IMAT, although muscle wasting around the edges of muscles is not tagged. Use the TAG lock feature, as described in the following paragraph, to lock the tagged IMAT. Continue this process for the remaining tissues by selecting TAG 5 (yellow colour) for VAT and TAG 7 (cyan colour) to evaluate the SAT. The "Grow 2D" feature can be useful for tagging the abdominal cavity as VAT. The intestine and visceral organs are not coloured nor should the skin be tagged as SAT (**Figure 5**). Use the TAG lock feature prior to selecting TAG 7 for the SAT. Once satisfied, navigate "File", and select "Save TAG".

Colouring tools within sliceOmatic that have been mentioned and may be useful are outlined below. To fill an area of the image, trace the edges of a large muscle area by painting a line. Once a large tissue area is enclosed, select "Grow 2D" and the smallest brush size to flood a large area of pixels with the selected TAG colour. This mode is most effective for VAT and SAT analyses, not the analysis of skeletal muscle or images with minimal VAT and SAT. If the limits of a tissue are hard to visualize, use the "Colour Scheme" tool to change the contrast of black and white to make the edges of a tissue clearer. Increasing the darkness of the image will improve muscle visualization whereas lightening an image will allow for better visualization of adipose tissue. To erase any errors, right-click and hold the mouse while hovering over the area(s) containing pixels coloured in error. Alternatively, select the "none" TAG and left-click and hold while hovering the mouse over the coloured pixels to be deleted. To undo previous

brush strokes, use the “Ctrl Z” feature on the keyboard. Once satisfied with a colour, use “TAG lock” to protect that colour and lock it in place. This feature ensures that no other colour can override the tagging that has been done previously. The TAG lock feature is especially important when colouring tissues that have overlapping HU (e.g., the three types of adipose tissue). Lastly, “Scale” will increase the size of the image, making it easier to complete the colouring with accuracy.

Determining Body Composition Measures

Once the images are analyzed, sliceOmatic will provide the TAG surface/volume measurement for each TAG (colour) used. Navigate “Tools”, select “TAG Surface/Volume”, and in the right-hand column, select “DB Surface” to obtain measurement information. The software will prompt for the files to be saved. Next, navigate “Mode”, select “DB File Management” and “All/Close Selected/ Update DB”. Outside of the software, open the saved file in a spreadsheet. The mean GLI (Grey Level Image) for a TAG is reported in HU and found in row 3 of the spreadsheet. The GLI value represents the physical properties of the scanned tissue (it is a marker of muscle radiodensity). Variables of interest are given in cross-sectional areas in cm^2, which is a direct unit of measurement from CT and are found in row one of the spreadsheet. Repeat this process in its entirety for each segmented image and transfer the data to a master spreadsheet.

Notes

The data on cross-sectional area can then be used to stratify people from least to most muscular or to compare muscularity with previously published population-specific cut points used for identification of low muscle mass [20, 21, 27-29]. Regression equations are also available for prediction of whole-body skeletal muscle and adipose tissue based on values retrieved from the L3 vertebra [30, 31]. Data containing the mean value of the pixels in HU is available for each TAG and depicts the mean radiodensity of each tissue. Reflective of attenuation, the mean HU is indicative of fatty infiltration of muscle and thus, muscle quality or presence of myosteatosis can be inferred [28, 32].

Body composition assessment from analysis of CT images can be conducted regardless of contrast agent (e.g., barium, iodine dyes) use during the imaging process [5]. Notably, contrast

does alter the radiodensity of tissues and thus will equate to different HU compared to an image that did not contain contrast; thus, use of contrast is an important consideration when analyzing and comparing results of body composition assessment by CT. If available, we recommend analyzing images without contrast.

To determine the type of series that is being viewed in sliceOmatic, navigate the "Tools" tab and select "2D Overlay". In the bottom right-hand corner of the screen, select "Tech". Technical information for the image will appear [18]. Frame thickness and spacing are important variables that can be found within the technical information and can vary depending on the CT equipment and the technician performing the scan. Frame thickness should be recorded in a separate spreadsheet and will be needed for body composition analysis. Frame thickness can also affect the technician's ability to select the appropriate L3 slice. As mentioned in the methods, the L3 slice with the thickest and most even transverse processes should be selected for segmentation [18].

Image quality can be affected by artifacts within the body, challenging the accuracy of body composition assessment, and in some cases the image may need to be discarded from analysis [33]. For example, cavity fillings, medical implants, and titanium rods can alter the quality of a CT image. If patient is wearing a watch during the scan, streaks are visible across the image, challenging the accuracy of the segmentation process and subsequently, body composition assessment. A build up of fluid (ascites) will cause poor contrast as the fluid has a very similar density to muscle [18]. The "Colour scheme" tool within sliceOmatic allows for contrast adjustment, which can be especially useful for analyzing low quality images. For example, images can be viewed in grey-scale, mixed, tint, or over (brightest option). Use the F1 through F4 keys to toggle through the grey, mixed, tint, or over options, respectively. Grey (F1) is best used for visualizing the boundaries between muscle and organs. Mixed (F2) is ideal during the segmentation (colouring) process. Tint (F3) is ideal when reviewing the image for errors or pixels that are not appropriately coloured. Lastly, the over option (F4) is ideal when using the images for presentations or when verifying that no pixels of skin have been tagged as SAT [18].

Anatomical knowledge is required for CT image analysis. Notably, CT images are inverted whereby the right side of the body appears on the left side of the image and vice-versa.

The option to identify individual muscle groups in sliceOmatic is possible by setting different TAG colours for specific muscles (e.g., psoas major, erector spinae, quadratus lumborum, abdominal obliques, and rectus abdominus), as shown in **Figure 1** [18].

Beyond the cost, expertise, and ionizing radiation exposure, the size of the person can also present as a limitation to CT analysis for body composition assessment [2]. The CT scanner field of view may not accommodate all persons living with excess body weight, resulting in CT images that are missing sections of tissues (e.g., SAT, skeletal muscle) [2]. The image should not be used for body composition analysis if both sides of the obliques/transversus abdominus, erector spinae, or rectus abdominus are cut off from the image [18]. If the person's body is pressed against the scanner, the CT image will produce an altered image containing photon starvation artefacts and may not be usable in analysis [33]. Additionally, CT images may not capture regional change in skeletal muscle and adipose tissue that results from weight change [4]. Whole-body CT scans are not common due to the ionizing radiation and weight change may be region-specific and thus not captured within in the landmark image of interest [4]. As discussed, whole-body composition can be estimated by a single cross-sectional CT image of the abdomen [10, 34]. If weight change has occurred, the data should be interpreted with caution.

Analyzing CT images for the purpose of body composition assessment will take an experienced technician approximately 20 minutes to segment one image whereas someone who has less experience will require about 45 minutes per image. This timeframe is in addition to the time needed for the landmarking process. As mentioned, it is important that the technician used for one study remain consistent throughout the analysis of images for that study to ensure consistency in technique across images. For a visual explanation of landmarking using sliceOmatic, we recommend viewing our YouTube video or the training modules available elsewhere [35, 36]. For detailed anatomical photos to assist with landmarking and segmenting, we recommend referring to the *Pocket Atlas of Sectional Anatomy Vol. II* [37].

In terms of organization, we recommend that the person analyzing the images create a folder for all tagged L3 images and include a subfolder for each participant. The subfolder should contain two files: the TAG and DICOM files. The TAG file is the final segmented file whereas the DICOM file is needed for any changes to be made; the TAG file cannot be uploaded into sliceOmatic for adjustments. Within a master spreadsheet containing data from all

segmented images, we recommend that notes are recorded if the following are present within the images: SAT cut-off and location; presence of a hernia (whether minor or major); ostomy (regardless of location); abnormal anatomy; pannus (skinfold); presence of artifacts.

Manual segmentation was discussed herein although the future of CT image analysis includes automatic segmentation for the purpose of body composition assessment and is now available [38]. Automatic segmentation of skeletal muscle, VAT, and SAT is taken from an axial CT image accurately, in comparison to manual segmentation using Automatic Body composition Analyser using Computed tomography image Segmentation™ (ABACS™) software (Voronoi Health Analytics) [33, 38-40]. This program has been internally [38] and externally [33] validated in comparison to manual segmentation of images. External validation in a cohort of patients with non-metastatic colorectal (n=3102) and breast cancer (n=2888) found that automatic segmentation by ABACS™ underestimates skeletal muscle by a mean of -2.35 cm^2 [33].

New technological developments recently released by the company, includes the ABACS™ plug-in, which is an artificial intelligence program integrated within the Data Analysis Facilitation Suite (DAFS) 3.0 platform and automatically segments landmark images of interest [39]. The entire body composition analysis workflow, including data curation, vertebral slice landmarking, tissue segmentation, manual editing/corrections and final tissue statistics computation can be performed using DAFS [41]. DAFS includes two key automation engines, the ABACS™ 3D which provides a volumetric segmentation of the entire CT scan containing any field-of-view within the thoracolumbar region, and the Automated Vertebral Annotator engine that enables automated landmarking of the thoracis to sacrum vertebral locations [41]. Such advances in software technology and use of artificial intelligence in body composition analysis make for a promising future within the field, ideally with integration of body composition into clinical care.

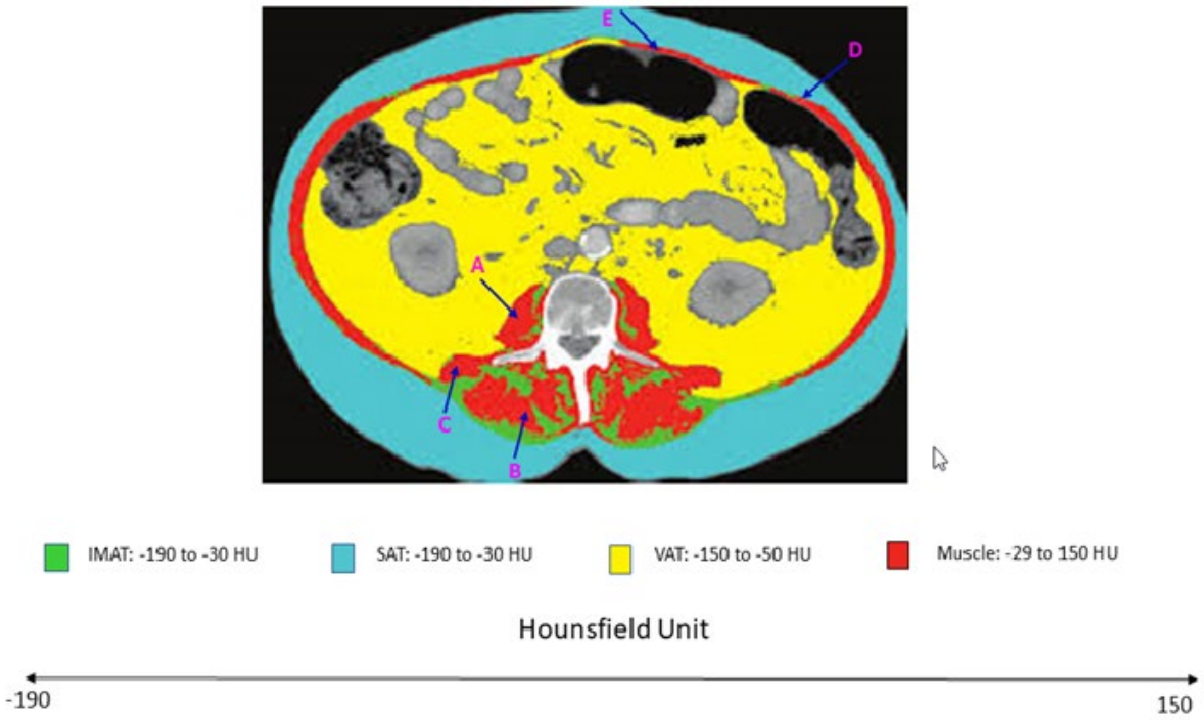

Figure 1. Body composition profile on a computerized tomography image at the third lumbar (L3) vertebra. Tissues are colored based on their respectively Hounsfield Units (HU). Abbreviations: IMAT: Intermuscular adipose tissue; SAT: Subcutaneous adipose tissue; VAT: Visceral adipose tissue; Muscle: Skeletal muscle. Arrows indicate different muscle groups: A) Psoas major; B) Erector spinae; C) Quadratus lumborum; D) Abdominal obliques; E) Rectus abdominus.

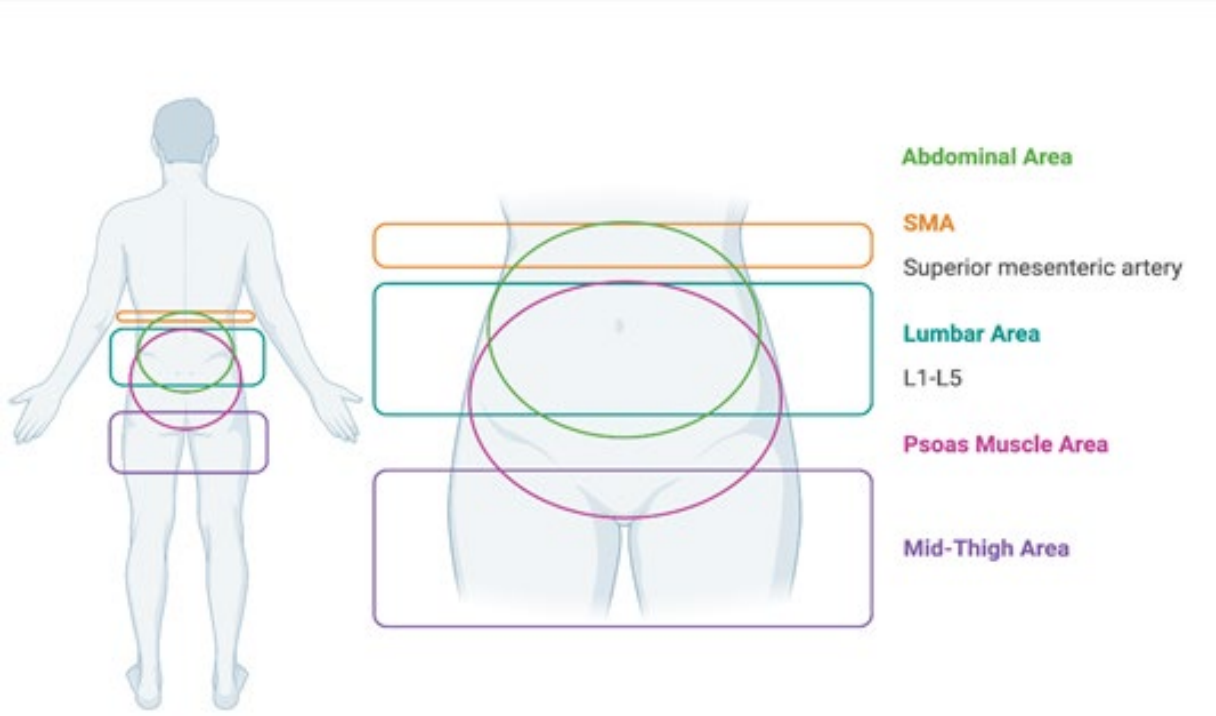

Figure 2. Muscle groups in the lumbar area.

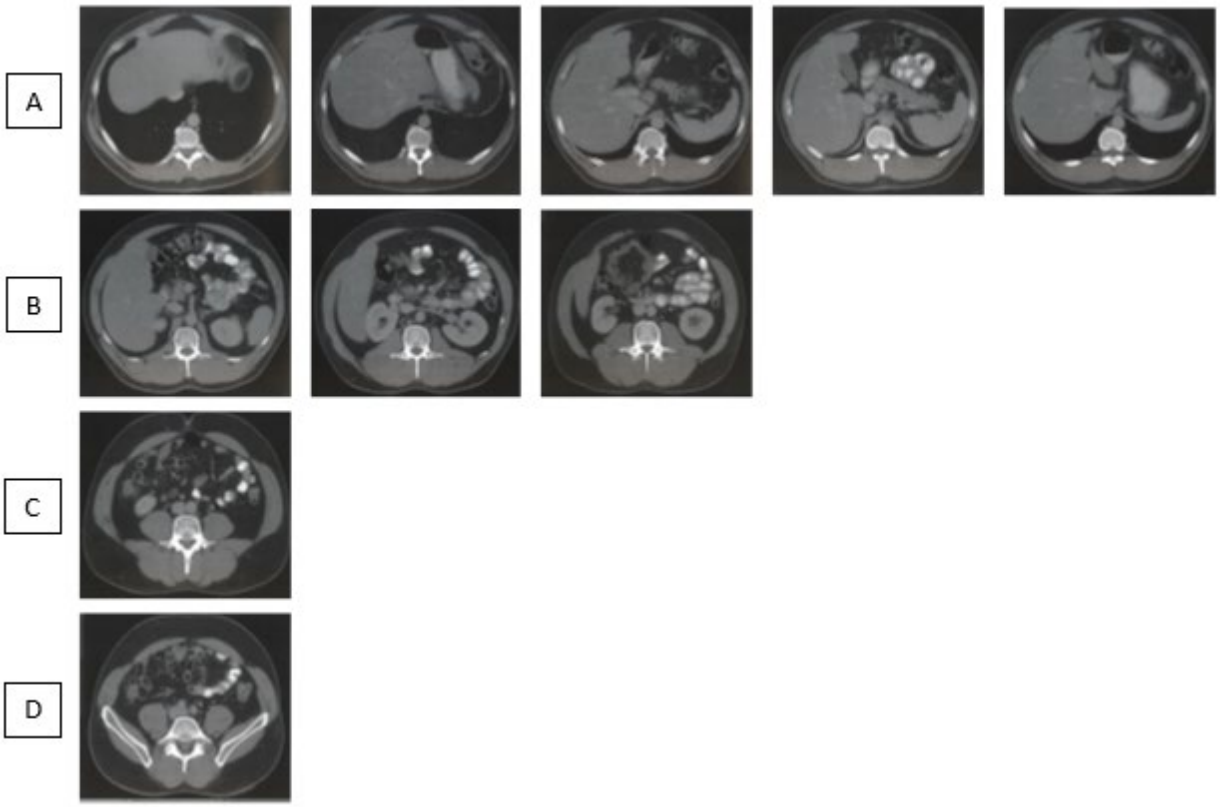

Figure 3. Axial images of thoracic and lumbar vertebrae without contrast. A: Thoracic vertebrae (T1-T12). Articular facets for ribs, long sharp spinous, and the lungs start to disappear. B: Lumbar vertebrae (L1-L3 from left to right). No articular facets for ribs, short blunt spinous process, and no ribs are visible. C: L4 vertebra. Iliac crest may be visible. D: L5 vertebra. The iliac crest is the main landmark.

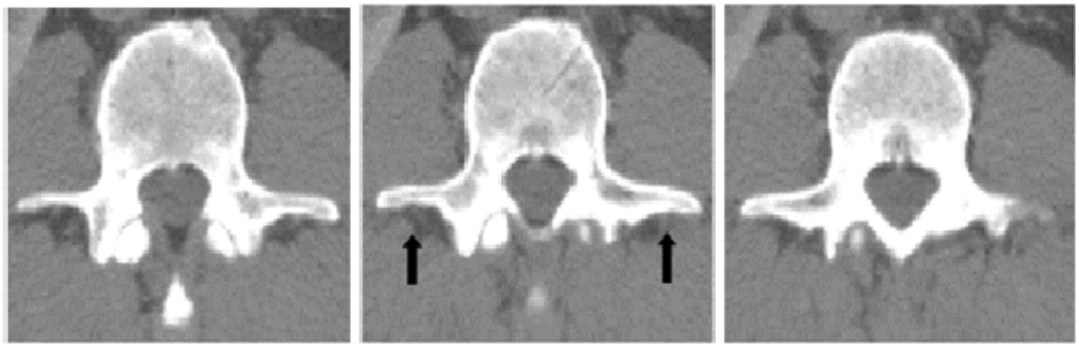

Figure 4. Three frames showing the transverse processes at the third lumbar (L3) vertebra level. Arrows indicate the thickest and most consistent transverse process within the series of images.

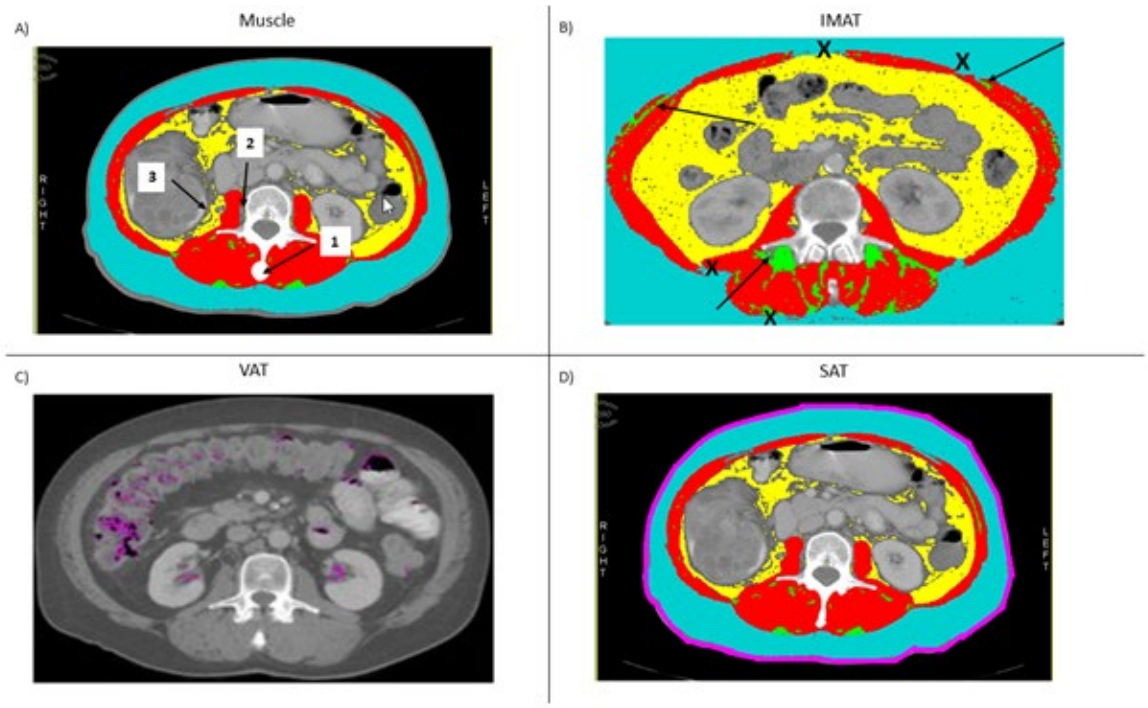

Figure 5. Potential problematic areas when tagging different tissues. Abbreviations: IMAT: Intermuscular adipose tissue; VAT: Visceral adipose tissue; SAT: subcutaneous adipose tissue. Skeletal muscle tissue is represented by red color, IMAT is represented by green color, VAT is represented by yellow color, and SAT is represented by cyan color. A) 1: The area underneath the neural spine (if present) should remain untagged; 2: Represents a tendon and should not be analyzed as muscle; 3: Non-muscle structures touching the psoas or other muscles should not be tagged. B) Arrows indicate areas to examine for presence of IMAT. The X's indicate areas that should not be tagged. C) Adipose tissue inside the organs (e.g., liver, kidney, and intestine) are not considered VAT. Purple colour indicates tissue that should not be included as VAT despite having the same density. D) Purple colour indicates skin. Skin is not analyzed as SAT.

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