THE EFFECT OF DIETARY PROTEIN ON SATIETY AND WEIGHT LOSS DURING INTERMITTENT FASTING IN OVERWEIGHT AND OBESE WOMEN

by

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Submitted in partial fulfilment of the requirements
for the degree of Doctor of Philosophy

at

Dalhousie University
Halifax, Nova Scotia
September 2023

DEDICATION PAGE

To my husband, my parents, my kids, and my siblings thank you for all of your support, guidance, sacrifice, and many memories. I dedicate this dissertation to you with an apology for every moment of my shortcomings because of my preoccupation.

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Abstract

Energy restriction, including IER regimens, is one of the most important obesity treatment and weight-control strategies. These regimens provide health benefits associated with weight reduction. With energy restriction regimens, however, noncompliance and hunger-induced fatigue are common issues that may interfere with this diet's success. According to evidence, dietary protein may impact satiety and therefore mitigate certain noncompliance-related difficulties. Therefore, this dissertation primarily investigated the effect of dietary protein on satiety and body weight, with a secondary focus on health indicators (i.e., lipid profile, HbA1c, and CRP) in overweight and obese women. The data showed that plant-based protein sources increase satiety at a level comparable to that of animal-based protein. Positive results were also observed with the higher protein diet: increased satiety, decreased body weight and waist circumference, and the improvement of other health indicators, including triglycerides and C-reactive protein. Nonetheless, the differences in effect between protein groups (high protein diet versus low protein diet) were not statistically significant, possibly due to the small sample size. We found that the telehealth method was effective in facilitating the research, despite some limitations in conducting dietary interventions using telehealth. Further studies with larger sample sizes are required to clearly demonstrate the effect of dietary protein content on satiety and weight under intermittent fasting conditions and over the long term among overweight and obese women.

LIST OF ABBREVIATIONS USED

IER – Intermittent Energy Restriction WHO – World Health Organization BMI –

BMI - Body Mass Index

GLP-1 – Glucagonlike Peptide 1 CCK – Cholecystokinin

PYY – Peptide YY

AMDR– Acceptable Macronutrient Distribution Range FFM– Fat-Free Mass

FMD – Fasting-Mimicking Diet

VAS – Visual Analogue Scale

α – alpha significance level

HP – high protein

LP – low protein

TEF – thermic effect of food

ADF – alternate day fasting

REDCap – Research Electronic Data Capture REDCap

ANOVA – Analysis of Variance

CRP – C-reactive protein

ACKNOWLEDGEMENTS

This dissertation, and ultimately who I am today, would not have been possible without the support of so many individuals. I am fortunate to have remarkable people around me, both professionally and personally. First, I appreciate all that Dr. Jo Bryant has done for me, especially the opportunities she has given me, beginning with her agreement to be my supervisor and continuing with her support. My knowledge and abilities have significantly benefited from the lessons about conceptualizing, writing, and conducting presentations. I would also like to express my deepest appreciation to my committee members Dr. Laurene Rehman, Dr. Younes Anini and Dr. Irene Ogada for their time, guidance, and support. Without them, this dissertation and my educational journey would have been impossible. I am also grateful for the moral support that helped me keep my spirits and motivation high.

Next, I would like to extend my deepest gratitude to Dr. Julie Zhu. She provided me with all the necessary support and tools to succeed in conducting my research. She overwhelmed me with kindness and enabled me to overcome the difficulties I faced, especially in facilitating blood tests and obtaining blood work results. I would also like to extend my sincere thanks to my research participants. Without them, it would have been impossible to conduct the research.

To my husband, my soulmate, and my companion in the journey of life and my pursuit of a doctorate, you believe that my success is your success. You were my source of strength and encouragement, even in the midst of the hardships we experienced. I owe you for all that you have provided for me, for your belief in my abilities, and for changing the course of my life. You made many sacrifices to help me succeed in my doctoral journey. Without you, I do not know where I would be, but I do know that I would not have achieved this success. You taught me the value of life and that every problem has a solution that begins with patience.

Mother, what words will reward you? I offer thanks and gratitude for your unparalleled giving and love. Your prayers and encouragement surround me. I was your focus, despite

your responsibilities and pain. You taught me not to despair and that hope exists in the presence of God. This dissertation is the least I can give you to express my thanks and gratitude because I know how much my success means to you. Father, you taught me the importance of sincerity and hard work. You have remained my idol through my struggles and success.

My siblings—thank you for your unconditional love and for believing in me more than I believe in myself. I am proud of you and grateful you are my siblings. Nadia, my tender sister, you have been an example of giving and altruism and my friend since childhood. Your kind words relieved my stress and anxiety. I would also like to thank Raed, my brother, for advising me and encouraging me to face the struggles of both work and life. I cannot begin to express my thanks to my brother Mishal for welcoming me into his home to support me in finishing the rest of the dissertation. I have always felt your support and love for me and my family. You bore my absence even in the most meaningful moments of joy and the most difficult of times.

Ghala and Faisal, this dissertation carries with it our dream and stories full of memories of joy alongside challenges, successes, and hardships. However, we are strong by God, and our dreams have not ended.

1.1. CHAPTER 1: INTRODUCTION

Increased obesity rates pose a threat to individual health and are a burden on the health care system (1). Significant evidence has shown that obesity is involved in the development of many chronic diseases, such as heart disease, diabetes, hypertension, and some cancers (2,3). The American Medical Association's 2013 decision to acknowledge obesity as a disease marks an important step forward in the acceptance of obesity as a disease and the advancement of evidence-based methods for its prevention and treatment (4). Obesity has a complex etiology, but the most prominent cause is the positive energy balance that occurs when energy intake surpasses energy expenditure (5). Restricted energy intake is considered a primary strategy to reduce body weight and fat mass. Complying with such diets, though, may be challenging because most of these diets increase hunger; thus, a failure to achieve a sustainable strategy for weight loss is likely (6,7). As a result, incorporating satiety-enhancing elements into the design of such diets is crucial for achieving a successful, sustainable approach to the prevention and treatment of obesity.

Many dietary weight loss strategies for overweight or obese individuals are considered therapeutic treatments (8–10). One of these dietary strategies is dieting based on intermittent energy restriction (IER), which is defined as a dietary strategy that depends on cycles of restricted energy intake alternating with habitual energy intake (9). Typically, the degree of energy restriction is severe, with energy intake usually limited to 500–800 kilocalories, or 25% of the total energy required to maintain body weight (11). Many animal studies involving IER have reported that it is an effective strategy for weight loss (12–15). Researchers can easily perform such a diet using animal models since they can control feedings so that the animals cannot access additional intake. In contrast, people experience many challenges due to physiological and environmental factors (16,17), thus raising the question of whether IER is a successful strategy for weight loss among obese or overweight adults.

The term "satiety" refers to the feeling of being full following the consumption of a meal; accordingly, it influences the duration of intervals between meals (18). The feeling of satiety is a consequence of a series of chemical signals sent from the GI tract to the brainstem (19). Researchers have suggested that satiety signals are affected by many factors, including macronutrient composition and nutrient-related hormones (20,21). Several studies have investigated the association between macronutrients and satiety, and most have indicated that protein has a greater impact than other macronutrients on increasing satiety and suppressing energy intake (20,21). In a review of 24 randomized controlled trials, Wycherley et al. concluded that protein contributed to reducing appetite more than carbohydrates and fat (22). Subjective reports of satiety have demonstrated a greater reduction of hunger, the desire to eat, and energy intake during a meal following high-protein intake than during a meal following high-fat and carbohydrate intake (22). Additionally, dietary protein contributes to an increase in the release of gastrointestinal appetite hormones, such as PYY, which help suppress appetite and also decrease concentrations of ghrelin (23).

1.2. Obesity and metabolic disease risk

According to the World Health Organization (WHO), "overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health."(24). Typically, one of the measurement tools for monitoring weight status within the population is body mass index (BMI), which is calculated by dividing weight in kilograms by height in metres squared (25). The WHO classification of underweight, normal, overweight, and obese based on BMI is displayed in Table 1. The WHO further subdivides obesity into three categories: Obesity class I: a BMI of 30 to 34.9 kg m^2; Obesity class II: a BMI of 35 to less than 40kg /m^2; and Obesity class III or "severe" obesity: a BMI of 40 kg/m^2 or greater (26): Globally, the National Institutes of Health of USA and many public health researchers affiliated with other organizations are using BMI to determine the overall population level of obesity (25). Many public studies have linked BMI to morbidity or other parameters of health status (25). Although BMI is a practical assistance tool for assessing a population's general health status, additional measurements are required for more accurate individual diagnoses. BMI does not provide an accurate measurement of body fat content (27). For example, some athletes' BMI values are high because of their larger muscle mass rather than their excess body fat (27).

In recent years, obesity has risen to prominence as a global public health concern. The prevalence of obesity and even being overweight is rising worldwide among adults across all age groups, sexes, and educational levels (1). For instance, according to a WHO document in 2021, globally, about 1.9 billion individuals aged 18 years and older are overweight or obese (28). By 2025, global obesity rates will reach 18% of the male population and 21% of the female population (29). In Canada, approximately 28% of Canadian adults were obese in 2020, while 36% were overweight (30). Statistics Canada reported that 30% of adult residents in Nova Scotia are classified as overweight, and 33.7% are classified as obese (31). Considering the prevalence of obesity, the WHO has classified it as a global pandemic and health problem. Evidence shows that obesity is a predictor of health risk and a decreasing quality of life in adults (32–35). Obesity is also considered a high-risk factor for developing many chronic diseases, including type II diabetes, cardiovascular disease, high blood pressure, and certain types of cancer (35,36), while weight loss reduces these risks or delays the progression of these diseases (37–39).

Ample research on nutrition and health has indicated that eating behaviours are some of the primary factors that contribute to the development of obesity (40), although environment and genetics also play roles (41). A positive energy balance, which occurs when energy intake surpasses energy expenditure, is the primary reason for excess body fat accumulation over time (41). Consequently, reducing energy intake is a primary goal for effective diets that aim to treat or prevent obesity. Evidence indicates that the characteristics of food intake and environmental factors that influence satiety could be a reasonable explanation for energy imbalance (42).

Table 1 the BMI classification by the WHO (30)

BMI (kg/m^2)	**Classification**
Underweight	<18.5
Normal	18.5–24.9
Overweight	25.0–29.9
Obese (class I)	30.0–34.9
Obese (class II)	35.0–39.9
Obese (class III)	≥40.0

1.3. Dietary protein requirement

Dietary protein is a macronutrient that is an important component of a healthy diet. Following protein consumption, hydrochloric acid in the stomach hydrolyzes the dietary protein during the digestion process, and proteases in the duodenum break down long polypeptides into short-chain polypeptides (43). This digestive process reduces proteins into amino acids or small peptides, which are then absorbed in the small intestine (43). Among dietary amino acids, essential amino acids play an indispensable role in several critical bodily functions, including hormone, antibody and enzyme synthesis, the preservation of skeletal muscle mass (43). Considering the important role of essential amino acids (44) and the body's inability to store them, it is critical to include an adequate consumption of protein in dietary requirements for human health.

Most exogenous protein is used for repair of body tissues, immune function, and turnover of proteins in the body, and not for energy per se. Therefore, a substantially reduced protein intake could result in suboptimal health. To estimate an adult's needed protein intake, relative (percentage of energy) amounts and absolute (g protein per kg body weight) are methods that are commonly used. For relative amounts, the dietary reference intakes (DRI), a system developed for Canada and the USA, proposed ranges for each macronutrient via the acceptable macronutrient distribution range (AMDR); the protein intake needs were determined to be 10%–35% of the total energy required to maintain body weight (45). For determination on an absolute basis, the recommended dietary allowance for protein is 0.8 grams of protein per kilogram per day for a sedentary adult (45). A healthy, sedentary or lightly active adult on an isocaloric diet likely receives enough protein if either the absolute or relative methods are used to calculate protein needs. However, if a person's energy intake drops below isocaloric levels, calculating protein requirements on a basis relative to total energy intake (such as in restricted energy diets) would result in suboptimal levels of protein. Indeed, most IER diets involve a deficient protein content (46).Therefore, determining the amount of protein as an amount proportional to an individual's body weight is a more accurate method of calculating an individual's protein needs, especially when formulating the minimum protein requirement on a restricted-energy diet (46,47). Indeed, research has indicated that maintaining a high protein level while consuming a restricted-energy diet is beneficial for preventing the loss of fat-free mass (FFM) due to a negative nitrogen balance.

The high protein might not induce more weight loss than lower protein but provide a benefit to body composition due to retention of muscle mass. For instance, a randomized controlled trial compared the effects of a chronically energy-restricted diet with a daily protein intake of 0.8 g/kg body weight/day to an energy-restricted diet with a daily protein intake of 1.2 g/kg body weight/day on body weight over six months (48). Although higher protein content induced similar weight loss amount (84.1 ± 12kg) to lower protein content (85.0 ± 13kg), the higher protein diet led to a greater reduction in fat mass while maintaining the FFM (48). Similarly, in randomized crossover study compared a HP diet (30% of the energy intake from protein) to a LP (20% of the energy intake from protein) in a restricted energy diet over eight weeks in thirty-five overweight or obese men and women. They found that higher protein content induced more benefit on decreased fat mass, maintained free-fat mass, and improved the lipid profile than did the lower protein content (49).

There is limited evidence on the impact of low-protein IER diets on aspects of health. Some studies have found that the low-protein content in restricted-energy diets may improve health markers in animals (50) A study that investigated the effects of a low-protein fasting-mimicking diet (FMD) on aging in mice and humans reported that intermittent restriction of amino acid and protein consumption may reduce comorbidities associated with ageing and thus improve health and lifespan (52). Nevertheless, the reasons for these health benefits (e.g., enhancing glucose regulation and insulin sensitivity) might not only be due to the lower protein intake but also be due to the result of the metabolic switch or autophagy produced by IER (53,54). The evidence regarding the effect of low-protein content in energy-restriction diets on body weight and energy intake is inconclusive. Few human studies have tested protein levels for IER diets; thus, it remains difficult to determine if there is a benefit in restricting protein intake for such diets. Thus, the optimal amount of protein in restricted-energy diets remains unknown. A systematic review that included 24 studies with a diet duration was 12.1 ± 9.3 weeks demonstrated that high protein diet induced more reduction in fat mass reduction of reductions in fat-free mass and triglycerides (22). Clifton et al. analyzed data from ted three randomized parallel trials that compared high protein which consisted of 27% of energy intake from protein (i.e. g) to normal protein diet which consisted of 16% total energy intake from protein (i.e. 60 g) on 215 obese individuals over 12 weeks. Clifton et al. observed that high protein had more health benefits in enhancing health indicators; in which HP induced a reduction in total cholesterol by 12% from the initial mean of total cholesterol than the normal protein group where the reduction was 6% total cholesterol from the initial mean of total cholesterol. Additionally, HP achieved more reduction in abdominal fat mass loss and triacylglycerol level (55).

1.4. Satiety

Satiation and satiety are prominent consequential factors that drive appetite control and thus food consumption, but they represent different time frames of fullness and feelings of hunger (See Figure 1) (56). Satiation, which refers to feeling full, or having no desire for more food while ingesting a meal, may occur at any point after beginning to eat. Satiety refers to experiencing fullness after the consumption of a meal (57). It is typically measured with a subjective satiety rating (i.e. a visual analog scale) for fullness, hunger, desire to eat, and prospective food intake, as well as by the time interval between a test meal (treatment meal) and a subsequent meal (58). Both satiation and satiety regulate energy intake, as the size of meals and their frequency over a day determine the total daily energy intake (58). Blundell et al. developed the Satiety Cascade concept, a theoretical framework that illustrates a complex interplay between a series of physiological processes and behavioural and environmental factors that occur in the time frame from the early pre-ingestive period to a subsequent meal (i.e., satiation and satiety periods, as presented in Figure 1) (59).

These factors are divided into 1) external factors that include sensory and cognitive factors and 2) internal factors that include post-ingestive and post-absorptive factors. An early review by de Graaf et al (2004) of the factors inherent to food consumption concluded that sensory aspects have a more significant role in determining the type of consumption, whereas physiological biomarkers may have a more significant role in determining the quantity of food intake (60).

1.4.1. External factors affecting satiety

A complex interplay of sensory and cognitive factors affects satiety and satiation, which, in turn, leads to the satiation level influencing the satiety level (60,61). Thus, it is difficult to separate satiation from satiety entirely, even though they have different time frames. For example, satiation is mainly influenced by the sensory effects of food, including palatability, texture, temperature, appearance, and smell (60,61). Cognitive factors, such as education, on and beliefs about food, also influence food consumption (62,63). This means that the way people react to the sight, odour, and taste of food and their beliefs about food strongly influence how they decide on the portion and content of the food to be ingested (62,63). What individuals consume, including both the size of the meal and its content, is also positively associated with the satiety level and the time of a subsequent meal (60). As such, many dietary studies have indicated that the content and sensory characteristics of a meal influence the interval between meals (i.e., satiety) (60,64,65). This influence implies that satiation can be considered a factor in satiety, in which a meal's size and content significantly influence satiety (60,64,65).

People eat for multiple reasons other than satiating their hunger: sensory hedonics, the stimulation of the senses, and relief from stress and boredom (66,67). There is no general rule for eating behaviour; individuals may eat even though they feel full, or do not eat when they are hungry (66,67). These complex interplays between satiation and satiety may be a reason for the contradictions among interventional studies investigating subjective satiety or food intake. Thus, it is critical to consider factors related to satiation, such as palatability and meal content, in the assessment of satiety or to develop foods with the aim of enhancing satiety features.

1.4.2. Internal factors affecting satiety

Appetite and satiety sensations undergo intricate interplays between gastrointestinal system hormones and the hypothalamus (60). An area in the hypothalamus regulates appetite and satiety, inducing the intake of food or the sensation of being full and ultimately affects body weight (60). Previous studies have indicated that protein-induced satiety is potentially associated with a significant change in concentrations of appetite-regulating hormones that contribute to enhanced satiety (68,69). Accordingly, the dysregulation of the function of appetite hormones may cause risks related to body energy balance (70). The signals that play significant roles in food intake and energy intake homeostasis have been classified into two categories: satiety and adiposity signals (60,71). Satiety signals include those sent by gastrointestinal-derived hormones, such as cholecystokinin (CCK), peptide YY (PYY), and glucagonlike peptide 1 (GLP-1), which are released from enteroendocrine cells (60,71). These satiety peptide hormones are considered predictive biomarkers of hunger and appetite. GLP-1, CCK, and PYY levels decrease during fasting periods and rise after food intake; thus, they are secreted in response to fasting and feeding status (60,71). These changes trigger receptors on duodenal sensory neurons, which then send signals to the brain through the vagus nerve to induce the feeling of satiety (60,71).

Ghrelin, which is called the “hunger hormone,” due to its role in increasing hunger, leads to increased food intake (72). Weight loss increases ghrelin levels, which leads to increased hunger as a compensatory mechanism in response to body weight loss (73). It is involved in short-term appetite regulation and is predominantly released in the stomach, where it provides a signal to the brain indicating hunger (72). Schubert et al. observed that high protein intake had significantly reduced plasma acyl and total ghrelin levels than other macronutrients. It operates in a cycle, rising during fasting prior to meals and then dropping on meal termination (74). The relevant research findings on the influence of dietary protein on ghrelin regulation in humans are contradictory (23). Some studies have observed plasma acylated and total ghrelin decrease following a high protein meal than other macronutrients (74,75). For example, Blom et al. observed that increasing protein at the expense of carbohydrates in liquid meals dramatically reduced ghrelin release (76). Opposing studies have reported that high protein intake increases ghrelin concentration (77,78). These contradictory findings may reflect that ghrelin is influenced by many factors such as growth hormone and insulin level (79). However, the mechanisms responsible for the post-meal decrease in ghrelin secretion have not been fully explored.

Leptin, which is often called the satiety hormone, and insulin are fat-related hormones that contribute to regulating body weight by influencing feeding behaviour and appetite and basal metabolic rate (19). Leptin is a hormone created by adipose cells; it signals satiety to the hypothalamus, and thus works to reduce food intake (19). It inhibits the secretion of neuropeptide Y, which inhibits the release of orexins, which stimulate appetite (19). Although individuals who are obese have a high level of leptin, it has been observed that they also have leptin resistance, and body weight reduction could contribute to reduced leptin levels (80–82)

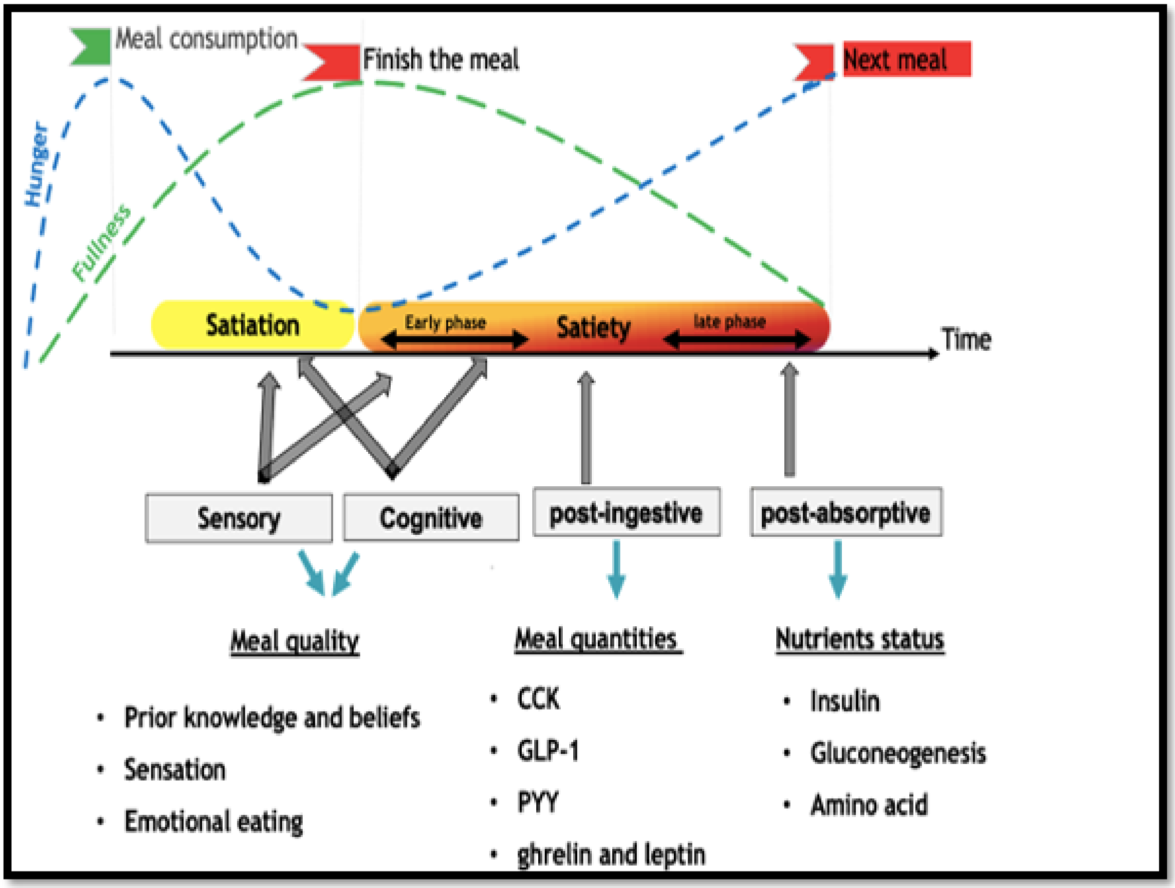

Figure 1: The frame of Satiety Cascade, developed by Blundell et al.
It shows the external and internal factors that affect satiety; the differences between the satiety and satiation (64,88)

1.5. Protein and satiety

1.5.1. Effect of high protein meal on satiety (short-term)

The impact of protein meals on satiety and appetite has been investigated (84–92) (See Table 2). Studies have tested, using a crossover study design, effects of varied protein concentration consumption on satiety by frequently assessing subjective satiety ratings (84–92), examining satiety hormones (85,86,88,89), or measuring subsequent food intake (84,89,90,92). Most of these studies compared meals that had significantly higher than normal protein concentrations.

Protein intake induced satiety to a greater extent than did other macronutrients in some studies that matched meals for total energy content (84,85,93). For example, Stubbs et al. used a crossover design to compare the effects of meals matched for energy content and density but contained either 20% or 60% of energy from protein in 16 healthy men (89). The higher protein meal enhanced satiety significantly more than the meal that contained lower protein meal ($P < 0.001$) (84). Similarly, in another intervention, the study subjects reported feeling fuller after a high-protein meal containing 68% energy from protein than after a meal containing 10% energy from protein (93). When comparing 25% protein with 10% protein, it was observed that satiety increased by more than 32%. This finding synchronizes with a reduction in hunger by about 40% (85).

Use of a visual analogue scale (VAS) for measuring satiety has revealed that meals with higher protein contents produce greater satiety than meals with the same amount of energy but low protein content (84,89,91,92). For example, a randomized study by Lejeune and coworkers observed that subsequent energy intake was significantly lower ($r^2 = 0.49$, $P < 0.05$) after a higher protein condition than a low one. Subjects also reported greater satiety after higher protein meals ($p = 0.05$) (94). Additionally, the high-protein meal induced a greater increase of GLP-1 concentrations over the day than did a meal with low protein content(94). Evidence has shown that increasing GLP-1 concentrations contributes to enhanced satiety via delayed gastric emptying, which leads to enhanced satiety by making one feel full for a prolonged time (60). Another study reported that a high-protein meal (41% energy from protein) led to a great reduction in hunger than did a lower protein meal (15% energy from protein) in 13 healthy men and women (95). A strength of this study was that both meals had identical fibre and flavour content, both of which are critical factors affecting satiety (95). Similarly, Porrini et al. compared a high-protein meal consisting of 56% protein, 19% carbohydrates, and 45% fat presented as meatballs against a high-carbohydrate meal consisting of 17% protein, 56% carbohydrates, and 27% fat presented as baked macaroni in 14 healthy men (92). Although both meals contained the same total energy, the food intake (ad libitum) was significantly lower after the high protein, meatball meal than the high carbohydrate meal (92). Although most studies have found a more significant difference in acute satiety after a high-protein meal than after a low-protein meal (84–87,89,92), other studies have not (88,90). For instance, a study comparing 43% to 10% of energy from protein meals, did not find a significant difference in satiety between the two meals (90). Possibly, the high-protein meal was more palatable than the low-protein meal. Evidence has shown that palatability can significantly contribute to bias in satiety responses because highly palatable foods stimulate hunger and increase food intake (96). Overall, most studies have demonstrated that high-protein meals have a more acute effect on satiety than do low-protein meals (84,85,93).

1.5.2. Effect of high protein diet on satiety (long-term)

High-protein diets (chronic condition) may produce greater satiety than do normal or low-protein diets in healthy individuals. (See Table 3). A randomized crossover intervention involved 19 men and women who averaged 41 years and a BMI of 26 kg/m^2. The subjects who consumed 34% of energy as protein indicated significantly greater satiety during weeks three and four than did those who consumed 18% of energy as protein (97). Furthermore, after 12 weeks, the subjects who consumed a higher protein diet decreased their energy intake by more than 400 kcal per day than baseline (97). Similarly, a randomized study was conducted on 65 overweight and obese adults (50 women, 15 men) aged 18–56 years with BMIs between 25 to 34 kg/m^2 (98). The subjects were randomized to consume one of three diets over six months: (1) a diet that consisted of 25% of total energy as protein, 45% of total energy as carbohydrates, and 30% of total energy as fat; (2) a diet, that consisted of 12% of total energy as protein, 58% of total energy as carbohydrate; or (3) their habitual diet. Those who followed the 25%-protein diet exhibited a significantly lower energy intake than those who followed the 12%-protein diet (98). Although the study did not examine the effects of a high-protein diet on hunger or satiety, the high protein group experienced a greater reduction in their body weight (35% of the initial mean of body weight) than the low protein group (which was 9% of the initial mean of body weight), which could be considered signs of increased satiety (98).

Habitual eating habits appear to influence appetite responses. Changes in customary dietary habits can, therefore, influence spontaneous satiety responses (99). Long et al. conducted a study to investigate whether the chronic consumption of a high protein diet reduced its satiating effect (100). Subjects were selected based on their daily intake of protein (100).

The subjects who typically consumed about 1.0 g of protein per kilogram of body weight per day were classified as the low-protein group (LP), and those who consumed 1.4 g per kilogram of body weight per day were classified as the high-protein group (HP) (100). Over two weeks, the protein intake level was manipulated for both groups. The HP group's protein intake increased to 2.0 g per kilogram of body weight per day and then decreased to 0.65 g/kg of BW per day 13 days. The protein intake for the LP group started at 0.65 g per kilogram of body weight per day. The HP group was found to have lower satiety than the LP group. Long et al. found an inverse correlation between the amount of usual protein intake and the response effect of proteins on satiety (100). One weakness of this study was that it did not compare the satiety between the groups' responses (HP vs. LP) with matching protein content meals, but several other studies have supported the theory that accustomed eating habits influence satiety-related outcomes (101,102). However, much uncertainty still exists about the relationship between habitual protein consumption amount and the effect of protein on satiety. Further research is necessary to determine whether a chronically high consumption of protein loses its effect on satiety.

Overall, higher protein meals seem to increase satiety more than low-protein content meals, and this impact could extend to the long term. Nevertheless, most clinical trials examining the effect of protein on satiety have not used a variety of foods (89,97,98,103,104). Further studies are required to investigate the effect of protein types on satiety by using various whole foods as part of a normal long-term diet.

1.6. Mechanisms behind the effect of high protein intake on satiety

Protein intake seems to play an essential role in enhancing satiety, either in the short term (105) or long term (106), through several different mechanisms. Two meta-analyses have found that a high-protein diet contributes to weight loss by the reduction of appetite and body fat (22,107). This finding may be attributed to proteins providing higher thermic energy than other macronutrients (108). Research has also indicated that protein intake reduces the hunger hormone (i.e. ghrelin) (109) and enhances weight-regulating hormones, including GLP-1, peptide YY, and cholecystokinin (110). More than other macronutrients, protein helps maintain a feeling of satiety, which may be because it slows digestion and gastric emptying (111). The mechanism of the impact of protein in enhancing satiety has not been completely elucidated; the observed variations in the pattern of satiety gastrointestinal tract hormone release might imply that they are involved in eating behaviour and satiety. The next section will discuss the possible mechanisms behind the effect of protein in enhancing satiety.

1.6.1. Amino acids

Studies examining the effect of amino acids on satiety have indicated that increased serum amino acid concentrations contribute to hunger suppression (112). The possible mechanism is that amino acids derived from dietary protein are detected by the gastrointestinal system. These peptides stimulate the production of gastrointestinal hormones that enhance satiety (113). One of these amino acids is tryptophan, which is important in the synthesis of serotonin and as a neurotransmitter involved in regulating satiety by delaying gastric emptying (114). It has been suggested that a deficiency of tryptophan may cause an increase in hunger (114). In a 14-day study, Ayaso et al. examined the effect of supplementing a diet with 5% tryptophan on eating behaviour and body weight in rats. A control group consumed a standard diet of rat chow which consisted of 18.2 kJ/g (56% carbohydrate, 21% protein and 23% fat), whereas two experimental groups both received this, with one group receiving 5% additional tryptophan or additional 5% of lysine. This increase in tryptophan led to a reduction in food intake. Additionally, the inter-meal interval of the tryptophan group was longer than the lysine and the control groups (114).

Histidine, another essential amino acid, reduces food intake through the conversion of histidine to histamine, which has a role in suppressing feeding and enhancing the metabolic rate in animal studies (115). Human studies have shown comparable findings. For instance, a study involving 1,689 adolescents aged 18 years found that the amount of daily histidine intake was inversely associated with total energy intake (116). This finding supported other studies that reported histidine is essential to the central appetite mechanism because of its control of energy balance (115). Additional evidence has shown that high histidine, arginine, and lysine concentrations could activate hypothalamic tanycytes, which are receptors in the brain that play a role in suppressing appetite (114).

1.6.2. Other dietary factors

Interestingly, evidence has shown that not all dietary proteins have the same effects on satiety (117). The varying properties among proteins, such as digestibility and the ratio of bioactive peptides within their amino acid sequences, cause proteins to have different effects on satiety (118). Casein, for instance, is classified as slow-digesting, whereas whey protein has a faster absorption rate in the gut (119). Thus, casein has a moderate, longer-lasting satiety impact, while whey protein has an greater acute satiety impact (119). Soy protein produces a lower satiety effect than milk protein because soy protein has faster digestion kinetics than milk protein (117,120). It has also been reported that the digestion rate of fish protein is lower than that of red meat and chicken protein (117,121). This lower digestion rate may explain previous findings that fish protein has a greater satiety effect than other animal-based proteins (117). Some types of fish have higher tryptophan content than turkey which improves the serotonergic activity which associated with the control of satiety (122). Additionally, fish and shellfish are rich in n-3 long chain polyunsaturated fatty acids (LCPUFA) which have been demonstrated to decrease appetite and promote feelings of fullness (123).

There is no decisive evidence that animal-based proteins have slower or faster digestion rates than plant-based proteins because other intrinsic properties might affect digestion kinetics and satiety. For example, high fat and soluble fiber in a meal could result in a slower gastrointestinal transit time, and digestion kinetics are faster for liquid meals than for solid ones (124,125). Additionally, it is not clear whether the differences in the availability of essential amino acids between animals and plant-based proteins would make a difference in the effect on satiety between animal-based and plant-based protein. This raises the question of whether plant-based protein provides comparable satiety as animal-based protein which will be investigated in Chapter 2.

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1.6.3. Gluconeogenesis

Evidence has suggested that gluconeogenesis, the process of producing glucose from protein in the intestine to compensate for a decrease in plasma glucose levels, is one of the potential mechanisms behind the satiating effect of high-protein diets (108). When high-protein diets are combined with a restricted-energy regime, typically the reduced availability of carbohydrates, a prime source of glucose, promotes gluconeogenesis (127–129). Plasma glucose levels may play an essential role in regulating hunger and food intake in the short term. Researchers have observed that reducing plasma glucose concentration increases feelings of hunger and drives food intake in rats (130,131). The stimulatory effect of gluconeogenesis attenuates hypoglycemia, thereby reducing hunger and increasing the spacing between meals (132). Under conditions of carbohydrate restriction combined with enhanced protein intake, this effect might be due to the upregulation of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase, enzymes implicated in gluconeogenesis (133). A randomized trial found that a high-protein diet free carbohydrates increased gluconeogenesis and reduced appetite more than a normal-protein diet did, although both diets were equivalent in total energy (134). Limited human studies have aimed to determine gluconeogenesis and appetite ratings in a high-protein diet condition. Further studies are needed to clarify what the effect of amino acid–induced gluconeogenesis in high protein with restricted energy on satiety and whether protein sources differ in their ability to stimulate gluconeogenesis.

1.6.4. Thermogenesis

Diet-induced thermogenesis, also known as the thermic effect of food (TEF), refers to the increase in the resting metabolic rate subsequent to food consumption. The thermic effect of food (TEF) accounts for approximately 10% of the total energy expenditure on average, and it could be a contributing factor to enhancing satiety and body weight control, especially in the long term (135). Research has indicated that diet composition impacts the TEF (136). Dietary intervention studies have observed that meal-induced thermogenesis is higher after protein consumption than after carbohydrate or fat intake (137). Protein intake produces a higher TEF than the isocaloric loading of carbohydrates or fat (137). The TEE of protein is 20-30%of the total energy content, for carbohydrates, is 5-10% of the total energy content and for fat is 0-3% of the total energy content (138).

The high thermic effect of protein has been ascribed to the energy costs of digestion and metabolism related to protein metabolism. Therefore, high-protein meals contribute more thermic effects than do meals with a low to normal content of protein. In a randomized clinical trial, Mikkelsen et al. observed that replacing 18% of carbohydrates with protein boosted energy expenditure by 3% until the fourth day of high protein dietary (139). This finding is consistent with a critical review of studies that investigated randomized studies on the effects of high-protein diets on TEF, which reported that increasing protein in a diet increases thermogenesis (140).

Evidence has indicated an association between diet-induced thermogenesis and satiety sensations. For instance, a randomized, controlled intervention that used a repeated-measures design compared the effects of high protein, high fat, and high carbohydrate meals and found that high-protein meals produced both greater thermogenesis and more of a sensation of fullness than other meals (141). Similarly, a randomized study (*n*=32) compared high-protein diets with high-carbohydrate diets over 12 weeks and found that increasing TEF in high-protein diets coincided with increased fullness sensations over the intervention period while the reverse was true in high-carbohydrate diets (142). Leidy et al. compared the effect of a meal with 30% of energy from protein (high protein) with that of a meal with 18% from energy from protein (normal protein) and concluded that high protein induced an increase in TEF, increased satiety and reduced desire to eat (143). One hypothesis that can explain the relationship between the TEF and the feeling of satiety is the direct heating effect of protein intake. A sentinel study by Westerterp-Plantenga and colleagues found that a high-protein intake increases the TEF, which leads to an increase in body temperature. Subjects that causes the suppression of appetite to avoid increased body temperature (144). Another possible implication is that increasing oxygen demand to compensate for increases in oxygen consumption coincides with an increase in the thermic effects of high-protein intake (87,144).

1.6.5. Insulin

The hormone, insulin, might be a factor that assists in the regulation of satiety in the short (145) and long term (19). Increasing insulin in the brain boosts the sensitivity of the brain to signals during the postprandial period (71). Hallschmid and colleagues examined the effect of brain insulin signalling on the regulation of appetite in the postprandial period (146). They found that insulin administration was associated with a reduction in food intake (146), which implies that insulin is a relevant signal in the short-term regulation of food intake.

The long-term effect of following a high-protein diet on insulin is likely associated with the total energy intake. It has been suggested that a high-protein diet could cause hyperinsulinemia in non-restricted diets, which eventually induces insulin resistance (147,148). Rietman et al., for example, reported that consuming high protein over six months or more in a balanced-energy diet led to increased insulin resistance (148). However, following a high-protein diet with a restricted-energy diet in long term had a positive impact on insulin sensitivity for prediabetics and individuals with type 2 diabetes (148). A randomized trial observed that following a high-protein diet combined with a restricted-energy diet over six months reduced fasting insulin ($P < 0.025$) significantly more than a low-protein diet (149). Likewise, other studies have found that a high-protein restricted-energy diet improved glucose metabolism and insulin sensitivity (150), thus implying that a high-protein diet combined with IER might be more beneficial than following a high-protein diet with a balanced-energy diet. Further long-term randomized trials should examine the effect of a high-protein diet on IER in the long term.

1.7. Dietary protein and body weight in a restricted-energy diet

There is a strong consensus that dietary regimes that focuses on energy restriction promote body weight reduction (10,15,151), but the optimal protein composition of the diet to achieve maximum weight loss is contested. Many studies have compared the effects of different concentrations of protein in restricted-energy diets on weight loss to discover an effective strategy to treat or prevent obesity. Most of these studies have found high-protein diets to be the most effective weight loss regime (46,47).

Some researchers have compared relatively high-protein intake combined with normal protein content concomitant with restricted-energy diets as weight-loss strategies (46,47). Their results suggested that the relative amount of the restricted-energy diet's protein content impacts the magnitude and rate of weight reduction (46,47). Similarly, other studies have observed that restricted-energy diets consisting of a relatively high protein level (providing the minimum requirement of protein) are more beneficial in reducing body weight (46,152,153) and induced more reduction in fat mass (152,153) than restricted energy diets with a low protein level. However, in contrast to these findings, Westerterp-Plantenga et al. reported that increasing the protein content above the normal level of protein requirement did not produce a greater reduction in body weight, although it helped maintain a higher level of FFM (154).

High-protein diets that are extremely restricted in carbohydrates, such as the Keto diet, the Atkins diet, and the Protein Power diet, have become popular because they initially greatly reduce body weight (155). This weight reduction may be the result of sodium and water loss and decreased hunger associated with ketosis status, which causes reduced energy intake (155). The long-term safety of such diets has yet to be determined (156). Interestingly, some studies have observed that a long-term increase in the protein intake of IER diets promotes body weight loss, regardless of the diets' carbohydrate levels (157).

1.8. Visual analog scale

Evidence emphasizes the dependability of VAS methods in terms of test-retest and inter-rater reliability. In ingestive eating behaviour research, VAS questionnaires are used to measure pre- and postprandial hunger, fullness, and desire to eat (58,158). Using the VAS approach to assess subjective satiety has been validated in the literature and considered as an adequate strategy to assess satiety and appetite. Evidence suggests that a 10% difference in satiety after few hours of postprandial duration is useful to predict subsequent energy intake (159). However, there are some considerations regarding using VAS to assess the satiety. One of these considerations is that repetitive inquiries on one's hunger level has the ability to enhance an individual's attentiveness toward their internal signals, which may afterwards result in a decrease in the amount of food consumed (160). On the other hand, consistently reminding an individual of their hunger may result in an amplified hunger reaction, perhaps leading to an elevated in subsequent food intake(160).

The VAS provides a valuable assessment of sensations of fullness, hunger and desire to eat that are difficult to evaluate via other approaches. Some researchers use 5-point Likert scales, or 9-point Likert scales; nonetheless, it is recommended to prioritize the usage of 100-mm or 10-cm lines (158). VAS is a tool that may be used to inquire about many aspects of appetite. It includes questions about hunger, fullness, prospective food intake, and desire to eat. These dimensions were first developed and verified by Rogers and Blundell (83). The use of the VAS line scale approach is more commonly applied in behaviour food intake research due to its cost-effectiveness, simplicity in comprehension and analysis, and its ability to predict prospective energy consumption. Integrating satiety physiological measurements with subjective satiety responses over the interval after a meal may provide more information on changes in satiety. However, measuring the satiety hormones is quite difficult and costly and there is no strong evidence that changes in satiety physiological biomarkers provide more clear information for satiety than changes in subjective rating scales (158).

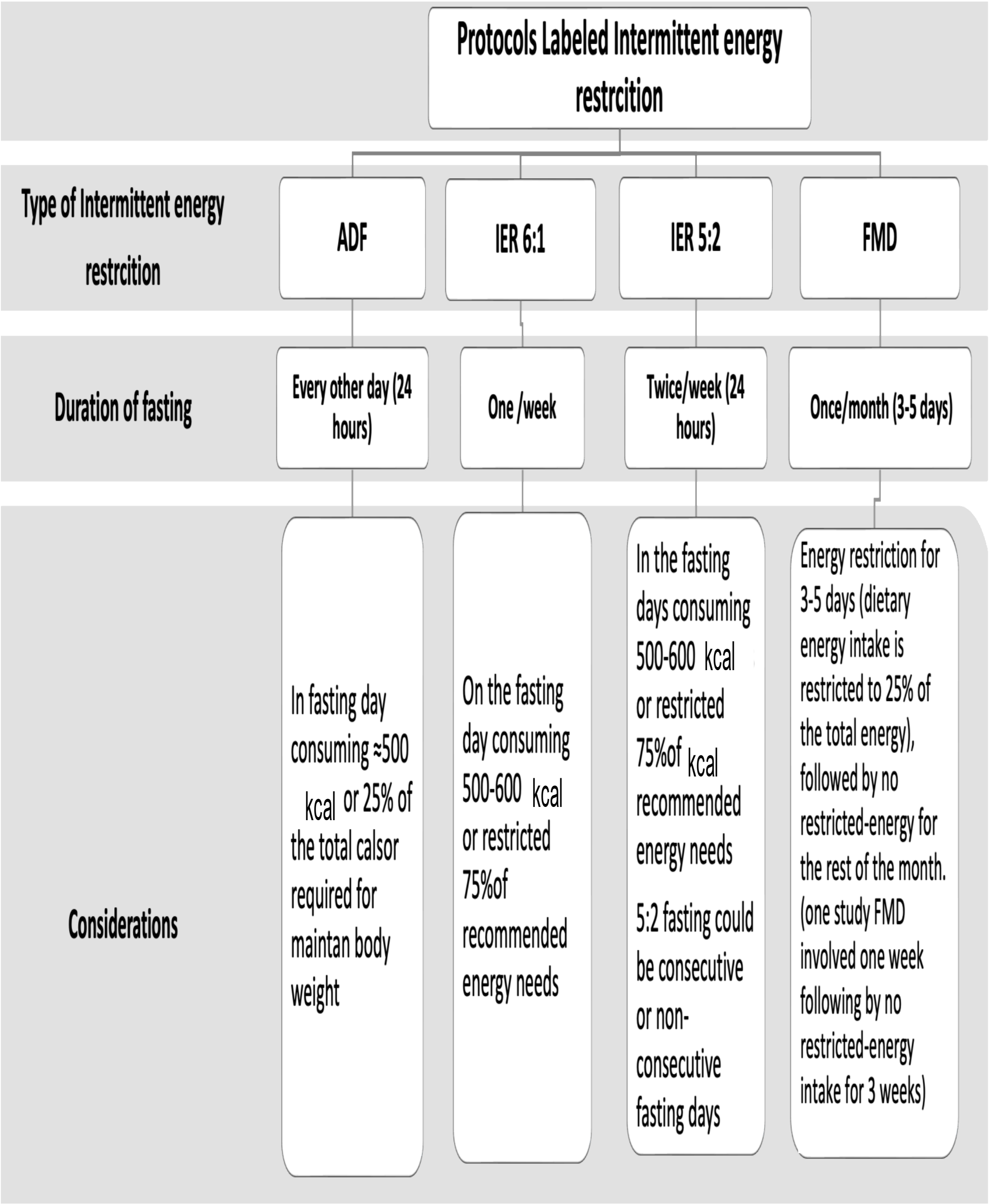
1.9. IER

1.9.1. IER definition, and types

There are many types of IER, including a fasting mimicking diet (FMD), alternate day fasting (ADF), and intermittent calorie restriction diets (5:2, 6:1 and 4:3) (161,162) (See Figure 2). These types of IER are named according to the fasting approach that is used, the amount of energy restriction and the period, or the cycle, of fasting (161). They differ from total fasting and are similar to each other in their dependence on dietary energy restriction for one to three days (called “fasting days”) alternating with normal energy intake days (called ad libitum) (161). On restricted-energy days, the amount of restriction of energy varies among studies. In most of the studies, on restricted-energy days the dietary energy intake is limited to ~20 to 25% of the total energy required to maintain body weight or consume 500–600 kilocalories per day, while during ad libitum days, eating as normally without restriction in energy (161). An FMD consists of energy restriction for 3–5 days before resuming a normal energy intake for the rest of the month and then repeating the cycle (162). Another version of an IER diet, the ADF diet, involves limiting caloric intake commonly to 500 calories or a reduction of 75% of the required energy to maintain body weight or less for one day, with ad libitum diet in the next day (161). Furthermore, an IER diet, which can be either a 5:2 diet or a 4:3 or a 6:1 diet, is a type of fasting that depends on consuming 20 to 25% of the recommended energy needs on one day (i.e., 6:1) or two days (i.e., 5:2) or three days (i.e., 4:3) during the week, consecutively or non-consecutively, with consuming the total energy required form maintaining body weight the remainder of the week (161,163).

1.9.2. IER and health

Evidence has demonstrated that IER is a beneficial strategy for weight loss, which is considered an important treatment for decreasing risk factors for many chronic diseases related to obesity (11,167). When comparing intermittent energy restriction regimens to daily energy restriction in a meta-analysis found very little difference in weight reduction (mean weight difference of 0.26 kg, 95% CI: -0.31 to 0.84; p=0.37) (166). This indicated to benefits of the IER alternate weight loss approach, and it is more flexible and easier to adopt than daily energy restriction (166). Weight loss for the majority of adults has many health benefits, including improvements in blood pressure, lipids profile, decrease in visceral fat and improvement in the markers of insulin sensitivity and the control of glucose levels (11). Evidence has shown that the IER approach can potentially improve compliance more than continuous energy restriction, as IER is more adaptable than daily energy restriction (168). Thus, it may be helpful to practice intermittent energy restriction as a sustainable strategy to maintain the positive effects of weight loss. Additionally, it was found that IER and continuous calorie restriction diets achieved comparable positive results in reducing biomarkers, such as insulin-like growth factor 1, IL-6, and TNF-, and decreasing oxidative stress, all of which are considered risk factors for developing many chronic diseases, such as type 2 diabetes and cardiovascular diseases (169). Evidence has shown that IER decreases oxidative stress, which is a primary risk factor for the development of metabolic disorders and many chronic diseases (169). Some studies that used animal models have observed that modified intermittent fasting induces an increase in the expression of the progenitor marker Ngn3, which is linked to an increase in the mass of the pancreas by enhancing the regeneration of pancreatic beta and alpha cells (170,171). Mechanisms by which IER deliver benefits to heath may include autophagy and the metabolic switch process. The damaged parts are destroyed and broken down into proteins that the cell itself devours. The cell then rebuilds new parts to replace the damaged ones (172). Some studies have suggested that rising ketone bodies as a result of autophagy and the metabolic switch process cause enhanced satiety and reduced food intake (173,174), which induce body weight loss. In the autophagy process, some damaged parts of the cell are replaced with new parts (175). However, excessively prolonged fasting in long term could cause excessive autophagy, which might lead to a negative impact on health. Thus, the exchange between the fasting period and the food consumption period during intermittent fasting allows for a balance between the process of autophagy and cell regeneration (176). Thus, the IER's protocol is critical to consider, since the occurrence of the metabolic switch or autophagy depends on the duration of fasting and the level of energy restriction. There are different protocols ranging from one to consecutive two of restrictive energy intake, and three to non-consecutive days of restrictive energy intake. However, to our knowledge, there were no human studies have examined the effect of (4:3 IF) on humans Although some animal studies found such a diet effective in improve health indicators (171). Thus, it is not clear the effect of the (4:3 IF) regimen on weight control and health indicators in humans.



Protocols Labeled Intermittent energy restrcition

Type of Intermittent energy restrcition	ADF	IER 6:1	IER 5:2	FMD
Duration of fasting	Every other day (24 hours)	One /week	Twice/week (24 hours)	Once/month (3-5 days)
Considerations	In fasting day consuming ≈500 kcal or 25% of the total calsor required for maintan body weight	On the fasting day consuming 500-600 kcal or restricted 75%of recommended energy needs	In the fasting days consuming 500-600 kcal or restricted 75%of kcal recommended energy needs 5:2 fasting could be consecutive or non-consecutive fasting days	Energy restriction for 3-5 days (dietary energy intake is restricted to 25% of the total energy), followed by no restricted-energy for the rest of the month. (one study FMD involved one week following by no restricted-energy intake for 3 weeks)

Figure 2 Shows different types of intermittent energy restriction.
Fasting-mimicking diet (FMD), alternate-day fasting (ADF), an intermittent energy restriction diet (5:2), and an intermittent energy restriction diet (6:1)
* (161)

Table 2 Studies that included characteristic of acute protein-induce satiety

Citation	**Population**			**Design**	**Blinding**	**Intervention diet**	**Duration, washout-period**	**Meal type**	**Satiety outcomes**
	N	**Sex**	**BMI** (kg/m^2)						
Ortinau 2014 (84)	20	W	22.2 ± 2.3	Randomized Crossover trial	Unclear	(14g protein, 0g fat, 25g carb,) VS. (0g protein, 19g carbohydrate,) vs. (2g protein, 9g fat,19g carb,).	3-h	Semi-solid	14 g protein significantly reduce hunger
Hochstenbach-Waelen 2009 (85)	24	M/W men (n =11) and women (n = 12)	22.2 ± 2.3	Randomized Crossover trial	single-blind	(25% protein, 20% fat, and 55% carbohydrate) **vs**. (10% protein, 35% fat, and 55% carbohydrate)	36-h/ ~4 wk.	Liquid	25% protein significantly increased satiety.
Smeets 2008 **(86)**	30	W/M (19 women and 11 men)	23.8 ± 2.8	Randomized crossover trial	Single-blind	(10% protein, 60% carbohydrate, 30% fat) **vs**. (25% protein, 30% fat, 45% carbohydrate)	3-h	Whole food	25% E protein significantly increased satiety
Barkeling 1990 (90)	20	W		Randomized crossover trial	Unclear	(43% protein, 2% fat, 36% carbohydrate) vs. (10% protein, 2% fat, 69% carbohydrate)	4-h	Liquid	43% protein significantly increased satiety

Table 2 Studies that included characteristic of acute protein-induce satiety

Citation	Population			Design	Blinding	Intervention diet	Duration, washout-period	Meal type	Satiety outcomes
	N	Sex	BMI (kg/m²)						
Westerterp-Plantenga 1999 (87)	8	W	23 ± 3 8	Randomized Crossover trial	Unclear	(29% protein, 10% fat 61% carbohydrate) **vs**. (9% protein, 61% fat, 30% carbohydrate)	24-h	Liquid	29% E protein significantly increased satiety
Erdmann, 2006 **(88)**	30	M/W (10 men, and 20 women)	Unclear	Randomized Crossover trial	Unclear	(12.4% protein, 7.9% fat, 79.7% carbohydrate) **vs**. (83% protein, 17% fat, 0% carbohydrate).	5-h	Whole food	No significant different
Stubbs 1999 (89)	16	M	mean of BMI = 23.5	Randomized Crossover trial	Unclear	(60% protein, 20% fat 20% carbohydrate) **vs.** (20% protein, 20% fat, 60% carbohydrate)	24-h		60% E protein significantly increased satiety
Vandewater 1996 **(91)**	40	W/M (27 women, and 13 men)	Unclear	Crossover trial	Unclear	(43% protein, 6% fat 51%, carbohydrate**) vs.** (20 % protein, 6% fat**,** 74% carbohydrate)	2-m	Liquid	43% E protein significantly increased satiety

Table 2 Studies that included characteristic of acute protein-induce satiety

Citation	Population			Design	Blinding	Intervention diet	Duration, washout-period	Meal type	Satiety outcomes
	N	Sex	BMI (kg/m^2)						
Porrini 1997 **(92)**	14	M	22.4 ± 1.9	Crossover trial	Unclear	(54% protein,10% fat, 19% carbohydrate) **vs.** 15 % protein,79% fat**,** 6 % carbohydrate)	2-h	Whole food	54% E significantly lower energy intake

W: women; M: men; E: energy; VS: verses.

Table 3 Included studies characteristic of high protein diet-induce satiety

Citation	**Population**			**Design**	**Blinding**	**Intervention diet**	**Duration, washout-period**	**Satiety outcomes**
	N	**Sex**	**BMI** (kg/m²)					
Layman 2003 (103)	24	W	30.3 ± 1.0	Parallel design	No	(30% protein, 32.5% fat, 41% carbohydrate) **vs.** (16% protein, 26% fat, 58% carb)	10 -wks.	30% E protein, significantly increased satiety
Long 2000 (100)	14	W/M (7 men and 7 women)	22.4 ± 3	Crossover trial	Unclear	(35% protein, 32.5% fat 32.5% carbohydrate) **vs.** (75 g of protein /BW or 1.96 g protein /BW).	13 days	35% E protein, significantly increased satiety
Lejeune 2006 (94)	12	W	21.1 ± 1.5	Randomized Crossover trial	single-blind	(30% protein, 40%,30% fa carbohydrate) **vs.** (10% protein, 60% carbohydrate, and 30% fat)	3 days/ 4wk.	30% E protein, significantly increased satiety
Weigle 2005 (173)	19	W/M (3 men, and 16 women)	26.2 ± 2.1	Crossover trial	Unclear	(15% protein, 35% fat, and 50% carbohydrate) for 2wk **vs.** (30% protein, 20% fat, and 50% carbohydrate) for 2wk followed by ad libitum diet (30% protein, 20% fat, and 50% carbohydrate) for 12 wk	16 weeks	30% E protein, significantly increased satiety

Table 3 Included studies characteristic of high protein diet-induce satiety

Citation	Population			Design	Blinding	Intervention diet	Duration, washout-period	Satiety outcomes
	N	Sex	BMI (kg/m^2)					
Moran 2005 (174)	57	W/M	34.0 ± 3.5	Randomized, Parallel design	ER	(34% protein, 29% fat, 37% carbohydrate) **vs.** (18% protein, 45% fat, 37 carbohydrate)	12-wk ER, 4-wk non-ER	30% E protein, significantly increased satiety
Skov 1999 (98)	65	W/M (15 men and 50 women)	30.8± 0.4	Randomized trial	ER	(25% protein, 30% fat, 45% carbohydrate) **vs.** (12% protein, 30% fa, 58% carbohydrate)	6 months	Energy intake lower in HP diet
Gibson 2019 (175)	48	W/M 19 men, and 29 women)	24.9 ± 2.7	Randomized Crossover trial	Double-blind	(33.6 g of protein and 42.4 g of carbohydrate) **vs.** (18.6 g of protein and 23.4 g of carbohydrate)	5 d/ 2 wks.	No significant different

ER: energy restriction, M: men; E: energy; VS: verses; E: energy.

1.10. Research problem

Evidence has demonstrated that IER is a beneficial strategy for weight loss, which is considered an important treatment for decreasing risk factors for many chronic diseases related to obesity (164,165). When comparing intermittent energy restriction regimens to daily energy restriction in recent meta-analysis found very little difference in weight reduction (mean weight difference of 0.26 kg, 95% CI: -0.31 to 0.84; p=0.37). This indicated to benefits of the IER alternate weight loss approach, and it is more flexible and easier to adopt than daily energy restriction(166). Weight loss for the majority of adults has many health benefits, including improvements in blood pressure, lipids profile, decrease in visceral fat and improvement in the markers of insulin sensitivity and the control of glucose levels (165). Evidence has shown that the IER approach can potentially improve compliance more than continuous energy restriction, as IER is more adaptable than daily energy restriction (167). Thus, it may be helpful to practice intermittent energy restriction as a sustainable strategy to maintain the positive effects of weight loss. Additionally, it was found that IER and continuous calorie restriction diets achieved comparable positive results in reducing biomarkers, such as insulin-like growth factor 1, IL-6, and TNF-, and decreasing oxidative stress, all of which are considered risk factors for developing many chronic diseases, such as type 2 diabetes and cardiovascular diseases (168). Evidence has shown that IER decreases oxidative stress, which is a primary risk factor for the development of metabolic disorders and many chronic diseases (168). Mechanisms by which IER deliver benefits to heath may include autophagy and the metabolic switch process. In the autophagy process, some damaged parts of the cell are replaced with new parts (169). The damaged parts are destroyed and broken down into proteins that the cell itself devours. The cell then rebuilds new parts to replace the damaged ones (169). Evidence have suggested that rising ketone bodies as a result of autophagy and the metabolic switch process cause enhanced satiety and reduced food intake (170), which induce body weight loss. However, excessively prolonged fasting in long term could cause excessive autophagy might lead negative impact on health. Thus, the exchange between the fasting period and the food consumption period during intermittent fasting allows for a balance between the process of autophagy and cell regeneration (171). Thus, the IER's protocol is critical to consider, since the occurrence of the metabolic switch or autophagy depends on the duration of fasting and the level of energy restriction. There are different protocols ranging from one to consecutive two of restrictive energy intake, and three to non-consecutive days of restrictive energy intake. However, to our knowledge, there were no human studies have examined the effect of (4:3 IF) on humans Although some animal studies found such a diet effective in improve health indicators (172). Thus, it is not clear the effect of the (4:3 IF) regimen on weight control and health indicators in humans.

1.11. Objectives

• The main objective of this project was to determine whether a high protein diet, while following an IER diet, will improve satiety more than a low-protein diet combined with IER.

• The secondary objective of this study was to compare the impact of a high-protein diet with that of a low-protein diet while following an IER diet, on the following health indicators: body weight, waist circumference, inflammation, glycemic control, and plasma lipids.

1.12. Hypotheses

• We hypothesized that consuming a high protein content regime while adhering to an intermittent energy restriction diet would improve satiety more than consuming a low protein content regime while on an intermittent energy restricted diet in overweight and obese women.

• Overweight and obese and women who follow an IER diet combined with enhanced protein intake would lose more body weight than those on a low-protein IER diet.

• High-protein intake combined with an IER diet would improve inflammation, glycemic control and lipid profiles of overweight and obese women.

1.13. Study scope and framework

This PhD dissertation was designed to provide a greater understanding of the effect of dietary protein on body weight status and health indicators (lipids profile, CRP, and A1c), emphasizing the effects of dietary protein on satiety in overweight and obese women. The first section of this introductory chapter highlighted the obesity problem and related obesity health risks. It then provided a brief definition of the related terms and an overview of the literature review topics relevant to the research. The effect of protein content on body weight and satiety and the mechanism of the effect of high dietary protein on satiety were discussed. Chapter Two consists of a systematic review comparing the satiety achieved through different dietary protein sources in different concentrations and textures in randomized trials. Chapter Three consists of a published paper that served as a pilot feasibility study to investigate the effects of dietary protein on satiety, CRP, body weight, and circumference in overweight and obese women who were adhering for a specific intermittent fasting diet. This pilot study's methodology and findings formed the basis for the research design on my subsequent larger study, which is presented in Chapter Four. Chapter Four investigated the effects of high protein versus low protein while adhering to an intermittent fasting diet on body weight, waist circumference, and health indicators (lipids profile, CRP, and HgAlc) using telehealth methodologies. Chapter Five describes the advantages and disadvantages of using telehealth for our study during the Covid-19 pandemic. Finally, Chapter Six consists of a discussion that synthesizes and analyzes the main aspects of the dissertation to provide a general overview, evaluation, and explanation of the current research, followed by recommendations for future research.

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CHAPTER2: COMPARISON OF PLANT- VERSUS ANIMAL-BASED PROTEINS ON SATIETY: A SYSTEMATIC REVIEW

2.1. Abstract

Introduction: Recent studies have investigated the effects of macronutrients on satiety, and most have indicated that protein, regardless of source, increases satiety and suppresses energy intake more than other macronutrients. However, the best sources of protein for achieving such goals remains unclear. This synthesis compares the effectiveness of plant-based protein versus animal-based protein on satiation.

Methods: A systematic literature search was conducted in PubMed, CINAHL, Academic Search Premier, CAB Abstracts, FSTA (Food Science and Technology Abstracts) and Embase for studies for published from inception 1998 to January 2019. Randomized controlled trials that compared the effects of plant- versus animal-based protein sources on satiation in humans were included. Risk of bias of included studies was assessed using the Cochrane risk-of-bias tool for randomized trials (RoB 2).

Results: The search identified 1,200 unique studies. Following review of studies (titles, abstract and, when relevant, full texts) 23 remained. In total 865 participants were included. Most of the included studies observed that plant protein is as efficient as animal protein in enhancing satiety. Most studies were assessed to be of moderate quality.

Conclusion: Although current data suggests that plant-based protein may be advantageous for satiety, further long-term studies are required to investigate the effects of various plant-based proteins on subjective satiety.

Keywords: protein sources, satiety, dietary proteins, satiation

2.2. Introduction

The worldwide rise in obesity has mainly been attributed to increasing energy intake among individuals (1). Typically, the recommended strategies for obese individuals include fasting and severe energy restriction, which are associated with increased hunger, consequently increasing the difficulty of adherence to these diets (2). Thus, it is crucial to comprehend the mechanism of appetite hormones and the factors that influence their function, particularly nutrient composition and consuming behaviour. Understanding these factors can aid in the development of dietary plans that promote satiety and reduce the likelihood of excess overeating.

The hunger and satiety control centre is located in the hypothalamus, which is affected by hormones that regulate food intake. The hormones Glucagon-like Peptide-1 (GLP-1) and Peptide YY (PYY) influence feeding behaviour by regulating appetite and the feeling of fullness (3). GLP-1 is an incretin hormone that enhances satiety by regulating blood glucose levels by increasing the amount of insulin released from beta cells after eating. It limits the secretion of the hormone glucagon, which raises the liver's glucose production and slows the stomach's emptying (4). One study found that mice suffering from GLP-1 deficiency consumed more fat, whereas mice injected with GLP-1 consumed less (5). Treatment with GLP-1 receptor agonists is currently employed for obesity remediation, especially in people with type II diabetes(6). PYY is also considered a satiety signal due to its inverse relationship with the caloric load. PYY concentration begins to rise after less than 20 minutes of eating and leads to a feeling of satiation once it reaches its peak (7).

Several studies have investigated the association between macronutrients and satiety, and most indicate that protein increases satiety and suppresses energy intake more than other macronutrients (8, 9). It has been shown that protein contributes to an increase in the release of gastrointestinal appetite hormones, such as PYY (10). Additionally, previous studies suggested that high protein intake may contribute to reduced ghrelin hormone; ghrelin typically increases hunger in response to a restrictive energy diet (11). A high-protein diet is recommended for controlling appetite (12), but the evidence regarding the contribution of animal-based protein versus plant protein to satiety is limited and inconsistent. Animal protein sources are usually considered to be of higher protein quality than plant protein sources because they contain all essential amino acids and have a higher protein digestibility corrected amino acid score than plant protein (13). However, animal foods tend to be higher in saturated fat, which has been associated with a high risk of cardiovascular disease (14). In addition, although most plant protein sources do not contain all the essential amino acids, or all of them in sufficient quantities, combining protein from different plant-based sources can result in consumption of all essential amino acids and in sufficient amounts. Therefore, a diet that excludes animal-based protein can provide enough total protein for healthy adults. Evidence has indicated that a plant-based diet is a healthy alternative to an animal protein diet (15). Additionally, plant sources contain a high amount of fibre, making them a possible alternative to animal-sourced protein in satiety regulation (16,17).

Despite the recognition of the role of protein in enhancing satiety, a need exists to investigate how effective plant-based proteins are compared to animal-based proteins for controlling energy intake. One reason is that the number of individuals who have adopted a plant-based diet or have increased the amount of plant-based food in their diet has risen (18) an increase that has occurred for multiple reasons. It may mostly have been driven by a desire to protect the environment and a concern for animal welfare (19). Religious or philosophical reasons may also have fostered the adoption of plant-based diets (20). Additionally, the reported health benefits of a vegan diet may be why individuals desiring a healthy lifestyle have adopted a plant-based diet (19). Therefore, this paper aims to explore whether the effects of plant and animal protein on satiety are different with considering the protein concentration and form.

2.3. Methods

2.3.1. Search Strategy

A systematic literature review was conducted to determine which protein sources are likely to result in the highest levels of satiety. This review was conducted in five databases: PubMed, CINAHL, Academic Search Premier, CAB Abstracts, and FSTA (Food Science and Technology Abstracts) and Embase. Additionally, a search was performed of reference lists of the original relevant papers to access further studies that might be eligible for the review. The review included primary research studies published in peer-reviewed journals. The search strategy was limited to studies in the English language. In PubMed the following search terms were employed : ‘satiety” OR “satiation” or “fullness” OR “satiety response” AND “clinical trial” AND “humans (MeSH)” AND “dietary proteins” OR “protein source”.

2.3.2. Selection and Exclusion Criteria

Once the initial search was completed, all articles were evaluated for quality and relevance to the research questions. Studies were eligible for inclusion if they: (1) included adults, (2) compared at least one type of animal and plant-based protein intervention on satiation or satiety, (3) used randomized controlled trials or randomized crossover studies, (4) included a treatment and follow-up duration that was at least 3 hours, and (5) reported the protein source, plus macronutrient composition (6). Visual Analogue Scales (VAS) were utilized to measure appetite sensations, and food and energy intake had to be measured via a validated approach. Studies were excluded if subjects took any medication that may have affected their metabolic state, satiety, or mood.

2.3.3. Data Extraction

Data extraction was performed using Covidence, which is a web-based software certified by Cochrane to streamline and facilitate the review procedure (21). All studies selected for inclusion were designed to compare at least one type of plant-based and animal-based protein. Extracted from each study were population characteristics, comorbidities, study design, blinding, types of protein diets, macronutrient intake distribution, duration, and washout period (Table 1). To clarify any unclear or missing information in the included studies, we contacted the authors.

Included studies were assessed for risk of bias using the Cochrane Risk of Bias tool for randomized trials (22). This review was conducted in accordance with the PRISMA guidelines (23).

2.3.4. Risk of bias assessment

The "Risk of Bias” assessment tool developed by the Cochrane Collaboration for RCTs was utilized to assess all included studies independently. This tool assesses the risk of bias in the following components of the studies: the randomization process, bias arising from period and carryover effects, bias due to deviations from intended intervention, bias due to missing outcome data, bias in the measurement of the outcome, and bias in the selection of the reported result.

2.4. Results

2.4.1. Studies Included

The preliminary database search identified 1348 studies that were potentially relevant to the topic; 148 of the 1348 studies were excluded due to duplication. After screening the title and abstract of the remaining 1200 studies, 1063 studies were excluded due to not being relevant to the topic. A full-text screening was performed on the 137 studies and eighty-four studies were excluded because they did not involve a plant-based versus animal-based protein comparison (Table1). Fourteen studies were excluded due to non-human trials, twelve studies were excluded due to the inclusion of children, and four studies were excluded due to the trials not being randomized. Consequently, in total twenty-five studies were included in this systematic review. A flow chart of the selection process and reasons for exclusion are shown in Figure 3.

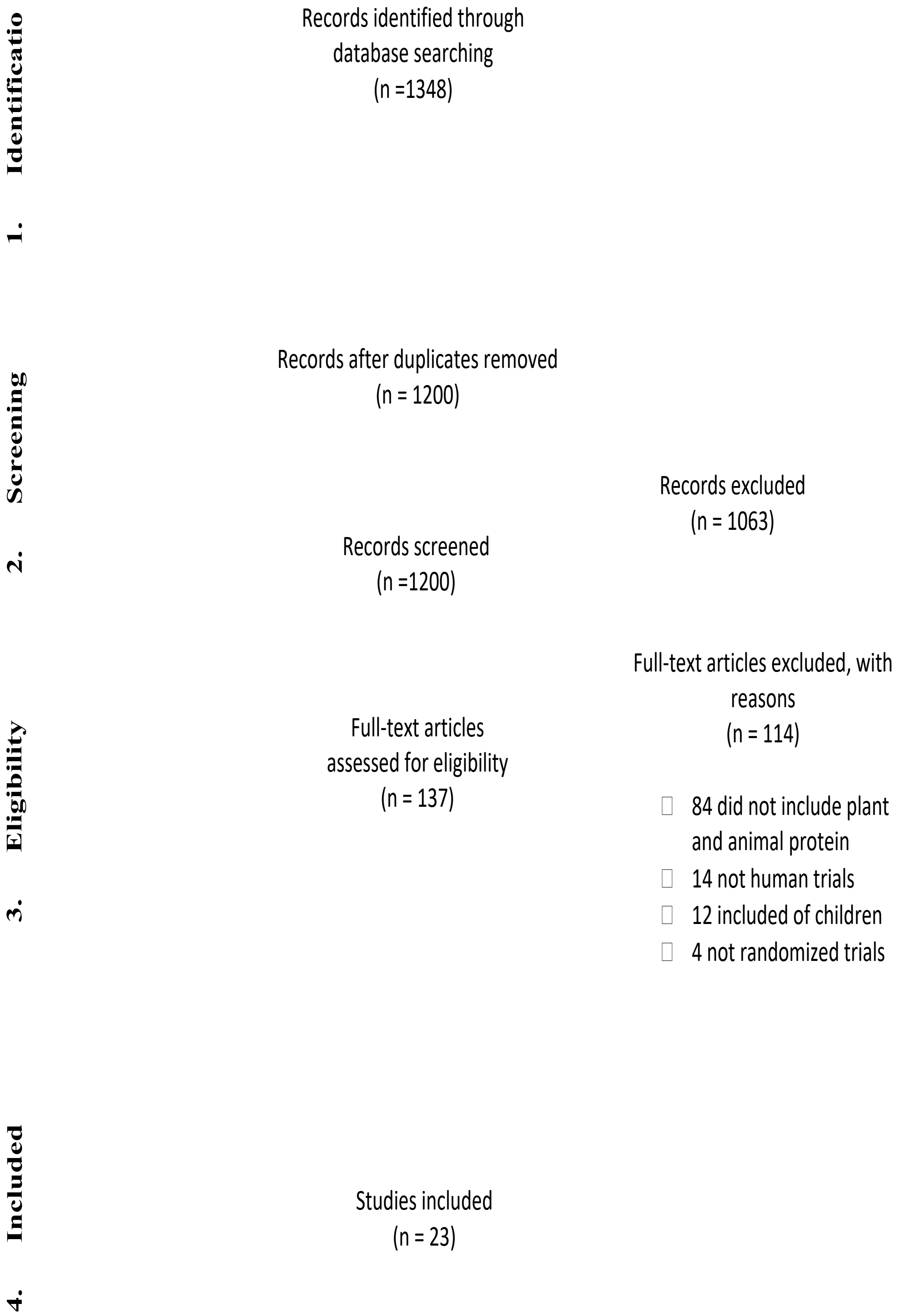

1. Identificatio
Records identified through database searching (n =1348)
2. Screening
Records after duplicates removed (n = 1200)
Records excluded (n = 1063)
Records screened (n =1200)
3. Eligibility
Full-text articles excluded, with reasons (n = 114)
Full-text articles assessed for eligibility (n = 137)
84 did not include plant and animal protein
14 not human trials
12 included of children
4 not randomized trials
4. Included
Studies included (n = 23)

Figure 3 The flow chart of the study selection

Table 4 Characteristics of included studies

Citation	Population	Design	Blinding	Intervention diet	Meal type	Duration, washout period
Abou-Samra et al, 2011 (24)	32 men, age 25 ± 4 y, BMI 24 ± 0.4 kg/m^2	Randomized crossover	Single-blind	**Pea protein meal:** 20 g protein, 0 g fat, <1 g carbohydrate; **casein meal:** 20 g protein, .3 g fat, .1 g; **whey meal:** 20 g protein, 0 g fat, <1 g carbohydrate; **egg albumin meal: 20**(g) protein, 0 g fat, 1.1 g carbohydrate	Liquid	9 hours,
Acheson et al, 2011 (25)	23 lean women and men; age 32 ± 6.3 y; BMI 22.7 ± 1.7 kg/m^2	Placebo-controlled, crossover randomized	Double-blind	**Casein meal:** 50% protein, 10% fat, and 40% carb; **Soy meal**: 50% protein, 10% fat, and 40% carb. Whey diet; **Carbohydrate diet** 1.2% protein, 3.3 % fat, and 95.5% carb.	Liquid	5.5 hours, ≥1–4 week
Alfenas et al, 2010 (26)	26 healthy adults 13 men and 13 women), aged 23.5 ± 3.95 y; BMI: 20.5 ± 1.46 kg/m^2	Randomized,	Unclear	**Whey protein**: Carbohydrate (g) 30.3 ± 6.9 fat (g) 5.8 ± 2.8, protein (g) 24.2 ± 3.9; **soy diet**: Carbohydrate (g) 30.5 ± 9.1 fat (g) 6.1 ± 2.5, protein (g) 24.3 ± 4.5	Liquid	7 days, ≥7 days

Table 5 Characteristics of included studies

Citation	Population	Design	Blinding	Intervention diet	Meal type	Duration, washout period
Baer et al, 2011 (27)	73 34 men and 39 women; age control group 51±9 y, whey group 45±9 y, soy group 53 ±9 y; BMI control group 31.1 ± 2.5 3 kg/m^2, whey group 31.0 ± 2.2 kg/m^2, soy group 30.9 ± 2.3 kg/m^2	Randomized crossover	Double-blind	**Control** diet14 ±1% protein, 58 ± 2%carbohydratet, 28 ± 2% fat**; whey diet** 24 ± 2% protein, 49 ± 2% carbohydrate, 27 ± 2% fat**; soy diet** 24 ± 2% protein, 48 ±1% carbohydrate, 28 ± 1% fat.	Liquid	23 weeks, non
Barnard et al, 2009 (28)	99 adults with type II diabetes, age (**vegan group** n=49, age 56.7, 35-82 y; BMI (33.9 ± 7.8), **control group** n=50 age (54.6 y, 27–80 y), (BMI: 35.9 ± 7.0 kg/m^2)	Randomized, parallel design, controlled.	Unclear	**Plant based diet**: 10% from, 15% protein, 75% carbohydrate; **animal-based diet**: 15–20% protein, <7% of energy from saturated fat, Carbohydrate and monounsaturated fats 60–70%	Solid	74 week, no
Bayham et al, 2014 (29)	20 healthy; 15 women, 5 men; age 40.7 ± 14.1 y; BMI 37.5 ± 4.1 kg/m^2	Randomized crossover	No	**Egg meal: 19**.8% protein, 35.6% fat, and 42.9% carbohydrate **Soy meal** 19.8% protein, 35.4% fat, 44.8% Carbohydrate	Solid	1 week, 1-2 week
Bowen et al, 2006 (30)	72 subjects; 25 lean men, age: 50.5± 2.4y) BMI (23.3± 0.2) kg/m^2 overweight n=47 age (56.8 ±1.1 y), BMI (30.1± 0.5) kg/m^2	Randomized, crossover	Unclear	**Soy diet and Whey diet:** 71% protein, 18% carb and 11 % fat	Liquid	3 hours, 7days

Table 5 Characteristics of included studies

Citation	Population	Design	Blinding	Intervention diet	Meal type	Duration, washout period
Dougkas et al, 2017 (31)	28 men age: (27.4 ± 4.2 y), BMI: 23.4 ±2.1kg/m^2	Randomized, crossover	single-blind,	**Animal meal:** 25% protein, 66% carbohydrates and 9% fat; **plant meal:** 25% protein, 66% carbohydrates and 9% fat	Solid	8 hours, ≥1 week
Douglas et al, 2005 (32)	21 adults (aged 23 ± 1 y), BMI: 23.8 ± 0.6 kg/m^2	Randomized, crossover	Double-blind	**Soy and beef diet**: 33% protein, 43% carbohydrates, and 24% fat	Solid	7 hours, 2–7 days
Jakubowicz et al, 2017 (33)	56 Type 2 diabetes participants, 26 men and 30 women aged 58.9±4.5 y, BMI 32.1±0.9 kg/m^2	Randomized parallel design	Blinding	**Whey protein diet:** 25% protein, 50% carbohydrates, and 25% fat; **whey with egg diet:**25% protein, 50% carbohydrates, and 25% fat; **soy diet**: 11% protein, and 25% fat and 64% carbohydrates	Solid	12 weeks
Jenkins et al, 2010 (34)	23 healthy 16 men and 7 women aged 56 ± 2 y, BMI 26 ± 1 kg/m^2	Randomized crossover	Blinding	Barley protein 33% protein, 61 % carbohydrate, 7% fat; casein diet: 34 %protein, 58% carbohydrate, 8 % fat	Solid	4 weeks, 2 weeks

Table 5 Characteristics of included studies

Citation	**Population**	**Design**	**Blinding**	**Intervention diet**	**Meal type**	**Duration, washout period**
Kehle et al, 2017 (35)	40 healthy men age: 23.3 ± 2.9 y, BMI: 22.2 ± 1.9 kg/m^2	Randomized, crossover	No	**Animal protein meal:** 18.3% protein, 50.3% carbohydrate and 31.4 % fat; **plant protein meal:** 17.8% protein, 52.6% carbohydrate and 29.6% fat	Solid	4 hours, ≥1 week
Klementova et al, 2019 (36)	(T2D, n = 20), obese men (n = 20), and healthy men (n = 20), aged 30-65 y, BMI: 25–45 kg/m^2	Randomized, crossover	Unclear	**Pork meal:** 16.7% protein, 44% carbohydrate, 38.6 % fat; tofu **meal:** 16.7% protein, 44% carbohydrate, 38.6 % fat	Solid	3 hours, unclear
Kristensen et al, 2016 (37)	43 healthy men, age: 24.49±4.8y; BMI: 23.09±2.1 kg/m^2	Randomized crossover, placebo-controlled	Double-blind	**Meat meal & Legume meal**; 19 % protein, 53% carbohydrate, 28 % fat; **Meat meal & Legume meal;** 9 % protein, 62 % carbohydrate, 29% fat	Solid	3 hours, ≥2 week
Lang et al, 1998 (38)	12 healthy men; age 22.6 ± 0.6 y, BMI 21.9 ± 0.5 kg/m^2	Randomized crossover	Single-blind	≈ 14.5% protein, 45.8 % carbohydrate and fat 39.6 %	Solid	24 hours,≥1 week
Li et al, 2016 (39)	34 11men and 23 women age (51 ±2, 56 ±4 y), BMI 87.0 ± 2.9, 88.1 ± 2.9) kg/m^2	Randomized crossover	Unclear	**Soy and whey**: 10% protein, 65% carbohydrate and 25 % fat **or** 20% protein, 55 % carbohydrate and 25 % fat, or 30% protein, 45% carb and 25 %fat	Solid	4 weeks, no

Table 5 Characteristics of included studies

Citation	Population	Design	Blinding	Intervention diet	Meal type	Duration, washout period
Melson et al, 2019 (40)	17 healthy, 11 women and 6 men; aged 27 ± 7 y, BMI 24.6 ± 0.9 kg/m^2	Randomized, crossover	Double-blind	**Whey meal** 40.8% protein, 52.2% Carbohydrate, and 6.8% fat**; Soy meal** 46.6% protein, 46.6% Carbohydrate, and 6.7 %fat	Liquid	3 hours, ≥ 72 hour
Morenga et al, 2011 (41)	70 women aged 18-65 y, BMI ≥ 27 kg/m^2	Randomized parallel design	Single bling	**Animal and plant protein diet**: 30 % protein, 40% carbohydrate vs. 50%, 20% protein	Solid	8 weeks, NA
Neacsu et al, 2014 (42)	20 men aged 51.6 ±11.4 y, BMI 34.8 ± 6 3.8 kg/m^2	Randomized crossover	Unclear	**Meat or Soy meal**: 30 % protein, 40 % carbohydrate and 30 % fat	Solid	2 week, no washout
Nielsen et al, 2018 (43)	35 healthy men, age 26.5 ± 5.5 y, BMI 23.3 ± 1.9 kg/m^2	Randomized crossover	Single-blinded	**Meat, beans, egg meals:** 19 % protein, 53% carbohydrate, and 28% fat	Solid	4.8 hours, 7 d≥ washout period
Tan et al, 2010 (44)	12 9 men and 3 women aged > 18 years BMI	Randomized, crossover	Unclear	**Plant and animal protein diet:** 30% protein, 40% carbohydrate, 30% fat	Solid	8 hours, 3 days for male and one month for female
Veldhorst et al, 2009 (45)	24 healthy 10 men and 14 women age: 25 ±2 y, BMI: 24.8 ±0.5 kg/m^2	Randomized, crossover	Single-blind design	**Casein, soy and whey meal:** 10%protein, 55% carbohydrate, 35% fat **or** 25%protein, 55% carbohydrate, 20% fat	Semi-solid (custard)	6 hours, 3 days

Table 5 Characteristics of included studies

Veldhorst et al, 2009 (46)	25 11 men and 14 women age:22 ± 1 y, BMI:23.9 ± 0.3 kg/m^2	Randomize, crossover	Single bling	**Casein-, soy-, or whey-protein die:**10% protein, 55% carbohydrate and 35% fat **or** 25% protein, 55%	Sami-solid	4 hours, one week

2.4.2. Characteristics of Trials

This review included twenty-three studies (See Table 4). All included studies were randomized trials that were performed using either a crossover (24–27,29–32,34–40,42–46) or parallel design(28,33,41). All studies compared one, two, or three types of plant-based protein versus animal-based protein (24–46). Considering that the included studies used varied energy proportions from proteins for their test meals, studies were classified by range (level) of concentration. Protein levels were classified as high at 20% or more and normal at 9% to 19%. Fourteen of the 23 studies adopted a high level of protein with 20% or more energy from protein (25,28,30–34,39–42,44–46). Ten studies adopted an average of 9%–19% of energy from protein (28,29,33,35–37,39,43,45,46). Fifteen studies used whole food (solid food) as the source of protein content (28,29,31–39,41–44) while eight studies used protein supplementations (24–27,30,40,45,46). The duration of the intervention varied from three hours to 74 weeks. While the washout period ranged between one day to one month, some studies did not have washout period (27,28,39,42), and one did not report whether there was a separation time between interventions (36,41).

2.4.3. Blinding

Five of the included studies were truly blinded (25,27,32,37,40) as participants were not aware of which type of protein they consumed due to the addition of some flavours that inhibited the differentiation between protein types. At the same time, the investigators were not aware of the test meal content during the experiment. Seven studies were single-blinded (24,31,38,41,43,45,46) with the investigators aware of the test meal content, but the subjects not aware of it. The remainder of the studies were either not blinded (29,35), or did not report whether they adopted a blinding design (26,28,30,39,42,44) (See Table 4).

2.4.4. Participants

The total number of participants included in his systematic review is 885. In the majority of included studies, the number of participants ranged from n = 9 to n = 99. Ages ranged from 18 to 65 years. Eight studies involved only men (24,30,31,35,37,38,42,43), while fourteen studies involved both men and women (25–29,32–34,36,39,40,44–46). One study included only women (41). Three studies included diabetic individuals (28,33,36), while the rest included healthy subjects. Weight status varied among the included studies and involved normal, overweight, or obese adults with BMIs between 20 to 35 kg/m^2.

2.4.5. Satiety measurements

All of the 23 included studies use visual analogue scales (VASs) to estimate various dimensions of satiety, hunger, and level of fullness ratings over different time points, starting at 30 minutes following the completion of the test meal consumption (24–46). For periods ranging from 1 to 4 hours after the test meal, a standard lunch was provided to the participants with instructions to consume as much as they needed to feel full. Eight studies included both blood sample collection to interpret changes in appetite sensations and postprandial responses of GLP-1 and PYY (2,6,11,14,16,17,19,21), which represents the measurements tools for satiety (47). See Table 5.

2.4.6. The effect of protein sources on satiety

Fourteen of the 23 studies adopted a high level of protein with 20% or more energy from protein (25,28,30–34,39–42,44–46). Twelve studies out of fourteen studies found that there was no significant difference between plant-based and animal-based proteins in the effect on satiety (28,30–32,34,39–42,44–46). However, two studies found that protein sources provided different effects on satiety (25,33). One of these studies found that plant-based protein provided more satiety than animal protein (25) while another study reported that animal-based protein provided higher satiety than plant-based protein (33). Ten studies adopted an average of 9%–19% of energy from protein (28,29,33,35–37,39,43,45,46). Seven studies out of these ten found that plant-based and animal-based protein provide comparable effect on satiety (28, 35,39,43,45,46). However, two studies found that plant-based protein provide higher satiety than animal-based protein (33,36,37); while one study reported that animal-based protein provided higher satiety than plant-based protein (33).

Fifteen studies used whole food (solid food) as the source of protein content (28,29,31–39,41–44). Three studies of fifteen studies found that plant-based protein induced satiety more than animal-based protein (29,36,37) and one study found that animal-based protein induced more satiety than plant-based protein (33). While eleven studies found that animal-based and plant-based protein induced similar satiety effect (28,31,32,34,35,38,39,41–44). Eight studies used protein supplementations (24–27,30,40,45,46). Six studies out of eight reported that there was no differences between plant-based and animal-based (25,26).

Table 5 Reported associations between protein sources and satiety

Citation	Satiety rating	Endocrine measure	Major finding
Melson et al (40)	11-point scale	NA	➔
Bayham et al (29)	VAS	PYY3-36	↑plant increase satiety more than animal plant protein on day1, day 7 ➔
Bowen et al (30)	VAS	CCK and ghrelin	➔
Acheson et al (25)	VAS	NA	Soy and casein ↑satiety more than whey die but with carb diet
Lang et al (38)	VAS	NA	➔
Abou-Samra et al (24)	VAS	NA	➔
Neacsu et al (42)	VAS	GLP-1, ghrelin, and PYY	➔
Nielsen et al (43)	VAS	NA	➔
Kristensen et al (37)	VAS	NA	Plant protein ↑satiety than animal protein
Veldhorst et al (45)	VAS	NA	➔
Jenkins et al (34).	2 bipolar semantic scales	NA	➔
Jakubowicz et al (33)	VAS	C-peptide and iGLP-1	↑Whey protein diet increased satiety than mixed and plant protein diets
Li et al (39)	100-mm	NA	➔

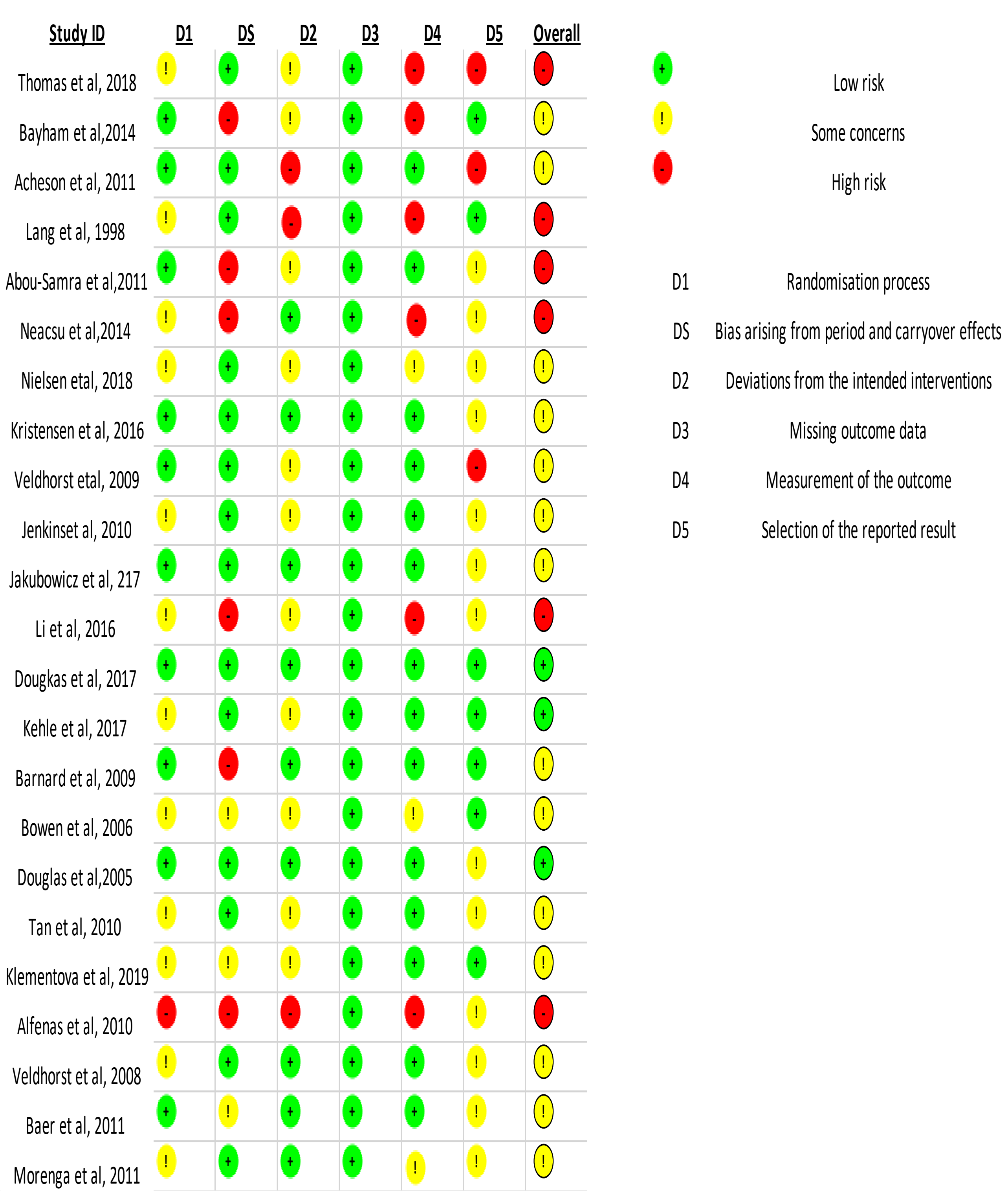
	quasilogarithmic VAS		
Morenga et al (41)	VAS	NA	→
Dougkas et al (31)	VAS	NA	→
Kehle et al (35)	VAS	GLP-1, PYY	→
Barnard et al (28)	VAS	NA	→
Bowen et al (30)	VAS	GLP-1	→
Douglas et al(32)	VAS	GLP-1 and PYY	→
Tan et al (44)	VAS	NA	→
Klementova et al (36)	VAS	GLP-1, amylin	↑ plant meal more than animal protein
Alfenas et al (26)	9-point bipolar category scale	NA	Soy diet less fullness and satiety but that did not change in energy intake
Veldhorst et al (46)	00 mm Visual Analogue Scales	GLP-1	→
Baer et al (27)	VAS	NA	→

↑indicates increase satiety more

→indicates no difference between plant and animal protein

2.4.7. The risk of bias assesment

Ten (43%) of included RCTs were identified on processes of randomization and allocation concealment that were determined to be at high risk of bias. The majority of studies (53%) were found to have a medium risk of bias in the selection of the reported result, while only 4% of RCTs were determined to be at low risk of bias (See Figure 4).



Study ID	D1	DS	D2	D3	D4	D5	Overall
Thomas et al, 2018	!	+	!	+	-	-	-
Bayham et al,2014	+	-	!	+	-	+	!
Acheson et al, 2011	+	+	-	+	+	-	!
Lang et al, 1998	!	+	-	+	-	+	-
Abou-Samra et al,2011	+	-	!	+	+	!	-
Neacsu et al,2014	!	-	+	+	-	!	-
Nielsen etal, 2018	!	+	!	+	!	!	!
Kristensen et al, 2016	+	+	+	+	+	!	!
Veldhorst etal, 2009	+	+	!	+	+	-	!
Jenkinset al, 2010	!	+	!	+	+	!	!
Jakubowicz et al, 217	+	+	+	+	+	!	!
Li et al, 2016	!	-	!	+	-	!	-
Dougkas et al, 2017	+	+	+	+	+	+	+
Kehle et al, 2017	!	+	!	+	+	+	+
Barnard et al, 2009	+	-	+	+	+	+	!
Bowen et al, 2006	!	!	!	+	!	+	!
Douglas et al,2005	+	+	+	+	+	!	+
Tan et al, 2010	!	+	!	+	+	!	!
Klementova et al, 2019	!	!	!	+	+	+	!
Alfenas et al, 2010	-	-	-	+	-	!	-
Veldhorst et al, 2008	!	+	+	+	+	!	!
Baer et al, 2011	+	!	+	+	+	!	!
Morenga et al, 2011	!	+	+	+	!	!	!

+	Low risk
!	Some concerns
-	High risk

D1	Randomisation process
DS	Bias arising from period and carryover effects
D2	Deviations from the intended interventions
D3	Missing outcome data
D4	Measurement of the outcome
D5	Selection of the reported result

Figure 4 Quality assessment of individual studies

2.5. Discussion

2.5.1. High protein content

Fourteen of the 23 studies adopted a high level of protein with 20% or more energy from protein (25,28,30–34,39–42,44–46). Studies on the effects of high plant and animal protein consumption on satiety and satiation are limited, and the results are inconsistent. Studies using adults with normal, overweight, or obese body weight observed no difference between the effects of plant and animal protein intake on satiety rating or satiety hormones, including GLP-1 and PYY (25,28,30–32,34,40–42,44–46) (See Table 5). Neacsu et al., for example, examined the effect of meat and soy diets on weight loss among obese males and found that both diets induced comparable effects on GLP-1, PYY, and subjective satiety (42). This study indicated that both diets similarly reduced body weight (42), likely due to a reduction in total energy intake. Similarly, a long-term study that compared bread enriched with barley protein or casein protein consumed for four weeks found that satiety ratings were similar among barley protein bread treatment and casein protein bread treatment (48). Previous results were broadly consistent with evidence that varying the high-protein source has little effect on satiety and food intake responses (49). For example, Bligh et al. concluded that even though adding fish and almonds to Palaeolithic-type meals more than doubled the amount of protein, the increasing satiety was similar regardless of the protein sources and protein content (50). Animal model experiments have shown that different protein sources do not cause a difference in appetite or food intake suppression (23, 24). However, Bayham et al. established that the effect of a high plant-protein diet (i.e., soy) on satiation surpassed that of an animal-protein source (i.e., egg protein) (29). It is critical to note, though, that the plant- and animal-based protein meals were not matched for fiber content and glycemic load content (29). Jakubowicz et al. conducted a randomized trial on 99 individuals with type 2 diabetes to compare the effects of protein sources on satiety over 12 weeks and reported that a whey-protein diet enhanced satiety more than a mixed source of protein and plant-based protein diets. Nevertheless, it is unclear whether they would have achieved the same results in healthy individuals (33).

This review found that high protein content, regardless of the protein source, contributes to enhancing satiety. High protein intake stimulates appetite in several ways. Some evidence has indicated that increased protein concentration in a diet leads to the increased production of ketone bodies, which play a principal role in satiety repression (53). Additionally, a high-protein diet could help to maintain plasma glucose levels through glucose produced by amino acids, in which decreasing blood glucose levels stimulates hunger (54,55). Ghazzawi and Mustafa have noted that high-protein diets enhance the regulation of glucose levels in the body because they contribute to regulating the enzymes that create glucose (56).

2.5.2. Normal protein content

Ten studies adopted an average of 9%–19% of energy from protein (28,29,33,35–37,39,43,45,46). The experimental data involving normal protein diets (9–19% protein) are consistent. Most of the included studies demonstrated that plant and animal protein diets similarly increase satiety. One randomized controlled study investigated, for instance, the effects of plant protein- and animal-based diets over 74 weeks on fullness and appetite response among type II diabetic individuals (28). A high level of satiety was attained on both diets but no significant difference in satiety was found between the diets (28). A few studies have reported that protein sources affect satiety levels (29,33,36,37). Klementov et al. noted that tofu meals provided greater satiety than pork meals in individuals with type II diabetes (36). Another study observed that subjects had a lower energy intake after consuming pasta with either tofu or mycoprotein than after consuming pasta with chicken (57), although these results are confounded because the tofu-based meal contained more fibre and energy than the chicken-based meal. Additional studies reported that satiety increased more after vegetable-based meals than after animal-based meals (37), perhaps because plant-based foods tend to be higher in fibre content. It is noteworthy that in most studies that found that plant-based protein increases satiety more than animal-based protein, the fibre content was higher in the in plant-based foods. Although the ability for fiber to increase satiety appears to vary with the type and source of the fiber (58), overall, fiber seems to mostly promote satiety and fullness, which could confound interpretations of the effect of protein source on satiety levels (59).

Not all studies have determined that plant protein benefits satiety more than does animal protein. Alfenas et al. reported that soy meals produce less fullness than animal-based meals (26). This finding may have arisen because more than half of the subjects did not complete the soy portion of the experiment, which could have biased the results. Soluble fibre slows passage of food and seems to be the main component. Insoluble fibre speeds passage in the gut. More research is needed comparing soluble vs insoluble fibre on satiety.

2.5.3. Supplemental protein and satiety

Most studies involving protein supplementation in a test diet reported no differences in the impact on appetite among soy, casein, and whey (22, 28, 32, 39, 44, 46). Nevertheless, Alfenas et al., who compared the effect of casein, whey, and soy protein on appetite, observed that during the casein session, the energy intake decreased and greater satiety was reported than during the whey and soy sessions (26). A short-term randomized crossover study showed that there was relatively less fullness after eating whey than there was after eating casein and soy **(25)**. These findings are consistent with evidence that whey undergoes more rapid digestion and gastric emptying than casein, thus reducing satiety (60,61). Thus, casein has a more significant effect on enhancing appetite in the long term than in the short term (60,61). The differences in physical properties, concentration differences of the amino acid, peptide size distribution, the degree of hydrolysis of peptides, and the level of purity of isolated compounds in whey, soy casein, and pea proteins could also play essential roles in these differing findings on fullness and hunger (62,63). A review investigating the mechanisms of protein-induced appetite modulation established that protein-induced satiety in protein supplements is influenced by the amino acid type and the level of supplement-induced thermogenesis (62). For instance, Veldhorst et al. compared whey, casein and soy meals that derived 10% of their energy from protein (46).. They reported that whey induced greater hunger suppression than casein and soy which derived 10% of their energy from protein. However, the difference between treatments vanished when the protein concentration was increased to 25% of the energy from protein (46).

2.5.4. Whole Food Meal and Satiety

This review found that animal and plant protein led to similar hunger suppression (27,29,30,33,35,36,38,40,41,46). Similarly, one short-term intervention conducted on healthy individuals to examine the effect of a normal protein level from different sources established that both animal and plant-based diets increased GLP-1 and PYY concentrations. They also noted that both diets similarly enhanced satiety (48). In contrast, two included studies reported that plant protein was more effective than animal protein in generating fullness (29,37). There are many potential reasons, such as confounding factors, for these inconsistent results among studies. For example, variations in the time spent consuming meals (64,65), the size of the meals (65), or the study design could have impacted satiation and satiety. Additionally, these inconsistencies may have occurred because these studies did not control for a confounding factor in appetite: that the plant meals contained more fibre than the animal meals. Dietary fibre can increase satiety and decrease energy intake (66). However, further complicating the effects of fibre, a comprehensive review of 136 studies on the effects of type of fibre on appetite and energy intake reported viscous fibre types to be the most beneficial (67). A separate study concluded that non-viscous soluble fibre also increased satiety (68). Another reason for inconsistent results is that adopting one type of measurement to determine satiety may produce inaccurate results and discrepancies. For instance, Bayham et al. observed increased PYY levels after plant meals but found no reduction in energy intake (29).

2.6. Limitations and implications

To our knowledge, no systematic review or in-depth analysis has compared plant- and animal-based protein diets in varying concentrations and protein forms (e.g., supplementation and whole-food meals). Appetite is considered a complex research topic because of its confounding variables, and it is an intractable problem to control all of them in research using free-living humans. Thus, this systematic review did not include a meta-analysis because of the diverse protocols of the included studies and VAS scoring approaches among the included studies were different. As a result, the results of this systematic review have limitations. Nonetheless, we minimized these limitations by assessing the quality, intervention methods, and standardization of the criteria of each study. Nonetheless, we minimized these limitations by assessing the quality, intervention methods, and standardization of the criteria of each study. The included studies had limited variations in plant- and animal-based protein types, with most research utilizing soy for plant protein. Few studies involved other legumes as the plant-based protein or red meat as the animal-based protein. Moreover, 90% of the included studies were short-term interventions. Longer-term interventions are needed to produce clear results and examine the effects of protein quality on satiety because many dietary interventions are effective in the short term but fail in the long term.

2.7. Conclusion

This systematic review provides evidence that plant protein sources could be an effective alternative to animal protein sources in enhancing satiety. Interestingly, protein sources provide a comparable enhancement of satiety regardless of texture (i.e., whole food compared to a liquid meal) and protein concentration (i.e., high versus normal protein levels). Nevertheless, further research is necessary to determine the effect of plant protein on satiety by controlling for such confounding factors as fibre content and energy density, and how protein source affects satiety in the long term. Doing so will clarify the association between protein sources and satiety.

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CHAPTER 3: INTERMITTENT ENERGY RESTRICTION COMBINED WITH A HIGH-PROTEIN/LOW-PROTEIN DIET: EFFECTS ON BODY WEIGHT, SATIETY, AND INFLAMMATION: A PILOT STUDY

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3.1. Abstract

Intermittent energy restricted (IER) diets have become popular as a body weight management approach. In this pilot study, we investigated if an IER diet would reduce systemic inflammation and if maintaining an elevated protein level while on an IER diet would enhance satiety. Six healthy women, aged 33–55 years with a BMI of 27–33 kg/m^2, were randomized to first adhere to either a low- or high-protein IER diet using whole foods for three weeks. They then returned to their regular diets for a week, after which they adhered to the second diet for three weeks. Each test diet consisted of three low-energy intake days followed by four isocaloric energy intake days. The diets differed only in protein content. High-sensitivity C-reactive protein (hs-CRP), glucose, satiety, body weight, and waist circumference were measured at the beginning and end of each dietary intervention. Most participants showed reductions in hs-CRP levels from baseline on both IER diets but reported greater satiety when adhering to the higher protein IER diet. Overall, the IER diets reduced body weight and appeared to decrease inflammation in these overweight women, and the higher protein version enhanced satiety, which may lead to greater long-term dietary adherence.

Keywords: intermittent energy restriction; obesity; dietary protein; satiety

3.2. Introduction

The worldwide prevalence of obesity is rising. According to the World Health Organization, approximately 1.9 billion individuals aged 18 years and older are overweight or obese (1). By 2025, global obesity rates will reach 18% for the male population and 21% for the female population (2). Evidence shows that obesity commonly generates adipose tissue dysfunction (3,4). The excessive accumulation of fat in adipocytes can result in a decrease in mitochondrial metabolism, and an increase in the release of pro-inflammatory adipokines, such as TNF-α and IL-6 (4). Additionally, this chronic low-grade systemic inflammation can act as an underlying risk factor for developing many chronic diseases, including type II diabetes, cardiovascular disease, hypertension, and cancer (4). Adipose tissue also synthesizes and secretes certain hormones, such as leptin and adiponectin, which play essential roles in appetite regulation (5).

Recent epidemiological studies show that dietary strategies involving intermittent energy restriction (IER) are beneficial therapeutic interventions for the prevention or treatment of inflammatory disease (6,7). IER diets restrict energy intake from one day to a few days a week, followed by intervals of refeeding in the remainder of the week. Various versions of IER diets restrict energy from 75% to as low as 10% of the total energy intake required to maintain body weight. IER diets have been demonstrated to improve metabolic performance and cellular modifications that contribute to reversing oxidative damage and inflammation (8,9). These diets may also be effective at regulating blood glucose levels and enhancing metabolic outcomes (9). In addition, recent evidence indicates that IER diets can serve as an alternative to continued energy restricted (CER) diets for weight loss and to improve health indicators like decreasing pro-inflammatory markers. For example, a recent randomized controlled trial compared an IER strategy to a CER diet in adults aged between 18 and 45 years with a BMI of 22.0–35.0 kg/m2. They reported similar benefits in terms of hunger and health markers such as total cholesterol and low-density lipoprotein cholesterol over the 12 weeks, although some indicators suggested that the IER diet may be more beneficial (10). A systemic review that compared the effect of IER to CER diets on weight loss also reported that both have similar effects on weight loss (11). Giving further credence to the efficacy of an IER diet, a recent systematic review, which included

27 randomized controlled trials on women and men who were overweight or obese, found that IER diets reduced both body weight and fat mass (12).

Many versions of IER diets are purported to be beneficial. Some of these alternate the intervals of energy restriction versus normal energy intake; currently, the optimal protocol for an IER diet is unclear. A study using an animal model has demonstrated that three consecutive days of energy restriction were associated with greater improvements in insulin sensitivity, inflammation, and even the regeneration of failed pancreatic cells (13). Nevertheless, the benefits and feasibility of such diets for human subjects have not been adequately identified and investigated. Interestingly, a recent study demonstrated that an IER diet modified the hypothalamic expression of critical genes that are involved in lipid metabolism, inflammation, and the regulation of the insulin and leptin pathways (14).

Non-adherence is a common issue with human dietary interventions designed for weight loss, especially in diets that depend on restricted energy intake (15). For instance, a systematic review and meta-analysis involving 45 randomized controlled trials that examined the effects of energy restriction interventions in obese individuals reported that nearly 28% of subjects dropped out due to non-adherence to their dietary interventions (16). Accordingly, increasing the ability to adhere to an IER diet is an important factor for its success (15,17). One of the critical elements for adherence may be increased satiety. Thus, including foods that increase the satiety in energy restricted diets, such as foods with higher protein content, may increase adherence (18).

An IER diet that increases the protein content of the diet while restricting the fat and carbohydrate proportions will result in a higher calculated total energy intake than a diet that decreases the intake of all three macronutrients. However, this difference in protein intake is unlikely to profoundly impact total energy availability because protein is used by the body sparsely as a primary source of energy (19), yet it is the macronutrient that provides the greatest satiety (20). Therefore, in the current study, our primary hypothesis was that a higher protein content combined with an IER diet will facilitate adherence to the diet because protein intake enhances satiety. Secondly, we hypothesized that an IER diet will reduce inflammation independent of protein content. Since this is a feasibility study, we examined the feasibility, effectiveness, and acceptability of an IER diet at low- versus high-protein content to improve health indicators such as CRP, body weight, waist circumference, and fasting glucose.

3.3. Materials and Methods

3.3.1. Participants

In the summer of 2018, we posted the study poster in LISTSERVs for recruiting participants in Halifax, Nova Scotia, Canada. We recruited six women between the ages of 33 and 55 years with a body mass index of 27–33 kg/m2. Only women were included in order to increase the homogeneity of the participants in the study considering the small sample size (21). An additional reason for selecting only women was that clinical trials have shown differences between men and women in appetite sensations and appetite responses to macronutrient content changes in diets (22,23). We also narrowed the age range of participants because evidence has demonstrated physiological differences in sensory satiety among age groups (i.e., adolescent, middle age, and elderly) (24,25). We also selected participants who were in a discrete range of overweight or obese measures. For the purpose of this study, overweight and obese criteria were determined by a body mass index (BMI) between 27 and 33 kg/m2. By excluding obese individuals who have a BMI greater than 33 kg/m2, we excluded those who were more likely to have undiagnosed obesity-related chronic disease (26). Additionally excluded from this study were pregnant or breastfeeding women because of their greater nutritional needs, as well as individuals predisposed to or with serious diagnosed health conditions. Participants taking prescribed medications that could affect their metabolism and possibly their immune function, such as those with special dietary requirements for a health condition (collected by self-assessed report), were also excluded. All participants were non-smokers who did not consume more than one alcoholic beverage per day or drink more than two cups of coffee per day, as both can alter metabolism levels. All participants were willing to eat the food used in this study, either the regular (meat included) meal options or the vegetarian meal options, and they were capable of preparing their own food during the study period.

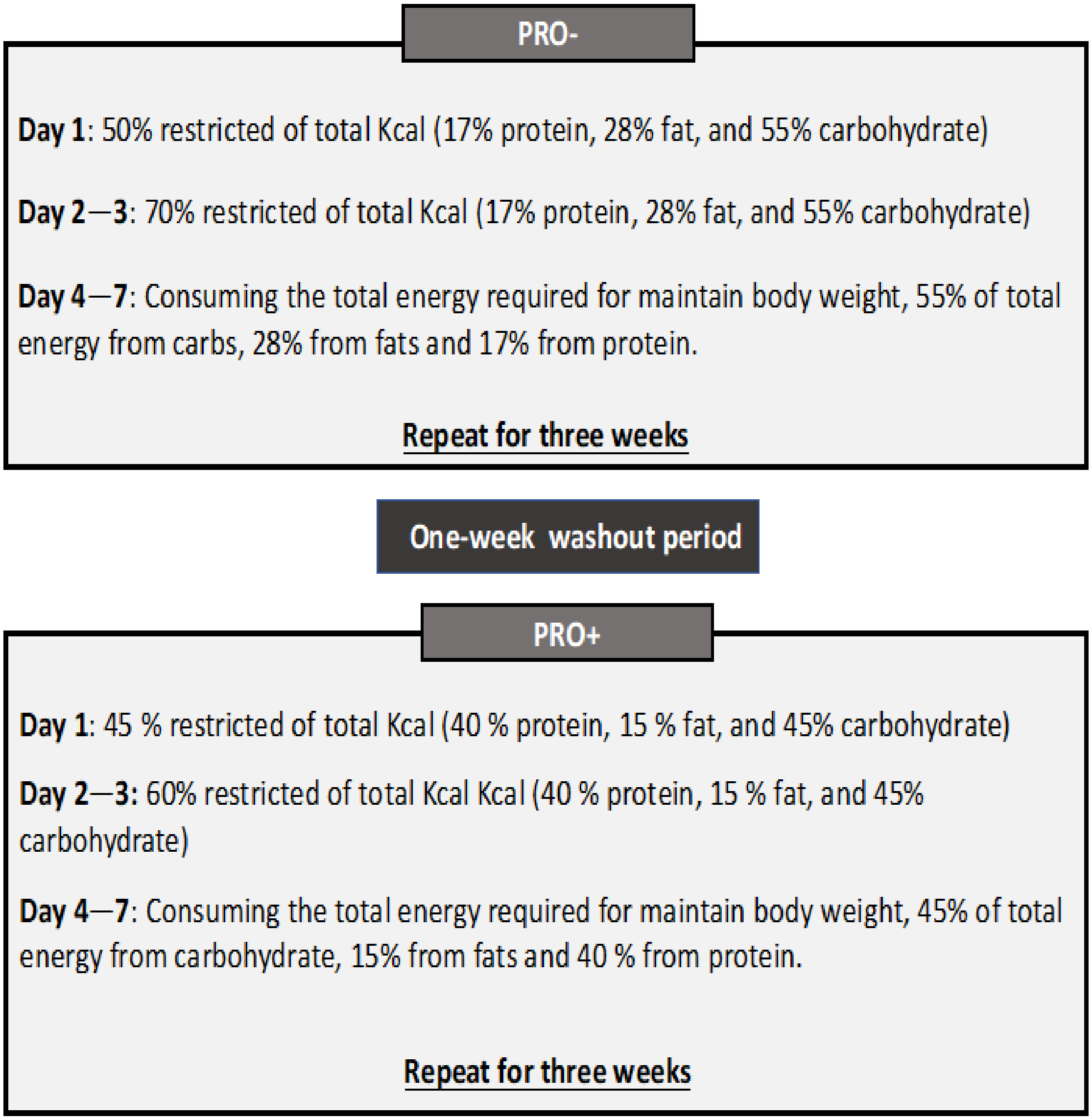
For the individuals who were interested in participating, we set up individual interviews for identity protection. This initial interview consisted of a brief description of the study, objectives, methodology, inclusion and exclusion criteria of the participants, and their answers to a prepared oral questionnaire, which provided the necessary information to ascertain a participant's understanding of the study before starting further screening eligibility. The researcher then measured the waist circumference, weight, and height of the volunteer and calculated their BMI; if the BMI measurement met the criterion, then the interview was conducted with each prospective participant. The main purpose of the interview was to go through the self-screening questions that were already been filled by participants. The researcher did not retain a participant's name until the researcher was certain of their eligibility and they agreed to participate. If eligibility was confirmed, and the volunteer fully understood the study and their role, they were asked to sign the consent form. Participant identification numbers rather than names were used on all materials, and this information was kept with consent forms in a separate locked cabinet. The study protocol was approved by the Dalhousie University Research Ethics Board (protocol number 2018-4477).

3.3.2. Study Design

The study utilized a cross-over design consisting of two three-week treatment periods with a one-week washout period with no dietary restrictions between treatment periods. The participants were randomized to begin with either the low- or high-protein IER diet. See Figure 5 and Section 3.3.3.for dietary details.

3.3.3. Dietary Interventions

The dietary plan consisted of three low-energy intake days followed by four days of consuming the amount of energy calculated to maintain body weight; this cycle was repeated for three weeks. The two treatment periods differed by protein content in days 1–3, which were designated as PRO- and PRO+ as shown in Figure 5. Between dietary periods, the participants had one week off so that the effects of the previous diet would wear off. Doing so helped us assess the effects of each diet separately. Since these are novel diets, this pilot study was used to inform us on the design of a future, larger study. For study purposes, we developed quick recipes, which use similar ingredients to those used in the classic Mediterranean diet, which is generally considered to be a healthy diet (27). The primary source of protein was a variety of animal- and plant-based proteins based on each participant's preferences. The recipes were same for both interventions and only differed by the macronutrient content as described in following section.



PRO-

Day 1: 50% restricted of total Kcal (17% protein, 28% fat, and 55% carbohydrate)

Day 2—3: 70% restricted of total Kcal (17% protein, 28% fat, and 55% carbohydrate)

Day 4—7: Consuming the total energy required for maintain body weight, 55% of total energy from carbs, 28% from fats and 17% from protein.

Repeat for three weeks

One-week washout period

PRO+

Day 1: 45 % restricted of total Kcal (40 % protein, 15 % fat, and 45% carbohydrate)

Day 2—3: 60% restricted of total Kcal Kcal (40 % protein, 15 % fat, and 45% carbohydrate)

Day 4—7: Consuming the total energy required for maintain body weight, 45% of total energy from carbohydrate, 15% from fats and 40 % from protein.

Repeat for three weeks

Figure 5 Study design.
CHO = carbohydrate; FAT = fat; PRO = protein.

3.3.3.1. PRO- Diet

The PRO- diet consisted of a 7-day cyclical diet. On the first day of the PRO- diet, the participants' dietary energy intake was restricted to 50% of the total energy required to maintain their current body weight. On days 2 and 3, energy intake was restricted to 70% of the total required energy. The proportion of energy intake from macronutrients remained at 17% protein, 28% fat, and 55% carbohydrates. The total energy on day one was approximately 1000–1300 kcal, and on days 2 to 3, it was approximately 700 to 800 calorie kcal. During days 4 to 7, the participants consumed a diet that maintained the same proportion of macronutrients (17% protein, 28% fat, and 55% carbohydrates) but in amounts calculated to maintain their body weight.

3.3.3.2. PRO+ Diet

The PRO+ diet, the experimental diet we developed for this study, differed substantially from the PRO- diet only in protein content on days 1–3 of each treatment week. The participants' dietary energy intake was restricted to 45% of the total energy required to maintain their current body weight. On days 2 and 3, energy intake was restricted to 60% of the total required energy. The proportion of energy intake from macronutrients remained at 40% protein, 15% fat, and 45% carbohydrates. The total energy in day 1 was approximately 1200–1500 kcal, and on days 2–3, it was 900 to 1300 kcal. During days 4 to 7, the participants consumed a diet that maintained the same proportion of macronutrients (40% protein, 15% fat, and 45% carbohydrate) but in amounts calculated to maintain their body weight.

3.3.4. Anthropometric Measures

The anthropometric measurements were obtained on the first day of the diet (baseline) and at the end of the third week (the end of treatment) of each treatment period. These measurements included weight, height, and waist circumference, all of which were measured according to standardized procedures. To measure height, the participants were required to remove their shoes and anything on their heads and then stand upright on the central point of a stadiometer platform with their backs against the wall and their feet together while looking straight ahead with their backs and shoulders touching the wall.

Their BMI was then calculated. Waist circumference was measured while the participants were in an upright but relaxed position using the World Health Organization method, which posits the location as “at the mid-point between the highest point of the iliac crest and the last floating rib” (28).

3.3.5. Blood Tests

Blood samples were collected via finger stick after a minimum of 12 h of fasting and tested for glucose and a hs-CRP test at baseline and at the end of each of the two treatment periods. The CRP high-sensitivity rapid test (CRP-K10, Schwerin, Germany) was used, which has a reference range for CRP as follows: negative, less than 10 mg/L; positive, which is divided into three levels: low, 10 mg/L or less than 30 mg/L; medium, 30 mg/L; and high, greater than 30 mg/L. These reference ranges were provided by the manufacturer of the test kits. Additionally, based on the manufacturer of the test kits, the relative sensitivity of the CRP-K10 kit depends on the CRP level. Specifically, for CRP values of 10 mg/L, the relative sensitivity is 99.4%; 94.3% for a CRP range of 10 mg/L to less than 30 mg/L; and 99.1% for CRP values of 30 mg/L or greater. For the measurement of blood glucose from serum, the One Touch Ultra (USA) was used, which has been demonstrated to have sufficient validity and reliability (29)

3.3.6. Hunger, Satisfaction, and Fullness

A visual analogue scale is a self-assessment tool that dietary researchers often use to assess the magnitude of hunger and fullness. The visual analogue scales used in this study provide a continuum of values in ascending order from 0 to 10, where 0 is the lowest level, and 10 is the highest level represented. These values are classified into specific categories, with each category representing the level of a participant’s experience of hunger, satisfaction, and fullness. In the current study, the participants indicated their value of each category on the scale, as illustrated in Figure 6. Each participant completed the visual analogue scale by marking the point on the scale that best represented the level of their feelings of fullness, satisfaction, and hunger during the energy-restricted days by end of each treatment period.

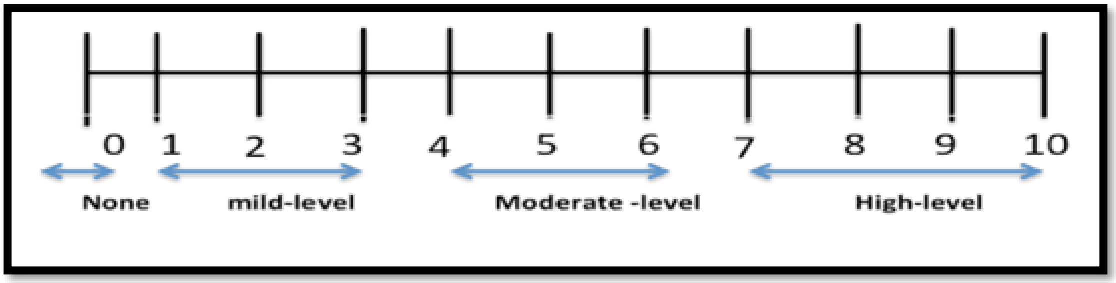


Figure 6 The categories for hunger, satisfaction, and fullness on the visual analogue scale

3.3.7. Adherence

Subject behavior was our greatest concern when considering enhanced adherence to the diet. Tactics used in this study to avoid high withdrawal rates included the use of whole foods rather than liquids, because solid foods offer greater prolonged satiety than liquid meals. Additionally, our study did not require specific times for food consumption; thus, the participants could consume meals based on their individual schedules.

Adherence is also enhanced by self-monitoring (15). Therefore, all participants were given a food journal and asked to record their food consumption on fasting days and then bring their journal to each lab visit. To further encourage compliance, each participant was contacted at least twice a week by phone or in person. During these communications and the lab visits, the participants were asked questions that gathered more information about how they were managing their diet, and to determine if they were experiencing any difficulties. Based on ongoing feedback, a researcher also customized the foods to the preferences of the participants to enhance adherence. All participants were also encouraged to use the Lifesum app for self-monitoring during non-restricted days. Additionally, each participant was provided with an individualized cookbook with recipes for days one to three of the PRO- and PRO+ diets; these recipes considered the participants' food choices but remained commensurate with the dietary plan of the study.

3.3.8. Statistical Analysis

Each numerical parameter (weight, waist circumference, BMI, and glucose) of pre-diet values was subtracted from post-diet values using SPSS (Version 24). All data were expressed as mean ± SD. Considering that the current study used a single case study design that involved a small sample size, the data were also presented descriptively and graphically.

3.4. Results

3.4.1. Participants

Six participants completed both phases of the study. An additional participant completed only a single treatment and was not included in the results. See Table 6.

Table 6 Baseline characteristics of study participants

Participant ID	**Age (y)**	**Body Weight (kg)**	**WC (cm)**	**BMI (kg/m^2)**
Case 1	49	78.2	93	28.9
Case 2	47	79.8	91	29.5
Case 3	37	79.9	80	29.2
Case 4	54	90.0	105	33.9
Case 5	51	71.9	84	29.4
Case 6	44	81.0	88	31.5

3.4.2. Body Weight

Weight loss occurred in 9 out of the 12 interventions, with an overall average loss of 2.40 kg on the IER diets. Similar losses occurred on both the PRO+ (2.45 kg) and PRO- (2.35 kg) diets (See Figure 7). The dietary records of Case 5, who showed a slight gain in body weight on both diets, indicated that she consumed an excessive amount of energy on the non-restricted days 4 to 7 compared to her isocaloric needs. Similarly, Case 3 reported that she ate unhealthy food during the restricted days of her PRO- diet, which may be the cause of her lack of weight loss.

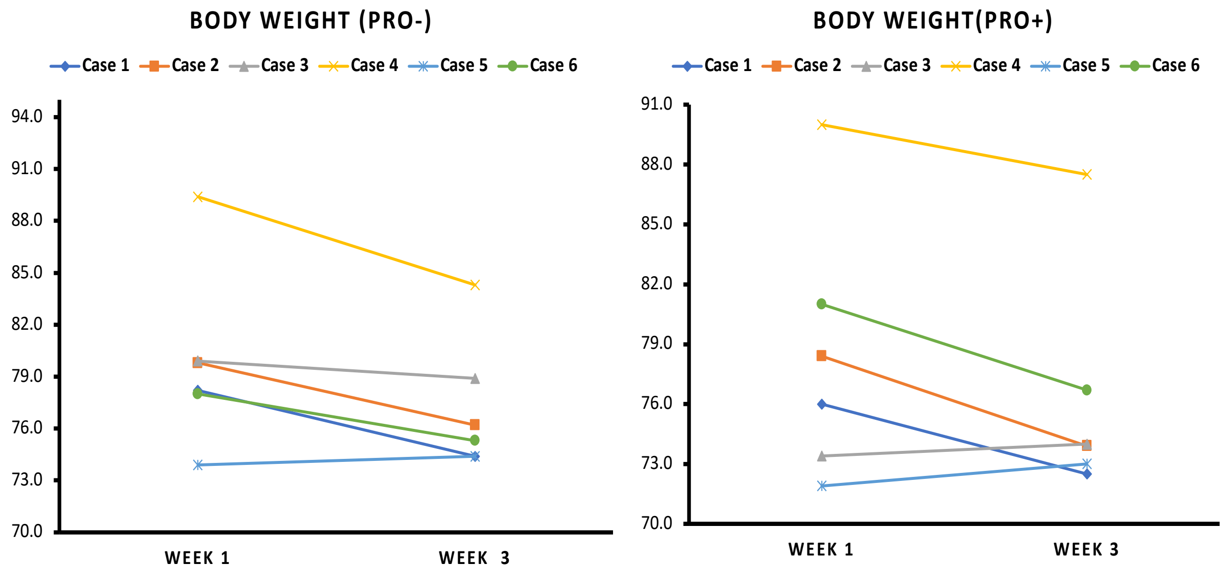


Figure 7: body weight changes on three weeks of the PRO+ and PRO- diets

3.4.3. Waist Circumference

Changes in waist circumference varied considerably among the cases, ranging from 0 to 4 cm, with an average loss of 1.88 cm over each of the 12 periods (see Figure 8). A plausible reason that Case 5 did not experience a reduction in her waist circumference from her PRO- intervention is that she consumed more than the total energy required to main body weight on some non-restricted days.

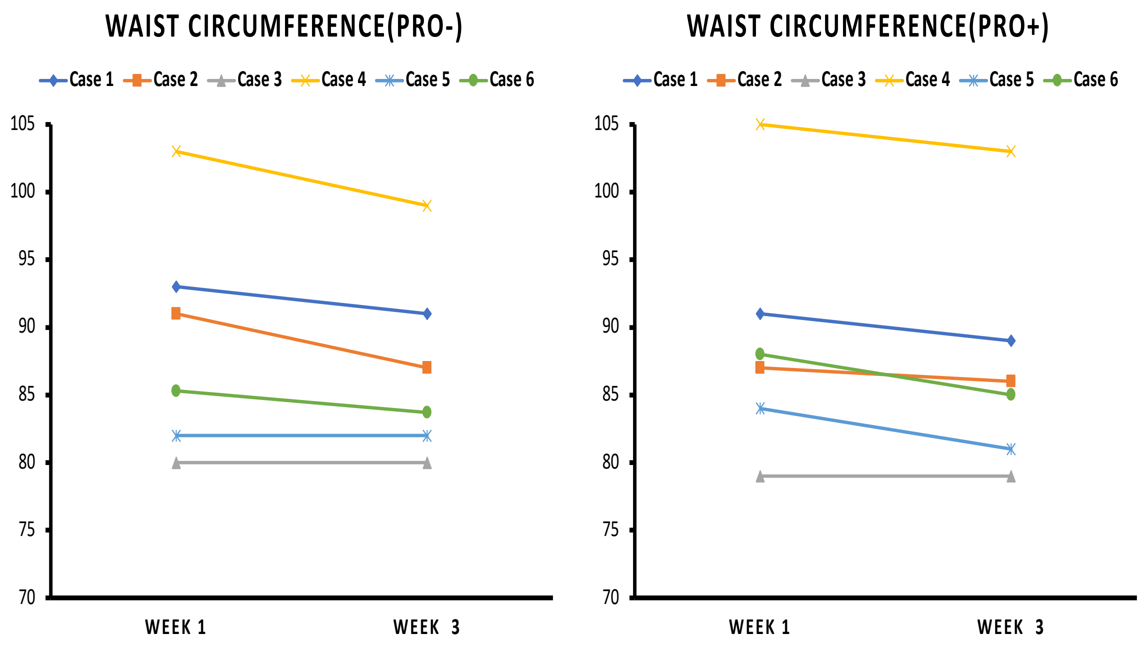


Figure 8 Waist circumference changes on three weeks of the PRO+ and PRO- diets.

3.4.4. CRP

Most participants showed reductions in CRP levels from the baseline value measured at their initial rotation (see Table 7). Three participants with a low level of CRP at the beginning of the first phase of intervention dropped to negative at the end of week three and maintained this negative status through their subsequent dietary rotation.

Table 7 CRP at baseline and the end of each intervention period.

	CRP		**CRP**	
	Baseline **(PRO-)**	**Week 3** **(PRO-)**	**Baseline** **(PRO+)**	**End Week 7** **(PRO+)**
Case 1	Negative	Negative	Negative	Negative
Case 2	Moderate	Negative	Negative	Negative
Case 3	Moderate	Negative	Negative	Negative

	CRP		**CRP**	
	Baseline (PRO-)	**Week 3 (PRO-)**	**Baseline (PRO+)**	**End Week 7 (PRO+)**
Case 4	Moderate	Moderate	High	Moderate
Case 5	Negative	Negative	Moderate	Negative
Case 6	Moderate	Moderate	Moderate	Moderate

Negative: CRP concentration of less than 10 mg/L; moderate inflammation: CRP concentration 10 mg/L or less than 30 mg/L; high inflammation: CRP concentration > 30 mg/L.

3.4.5. Fasting Glucose

There were no discernible trends in fasting glucose levels throughout the intervention period (see Figure 9). This might have been because the participants' fasting glucose levels were within normal blood glucose levels both at baseline and at the end of the interventions. One participant, who had a higher than normal glucose level at baseline, decreased in fasting glucose from baseline to the final measurements in the second phase of the interventions.

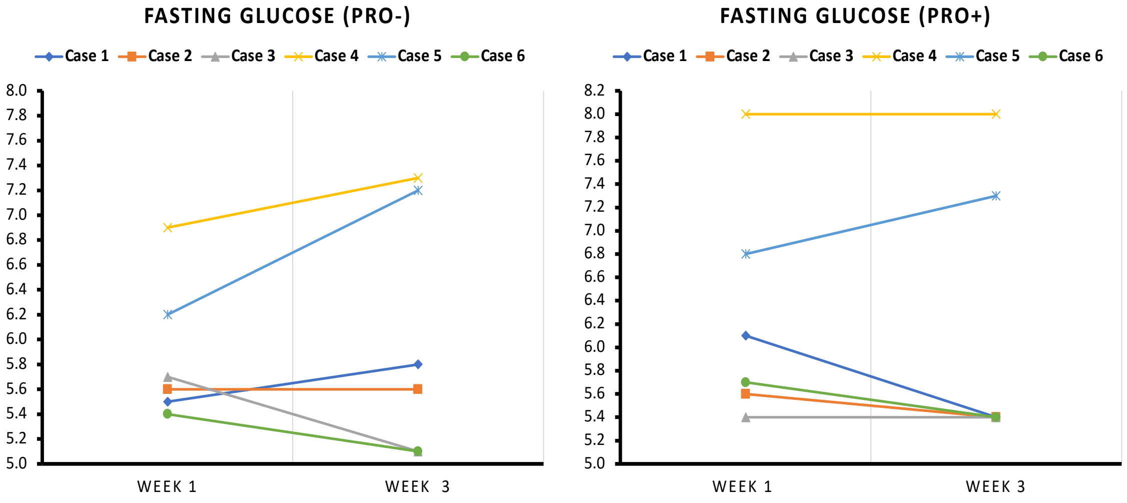
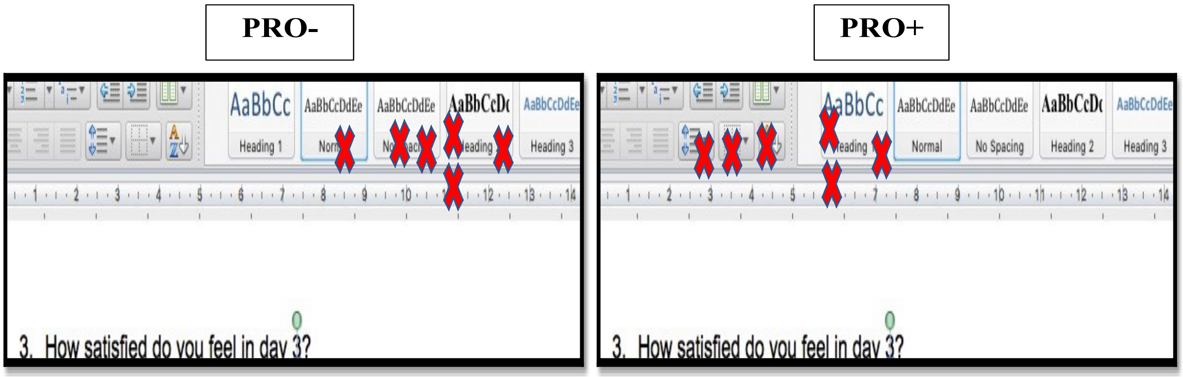


Figure 9 Glucose changed after following the dietary interventions

3.4.6. Satiety

The participants reported greater satiety on the PRO+ diet than on the PRO- diet (see Figure 10). The participants indicated that they were successfully adhering to both diets (PRO+ and PRO-) but found the PRO+ diet easier to adhere to because it produced less hunger. All participants reported that, on the PRO+ diet, they felt more fullness than on the PRO- diet. Two participants in the PRO- diet group mentioned that on the third day of the restricted portion of the diet, they had an increased desire to eat, whereas two participants in the PRO+ diet group reported feeling full before finishing their meals.



3. How satisfied do you feel in day 3?

3. How satisfied do you feel in day 3?

Figure 10 Participants' responses to a visual analog scale questionnaire for comparing the difficulties in adherence to PRO- and PRO+ diets

3.4.7. Effect of Order of Rotation on Results

Participants who started with the PRO- diet achieved greater reduction in body weight and waist circumference than those who started with the PRO+ diet. There was no effect of the order of rotation of dietary intervention on fasting glucose and CRP results.

3.4.8. Additional Observations

Six participants completed the entire set of interventions. Only one participant did not complete the second phase of the intervention for reasons unrelated to the study. None of the participants reported adverse events during the PRO+ or PRO- diets. While following the PRO- diet, one participant reported slight headaches on days one and two of the restricted intake portion. No other adverse conditions were reported. Some of the participants found the Lifesum app was useful in teaching them how to select healthy food. All participants mentioned that they were committed to consuming the total recommended energy.

3.5. Discussion

3.5.1. Weight Loss and Waist Circumference

In this study, both diets induced a reduction in body weight and waist circumference, even though the high-protein diet contained higher energy density than the low-protein diet. These findings support a previous study that found that positive losses of waist circumference did not differ between two levels of moderate protein intake in participants on a low calorie diet (30). Similarly, others have tested the effects of protein level while energy intake is restricted and reported similar results in weight loss (26). Interestingly, the higher protein intakes result in increased retention of muscle mass at the expense of fat mass (26). However, a very high-protein diet may have no further benefit, as increasing the protein content above the normal level of protein requirement has not produced a further reduction in body weight, although it helped maintain a higher level of free fat mass (31).

3.5.2. CRP

This pilot study suggests that three days of an energy restricted diet, whether it is high- or low-protein, can result in improvement in CRP for OW/OB women. Previous studies have used anti-inflammatory diets to investigate the effects of macronutrient proportions on inflammatory processes (32,33). However, to our knowledge, no study has tested the effect of protein content on hs-CRP. Instead, various studies have investigated aspects of carbohydrate and fat intake on inflammation. Thus, previous studies have failed to fully inform guidelines for people with significantly high levels of hs-CRP.

Aspects of dietary carbohydrate content seem to exert effects on hs-CRP. For example, a study using 29 overweight women with an average BMI of 32.1 ± 5.4 kg/m2 found more benefits for reducing hs-CRP using a low-carbohydrate diet compared to a low-fat diet (34). Interestingly, many of these studies found that macronutrient content is likely a more critical factor in reducing inflammation markers than weight loss. For example, a study with OW/OB patients aged 18–40 years reported that low glycemic load diets more effectively reduced the level of hs-CRP than a low-fat diet, although both diets similarly impacted weight loss (35). These findings are consistent with those of a 12 month randomized trial that found that a low glycemic diet was more effective in reducing high levels of hs-CRP than a low-fat diet, despite the similarities in weight loss outcomes in both groups (36). Another study compared the two versions of Mediterranean diets to a low-fat diet, and reported that the Mediterranean diets reduced hs-CRP without weight loss more effectively than the low-fat diet (37). Similarly, in the current study, most of the participants demonstrated decreases in their hs-CRP levels, although some of them showed slight weight increases. However, this is inconsistent with a 2007 systematic review that concluded that weight loss led to a reduction in CRP regardless of which intervention approach was used (38). It is important to mention that this review excluded the interventions that did not have weight loss as an objective. Further studies are required to obtain a clear conclusion about the role of the dietary intervention type, especially from protein level and weight loss on CRP levels.

3.5.3. Glucose

There was no significant reduction in fasting blood glucose for most of the participants. A possible reason for this finding is that most of the participants began this study at a normal level of the fasting blood glucose. Indeed, the beneficial effects of energy restriction interventions are more likely to manifest in individuals with insulin resistance than in healthy individuals (39). Additionally, the apparent lack of correlation between weight loss and decreasing fasting glucose in our findings could also be attributed to the short study length, which may have been inadequate to show the effects of weight loss on enhancing fasting glucose. Most energy restricting studies that have demonstrated that the capacity to be effective for controlling glucose levels and enhancing metabolic outcomes were conducted over periods of seven weeks or more (40–42). Lim et al., for instance, reported that, after eight weeks of restricted energy intake by type 2 diabetic patients, there was an enhancement in the function of beta cells (43), which has a curvilinear relationship with fasting blood glucose level (44). Similarly, one large diabetes prevention study with middle-aged overweight women and men with impaired glucose tolerance used intensive lifestyle interventions for eight weeks, including reducing fat consumption to less than 30%, saturated fat intake to no more than 10% of the total energy consumed, and total body weight by at least 5% (45). The study found that this dietary intervention prevented the progression to diabetes by 58% (45). Thus, it is probable that a longer study than ours and one with participants with higher baseline glycemic values would be needed to test the effects of protein level on fasting glucose levels while on an IER diet.

In the current study, Case 4 initially had a glucose level that was stable at 8 mg/dL in week one and remained unchanged at the end of week three (during the PRO + diet intervention), although with a slight body weight loss. During the subsequent PRO- diet intervention, though, she lost 5% of her body weight, and her glucose level decreased to 6.8 in the fifth week even though she did not take medication to regulate blood glucose. These findings correspond to evidence suggesting that 5% weight loss in OW/OB individuals induces improved metabolic function and the diminution of metabolic, disease-associated risk factors such as fasting blood glucose (46,47). Similarly, several studies have revealed that weight loss contributes to a decrease in visceral fat and improves markers of glucose metabolism (13,25,26). These results match those observed in an earlier study, which concluded that OW/OB people can reduce their risk for diabetes with every kilogram of body fat they lose (48).

3.5.4. Adherence

The participants in this study completed both phases of the diet without exception, and only one participant withdrew by the end of Phase 1 for reasons unrelated to the study. We therefore assume that our methodology provides the ability to adhere to an energy-restricted diet. The participants reported that they experienced more fullness and satiety on the PRO+ diet than on the PRO- diet. The reason for this may be the role of protein in increasing satiety. Several studies have investigated the association between macronutrients and satiety, with the majority indicating that protein increases satiety and suppresses energy intake more than other macronutrients (20,49), likely because protein contributes to an increase in the release of gastrointestinal appetite hormones, such as PYY, and also increases concentrations of ghrelin (20). A previously published systematic review recommended a high-protein diet for controlling appetite (50).

3.6. Limitations

There were certain limitations to this study, such as the small sample size. This study included only women who have a BMI between 27 and 33 kg/m2 and were aged 33–55 years in order to increase the homogeneity of the samples. The reason for selecting the age group is that evidence has demonstrated physiological differences in sensory satiety among age groups (i.e., adolescent, middle age, and elderly) (24,25). Further research is needed to investigate the effects of IER diets on obese men because the clinical trials have shown differences between men and women in appetite sensations and appetite responses to changes in macronutrient content in diets (22,23).

3.7. Conclusions

This pilot study demonstrated that an IER diet, whether the protein content is low or high, is a feasible strategy for obese women. Most participants lost weight and reduced their waist circumference. Additionally, most of them improved their CRP. Although both PRO+ and PRO- diets reduced CRP levels among the participants, the IER PRO+ diet resulted in greater satiety than did the IER PRO- diet and was preferred by the participants. This suggests that a higher protein content while consuming a IER diet may lead to greater long-term adherence. These positive findings hold promise for potentially similar exciting advances in larger and longer studies that involve an IER high-protein diet. To provide more data, a large study should investigate the effects of intermittent fasting combined with a high-protein diet on satiety, weight loss, and various health indicators, such as blood glucose, lipid profile, and pro-inflammatory markers, in overweight and obese adults.

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CHAPTER 4: THE EFFECT OF DIETARY PROTEIN ON SATIETY AND WEIGHT LOSS DURING INTERMITTENT FASTING IN OVERWEIGHT AND OBESE WOMEN

4.1. Abstract

Background: Obesity is one of the most critical health concerns of our time. Although intermittent energy restriction (IER) is a successful strategy for reducing body weight and fat mass, adherence to IER diets may be challenging because most of them increase hunger.
Aim: This study aimed to determine whether a high-protein diet combined with an IER diet would improve satiety and reduce body weight more than a low-protein diet combined with an IER diet.
Methods: Participants were randomly assigned into one of two study groups, either a high-protein (HP) diet combined with IER, or a low-protein (LP) diet combined with IER, for eight weeks. Body weight, waist circumference, blood lipids, C-reactive protein (CRP) and subjective satiety were assessed at baseline and week 8 (post-intervention).
Results: A total of 22 women, 45.6 ± 5.4 years, with a mean (SD) body mass index (BMI) of 30.1 ± 2.2 kg/m^2 completed the interventions (n=11 in each group). Body weight was significantly reduced by both IER diets (Overall, 5.77%; HP, 5.30%; LP, 6.27%, of body weight), with no difference between diet groups (p=0.35). Similarly, waist circumference was reduced for all participants (-8.04 ± 5.99 cm); although the HP group lost more (-9.26 ± 7.86 cm) that the LP group (-6.82 cm ±3.21), the difference was not significant (p=0.87). Reductions in triglycerides and changes in CRP after the intervention were not significant (p=0.95; (p=0.74). No changes were observed in LDL, HDL, and total cholesterol in either group. Overall, AUC showed that the HP IER diet lowered the desire to eat more than the LP diet did, although this was not statistically significant.
Conclusion: Both IER diets effectively reduced body weight and waist circumference in these middle aged, overweight or obese women. A high protein content combined with an IER diet may reduce waist circumference and the desire-to-eat score better than a low protein version. However, the protein content of the IER diet did not affect LDL, HDL, cholesterol or HbA1c measures. A longer study is needed to determine if the reduced desire to eat provided by the HP IER diet would result in increased adherence to an IER

diet. This study advances the understanding of the effect of protein content levels on satiety and health indicators in women adhering to an IER
diet.

Keywords: Dietary protein, intermittent energy restriction, obesity, satiety, energy restriction.

4.2. Introduction

Dietary protein is an important component of a healthy diet. Following consumption, dietary protein is hydrolyzed during the digestion process via hydrochloric acid in the stomach, and proteases in the duodenum to break down long polypeptides into short-chain polypeptides (1). Thus, this digestive process converts protein into amino acids or smaller peptides, which are then absorbed in the small intestine (1). Among the dietary amino acids, essential amino acids play an indispensable role in several critical bodily functions, such as hormone synthesis, the preservation of skeletal muscle mass, and the formation of several biological fluids (2). Considering the important role of essential amino acids (2) and the body's inability to store them, it is critical to include the adequate consumption of protein in dietary requirements for human health (3).

Obesity is frequently linked to a number of risk factors for cardiometabolic (4) and other chronic diseases (5), such as insulin resistance, beta-cell dysfunction (6), and atherogenic dyslipidemia (high triglyceride and LDL-cholesterol, and low HDL-cholesterol concentrations) (7). Dietary protein consumption may plays a greater role in enhanced satiety and body weight management than do other macronutrients (8–10). A high protein diet tends to increase metabolism because it has a thermic impact, decreases appetite and hunger through a variety of processes, and importantly, has influence on some hormones that control weight (11).

One dietary method that may be used as therapy for obesity treatments is intermittent energy restriction (IER), which involves alternating cycles of limited energy consumption with periods of regular energy intake (12). Numerous animal research studies investigating Intermittent Energy Restriction (IER) has consistently shown its efficacy as a weight reduction method (13–16). Individuals encounter several difficulties as a result of physiological and environmental elements (17,18), hence prompting inquiry into the efficacy of Intermittent Energy Restriction (IER) as a weight reduction approach for obese or overweight adults.

This study investigated the effects of dietary protein level in an energy restricted diet on body weight in overweight and obese women, on other health indicators, and on satiety.

4.3. Methods

4.3.1. Participants

The current study aimed to include 40 overweight and obese women with an age range of 35 to 55 years. Only women were included in order to increase the homogeneity of the participants because previous clinical trials have shown differences between men and women in appetite sensations and appetite responses to macronutrient content changes in the diets (19,20). The rationale for selecting this age group was that physiological differences exist in sensory satiety among age groups (i.e., adolescent, middle age, and elderly) (21,22). The overweight and obese criteria were determined by body mass index (BMI) between 27-33 kg/m^2. By excluding obese individuals with a BMI above 33 kg/m^2, we intended to recruit from a lower-risk population who may have undiagnosed obesity-related chronic diseases (23). The inclusion criteria for participants were:

1. Willing to eat the foods recommended in this study, whether these foods were part of the regular, vegetarian, or lactose-free diet options.
2. Able to prepare their own food during the study period.
3. Have a device that could connect to the internet, such as a cell phone or iPad to facilitate the collection of data, receive their personalized meal plan and attend the online meetings. This study used the telehealth method, and thus necessitated participants' access to the internet.

Potential participants were not eligible to participate if: they had a serious health condition; had been diagnosed with diabetes; were undergoing medical treatment for regulating blood glucose; were taking prescribed medication that would affect metabolism; were taking medication for immune function; or were taking antidepressant medication, diuretics, or laxatives. In addition, those on a special diet that was incompatible with our dietary intervention were excluded from the study. Such diets might be for kidney disease, chronic gastrointestinal issues, vascular diseases, diabetes mellitus, cancer or some autoimmune conditions. Pregnant and breastfeeding women were excluded because of their greater nutritional needs (24). Additionally, we excluded women who smoke.

4.3.2. Sample size calculation

Visual analog scales (VAS) are reliable tools to evaluate hunger and satiety at time of food consumption (25). A change in the VAS of 10 mm is usually considered clinically significant (26). Based on the statistical power software, G*Power (27), the sample size for the study was calculated based on the average expected difference observed in VAS ratings in relevant previous studies (22–24). The Power calculations (G*Power v.9) estimated that a sample size of 28 would be required to detect an interaction in subjective satiety rate ($\eta 2p = 0.06$) between 2 groups and 4 repeated measurements effect size of 0.25, with $\alpha = 0.05$ and $1-\beta = 0.8$. Thus, 14 participants per group were expected to be sufficient to detect minimum significant differences in the dependent variables between groups (28–30).

Non-adherence or drop-out issues are common among restricted energy diets. A systematic review and meta-analysis that involved 45 randomized controlled trials examining the effects of dietary interventions on weight loss in obese individuals reported that nearly 28% of the subjects dropped out due to not adhering to the dietary interventions or other reasons (31). Thus, recruiting 40 subjects would minimize the effect of some non-adherence or drop-out issues. We expected that 28 of 40 participants would complete their dietary intervention in the study.

4.3.3. Recruiting procedure

A medical practitioner, who is an Internal Medicine specialist, Dr. Julie Zhu, identified and informed patients who were likely eligible to participate about the study and gave them the flyer, which contained the contact information of the study's principal investigator (PI). Also, in order to disseminate more widely the opportunity to take part in our study, we placed the poster for this study on several Nova Scotia community LISTSERVs, such as ones for Dalhousie University employees and Nova Scotia teachers. We additionally posted the information on Facebook and Twitter groups in the Halifax area. Individuals who contacted the PI, were provided with brief information about this study, the eligibility criteria, and what the study would entail for them. The PI then followed up with individuals who were interested in participating by Nova Scotia Health Authority (NSHA email), to answer questions that may have arisen and ascertain whether they would like to receive a copy of the protocol to read. Those interested in joining the study and appeared to meet the eligibility criteria, were sent the link to the informed consent form via Research Electronic Data Capture (REDCap), which covered important information including the requirements to take part in the study. This email also included the link to the self-screening form and links to videos that explained how to take their body measurements (body weight, waist circumference and height). In the email, individuals who were interested in participating were asked to complete the self-screening form by following the instructions on taking body measurements that were explained in the videos. This saved time for people who were interested in participating and was used to verify eligibility to participate. Then, those who were still eligible and interested in participating in the study received a request to schedule a remote initial individual interview, which took 15-45 minutes via Zoom Healthcare. The main purpose of this interview was to go through the screening questions that had already been filled out by the participants as a double-check process by the PI to make sure they answered the questions correctly and determined their eligibility. In addition, during this initial interview, the PI provided the participants with important information about the study such as the study objectives and methodology. The PI then asked each participant some questions about the study in order to ensure that she understood the study. Finally, the PI informed each participant that the study would include online interview sessions for data collection purposes and explained the session procedures (timeline, duration, and protocol of sessions; how to access the website where the interview would be held). Prior to the online meeting procedures, participants were asked for verbal consent to communicate via email in order to obtain their email addresses. When eligibility was confirmed, and the prospective participant fully understood the study and their role, they were asked to electronically sign and submit the consent form via REDCap. For those not meeting the criteria, the screening document was deleted immediately.

4.3.4. Research plan

4.3.4.1. Study design

This study was designed to examine the effects of dietary protein level on satiety and weight loss, while adhering to a specific intermittent energy restricted format on multiple outcomes. The study design implemented a single-blind, parallel design, in which participants were assigned randomly to either a higher or lower protein diet, both with intermittent energy restrictions. The IER format used required a low energy intake for three consecutive days, followed by normal energy intake for four days, for eight consecutive weeks. The differences in protein intake occurred in the three days of low energy intake each week, and not on the other four days. The "single-blind" aspect of the study refers to the arm of the study to which a participant was randomized; participants were not informed if they were in the low versus high protein arm (See Figure 11). This study depended on the telehealth method for obtaining anthropometric measurements (i.e., body weight, height, and waist circumference), and subjective satiety measurements.

4.3.4.2. Randomization

The randomization was stratified by BMI category (i.e., dichotomized as 25-29.9 kg/m^2 and 30-34.9 kg/m^2) and age (i.e., dichotomized as 35-44 y and 45-55 y) via utilizing RedCap®, which is a validated online randomization tool for researchers (32). The RedCap® tool randomly assigned the initial participants to one of two groups (33). The assignment to groups was in the order of acceptance into the study and participants were randomized from each successive stratum one by one until reaching the target sample size, which was 20 for each group.

4.3.4.3. Blinding

The advertisement for the study, discussion in recruiting meeting, and information in the consent form only referred to examining the effect of intermittent energy restriction as part of the dietary intervention. Participants were blinded to the aspect of protein content differences in the intermittent energy restriction diet on study outcomes. The justification for this blinding was as follows: High protein diets are currently elevated as healthier regimens on social media and on commonly frequented health websites. If the different protein content was known to the participants through the consent form and other sources, then they would easily guess if they were in the high protein group or low protein group even if not informed directly to which group they were randomized. Therefore, blinding of the participants reduced the possibility of bias when they assessed their hunger and fullness (34,35). The food recipes for both groups were the same recipes but differed in the amount of protein content.

4.3.4.4. Dietary interventions

Upon agreeing to participate, and after their baseline measurements were collected, participants were contacted individually to set up an online meeting on Zoom Healthcare. In this meeting, the PI: 1) Discussed their questions and concerns related to the recipes; 2) Explained how to download and use the Lifesum App on their cell phone or tablet; and how to plan their diet for four non-restriction-days; and 3) Explained the protocol of the test meal subjective satiety questionnaire. Then, participants received by email their personalized meal plan based on their group (i.e., HP diet or LP diet).

Each participant was randomly assigned to one diet group, either intermittent energy restriction low protein diet (LP) or intermittent energy restriction high protein (HP). Both diets consisted of three energy restriction days followed by consumption of an isocaloric diet for four days. For calculating the total energy requirement for the participants the following equation was used:

METs X 3.5 X BW (kg) / 200 = kcal/min

The MET values depended on the level of physical activities are as follows:

- A PAL value between 1.40-1.69: sedentary or light active lifestyle.

The diets (i.e., HP diet and LP diet) differed in the protein content on the three energy restriction days as described below. However, HP group consumed about 316 more total kilocalories per person daily for three days every week for eight weeks due to their higher protein intake.

Intermittent energy restriction low protein diet (LP)

On the first three days of the week, the LP diet restricted participants' dietary energy intake to 25% of their total energy required to maintain their current body weight. The energy content in this diet contained 10% protein, 30% fat and 60% carbohydrates. For these three restricted-energy days, each participant was provided with an individualized cookbook with recipes for days one to three (the restricted-days). Also, participants received a digital food scale so they could measure their food amounts. During days four to seven each week, the participants consumed an isocaloric diet (estimated energy to maintain body weight), which consisted of 40% of total energy from carbohydrates, 30% from fats and 30% from protein.

Intermittent energy restriction high protein diet (HP)

The HP diet, the novel diet we developed for the purposes of this experiment, was also a seven-day cyclical diet. From day one to day three each week, participants consumed of 45% protein, 15% fat and 40% carbohydrates as proportions of total energy intake. Thus, their protein intake (45% of total energy) was similar in amount to that consumed on days four to seven.

On days four to seven of the HP diet, participants consumed the same isocaloric diet as on the LP diet 40% of total energy from carbohydrates, 30% from fats and 30% from protein. Nutrium (36), which has been validated as a nutrition dietary assessment software, was used to develop a personalized diet plan for the three restricted days. Via the Nutrium software, the PI was in contact with the participants individually. Nutrium was used for several functions, including delivering meal plans for the three-restriction days and providing one-to-one consultations. The data that was collected through the Nutrium APP was limited to body weight, height, and meal plans. Only participants' ID codes were used in the Nutrium APP, and not initials or names.

For non-restricted days, participants were asked to download the free, easily searchable and valid dietary mentoring instrument, the Lifesum app (37), onto their cellphone or tablet in order to help them to log their food consumption. They were encouraged to select healthy foods and were assisted in their planning of a healthy diet by using the Lifesum app for non-restricted days over eight weeks. Participants' energy intake to limited to the total energy required to maintain body weight. The Lifesum app assisted the participants in avoiding the consumption of more than the energy needed to maintain body weight in non-restricted days diet. The Lifesum app allows individuals to track their daily energy intake by searching its extensive nutrition database. Foods can be entered into the Lifesum app either via a scanned barcode or simply by inserting the food information manually. Researchers did not have access to participants' Lifesum app data; therefore, no data were collected by the researchers from the participants' Lifesum app. no data was collected on the participant experience, either overall or on the use of Lifesum. The PI asked participants whether they consumed an excessive amount of energy intake required to maintain their body weight. When the PI met the participant to explain the diet dietary intervention, the PI informed participants that they had to report if they consumed energy intake more than the total energy requirement to maintain their current body weight. On days four to seven (i.e. non-restricted days) of the HP diet, participants consumed the same isocaloric diet as on the LP diet 40% of total energy from carbohydrates, 30% from fats and 30% from protein within the total energy needed to maintain body weight.

Before the PI gave the participants their personalized cookbook recipe, the PI contacted participants individually to set up an online meeting on Zoom Healthcare. The main purposes of this meeting was (1) to discuss their questions and concerns related to the recipes; (2) to explain how to log their food intake into Nutrium for the three restriction days; (3) to describe how to download and use Nutrium; (4) to explain how to download and use the Lifesum App on their cell phone or tablet, and how to plan their diet for four non-restriction-days; and (5) to explain the protocol of the test meal subjective satiety questionnaire. Then participants received by email their personalized meal plan based on their group (i.e., HP diet or LP diet) via NSHA email. Additionally, the PI encouraged participants to contact the PI and request an online meeting at any time point of the intervention to discuss their questions, concerns or any other observations regarding the dietary intervention. Also, the PI informed the participants that they could request changes to the recipes or edit them at any time point of the dietary intervention. The meeting duration depended on how long it took to complete the discussion; however, usually the minimum duration of the meeting was 15 minutes and the maximum was one hour. The number of sessions with a participant depended on how many times they requested a meeting. In addition, the PI sent weekly emails to participants individually to ask them questions about their practising of their diet and if they had questions or concerns. They were expected to report if they did not adhere to their diet, changed the meals or their energy intake on non-restricted days was more than the total energy needed to maintain their body weight.

4.3.5. Data collection

4.3.5.1.Anthropometric measurements

The current study depended on the remote assessment self-report method for obtaining anthropometric measurements (i.e., body weight, height, and waist circumference). Each participant was asked to report her body weight and waist circumference on the first day of the intervention and on the last day of week eight via REDCap. Subjective satiety measurements were collected on the third days of week one and week eight. Participants were informed that monitoring would be remote and not conducted physically except for their blood sample collection, for which participants could choose the location of the blood collection service.

Body weight

The participants received an instructional video of how to use their home scale. Moreover, in order to avoid inaccurate self-reported weight, participants were instructed on the required conditions for obtaining accurate readings on a scale such as:

- Weigh in the morning before eating.
- Wear indoor clothes or no clothes, without shoes.
- Use the scale on a hard and flat surface; the scale will not give an accurate reading on the carpet.
- The product should be on stable and vibration-free surface during use
- Examine the battery of the scale before use because a low battery could cause incorrect readings.
- Use with dry feet, for safety.
- Keep the scale away from water or moisture.
- Repeat the body weight measurement three times in a row to ensure the repeatability of the scale’s reading.
- Measure to the nearest 0.1 kg.

Height

Participants received a video link that explained how to measure their height. They self-reported their height to the nearest 0.1cm, according to the recommendations for remote anthropometric assessment provided by the Health and Retirement Study protocol, which has been validated (38).

4.3.5.2. Subjective satiety measurement

A Visual Analogue Scale (VAS; 0–10 cm) is a self–assessment tool used by dietary researchers to assess the magnitude of a person's hunger, satisfaction and fullness. A VAS provides a continuum of values in ascending order from 0 to 10. These values were classified into specific categories with each category representing the level of a participant's experience of hunger, satisfaction, and fullness. Participants were asked to fill out the VAS (0–10 cm) by marking the point on the scale that best represented the level of their feelings of fullness, satisfaction, and hunger during the third day of energy-restricted days on weeks one and eight. The hunger-fullness questionnaire was presented on REDCap and their responses were recorded and saved with a time and date so that compliance to the study protocol could be determined. The satiety VAS instruments involved the following questions: (1) How strong is your desire to eat? (Weak to Strong); and 2) How full do you feel? ("Feel completely empty" to "I cannot eat anything more").

Test meal

We used a standard test meal to help measure subjective satiety. The components used to reflect the changes in participants' responses to protein content in their test meals were the VAS for each of "desire to eat" and "fullness" at specific time points following a standardized meal, which would reflect the satiety level of participants. A minimum of 24-h before the test meal day, the PI held a remote individual meeting with each participant to review the test meal instructions and answer her questions. Participants were asked to prepare the test meal by themselves; thus, the test meal was formulated to be easy to prepare and comprised of commonly eaten food. It consisted of the same group's protein content: HP (45% protein, 15% fat and 40% carbohydrates), or LP (10% protein, 30% fat, 60% carbohydrate). Participants were instructed to fill out the hunger-fullness questionnaire following an overnight fast between 9-12 hours and immediately before consuming a breakfast test meal. After filling out the hunger-fullness questionnaire, they were asked to consume their breakfast test meal in its entirety within a maximum of 5-15 minutes. Then, participants were asked to fill out the hunger-fullness questionnaire at 30, 60 and 90 minutes following meal consumption.

4.3.6. Data analysis

All statistical analyses were performed using SPSS (Version 25). Baseline data and demographic characteristics were expressed as the mean ±SD or median as appropriate. The Shapiro-Wilk test was conducted to test the normality of the distribution of the data prior to analysis. If the data were not normally distributed, a natural log transformation was applied to obtain a normal distribution. Areas under the curve (AUC) for fullness and desire to eat were calculated. Also, AUC (0–90 min) were calculated by the trapezoidal rule and were used as an estimate of response to a desire to eat and fullness. A factorial ANOVA (time × diets) was performed to compare the effects of diets on satiety scores, body weight, and waist circumference, and to detect whether there was a significant difference between groups on satiety scores at pre-test, 30, 60 and 90 minutes. When main effects were detected, then independent t-test post hoc analyses were performed in order to detect the minimum significant difference between diets and to compare the differences in satiety between the diets at each time point. A paired t-test was used to test whether there was a significant difference between each measurement (body weight, waist measurement, desire to eat, and fullness) taken before and after the intervention program within groups. For nonparametric data (HDL and CRP), the Wilcoxon test was conducted. Statistical significance was accepted at $P \leq 0.05$.

4.4. Results

4.4.1. Participant recruitment and follow-up

The recruitment of the participants began in June 2022 and 189 people expressed interest to participate. Of these 189 individuals, 104 women filled out the self-screening questionnaires. From these 104 self-screening questionnaires, 40 prospective participants were not eligible because their age or BMI did not meet the study criteria. Additionally, 3 participants were excluded because they smoked or had a serious chronic disease.

A total of 61 participants were recruited and randomly assigned to either the LP or HP group, at a ratio of 1:1. A total of 39 participants from both groups subsequently withdrew from the study (21 in the LP and 19 in the HP). Twenty-two subjects completed the dietary intervention and their baseline characteristics are shown in Table 8 and Table 9.

Withdrawals from the study were due to many issues. Eleven participants tested positive for COVID-19, experienced flu symptoms, or withdrew due to Hurricane Fiona, which caused power outages which all made it too difficult to adhere to the diet. One participant withdrew because she experienced difficulties in preparing the food, while six participants dropped out for personal or otherwise undisclosed reasons. Five participants simply lost interest in the study. Eight participants decided to not participate due the extended waiting time for their initial blood tests, two participants left Nova Scotia and one felt unable to continue because she began a new job. Five participants did not participate because if they waited for the blood test appointment, the Christmas celebration would have occurred during the dietary intervention period, and they wanted to complete the diet before the holiday.

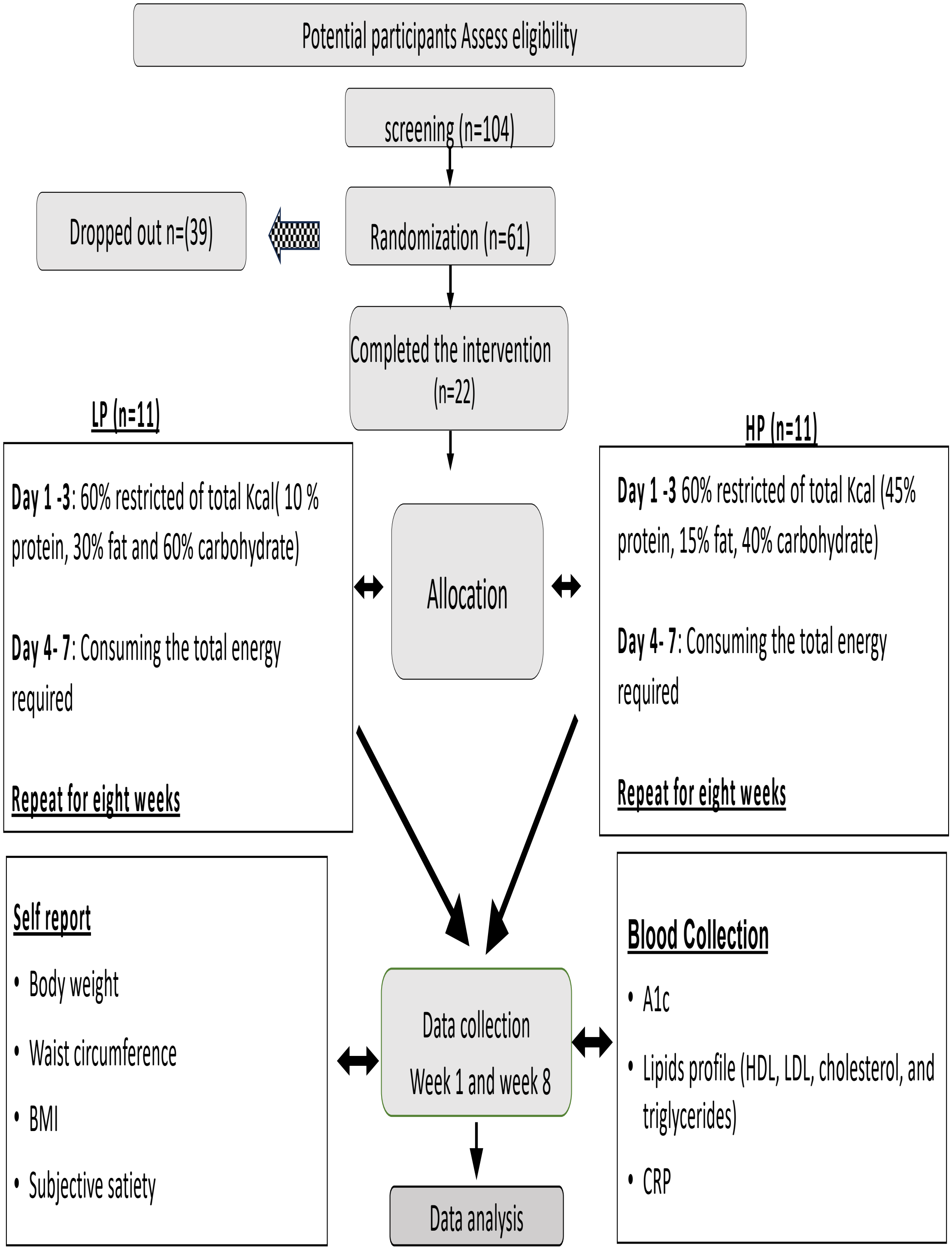
Potential participants Assess eligibility
screening (n=104)
Dropped out n=(39)
Randomization (n=61)
Completed the intervention (n=22)
LP (n=11)
HP (n=11)
Day 1 -3: 60% restricted of total Kcal(10 % protein, 30% fat and 60% carbohydrate)
Day 4- 7: Consuming the total energy required
Repeat for eight weeks
Allocation
Day 1 -3 60% restricted of total Kcal (45% protein, 15% fat, 40% carbohydrate)
Day 4- 7: Consuming the total energy required
Repeat for eight weeks
Self report
Body weight
Waist circumference
BMI
Subjective satiety
Data collection
Week 1 and week 8
Data analysis
Blood Collection
A1c
Lipids profile (HDL, LDL, cholesterol, and triglycerides)
CRP

Figure 11 The study design

Table 8 Demographic characteristics by study group (age, body weight, height, and body mass index)

	LP (n=11) (Mean ± SD)	**HP (n=11) (Mean ± SD)**	**Total (n=22) (Mean ± SD)**	**P-value**

Age (Year)
35-44 y
45-55 y
	48.91 ± 4.18
	n= 8 (73%)
	n=3 (27%)
		42.27 ± 4.54
		n=1 (10%)
		n=10 (90%)
			45.59 ± 5.44
			n=9 (41%)
			n=13 (59%)
				0.002

Body weight (kg)	82.30 ± 13.29	87.03 ± 7.38	84.68 ± 10.78	0.157
Height (cm)	164.81± 12.29	170.36 ± 5.42	167.59 ± 9.71	0.194

Body mass index (kg/m^2)
Overweight: 25.0–29.9 (kg/m^2)
Obese: 30.0 -34.9 (kg/m^2)
	30.18 ± 2.52
	n=5 (45%)
	n=6 (55%)
		30.05 ± 1.92
		n= 3 (27%)
		n=8 (73%)
			30.09 ± 2.20
			n=8 (36%)
			n=14 (64%)
				0.852

Table 9 Blood characteristics by study group (lipids profile, CRP and HbA1C)

	LP		**HP**		**Total**		**P-value**
	n	**Mean ± SD**	**n**	**Mean ± SD**	**n**	**Mean ± SD**	
Triglycerides (mmol/L)	10	1.61 ± 1.02	7	1.67 ± 1.81	17	1.63 ± 1.34	0.982
High density lipoprotein (mmol/L)	10	1.53 ± 0.69	8	1.35 ± 0.48	18	1.45 ± 0.60	0.505
Low density lipoprotein (mmol/L)	10	3.28 ± 0.82	8	3.15 ± 0.72	18	3.22 ± 0.76	0.564
Total cholesterol (mmol/L)	9	5.29 ± 0.89	8	4.91± 0.86	17	5.11 ± 0.87	0.234
C-reactive protein (mg/L)	10	3.25 ± 1.43	7	4.56 ± 3.42	17	3.79 ± 2.45	0.246
A1c (mmol/L)	3	5.07 ± 0.06	6	5.38 ± 0.39	9	5.28 ± 0.35	0.387

4.4.2. Effect of dietary protein with energy restricted energy diet on body weight status and waist circumference

4.4.2.1. Body weight status

Eight weeks of compliance to an IER diet was tested for change in Body weight. A reduction in the mean body weight was observed after the dietary intervention in both high- and low-protein diets (Table 10). Reductions of 4.68 kg and 5.16 kg were recorded in the mean body weight for high and low protein diets, respectively, after the intervention, which amounted to 5.30% and 6.27% respectively of the initial mean body weights (Table 10 and Figure 12).

Table 10 Body weight before and after the dietary intervention, by study group

Study group n=11, each group	**Pre-intervention (Mean ± SD) (kg)**	**Post-intervention (Mean ± SD) (kg)**	**Change in body weight (kg)**	**P- value**
HP	88.22 ± 6.21	83.54 ±7.02	4.68	<0.001
LP	82.31 ± 13.29	77.15 ± 13.31	5.16	<0.001
HP + LP	85.26 ± 10.57	80.34 ± 10.88	4.92	<0.001

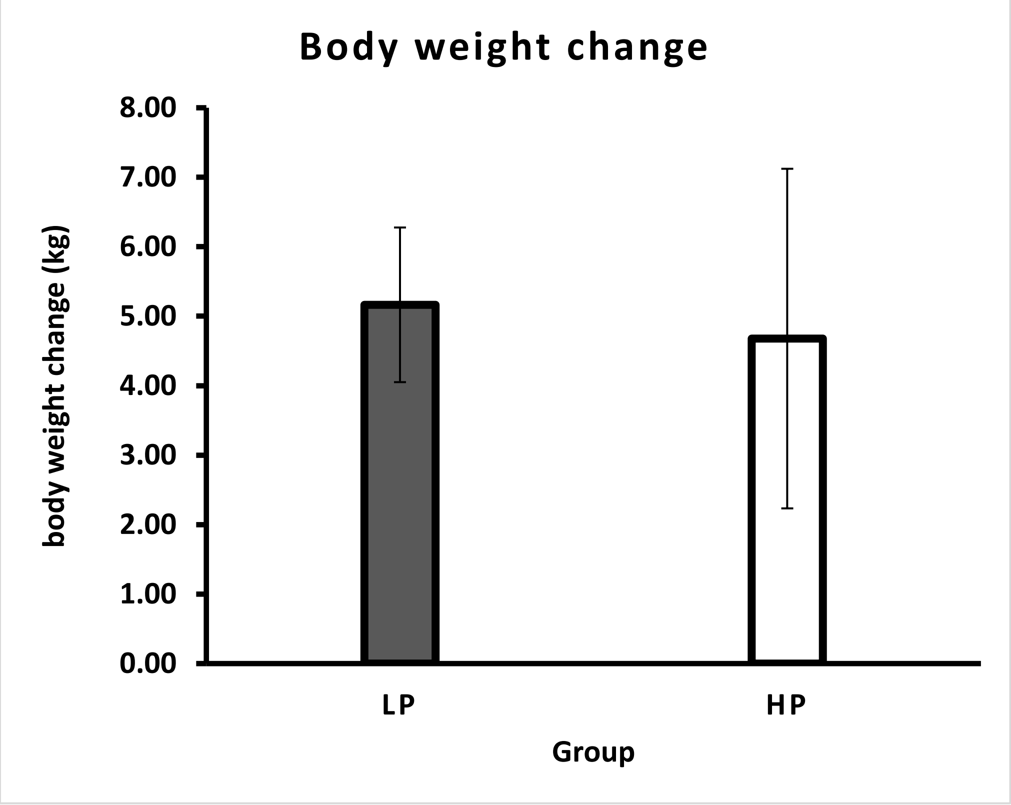

Figure 12 Changes in body weight by study group.
There was no significant difference between group in body weight change (p= 0.346)

4.4.2.2. Waist circumference measurement

Eight weeks of compliance to an IER diet was tested for change in waist circumference. A reduction in the mean waist circumference was observed after the dietary intervention in both high- and low-protein diets. For the high protein intake, a significant reduction was observed when waist circumference before intervention (102.91 ± 6.42cm) was compared to the waist circumference after intervention (93.65 ±7.55cm); [t (10) = 3.91, p <0.001]. Similarly, for the low protein diet, the results indicated a significant reduction in waist circumference when mean measurements before intervention (102.2±8.8) cm and after intervention (95.65 ± 8.10cm); [t (10) = 7.04, p <0.001] were compared (Table 11). There was no significant difference between groups in waist circumference (Figure 13).

Reductions of 9.26cm and 6.82cm were recorded in the mean waist circumference measurements for the HP and the LP groups, respectively, after the intervention, which amounted to a decrease of 8.99% and 6.67%, respectively, from the initial average waist circumference measurement (Table 11 and Figure 13).

Table 11 Waist circumference before and after the dietary intervention, by study group

Study group n=11, each group	**Pre-intervention (Mean ± SD) (cm)**	**Post-intervention (Mean ± SD) (cm)**	**Change in waist circumference (cm)**	**P- value**
HP	102.91± 6.42	93.65 ± 7.55	9.26	<0.001
LP	102.21 ± 8.84	95.39 ± 8.05	6.82	<0.001
HP + LP	102.56 ± 7.55	94.52 ± 7.67	8.04	<0.001

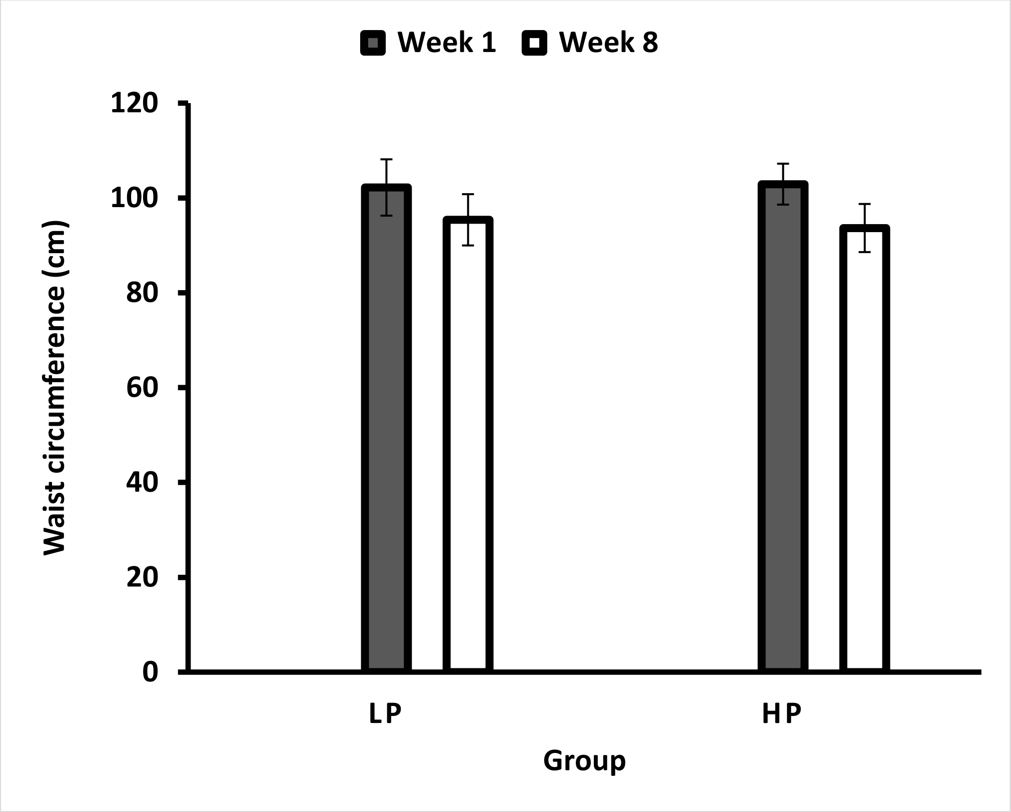

Figure 13 Waist circumference before and after the intervention for HP and LP groups. There was no significant difference between groups (p= 0.868).

4.4.3. Effect of dietary protein with energy restricted energy diet on satiety

4.4.3.1.Desire to eat

The level of desire to eat was also determined for the study groups over time (pre-test, 30 minutes, 60 minutes and 90 minutes from the test meal). A score of 0 represented "not desire to eat at all ", while 10 represented "extreme desire to eat". Overall, in the HP group, the desire to eat expressed as area under the curve (AUC) was lower than in the LP group (Figure 14) from 0 to 90 minutes and from week 1 to week 8 which means the HP group experienced less desire to eat than the LP group. ANOVA and AUC for fullness indicated that there was no significant diet effect when comparing the HP and LP groups (Table 12 and Figure 14).

Table 12 Desire to eat at pre-test, 30 minutes,60 minutes and 90 of test meal, by study group, by study group

Study group n=11, each group	Pre-intervention (Mean ± SD)	Post-intervention (Mean ± SD)	Changes in desire to eat	P- value
Pre-test				
HP	4.64 ±2.34	3.91 ±1.97	- 0.73	0.251
LP	4.36 ±2.46	4.18 ±2.09	-0.18	0.438
HP + LP	4.50 ±2.35	4.05 ± 1.99	-0.45	0.277
30 minutes				
HP	2.82 ±2.44	3.18 ± 2.78	-0.36	0.305
LP	3.18 ±2.48	3.55 ± 2.07	0.37	0.345
HP + LP	3.00±2.41	3.36 ± 2.34	0.36	0.257
60 minutes				
HP	2.82 ± 2.18	2.27 ± 1.49	- 0.55	0.206
LP	3.82 ±1.66	3.82 ± 2.27	0.00	0.500
HP + LP	3.31 ±1.96	3.05 ± 2.04	0.26	0.313
90 minutes				
HP	2.73 ± 2.41	3.82 ±3 .25	1.09	0.105
LP	4.27 ± 2.15	4.82 ± 1.89	0.55	0.299
HP + LP	3.50 ± 2.37	4.31 ± 2.64	0.81	0.068

4.4.3.2. Fullness score

The level of fullness after the test meal was also determined for the study groups over time (pre-test, 30 minutes, 60 minutes and 90 minutes from test meal). A score of 0 represented "not full at all", while 10 represented "extremely full". Overall, in the HP group, fullness expressed as area under the curve (AUC) was greater than in the LP group (Figure 15) from 0 to 90 minutes and from week 1 to week 8, which means HP group experienced more fullness than LP group. Both ANOVA and AUC for fullness indicated that there was no significant diet effect when comparing the HP and LP groups (Table 13 and Figure 15).

Table 13 Fullness score at pre-test, 30 minutes,60 minutes and 90 of test meal, by study group

Study group n=11, each group	**Pre-intervention (Mean ± SD)**	**Post-intervention (Mean ± SD)**	**Changes in fullness**	**P- value**
Pre-test				
HP	5.36 ± 1.75	4.91 ± 2.26	- 0.45	0.314
LP	4.27 ± 2.65	3.91 ± 1.97	- 0.36	0.377
HP + LP	4.82 ± 2.26	4.41 ± 2.13	- 0.41	0.285
30 minutes				
HP	7.00 ± 2.32	7.64 ± 1.86	0.64	0.154
LP	6.64 ± 1.63	5.73 ± 2.49	- 0.91	0.160
HP + LP	6.82 ±1.97	6.68 ± 2.36	0.14	0.401
60 minutes				
HP	6.82 ± 2.22	6.91 ±1.81	0.09	0.441
LP	6.27 ± 1.42	6.64 ± 1.43	0.37	0.246
HP + LP	6.55 ± 1.85	6.77 ± 1.602	0.22	0.280
90 minutes				
HP	6.55 ± 2.54	6.27± 2.61	- 0.28	0.366
LP	5.09 ± 1.70	5.36 ± 1.69	0.27	0.318
HP + LP	5.82 ± 2.24	5.82 ± 2.19	0.00	0.500

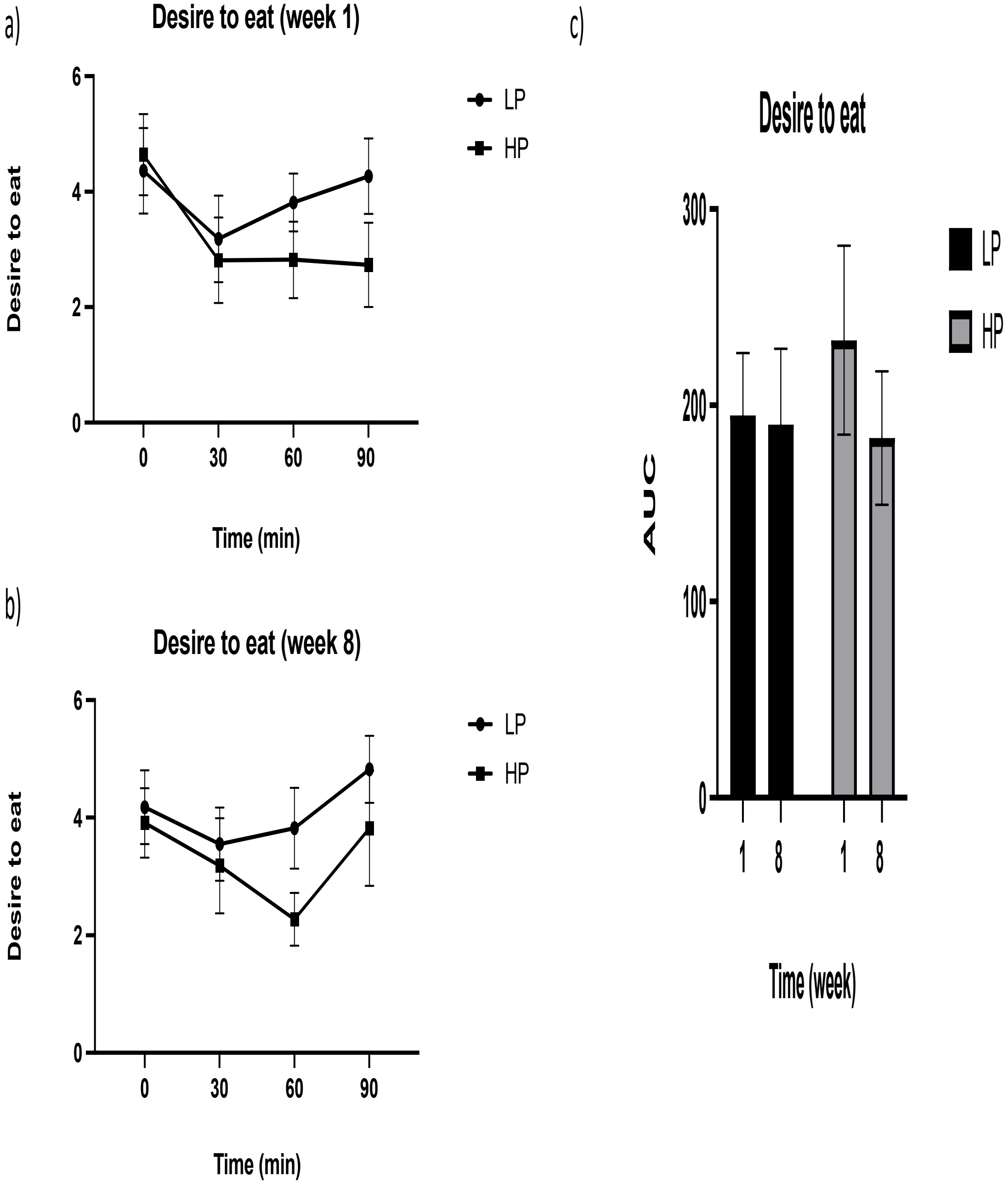

Figure 14 : Changes and area under the curves (AUC) in t the desire to eat (a, b, and c). Parameters were assessed using visual analog scales, scored between 0 and 10. HP or LP groups were completed at pre-teat meal and at 30, 60 and 90 minutes after the test meal. n=11 HP, n = 11 LP at week 1 and week 8. There was no significant difference between groups at week 1 (p=0.588) in desire to eat rate or at week 8 (p=0.564).

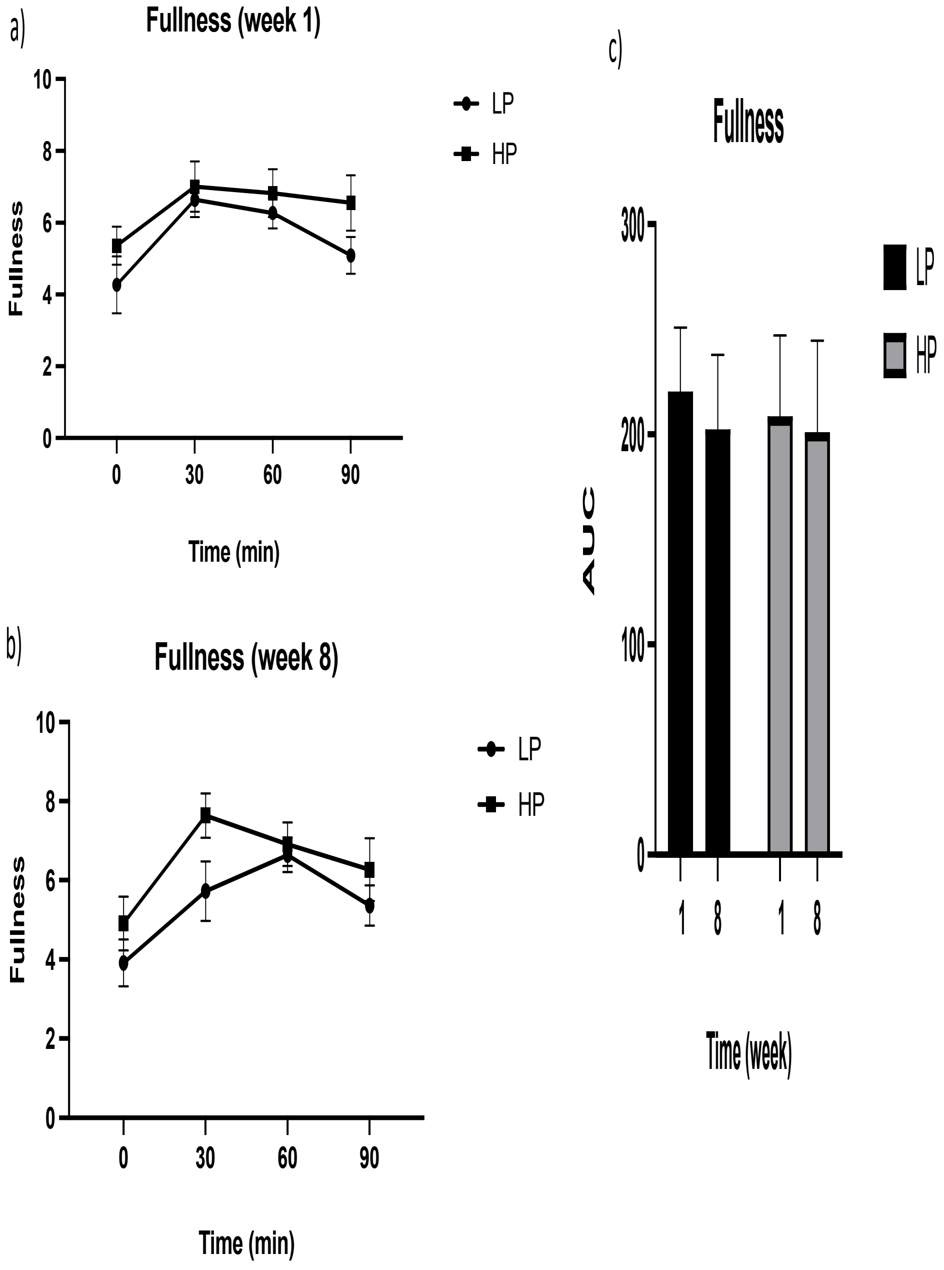

Figure 15 Changes and area under the curves (AUC) in the fullness (a and b, and c). Parameters were assessed using visual analog scales, scored between 0 and 10. HP or LP groups were completed at pre-teat meal and at 30, 60 and 90 minutes after the test meal. N=11 HP, n = 11 LP at week 1 and week 8. There was no significant difference between groups (p=0.541) in the fullness at week 1. Similarly, there was no significant difference between groups (p=0.379) in fullness in week 8

4.4.4. Effect of dietary protein with energy restricted energy diet on health indicators

4.4.4.1. High-density lipoprotein cholesterol

Eight weeks of compliance to an IER diet was tested for change in HDL cholesterol. Overall, both groups recorded very little reduction in HDL cholesterol, and it was not statically significant (Z = -0.071, p = 0.94). Eight weeks of the IER LP diet intervention did not result in a statistically significant change in HDL concentration (Z = -0.89, p = 0.374). Similarly, there was no significant difference in HDL concentration (Z= -0.91, p = 0.362) after eight weeks of a high protein diet. See Figure 16 and Table 14.

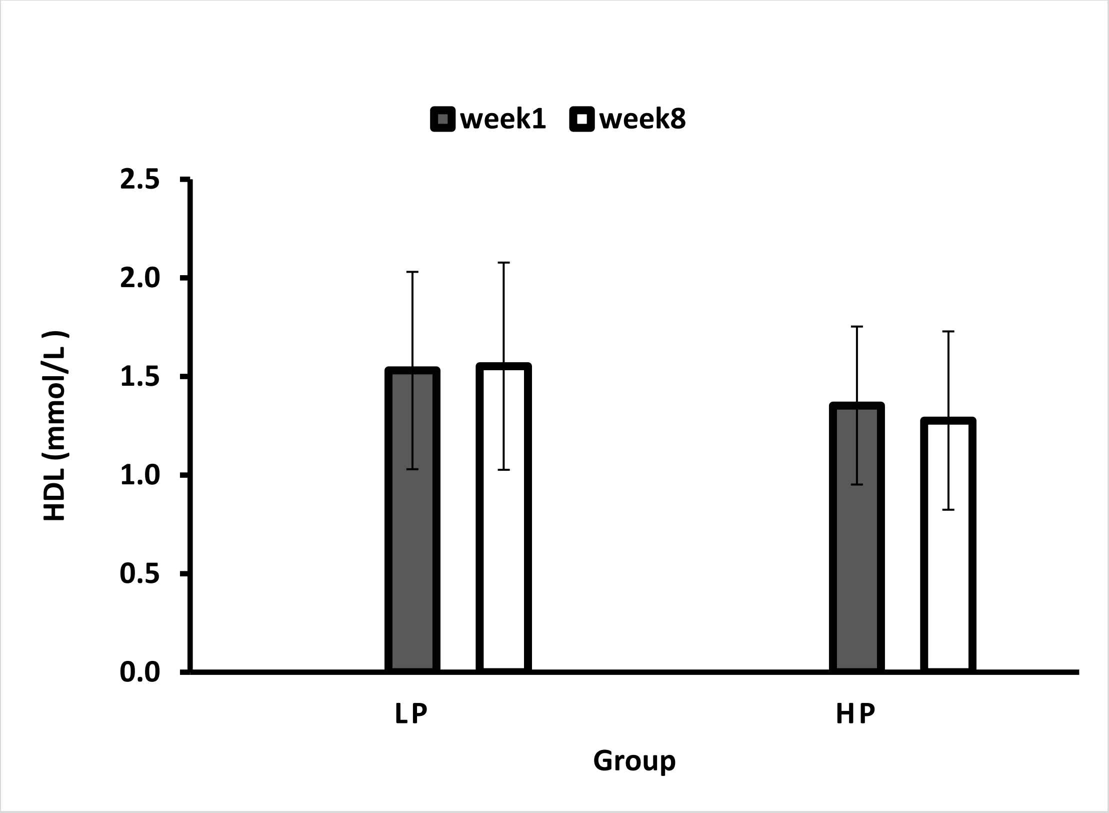

Figure 16 HDL level before and after the intervention for HP and LP groups.
There was no significant difference between groups (p= 0.459).

4.4.4.2. Low-density lipoprotein cholesterol

Eight weeks on the IER diets resulted in no significant baseline to post changes in LDL cholesterol for either the HP and LP groups (Table 14 and Figure 17). In the LP group, results showed no significant reduction between LDL level before intervention (3.28±0.82) mmol/L and LDL level after intervention (3.26±0.59) mmol/L; [t (9) 0.172=, p =0.434]. In the HP group, results indicate no significant reduction between LDL level before intervention (3.15±0.72) mmol/L and LDL level after intervention (3.21±0.44) mmol/L; [t (7) =, p =0.352]. Therefore, there was no difference in LDL changes between groups (Figure 17).

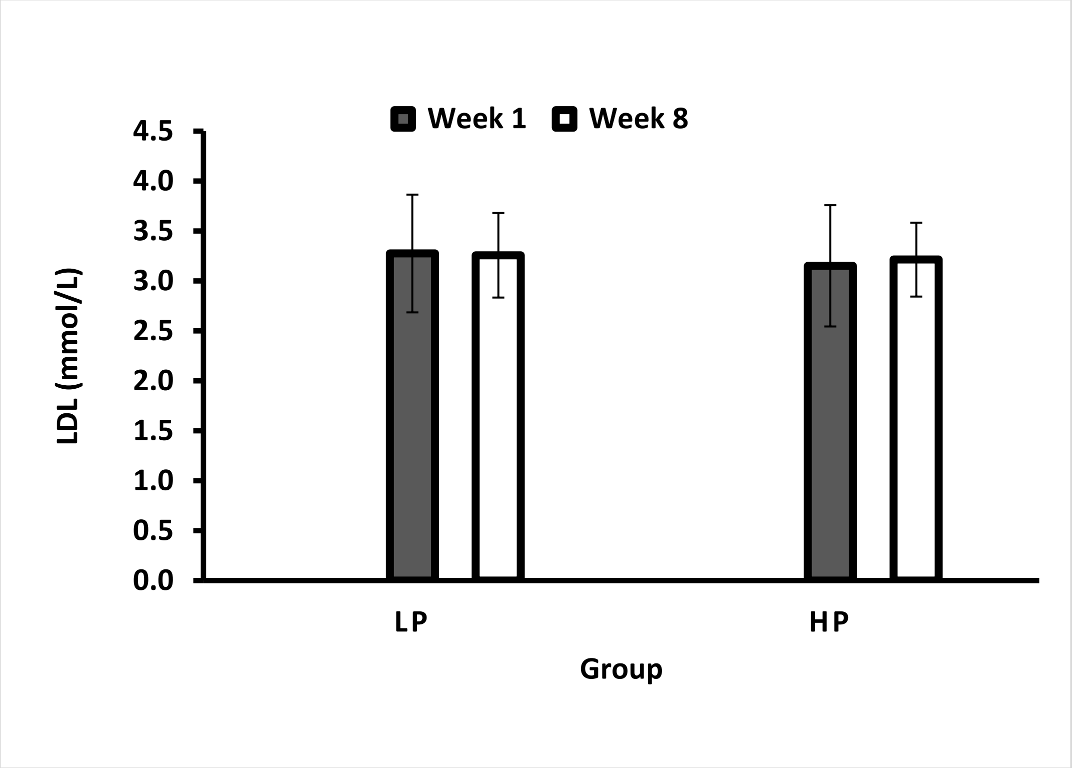

Figure 17 The LDL cholesterol level before and after the intervention for HP and LP groups.
There was no significant difference between groups in the LDL cholesterol (P=787).

4.4.4.3. Triglycerides

Overall, the IER diets result showed a significant effect on triglycerides. Eight weeks on the IER diets resulted in a significant baseline to post changes in the triglycerides for the LP group (Table 14 and Figure 18). In the LP group, results indicate a significant reduction between triglycerides level before intervention (1.61±1.02) mmol/L and triglycerides level after intervention (1.09±0.52) mmol/L; [t (9) = 2.91, p = 0.009]. However, the results indicate no significant changes in triglycerides level between before intervention (1.67±1.81) mmol/L to after intervention after (0.99±0.42); [t (6) = 0.93, p = 0.19] HP group. (Table 14 and Figure18). There was no difference in triglycerides changes between groups (Figure 18).

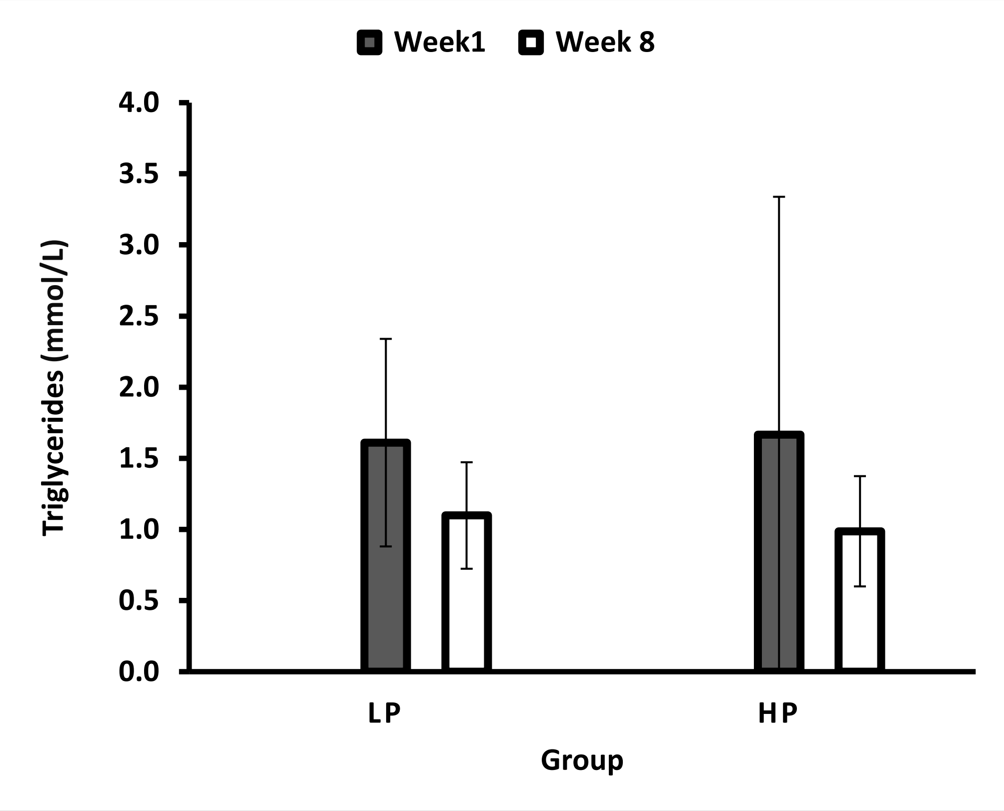

Figure 18 Triglyceride level before and after the intervention for HP and LP groups. There was no significant difference between groups in the Triglycerides (p= 0.948).

4.4.4.4.Total cholesterol

Overall, the IER diets resulted in no significant changes in the total cholesterol (P=0.277). A small increase of 0.05 mmol/L in total cholesterol was recorded for the HP group, while the LP group recorded a reduction of 0.19 mmol/L, which amounted to 1.02% and 3.59% respectively of the initial average of total cholesterol. The results indicated that the LP diet resulted in a significant reduction in cholesterol levels, from before intervention (5.29±0.89) mmol/L to after intervention (5.10±0.73) mmol/L; [t (8) = 1.81, p = 0.05]. For the HP group, no significant reduction was recorded between cholesterol level before intervention (4.91±0.86) mmol/L and cholesterol level after intervention (4.96±0.49) mmol/L; [t (7) =-0.25, p= 0.406]. (Table 14 and Figure 19).

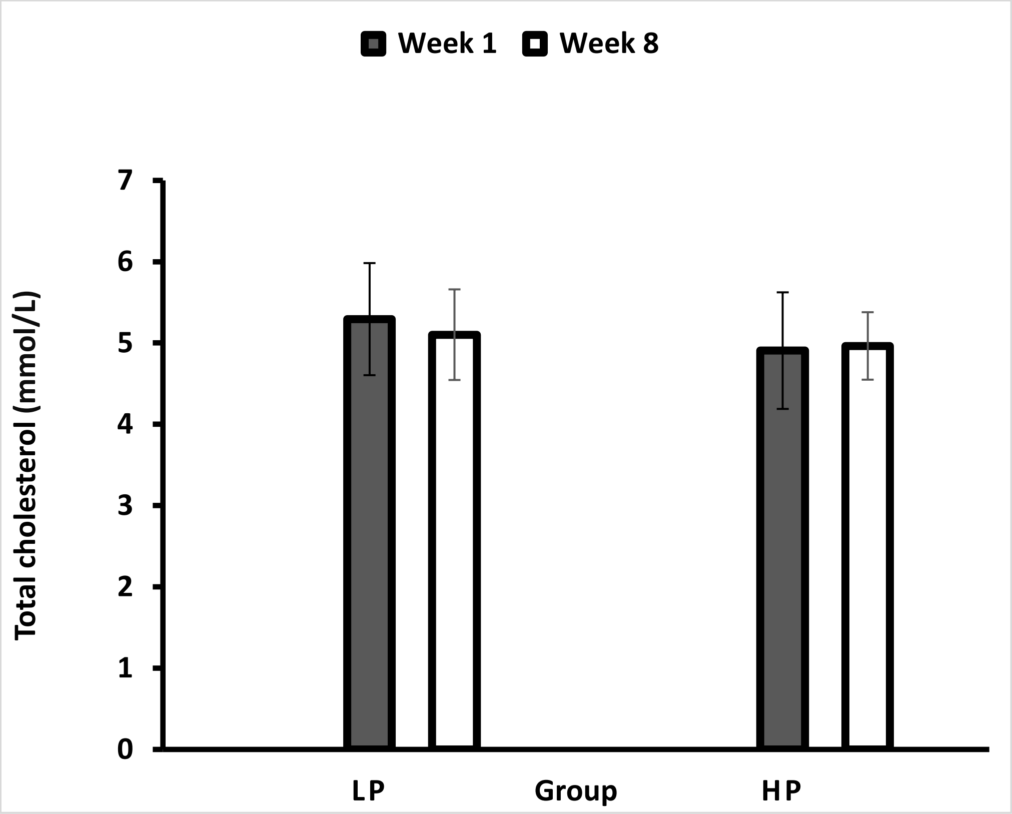

Figure 19 Total cholesterol level before and after the intervention for HP and LP groups. There was no significant difference between groups (p= 0.465).

4.4.4.5. C-reactive protein

Eight weeks of compliance to an IER diet was tested for change in CRP and the results showed no significant changes within groups. Eight weeks of low protein diet intervention did not result in a significant change in CRP concentration (Z = -0.225, p = 0.799). For the HP group, the results indicated no significant reduction between CRP level before intervention (4.56±3.42) mg/L and CRP level after intervention (4.17±3.35) mg/L; [t (6) =0.8, p =0.212].

The HP recorded a little reduction of 0.39 mg/L in CRP which amounted to a reduction of 8.55% of the initial average of CRP. While the LP group experienced an increase of 1.29 mg/L in CRP, which amounted to an increase of 39.69% of the initial average of CRP (Table 14 and Figure 20).

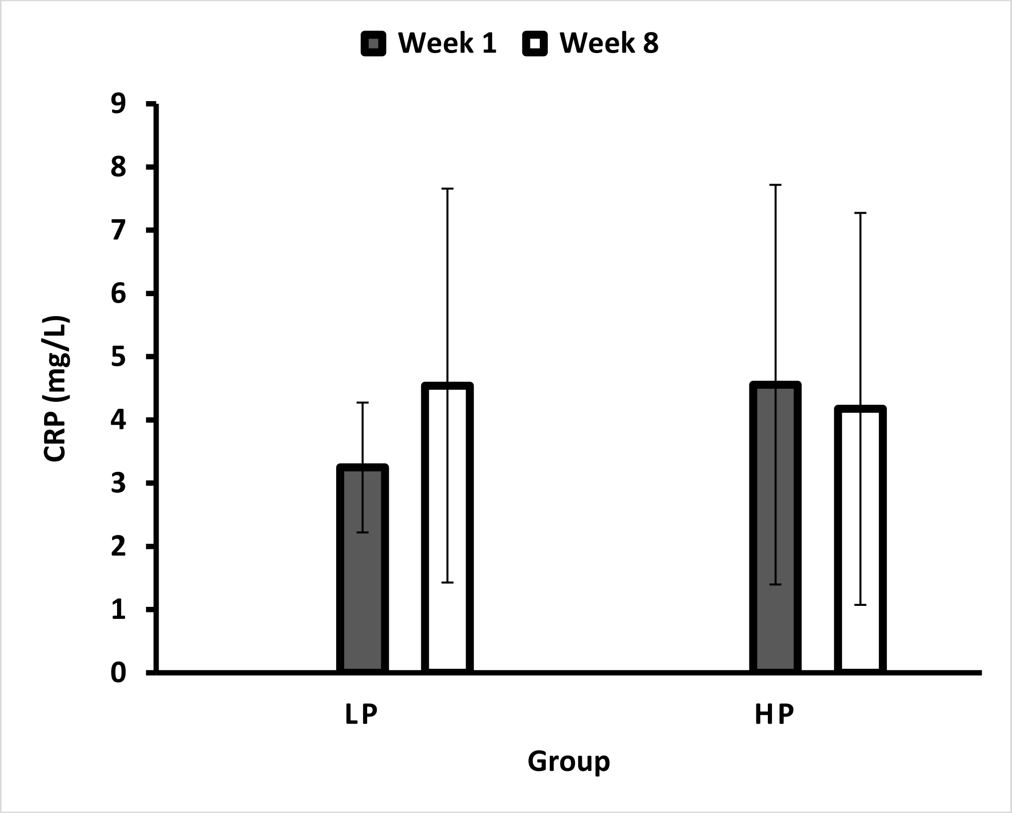

Figure 20 CRP level before and after the intervention for HP and LP groups.
There was no significant difference between groups in CRP (p= 0.742).

4.4.4.6. Hemoglobin A1c (HbA1c)

Only n=6 HP and n=3 LP participants completed the HbA1c tests. There was an overall 0.38% reduction in the initial mean HbA1c for both groups combined (LP+HP). No change was observed in HbA1c levels in the LP group, after the intervention, while the HP group recorded a 0.56% reduction of the initial mean HbA1c (Table 14 and Figure 21).

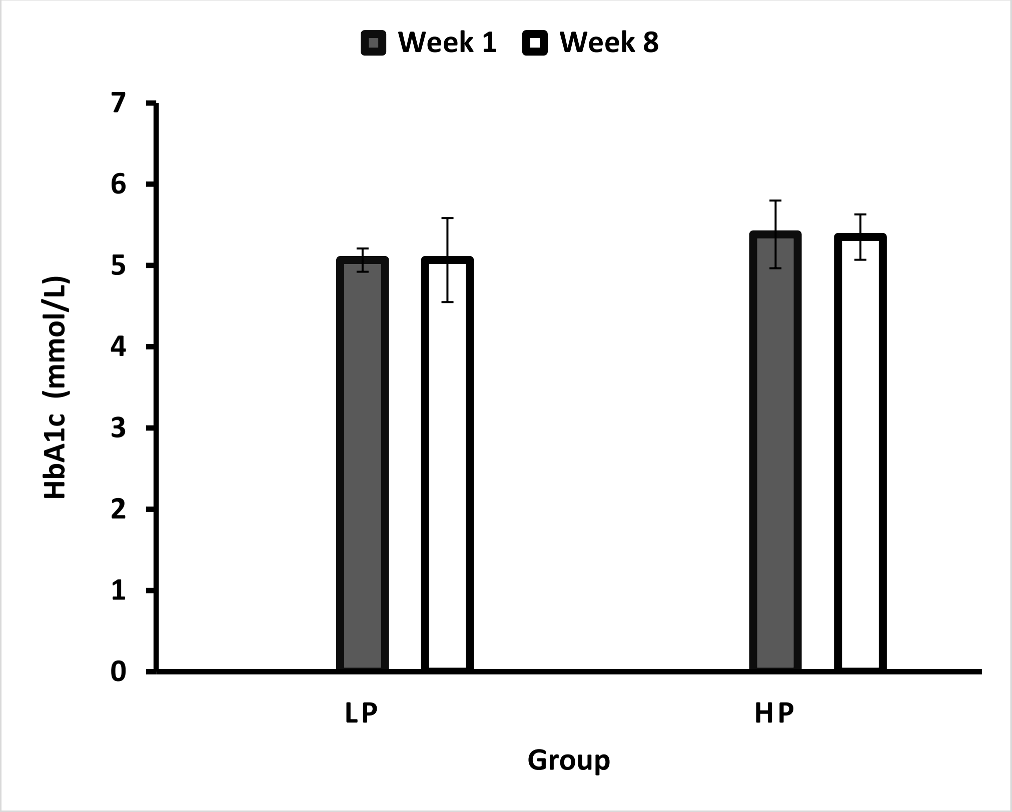

Figure 21 HbA1c level before and after the intervention for HP and LP groups. There was no significant difference between groups in HbA1c (p=0.182).

Table 14 Changes in biochemical characteristics according to diet group 8 weeks of dietary intervention

	LP				HP				LP+HP			
	Baseline, (n)	**Wk-8**	**Δ 8 wk from baseline**	***p***	**Baseline**	**Wk-8**	**Δ 8 wk from baseline**	***p***	**Baseline**	**Wk-8**	**Δ 8 wk from baseline**	***P***
HDL cholesterol (mmol/L)	1.53 ± 0.69 [1.08,1.69]	1.55 ± 0.73 [1.1,1.73]	0.02	0.374	1.35 ± 0.48 [1.01,1.64]	1.28 ± 0.54 [0.96,1.62]	- 0.07	0.362	1.45 ± 0.60 [1.06,1.64]	1.43 ± 0.65 [1.07,1.68]	- 0.02	0.943
LDL cholesterol (mmol/L)	3.28 ± 0.82	3.26 ± 0.59	- 0.02	0.434	3.15 ± 0.72	3.21 ± 0.44	0.06	0.352	3.22 ± 0.76	3.23 ± 0.52	0.01	0.422
Triglycerides (mmol/L)	1.61 ± 1.02	1.09 ± 0.52	-0.52	0.009	1.67 ± 1.81	0.99 ± 0.42	- 0.68	0.194	1.63 ± 1.34	1.05 ± 0.47	- 0.58	0.037
Total cholesterol (mmol/L)	5.29 ± 0.89	5.10 ± 0.73	- 0.19	0.054	4.91± 0.86	4.96 ± 0.49	0.05	0.406	5.11 ± 0.87	5.04 ± 0.61	- 0.07	0.277
CRP (mg/L)	3.25 ± 1.43 [1.54,4.7]	4.54 ± 4.36 [1.15,4.67]	1.29	0.79	4.56 ± 3.42	4.17 ± 3.35	- 0.39	0.212	3.79 ± 2.45 [1.67,4.98]	4.39 ± 3.86 [1.2,8.44]	0.6	0.49
HbA1c (mmol/L)	5.07 ± 0.06	5.07 ± 0.21	0.00	0.500	5.38 ± 0.39	5.35 ± 0.27	- 0.03	0.288	5.28 ± 0.35	5.26± 0.27	- 0.02	0.332

Values are mean ± standard deviation (SD) or median [percentile 25-percentile 75] as applicable. *P* refers to differences calculated paired samples or Wilcoxon test, as appropriate.

4.5. Discussion

4.5.1. Effect of protein content on body weight

In the current study, both high- and low-protein diets induced a significant loss of body weight; combined, participants lost (0.62 kg/wk), with the LP diet leading to an insignificantly greater reduction (0.65 kg/wk), compared to the HP (0.59 kg/wk). That the two groups lost similar body weight is not surprising, even though the HP group consumed about 316 more total kilocalories per person daily for three days every week for eight weeks due to their higher protein intake. This small daily difference would have amounted to 6384 kcal over the 8 weeks period. According to calculations originally proposed by Mellinkoff in 1956, an energy deficit of 7700 kcal per week is required to lose 1 kg of body weight (39) However, research by Redman and colleagues determined that weight loss due to a reduced energy intake is not linear over time, with a deficit of 4858 kcal per week needed for early weight loss, and 6569 kcal needed by 6 months as the body adjusts to decreased energy intake (40). Despite the different estimates of caloric deficit needed to lose 1 kg of body weight, the small difference provided by retaining the minimum protein requirement of 1.2 g/kg body weight resulted in only a 0.5 kg greater weight loss by the LP group than the HP group. A longer study, preferably with more participants, would be required to determine if the weight loss trajectories of the LP and HP groups merged or diverged. However, a year long Australian study with 68 overweight or obese (OW/OB) men who successfully lost weight on energy reduced diets did not find a difference in weight loss between high and low protein versions (41). Indeed, our previous study with similar women who adhered to the same IER diet as this study but only for 3 weeks, lost similar amounts of body weight on both the HP and LP versions (0.82 kg/wk HP; 0.78 kg/wk LP) (42). These losses were greater than in the current study, which might represent a lessening of weight loss over the longer period of time. Indeed, the 12-month study (41) reported a substantial lessening of weight loss over time. A recent systemic review and meta-analysis conducted by Hansen et al. in 2021 compared the effects of high protein versus low protein diets on weight loss (43). They found that high protein has a moderate beneficial effect on body weight control; in which, the higher protein diet-induced body weight reduction by 1.6 kg (1.2; 2.0) (mean [95% confidence interval]) compared to the lower protein group.

The differences in the weight loss results between the current study, our previous study and the Hansen et al. meta-analysis might be due to the effect of the differences in intervention components such as the long duration of that study. Duration of a dietary intervention may affect the efficacy of the intervention on weight management because compliance may decrease over time.

Previous research has reported different effects of protein content on weight loss. A review of long-term clinical trials that examined protein level on weight loss concluded that there was a positive effect of a higher protein intake on body weight and fat mass reduction in both energy restricted and standard-energy diets (11). They also reported fat free mass (FFM) is retained better on a low energy high protein diet (13). Additionally, Wycherley and colleagues conducted a meta-analysis that included 24 randomized controlled trials that involved 1,063 adults and found that the high-protein diet group (27%–35% of total energy intake consumed as protein) experienced a greater reduction in body weight than the standard protein diet group (16%–21% of total energy intake consumed as protein) (44). The contradiction between our findings regarding body weight and those of previous studies might be due to our study's small sample. The difference between our protocol, such as the duration of the study, and that of other studies is another possible reason. Thus, caution should be exercised when interpreting these results because different results could have been found in a larger sample size. A large intervention study is necessary to reach a clear conclusion regarding the effect of protein content levels on body weight.

4.5.2. Waist circumference and protein content

The IER diets in this study resulted in a reduction in waist circumference in both groups (mean -8.04 ±1.01 cm/wk). This waist loss may be considered clinically significant because evidence suggests that a reduction in waist circumference by 3 cm improves health in those with metabolic syndrome (45,46). Although the HP group showed a greater reduction in waist circumference (-8.3 cm; 1.04 cm/wk) than the low-protein group (-6.8 cm; 0.85 cm/wk), this difference was not statistically significant. Similarly, in our previous 3 week study with comparable participants on the same IER diets, no difference in waist circumference between HP and LP groups was found (HP, -0.64 cm/wk; LP, -0.61 cm/wk).

Other researchers have also reported a lack of additional benefit from HP versions of weight lost diets to decreases in waist circumference. A randomized controlled trial found no statistically significant difference in waist circumference loss in OW/OB individuals between a HP (30%; n= 33) versus normal protein (15%; n=43) diet combined with a restricted-energy diet after three months (47). Similarly, Witjaksono et al. tested the effects of a HP (22-30% PRO versus a LP (12-20%) weight loss diet and also reported significant reductions in waist circumference, although these were not different between groups (44).

In contrast, other researchers reported that a higher protein level in a weight loss diet was more beneficial to loss of waist circumference. For example, a 12-week randomized controlled trial reported that an energy restricted, higher protein diet (25% protein) induced a significantly greater reduction in waist circumference than did a standard protein diet (15% of total energy from protein) (48). Why some studies demonstrate a benefit of high protein over lower protein for waist circumference reduction is not clear. Possibly the duration of the interventions and the amount of energy restriction could be contributing to the dissimilarities of the findings among such studies. Additionally, the differences in the level or source of protein content might be a reason for the difference in findings between the previously mentioned studies.

Data from studies on protein intake by adults who are not on experimental diets suggests a benefit to higher protein to waist circumference. For example, a cohort study that included 22,433 middle-aged men and women investigated the effect of dietary protein on waist circumference over five years and found an inverse association between protein intake and increases in waist circumference, particularly in individuals with the greatest initial BMIs and waist circumferences (49).

The reduction of waist circumference is crucial from a clinical perspective. Waist circumference is positively associated with the amount of visceral adipose tissue (50), which is considered a major risk factor for atherogenic profiles, diabetes (51), and cardiovascular disease (52). Thus, reducing waist circumference is a treatment goal for lowering health risks.

Our study was conducted remotely and therefore body composition data could not be collected. However, other studies have investigated the role of dietary protein in body composition. A review reported that consuming a HP, energy restricted diet can benefit body composition beyond that achieved by a lower protein diet due to the retention of more free fat mass (53). Similarly, a randomized controlled trial not included in the above review compared the effect of different levels of protein content (20%, 27%, and 35% of total energy as protein consumed) in a restricted energy diet on 80 women with a BMI of 27.5–45 kg/m2 over three months (54) and observed that the highest protein content group achieved the greatest reduction of fat mass and visceral fat. However, there was no significant difference in body weight reduction between groups. Although we did not measure fat mass, the reduction in waist circumference is often interpreted to imply a reduction in abdominal visceral fat (55). Further interventions to investigate the effect of dietary protein content on free fat and fat masses are necessary to explore the effect of dietary protein content in restricted-energy and especially IER diets on body composition changes.

4.5.3. Satiety

The current study aimed to examine the effects of low versus high dietary protein intake combined with an IER diet on appetitive response in overweight and obese women. The satiety parameters included the desire to eat and fullness scores. Participants in the HP group reported a lower desire to eat score than the LP group from week one to week eight at pre-test meal 30-, and 60-minute time points, although these differences were not statistically significant. However, by 90 minutes, the effect of the HP diet on the desire to eat was diminished. Similarly, examination of the AUC in our data showed that the HP diet resulted in a lower desire to eat than the LP diet but, again, it was not statistically significant. It is critical to consider that controlling the desire to eat plays an important impact in satiety management because the physiological condition of hunger affects the level of desire to eat (56). Although the ANOVA data at most time points and the AUC data both showed high protein diet resulted in a lower desire to eat than the low protein diet, there was no significant difference between groups. Total AUC is commonly regarded to be a better measure of satiety because it considers the responses for full periods of time instead of focusing on individual time points. Indeed, a higher protein level than the amount that is used in the current study of protein might have been more efficacious on satiety. For example, a randomized crossover study compared the effect of different amounts of protein intake on the desire to eat over 18 days and observed that the desire to eat was lowered by increasing the protein content by 125% of the recommended dietary allowance but not by increasing it by 93% and 63% (57).

Evidence shows that food taste is a critical factor impacting such components of satiety as fullness and the desire to eat (58). The taste of food is essential for prompting the brain to send either negative or positive satiety signals. Taste stimulates the desire to eat, thus influencing whether people feel compelled to eat more (58). Brondel et al., for example, examined the effect of adding well-liked condiments to French fries and brownies on satiety and food intake (59). They found that people ate more food when the condiments were added, especially if additional food with the added condiments was offered after the basic foods were consumed (59). Consequently, in this study, we considered the participants' favourite flavours in the test meals to minimize the bias of their desire to eat and satiety responses. Participants were asked to select the test meal flavour while retaining the components required for the meal (total energy range and the macronutrient composition). Additionally, the literature has also suggested that BMI is positively correlated with the desire to eat (60). Thus, one strength of our study is that we narrowed the criteria of BMI for the participants to increase the homogeneity of the results.

The VAS fullness score was used in our study to determine if participants remained feeling full longer after eating an HP test meal. Comparisons of the effect of protein content on fullness rate between groups at time points pre-test meal, 30, 60 and 90 minutes did not show that there were no statistically significant differences between groups. However, the AUC for fullness for the HP group was greater than for the LP group in absolute terms but it was not statically significant. This study's results differ from our previous study in which the participants experienced more satiety with the HP diet than LP diet (42). A possible reason for the different findings is that in the current study, we used different subjects for the HP and LP diets, whereas in our previous study, the cross-over design allowed the participants to contrast their satiety on the two diets. The crossover design is more efficient in comparison to using a parallel design because it eliminates the between-subject variability and increases the sensitivity, due to each participant being his/her own control. However, the two studies did not use comparable methods to test elements of satiety; this study used a test diet before and after their HP and LP diets, whereas in our previous study, the participants compared their HP to LP dietary experiences without the use of a test diet. Nevertheless, many other studies have suggested that high-protein intake positively impacts fullness. For instance, Veldhorst et al. compared the effects of a high-protein meal (25% of total energy from protein) versus a normal-protein meal (10% of total energy from protein) on subjective satiety in healthy adults. They designed their test meals to have similar organoleptic (colour, taste, smell, texture) characteristics They observed that a higher protein content produces more fullness and less hunger (61). Similarly, a study compared two 24-hour diets (29% protein, 10% fat, 61% carbohydrate versus 10% protein, 60% fat, 30% carbohydrate) and noted less hunger and more fullness with a high-fat diet than with a high-protein diet (8). The connection between satiety, including fullness, and weight management is based on evidence that measures of satiety can predict total energy intake and weight reduction in obese adults (62). Therefore, that high protein diets may improve satiety suggests that it may decrease energy intake, which concurs with a review that reported that high-protein intake decreases both the desire to eat, and hunger (63).

Some evidence has indicated that early benefits from a high-protein diet and weight loss on satiety responses might attenuate over time. A randomized study examined the effect of a high-protein diet (30% of total energy) versus that of a low-protein diet (15% of total energy) with energy intake restricted to 30%–35% of the total energy required for weight maintenance over six weeks (64). These researchers reported that the high-protein group experienced greater satiety and less hunger than the high-carbohydrate group in weeks three and four (64). However, the differences between the groups decreased in weeks five and six, although the high-protein group maintained a higher satiety level (64). The reduction in satiety might be due to the physiological compensatory response that occurs when increasing food consumption after body weight reduction. Evidence suggests that compensatory metabolic responses resist energy deficiency in order to attenuate disturbances in energy balance (18). In doing so, they decrease energy expenditure and appetite-enhancing hormones (18).

4.5.4. C-reactive protein

In the current study, we hypothesized that the HP group would have a greater reduction in CRP than the LP group. To some extent, our findings supported this hypothesis. We observed that the protein content affected the CRP levels as the CRP decreased in the HP group by 0.39 mmol/L (8.55%), while it increased in the LP group by 1.29 mmol/L (39.69%), although the difference between the groups did not reach statistical significance.

A few dietary intervention studies have examined the effect of dietary protein on such markers of inflammation as CRP. We previously examined the effects of very similar HP versus LP IER diets on OW/OB women and determined that the IER diet appeared to reduce CRP after three weeks; however, that study was not sufficiently powered to determine a difference between HP and LP groups (42). Azadbakht et al. also conducted a randomized controlled trial that compared the effect of a high-protein diet (25% of total energy from protein) versus a low-protein diet (15% of total energy from protein) on 60 overweight and obese women over three months (48). They reported that, although the high-protein diet induced greater body weight loss and waist circumference reduction, both diets induced a reduction in CRP regardless of the amount of protein content (48). Likewise, a systematic review that investigated the effect of weight loss intervention (surgical, lifestyle, dietary, and exercise intervention) on CRP concentration in controlled trials concluded that body weight reduction alone is effective for reducing CRP concentration, independent of the intervention (65). This finding might be the reason for no significant difference between groups in CRP in our study, since there was no significant difference in body weight loss between groups.

Previous studies suggested that the elevated CRP measures of the participants in our current study could have had a wide range of etiologies, such as a high BMI (66), sleep disorders and even periodontal disease (67). Perhaps a more likely reason for observing the high CRP levels in the current study is that the study was conducted during the COVID-19 pandemic. Evidence suggests that a heightened immune system from COVID-19 stays activated for as long as eight months, even after recovery from the virus (68). Similarly, a recent study showed that even a few months after a mild case of COVID-19, macrophages altered inflammatory and metabolic expression, and the immune system became more sensitive (69). They observed that the number of pro-inflammatory eicosanoid molecules increased after several months of COVID-19 recovery (69). According to Nova Scotia Health's current (effective 3/23/2023 to 3/23/2024) Laboratory Test Reference Ranges, CRP results should be interpreted as follows for levels of cardiovascular risk: low, <1 mg/l; average, 1-3 mg/L; high, >3 mg/L (70). The mean results for all groups of CRP results in our study lay in the high category but with considerable variability, which suggests that some participants, although not all, had been exposed to COVID-19. Therefore, the effects of protein level on inflammation were likely overwhelmed by those of viral inflammation.

The link between high-protein intake and inflammation as informed by CRP levels is inconclusive. Peng and colleagues provided participants with food for an intervention comparing 15% versus 25% of energy from protein for 12 weeks; participants lost body weight but increased their hs-CPR (71). This difference might be due to the variances in dietary patterns and dietary protein sources among the study's population. Lee et al. reported that dietary pattern was indeed reflected in CRP results (72). One cross-sectional study reported a significant positive association between a high intake of red meat and CRP levels (73). However, another cross-sectional study found a positive association between CRP and processed meat but not with red meat or poultry (74). Long-term intervention controlled trials may be able to accurately determine the effect of dietary protein content on CRP.

4.5.5. Lipids profile

Overall, the current study found no differences in the effects of high-protein versus low-protein IER diets on most lipids (i.e., LDL, HDL, and cholesterol), with neither diet having a significant effect. However, we observed a 40.72% decrease in triglycerides in the HP group and a 32% reduction in the LP group, although only the triglyceride reduction in the LP group was significant (p=0.009). At baseline, the means of neither group met the level attributed to high risk (>1.7 mmol/L), although both were close to it. In individuals with metabolic syndrome, such reductions (40.72% and 32%) would be clinically meaningful (75). Indeed, a systematic review and meta-regression analysis of randomized controlled trials stated that reducing triglycerides lowered the risk of major vascular events in randomized controlled studies (75).

Weight loss alone typically results in lowering circulating levels of triglycerides, with one meta-analysis specifying that, on a population basis, for every 1 kg lost in an obese person, triglycerides would be lowered by 0.21 mmol/L (76), which is about double the reduction in triglycerides per kg of body weight in our study. Evangelista and coworkers conducted a randomized controlled study that involved restriction of energy intake in 76 overweight and obese subjects to compare the effect of high-protein (30% protein) and normal-protein diets (15% protein) over three months (47). Their reduction in triglycerides per body weight loss was higher in their HP group although both groups demonstrated much lower triglycerides per body weight loss that those in our study. Overall, the effects of dietary protein level on circulating triglycerides remains confounded by factors that have not yet been clearly defined.

We found little effect of the IER diet or protein level on total cholesterol, LDL cholesterol, or HDL cholesterol in our study. Others have reported both similar and different results. Evangelista et al. tested a 15% versus 30% protein diets and found no changes in HDL or LDL cholesterol due to either energy restriction or protein level, but a significant, 11.7% drop in total cholesterol in the high protein group (41). Mateo-Gallego et al., compared 20%, 27%, and 35% of total energy as protein, and reported that increasing the protein content resulted in mixed effects on the lipids profile (54). No changes were found in total, HDL, and LDL cholesterol in the 20% and 27% protein groups but in the group who consumed 35% of total energy as protein had significant reductions in total cholesterol and LDL cholesterol, but an undesirable reduction in HDL cholesterol (54). Farnsworth and coworkers tested 16% versus 27% energy from protein energy reduced diets for 12 weeks and reported significant reductions in both total and LDL cholesterol, and an increase in HDL cholesterol. (77). Nevertheless, Azadbakht et al. compared restricted-energy diets formulated to provide 1,300 and 1,600 kilocalories for women and men, respectively, with high-protein (24% of total energy from protein) and low- protein diets (15% of total energy from protein) over 12 weeks; they reported no significant difference in blood lipid levels between the groups (48). Similar to Azadbakht, Johnston et al. compared a high-protein diet (32% total energy) to a standard protein diet (15% total energy) in a randomized trial (64). They measured LDL cholesterol and total cholesterol and found that, while HDL ratios were not significantly affected in either group, total cholesterol decreased dramatically in both groups (64). A reason for differences in results among studies is not clear. Possible causes include differences in the absolute amounts of protein, the cohorts used, and the protocols themselves. Additionally, certain dietary constituents can result in different outcomes. For example, when comparing a high-protein diet with a high glycemic index to one with a low glycemic index, an increase in total cholesterol and LDL cholesterol concentrations was found, unlike in the observed results of a high-protein diet with a low glycemic index (78). These different findings could imply that changes in the lipids' profile are more closely associated with the glycemic index level than with protein content (78).

Similar to intervention studies, relevant cross-sectional studies have produced different findings concerning the association between protein content levels and lipid concentrations. For instance, when a cross-sectional study that involved 23,876 adults compared those with an intake of up to 0.8 g of protein per kg/day with those who typically consume 1.5 g of protein/kg/day, the latter group was associated with higher HDL cholesterol concentrations (79). Nevertheless, a systematic review found little or no association between protein content and lipids concentration (80). The reason for these different findings could be that changes in dietary patterns in different countries and pattern sources may lead to varying relationships between dietary protein lipids profiles. Moreover, protein sources are another reason for these different findings. A systematic review and meta-analysis of randomized controlled trials concluded that replacing animal protein with a plant protein is associated with reducing LDL cholesterol and non–high-density lipoprotein cholesterol (81). It is important to conduct further studies examining the effect of IER diets with high protein levels to obtain a clear conclusion regarding the effects of dietary protein with IER on plasma lipid profile because improving plasma lipid profile, especially in obese individuals, is highly associated with reduced risk of cardiovascular diseases (82).

4.5.6. Hemoglobin A1c (HbA1c)

We hypothesized that a high-protein diet would induce greater improvement in HbA1c than a low-protein diet since evidence indicates that middle-aged overweight and obese individuals tend to have slightly elevated HbA1c. In contrast, our study found no change in HbA1c level in either group and no significant difference in HbA1c between the two groups. Our findings are also inconsistent with a meta-analysis comparing the effects of a high versus moderate protein diets on glucose metabolism, including HbA1c, in individuals with type 2 diabetes (83). Their findings indicated that HP diets lead to a greater reduction in HbA1c concentration. Similar to the meta-analysis findings, a randomized controlled intervention compared diets consisting of 18% versus 35% protein with a restricted-energy diet (1,200–2,000 kcal per day). The HbA1c concentration in both groups was significantly reduced at 3 months, and more greatly reduced in the HP group. Further improvements in HbA1c declined by 6 months; although still significant for each group, the differences between protein diets groups no longer remained. However, the efficacity of the HP diet remained apparent from the results of a different measure of glycemic control, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), which indicated that the HP diet exceeded that of the LP diet on glycemic control (84). Enhanced glycemic control would diminish the risk of microvascular complications for individuals with type 2 diabetes and prediabetes (85). Evidence indicated that every 1% decrease in glycated HbA1c is associated with enhanced long-term results (86).

It is critical to mention important factors that may have caused our study to differ from previous findings included in the meta-analysis, which may have caused a bias in our findings (83). First, besides having a small sample size, our study was missing a significant amount of blood-based data, making it difficult to detect minimal differences between the groups. Additionally, most participants had normal HbA1c levels at baseline, and improvement is more likely to appear in individuals with abnormal HbA1c levels. The available data concerning the effect of a high-protein diet on HbA1c were inconclusive and required confirmation in further studies. For example, in the previously mentioned meta-analysis(83), although high protein positively impacted HbA1c, it did not impact fasting blood glucose levels, whereas the more recent intervention found differences among all measures of glycemic control (fasting glucose, HbA1c, and HOMA-IR), especially over time (87). A possible confounding factor in using HbA1c as the measure of glycemic control is that a higher than usual intake of branched chain amino acids have been positively correlated with increased HbA1c (88).

4.6. Limitations and implications

Conducting this study remotely resulted in limited control over environmental conditions in measuring subjective satiety responses. However, this study has specific criteria which would assist in obtaining homogeneity of the results; for example, evidence shows that men have different physiological responses to satiety than women. Similarly, age and BMI influenced the results. Therefore, the results of the current study are limited to women with similar BMI and age and cannot be extrapolated to other populations. Further research investigating the effects of IER on men and women over age 55 and those with greater obese would be beneficial. Another limitation of the current study is that no data was collected from Lifesum app to confirm that the total energy intakes of the participants were within the total energy needs to maintain body weight from day four to seven. Moreover, the lack of human studies and the wide range of protocols for IER make it difficult to find a clear strategy for practicing IER for this cohort so that doctors and dietitians can properly direct their patients. However, this study may contribute to the literature by confirming the results of others and filling identified gaps in previous studies regarding the effect of protein content in IER on improving satiety, glycemic control, and lipids profiles. Most of the intervention trials that examine the effects of intermittent energy restriction on health indicators (lipid profile, glucose metabolism, weight loss) lack detailed information about diet. These studies mainly focused on comparing intermittent energy restriction to continuous energy restriction or another objective that differs from what the current study. Therefore, we compared our results with previous studies that examined dietary protein levels combined with forms of restricted energy diets, as intermittent energy restriction is considered one type of restricted energy diet.

4.7. Conclusion

This study used telehealth methods to investigate whether an eight-week HP diet combined with IER would improve satiety and induce a reduction in body weight and waist circumference more than LP diet. It also investigated whether an HP diet would be more effective in enhancing health indicators, including the lipids profile, HbA1c, and CRP, than an LP diet. Both diets led to considerable body weight and waist circumference reductions but these were not significantly different between groups. High CRP levels suggested that most participants were still recovering from COVID-19 infection. Triglyceride levels were substantially reduced, especially by the high protein condition; although not statistically significant, this finding is of clinical importance. Neither the IER or protein levels affected LDL-cholesterol, HDL-cholesterol, total cholesterol or HbA1c values. Despite these lacks of differences, our finding that the HP group felt greater satiety after their test meal suggests that a HP version of an IER diet might increase its sustainability over the months needed to fully benefit from reduced body weight and other health benefits provided by adherence to an IER diet.

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CHAPTER 5: BENEFITS OF AND BARRIERS TO UTILIZING TELEHEALTH TO DELIVER DIETARY INTERVENTIONS

5.1. Abstract

Telehealth is used in health care and many types of health-related research as a safe alternative to the traditional face-to-face approach to healthcare, especially in light of recent precautions for preventing the spread of COVID-19. Limited dietary intervention studies have examined satiety using telehealth. This paper aims to discuss the pros and cons of telehealth based on my experience conducting a dietary intervention study to test the effect of dietary protein content on satiety, body weight, and certain health indicators. Telehealth was cost-effective and the data was easy to manage. However, study protocol plays an essential role in both the effectiveness and level of the difficulty when using telehealth. To ascertain the accuracy and reliability of telehealth methodology, further research that compares telehealth to traditional methods when conducting dietary intervention would be beneficial.

Keywords: telehealth, remote intervention, self-report.

5.2. Introduction

The COVID-19 pandemic significantly impacted many aspects of health care, politics, and social interactions worldwide. Canada, like many countries, instituted quarantines and travel restrictions to prevent COVID-19 transmission (1). The pandemic and imposed restrictions constituted a strong reason to shift to alternative methods, whether in healthcare or human research, to reduce the spread of COVID-19. One of these methods is telehealth. The World Health Organization (WHO) defines telehealth as "the cost-effective and secure use of information and communications technologies in support of health and health-related fields, including healthcare services, health surveillance, health literature, and health education, knowledge, and research" (2). This approach has become highly accepted and recommended in some cases among health care providers, especially to ensure social distancing is imposed to reduce the spread of COVID-19 (3,4). Thus, numerous research areas have become dependent on using telehealth as an effective option to conduct research, as it does not require direct interaction between the patient and researcher or the healthcare provider (5).

In light of the spread of the coronavirus and recent WHO recommendations (Jan 10, 2023) (6), the dependency on telehealth by many dietary intervention researchers has increased. Recently, many methods, programs, and software applications have been developed to facilitate conducting telehealth methodology in nutritional research. Technological advances appear to promise to reduce the cost burden, access more target populations, and improve the efficiency of data collection in nutrition research (7). With these benefits, many internet and web-based applications have been classified as valid and reliable to guarantee the confidentiality of patients' information (8). A recent review concluded that telehealth benefits obesity management and intervention, and that the technology was effective and uncomplicated, depending on how the intervention was designed (9). This paper briefly summarizes the benefits and limitations of conducting a dietary intervention remotely and provides recommendations for relevant future research.

5.3. Barriers to utilizing telehealth

5.3.1. Blood test appointments

Based on the current study's protocol, the participants were required to undergo blood tests to establish pre- and post-dietary intervention baseline values. As the current research was conducted remotely with participants in various areas of Nova Scotia, the participants did not have blood tests taken in a research lab; rather, an electronic laboratory requisition form for use in a public blood laboratory was delivered to the participants. All parameters of the blood tests were part of routine bloodwork for patients and were requisitioned as such from the public healthcare laboratory, with no cost to the patient or the study. The patients received a blood test requisition from their physician or from our study's physician, Dr. Zhu, which they could take to any blood clinic across the province.

Conducting blood tests outside of a research lab had both advantages and disadvantages. One positive aspect was that participants could choose from a wide range of blood collection clinic sites since participants were located across the province. This approach was cost-effective and convenient for the participants, especially those with mobility limitations or living far away from the Halifax Regional Municipality. It also eliminated the need for parking in downtown Halifax and waiting in the phlebotomy waiting room during the pandemic. Despite these advantages, we experienced missing lab test results for some parameters, which reduced our ability to interpret the data. For example, a policy in blood collection clinics in Nova Scotia restricts the duration between blood tests for hemoglobin A1c (HbA1c) to a minimum of 80 days. Therefore, our request for retesting after eight weeks was denied for some of our participants, despite evidence that two months is adequate to show changes in A1c (10), When lab results were returned without all expected parameters measured, it was impossible to repeat blood tests because they were conducted in the public blood test collection clinics, from which results often arrived weeks after the blood draws. This was also the situation when improbable results were received. Previously, for a pilot study conducted in our laboratory, we could quickly repeat blood tests. Another issue with data abnormalities arose with the c-reactive protein (CRP) test. Many factors affect CRP test results, such as certain medicines and health conditions that can induce CRP levels to be lower or higher than normal. One participant in our study, for example, had high levels of CRP at the end of week eight. The subject reported that she had a shoulder–joint infection, which could have caused this increased CRP levels.

The COVID-19 pandemic negatively affected healthcare services in Nova Scotia (11,12). Prior to the pandemic, wait times for healthcare services in Nova Scotia were the longest in Canada (13) but became far worse as COVID-19 reached the province, with 32.9% of Nova Scotia residents experiencing appointment cancellations or postponements as a result of COVID-19 (14). Furthermore, some blood collection clinics were discontinued in Nova Scotia. This discontinuation increased the burden on the remaining blood collection clinics and directly contributed to delays in our ability to book the blood tests required before commencing dietary interventions. For example, in only one week in August, 2020, the Nova Scotia Health (NSH) central zone received around 49,000 calls to book blood collection appointments, which greatly exceeded usual levels and swamped their phone lines (15). This increase in requests for bookings combined with a decrease in capacity in Nova Scotia of 4,000 appointments per day compared to the pre-pandemic period (16), resulted in a delay of at least two to three weeks in booking any blood test appointment. Moreover, when patients could not attend their blood tests, they would then need to wait for another two to three weeks for the next opportunity to do so. Accordingly, the delay in conducting blood tests, in some cases, was up to four weeks. Thus, because of delays, booking blood tests was one of the most significant challenges in collecting data in the current study. This delay in booking blood tests also significantly damaged our ability to retain consented participants. Eight participants decided to not participate while waiting several weeks for their blood tests, five participants simply lost interest, two temporarily left Nova Scotia, and one acquired a new job that seemed incompatible with participation in the study. An additional five participants declined to participate because the weeks waiting for their initial blood test appointments would extend their time in the dietary intervention to include the Christmas season.

5.3.2. Satiety measurements

Eating behaviour and food intake research can be performed under laboratory conditions or in free-living situations. Many researchers prefer conducting such studies in a laboratory setting rather than in a free-living environment, arguing that the former provides controlled circumstances free of the turbulence of a natural social environment (17). Therefore, laboratory settings are considered to provide data with highly meaningful external validity, leading to a greater ability to generalize outcomes. In contrast, a free-living setting cannot have as strict controls as a laboratory environment (17). A free-living setting is considered meaningful in ecological validity but likely provides large variations and less accurate outcomes than lab-setting outcomes (18). However, no strong evidence exists that findings achieved in a laboratory study are extrapolatable outside the boundaries of the laboratory setting in free-living humans (19).

Eating is a complex behaviour that is influenced by many factors, such as social norms, educational, and psychosocial factors. Thus, dietary intervention experiments conducted in a laboratory setting likely involve unnatural circumstances. Individuals in real-life conditions, for instance, do not usually have restricted meal times, nor do they eat in a room with monitoring, isolated from surrounding external interactions (20). Thus, eating experiments under laboratory conditions might not be optimal for generalizing findings to the real world. Indeed, compromising accuracy in favour of naturalness in experimental settings based on a study's aims would make the outcomes valuable for reflecting the environmental context and target population (20). Accordingly, in the current study's methodology, the researcher endeavored to incorporate more exacting laboratory-like aspects into the free-living situations of participants. to minimize the gap between the strictly controlled and free-living research designs. For instance, the test meal ingredients were standardized and easy to prepare, which helped participants to correctly follow the instructions. Participants were also instructed to consume the meal at a specific time, and to abide by time limitations. They received a detailed written protocol for judging their satiety in a virtual meeting. The PI remotely monitored the participants to ensure that the instructions were correctly followed. Participants consumed the satiety meal and performed their daily work routines. Thus, the satiety measurement was conducted in a free-living environment with some control over confounding external factors.

5.3.3. Food intake

Since the study was conducted remotely, a food laboratory could not be used. Therefore, it was challenging to measure satiation following a test meal by including a subsequent ad libitum meal in the study protocol. If satiety was examined in a laboratory setting, the protocol would likely have followed this sequence: subjects would (1) consumed a test meal (high or low protein), (2) completed subjective satiety tests at standardized time points, and then (3) researchers would have provided participants with an ad libitum meal. Measuring the food consumed during the ad libitum meal would help to evaluate the effect of test meal on satiety. If one test meal resulted in less food consumed during the subsequent ad libitum meal, then that test meal would have produced greater satiation.

Although including an ad libitum meal with subjective satiety tests would provide more data to examine the effect of dietary protein content on satiety (21), we did not include an ad libitum meal in our study protocol because we did not believe that there was an acceptable method to assess this subsequent food intake due to some concern of the accuracy of self-report. Food intake can be estimated in remote studies via self-report, weighted food records or by analysis of digital images of the food taken participants. Weighted food records are generally considered to be the gold standard (22) but would require participants to weigh the food prior to consumption and the resulting food waste. Although considerably more accurate when performed by a researcher than self-reporting, when the participants are required to perform the weighing, this method is cumbersome to them and can distort their eating behaviour (23). Assessment of dietary intake in remote studies via the use of photography seems promising because it would reduce the burden on participants. Olafsdottir and coauthors assessed food intake of school children in cafeterias by both the weighted plate and photography method and reported a close correlation (24). However, all plates were the same and presented at the same angle for photography, photographed by the same camera, and foods served were similar, which are circumstances that would not be present in our study. Indeed, only a limited number of studies have depended on digital photographs to calculate energy intake under free-living circumstances. Secondly, energy intake estimated through digital photographs has resulted in considerably more errors than weighed records (25). One study reported that the total energy intake estimated from digital photographs was significantly lower than that estimated from weighing food (26). Missing data can be another challenge due to the low quality of photos or delays in sending pictures.

5.3.4. Anthropometric measurements

Remote determination of body weight and height require measurement with instruments, rather than self-reporting based on self-perception because they are occasionally misreported. For instance, obese women are more apt to self-report their body weight as lower than their actual body weight than non-obese women (27). In contrast, women tend to be more accurate in their self-reported height than men, who over-estimate height (28). Underestimating body weight has also been correlated with higher socioeconomic status, self-perceived health, and a healthy lifestyle (29). In this study, participants were required to weigh themselves on their own scales rather than simply reporting what they thought they weighed. Interestingly, on the eligibility self-screening questionnaire many women self-reported their body weight as less than what they stated on the first day of the diet, which required that they used a scale to determine. Such differences might have occurred because participants were sent instructions on measuring body weight and these were discussed in the pre-diet meeting. However, it is challenging to ascertain that they accurately reported their weight or that their scales were accurate. Although body weight before and after the intervention was more important than actual accuracy of the scales, providing an accurate scale would have been preferrable to standardize the error that may have resulted from the type of body weight scale used. We could not provide the participants with a scale because the cost of such scales is $30 to $150 for commercial and $80 to $130 for research-grade scales (3). Providing high-quality body weight scales for participants would have cost more than the available research budget, especially considering delivery costs to remote locations. Evidence indicates that home scales provide adequate and acceptable accuracy and are used in public health research (30). Additionally, studies have demonstrated that most inaccuracies in self-reported body weight are probably attributable to human bias or human error rather than the home scale itself (30).

To increase the validity and minimize the error inherent in self-reported body weight, height and waist circumference values, the participants received instructions on how to take these measurements. For example, to avoid inaccurate self-reported weights, participants were instructed on the following required conditions participants were instructed on the following required conditions for obtaining accurate readings on a scale (31): 1) participants should weigh themselves in the morning before eating without shoes while wearing indoor clothes or no clothes; 2) the scale must be used on a hard, flat surface, as it will not provide an accurate reading on a carpet; 3) the scale should be on a stable, vibration-free surface during use; 4) the scale's batteries should be tested before use because a low battery could cause inaccurate readings; 5) for safety, it is recommended that one's feet be dry; 6) the scale should be kept away from water or moisture; and 7) the weight reading should be repeated three times consecutively to ensure accuracy. Participants also received a tensioned measuring tape specifically made to measure waist circumference, and they were provided with a video that demonstrated how to measure both height and waist circumference measurements based on the WHO method.

The objective anthropometric measurements of body weight, waist circumference, and height represent the most frequently used metrics in health-related research (32). Body weight and height are clinically utilized to estimate nutritional and health status (33). Additionally, many public studies have linked body mass index BMI to the risk of developing health conditions, including type II diabetes (34) and cardiovascular diseases (35). Consequently, undertaking further research to investigate the reasons for bias in self-reporting body measures and determining how to minimize them would likely be useful.

5.3.5. Food scale and waist circumference delivery

To increase compliance, validity, and reliability, each participant received a digital food scale and waist circumference measurement tape. A food scale improves diet compliance and helps participants measure food amounts. It also acts as a tool to educate them on measuring portion sizes and allows for greater accuracy in determination of total energy intake. However, delivering the food scales to remote participants required cost and effort; many participants lived outside Halifax Regional Municipality. The delivery cost via Canada Post ranged from $24 to $37, which exceeded the cost of the equipment. In future studies, giving each remote participant a gift card to buy a scale and tape might be a more efficient, cost-effective way of having them obtain the instruments, although this would increase the complexity of their participation in a study. Additionally, the scales and tapes delivered to participants who withdrew from the study were sometimes impossible to recover and therefore could not be used for further participants.

5.3.6. Other difficulties

The rate of dropouts in the current study exceeded 50%, which is higher than previously reported in dietary intervention studies (36,37). The study itself did not seem to be a factor in their withdrawal, as no participant reported withdrawing because of the difficulties of the dietary intervention and no adverse events connected to the study were reported. However, this study took place during the COVID-19 pandemic and many participants became infected with the coronavirus, leading them to end their participation in the study. As the COVID-19 infections waned, a spike in influenza infections occurred across the province early in the fall of 2022 (38–40), which resulted in the withdrawal of some participants. Adding to the retention difficulties, Hurricane Fiona hit Nova Scotia on September, 24, 2022, causing widespread destruction and prolonged power outages (41). The power outages caused several participants to withdraw from the study because they were not able to prepare their study diets. Finally, one participant withdrew because she found it too difficult to prepare her study food separately from that of her family.

In summary, one of the challenges in conducting this research was not taking measurements in-person by the investigator and depending on self-reporting to obtain measurements of body weight and waist circumference, thus the possibility of bias in self-reporting. To minimize this possible bias, we gave the participants clear instructions about how to measure their body weight and waist circumference and gave the participants valid tools for measuring body weight. In next rearch, giving each remote participant a gift card to buy a scale and tape might be a more efficient, cost-effective way of having them obtain the instruments. Using the telehealth method to measure satiety was challenging because it was impossible to control the environment of test, which may have produced errors in self-reporting of subjective satiety responses. However, using reliable and valid software or app that such as REDCap allowed the PI to monitor participants' responses to ensure the participants filled out the VAS time points on the correct time points.

5.4. The benefits of telehealth method in the study

Telehealth provides many benefits to nutritional research, including the ability to provide education and self-management assistance to facilitate dietary changes that enable and maintain lifestyle changes. It provides rapid options to reach out to patients regardless of their geographical locations and can overcome obstacles to participating in face-to-face dietary intervention. Additionally, a systemic review showed that using telehealth for dietary interventions is more cost-effective than a face-to-face approach (42). The current study used a safe online tool, REDCap, which provided data management and data collection for our research investigations. The REDCap method facilitated the gathering of data in one secure place and allowed it to be easily exported to statistical software such as Excel and SPSS.

In telehealth, the use of virtual appointments instead of in-person meetings accommodates busy schedules. For the present study, we used Zoom Healthcare, which is specifically approved for healthcare providers in Nova Scotia. Zoom Healthcare is classified as an easy-to-use, secure method to guarantee patient privacy and security. Virtual meetings also facilitated rescheduling and expanding the time window to meet patients to include weekends and evenings at the participants' convenience. Such meetings helped the researcher schedule multiple individual meetings in one day, especially during the recruitment phase, while maintaining the privacy of participants’ identities.

The telehealth method also facilitated quickly arranged meetings with patients when they had questions or required clarification. Successful body weight management and dietary intervention programs typically include patient follow-up visits via regular individual meetings or consultations to increase commitment to dietary intervention and support behavioural changes. Evidence suggests that psychological and behavioural dimensions are critical to the maintenance of long-term weight loss involving IER diets (43). Follow-up meetings provide such psychological and behavioural support (44). In the absence of such support, participants are more likely to regain body weight (44).

The Lifesum app is a Calorie tracking software that helps participants create healthy meals and also acts as an educational tool to show them how to meet their DRI requirements based on their choices (45). Additionally, the Lifesum app gives them a large menu. The Lifesum app provides tailored feedback, recipes, and meal plans to fit users' lifestyles. There were extra options on the Lifesum app that were not used because no data was collected on non-restriction days. However, these options might be useful to consider in the next large study. One of these options is that participants have the option to establish communication with the researcher via the use of the application, which serves as a means to enhance their level of motivation in relation to their predetermined goals. The Lifesum application has a feature that facilitates intermittent fasting. This program allows users to customize a fasting diet according to their own needs by including features such as setting a target energy intake for certain days or weeks. This program enables users to monitor their progress and get reminders to stay focused on their tasks in addition to other supplementary attributes aimed at fostering user motivation and adherence to dietary routines. Lifesum offers specialized meal plans tailored to accommodate intermittent fasting practices.

For restricted days, in the main research study (Chapter 4), the Nutrium software was used to create and organize personalized meal plans for each participant at a highly confidential level (46). Each participant had her own file that had their favourite foods and disliked foods to consider when designing their meal plan. Nutrium software uses a large food database with more suggestions for healthy meals that many researchers, or dietitians have used. Also, Nutrium software allows the researcher or dietitian to create eatable cookbook recipes so he/she can edit them based on each participant's energy intake and macronutrient contents. The Nutrium software has an option that allows participants to contact researchers directly and monitor them. However, I could not use this option because we used NSHealth email as the main method to contact the participants as a requirement to meet the NS Health Authority ethical approval. However, using this option of contacting participants via Nutrium might be useful to consider in the next large study.

Using a self-administered 24-hour diet recall software that is automatically coded allows researchers to manage studies and obtain nutrient and food group data files would be useful to overcome the shortcomings of conducting dietary intervention studies remotely online work while maintaining internal validity.

5.5. Conclusions

Conducting dietary interventions via telehealth has many benefits. It facilitates reaching out to participants, regardless of their geographical locations, and the collection of data. However, it is of critical importance to consider the available resources, such as blood collection, when designing a remote study in order to minimize subsequent challenges whenever possible. While the researcher was aware that recruitment and retention would likely be impacted by the COVID-19 pandemic, the resultant faltering of the blood collection system in Nova Scotia in 2022 was not foreseen. This, in turn, lead to some missing data in blood parameters, delays in conducting blood tests, and a decreased ability to retain participants. Despite the reduction in participants, telehealth still prevailed by allowing the completion of this research when all in-person, non-critical human research was required to be paused. Therefore, telehealth has demonstrated benefits in uncertain situations. Future remote intervention studies are needed to evaluate the use of telehealth for specific aspects involved in modernizing dietary interventions, such as the validity of using digital photography to estimate energy intake for measuring satiety.

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CHAPTER 6: SUMMARY AND FUTURE DIRECTIONS

6.1. PhD thesis summary

The prevalence of adult obesity in Canada has risen significantly regardless of sex, age, or geographic location. Trends show that between 2005 and 2017, the proportion of the population categorized as obese grew from 22.2% to 27.2% (1). Energy or caloric restriction, which can follow many different protocols, is one of the key methods for treating obesity and regulating weight. Such diets provide health benefits due mostly to body weight loss. Noncompliance and fatigue resulting from hunger are the most common issues for practitioners to address with this type of diet. Evidence suggests that dietary protein can impact satiety and thus potentially offset some challenges associated with non-compliance. However, more research is necessary to investigate the effect of dietary protein levels on satiety in restricted energy diets. Therefore, the current research project primarily focused on investigating the effect of dietary protein on satiety and body weight, with a secondary emphasis on health indicators (e.g., lipid profile, A1c, and CRP).

Chapter one provided an understanding of the research topic, definitions of research items, and delineations of the research problem and its scope. This chapter explained the importance of the research topic, which seeks to contribute to the resolution of a critical issue, which is obesity. Additionally, the various interpretations as to what constitutes a high protein diet in research that combined it with a restricted energy diets were discussed. Additionally, chapter one highlights the gaps in the relevant literature. One of the gaps in the literature is the paucity of studies that have examined the effect of high protein intake on weight management and health when combined with a restricted-energy diet.

Chapter two assessed through a systematic review, the available research that examined the effect of plant-based versus animal protein sources on satiety using different textures (i.e. liquid and solid), different durations (singular meals to dietary patterns), and different concentrations of protein. This systematic review provided some evidence that there is no differential effect of dietary protein sources (plant- versus animal-based protein) on satiety, regardless of the textures and the concentrations of the protein. Additionally, this systematic review is the first thorough analysis of the effects of varied protein concentrations, contents, and textures on satiety in diets of plant versus animal protein. However, as many confounding variables were difficult to control, appetite became a complicated issue, restricting our findings in the systematic review. We could reduce these constraints, though, by a uniformity of criteria for including research. We also noted that there was no variety in the kinds of vegetable proteins used in the included studies, most of which concentrated on soy. Only a small number of studies have focused on varied types of legumes. Also, since most included studies used only short-term interventions, longer-term intervention studies are necessary.

Chapter three consists of an accepted manuscript for a preliminary study that assessed the feasibility of combining intermittent energy restriction with a high-protein/low-protein diet, and measured the effects on body weight, satiety and inflammation. The case-based approach used in this study with a cross-over design helped to assess the experiment's study design and methodology and additionally, the acceptability of the meals for the diets. A small sample size of six healthy overweight or slightly obese women assisted in testing the acceptability of the diet and the implementation process. Overall, positive results were observed from both the low and high-protein (HP) diets; reduced body weight, waist circumference, and C-reactive protein (CRP), an indicator of inflammation, were measured following both diets. However, participants reported a preference for the high protein diet over that of the low protein diet.

The second study is presented in chapter four. Based on the information that we gained from the pilot study, we did some modifications to the pilot study protocol. For example, although the dietary intervention was similar to the pilot study (three-day fasting followed by four days of non-fasting) we increased the sample size and created more recipes. Additionally, we expanded the duration of the intervention and the health indicators that we examined. The study was designed as a parallel-group, randomized study. We blinded the participants to the main purpose of the study to reduce potential bias in their subjective satiety responses.

Chapter four sought to determine if following a higher protein diet intervention for eight weeks enhanced satiety and promoted a reduction in body weight and waist circumference. It also investigated whether a high protein diet would be more effective in enhancing health indicators, including the lipids profile, A1c, and CRP, than a low protein diet for the same duration when combined with intermittent energy restriction in healthy overweight and obese middle-aged women. This eight week study was conducted using telehealth methodology. Participants in both protein groups consumed a low energy intake for three days, followed by four days of consuming the total energy required to maintain body weight. The groups differed in their intake level of protein. Overall, participants in both dietary intervention groups exhibited reduced body weight and improved lipid profiles, with no significant differences observed between the groups. The HP group reported greater feelings of fullness than the LP group. Both diets induced reductions in body weight, but the LP group noted a slightly higher body weight reduction. However, the HP group reported a greater reduction in waist circumference than the LP group. There was no significant difference in the effect of dietary protein between the groups in A1c, LDL, and HDL, but the HP group showed slightly more improvement in triglycerides, and CRP.

Chapter five provides a reflection on the advantages and disadvantages of using the telehealth method in the second study, that was outlined in chapter four. There were some difficulties in conducting dietary interventions via telehealth; nonetheless, the telehealth method was effective in facilitating the study. The telehealth-based nutritional intervention had several advantages. Contacting participants regardless of their location and collecting data was easier. The telehealth method allowed for the completion of this study when all in-person, non-critical human research had to be postponed due to COVID-19. Therefore, telehealth has proven useful in difficult circumstances. Future remote intervention studies are required to assess the utility of telehealth for nutritional therapies.

6.2. Summary of Research

Both interventions were intensive studies with small sample sizes, but successfully demonstrated that energy restricted intermittent fasting can be implemented for positive health benefits in overweight and slightly obese women. Further benefits were obtained when the protein level was not decreased during the days of intermittent fasting. For example, in the larger study (Chapter 4), the participants in the high protein group reported having less desire to eat than those in the low protein group, which supports many relevant studies that have determined that high protein improves satiety (2–4). We also found that a high protein diet with a restricted-energy diet induced a reduction in body weight similar to that of the low protein group, even though the high protein diet contained relatively more energy content than the low protein diet. Recent results indicate that a high protein diet led to a greater reduction in waist circumference than in the low protein group, which agrees with previous studies' findings (4–6). Conversely, many studies have reported findings regarding health indicators that the present analysis support. Many relevant previous studies have also observed that increasing protein at the expense of carbohydrates can lead to a greater decrease in triglyceride levels (5) , but no effect of dietary protein content on LDL, HDL, and cholesterol (5,6). Some studies have found that higher protein consumption improves glycemic control more efficiently than lower protein consumption (7,8). However, this observation was not apparent in the present analysis, possibly due to the missing A1c data.

6.3. Future research

Future research on the effect of dietary protein on satiety should include examining the effect of appetite-related hormones with subjective satiety tests on a larger sample. The benefit of this research would be a broader understanding of the effect of dietary protein intake on satiety and related metabolic effects. For restricted-energy studies focusing on the effect of dietary protein on body weight loss, incorporating a weight maintenance phase might enable a determination of the effect of protein intake on satiety apart from weight loss. A meta-analysis that consisted of 29 long-term weight loss interventions found that 80% of subjects experienced a regain of more than 50% weight loss within two years (9) . This finding implies that only approximately 20% of patients can maintain their weight loss in the long term. Nutritionists have suggested that increasing protein intake could be beneficial for maintaining the body weight phase for several reasons (10). . Clinical studies have indicated that high protein intake assists in maintaining free fat mass (11,12) and increases thermogenesis and energy expenditure (11,13–15). Additionally, nutritional intervention studies have shown that high protein consumption has a greater impact on improved satiety than the consumption of other macronutrients (16). Nevertheless, the long-term role of a high protein diet has not been adequately established. Additional research is necessary to support the development of effective dietary interventions to prevent and treat individuals with obesity.

Many relevant studies have defined dietary protein interventions as HP or LP, based on the percentage rather than the absolute value of protein. Thus, HP classification might reflect total energy restriction rather than the actual amount of protein. To compare among study results, it is critical to have a standard definition of high, normal, and low protein in restricted-energy diets. With the wide variability in versions of HP diets, the long-term impact of HP on health and body weight and the impact of habitual HP consumption on the effectiveness of HP in weight management and health remain unclear. Further research is also required to determine the optimal and maximum protein content in the composition of a restricted-energy diet. Additionally, research is required that controls for such confounding factors in dietary content as fibre content and palatability, as well as for behavioural confounders such as habitual diet, alcohol and physical activity on the relationship between health and protein intake, protein sources, and satiety.

Another key area for future research is exploring telehealth to conduct nutritional interventions. The potential to connect with people, regardless of location provides opportunities for a much larger reach of the population. Further, it made data collection and access easier. However, further studies are necessary to evaluate the effectiveness of the telehealth approach in conducting dietary interventions and the reliability and accuracy of employing self-reported energy intake, body weight, and satiety.

The current study showed that retaining a higher protein content in the diet when following an intermittent fasting system is a promising means of short-term weight reduction. This study can serve as a resource for nutritionists when suggesting options to clients. Although the current findings need confirmation, they suggest that such a diet could lead to even better outcomes in weight reduction in the longer term. Further research must be conducted on how the dietary protein content affects satiety under semi-fasting conditions and body weight management in the long term. Understanding how macronutrient content affects satiety may be one of the most crucial aspects of preventing and treating obesity. This research (Chapter 5) also highlighted the benefits and barriers of using telehealth in nutrition. Therefore, it may serve as baseline information for relevant future studies.

6.4. Limitations and implications

Noting the study limitations is not only a critical ethical aspect of scientific research, but it also provides other researchers with a better understanding of the results, conclusions, and potential biases that the exclusion criteria and the methodology may have caused. Presenting the limitations allows the reader to consider future opportunities in relevant research and expand scholarly inquiry. Thus, this section provides the limitations of each of the analyses included in this dissertation. The intervention trials discussed in chapters three and four were short-term interventions. Such short-term intervention designs are appropriate for investigating the effects of dietary protein on body weight and composition changes, satiety, and health indicators. Nevertheless, they might be insufficient for assessing longer-term effects, especially because short-term dietary weight loss interventions tend to be moderately successful yet, frustratingly, fail over longer periods. Longer studies need to address the promise of increased satiety from higher protein content on changes in body weight and composition.

The processes through which increasing long-term dietary protein consumption regulate body weight are complex and not fully understood. The literature review suggested that a high protein diet in long-term might lessen the effect of a high protein intake on satiety and body weight management (17). Furthermore, the success of long-term weight loss maintenance is a critical concern in weight loss strategies, including when adhering to IER diets (18). Evidence suggests that compensatory metabolic responses resist energy deficiency to attenuate disturbances in energy balance (19). In doing so, these compensatory responses decrease energy expenditure and appetite-enhancing hormones (19). High protein long-term interventions with intermittent energy restriction would therefore provide more information on the effect of high protein on satiety, body weight management, and health indicators. Moreover, including a weight loss maintenance phase after a weight loss phase in a high protein, energy-restricted diet is an essential component of the overall weight loss and maintenance process.

One significant limitation in the relevant literature is the lack of consensus on what constitutes high, normal, and LP in restricted-energy diets. Another limitation of the research presented in chapters 3 and 4 is that men as well as women of different ages and BMIs were excluded from the research, which limits the ability to generalize study results. However, the reason for excluding these categories is that literature has indicated that these groups differ in physiological reactions to satiety. Thus, establishing certain specific criteria for inclusion in the study helps achieve homogeneity of results. Furthermore, due to the lack of human research and the diversity of IER regimens, identifying a clear plan for implementing intermittent fasting for this population is challenging. Nevertheless, this research aimed to contribute to fill some of the gaps left by earlier research on the impact of protein content on IER regimens' improvement of satiety, glycemic management, and lipid profiles.

A further limitation of the research reported in chapter four was its limited sample size. As a result, it was not possible to identify minor variations between groups. Moreover, since the inclusion criteria were stringent, more than 50% of applicants did not meet the requirements for participation, thus making recruitment difficult. Finally, as this study was conducted remotely, there was little environmental control for assessing subjective satiety reactions.

6.5. Conclusions

The projects outlined in this dissertation focused on the effect of protein content on satiety and body weight loss in diets that depend on IER regimes. They also investigated the effect of protein content in IER diets on the following health indicators: LDL cholesterol, HDL cholesterol, triglycerides, CRP, and A1c. Promising findings were noted with higher protein diets raising satiety, lowering body weight and waist circumference, and improving other health indicators such as triglycerides and CRP. Nevertheless, the differences in effect between protein groups was not statistically significant, possibly due to the small sample size. Despite some challenges, the telehealth method successfully served as a method to facilitate the study.

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Appendix

Publication 1

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Article

Intermittent Energy Restriction Combined with a High-Protein/Low-Protein Diet: Effects on Body Weight, Satiety, and Inflammation: A Pilot Study

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Abstract: Intermittent energy restricted (IER) diets have become popular as a body weight management approach. In this pilot study, we investigated if an IER diet would reduce systemic inflammation and if maintaining an elevated protein level while on an IER diet would enhance satiety. Six healthy women, aged 33–55 years with a BMI of 27–33 kg/m^2, were randomized to first adhere to either a low- or high-protein IER diet using whole foods for three weeks. They then returned to their regular diets for a week, after which they adhered to the second diet for three weeks. Each test diet consisted of three low-energy intake days followed by four isocaloric energy intake days. The diets differed only in protein content. High-sensitivity C-reactive protein (hs-CRP), glucose, satiety, body weight, and waist circumference were measured at the beginning and end of each dietary intervention. Most participants showed reductions in hs-CRP levels from baseline on both IER diets but reported greater satiety when adhering to the higher protein IER diet. Overall, the IER diets reduced body weight and appeared to decrease inflammation in these overweight women, and the higher protein version enhanced satiety, which may lead to greater long-term dietary adherence.

Keywords: intermittent energy restriction; obesity; dietary protein; satiety

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Citation: Alzhrani, N.E.; Bryant, J.M. Intermittent Energy Restriction Combined with a High-Protein/Low-Protein Diet: Effects on Body Weight, Satiety, and Inflammation: A Pilot Study. *Obesities* **2023**, *3*, 180–192. https://doi.org/10.3390/obesities3020015

Academic Editor: Sara Baldassano

Received: 3 April 2023
Revised: 6 May 2023
Accepted: 16 May 2023
Published: 19 May 2023

1. Introduction

The worldwide prevalence of obesity is rising. According to the World Health Organization, approximately 1.9 billion individuals aged 18 years and older are overweight or obese [1]. By 2025, global obesity rates will reach 18% for the male population and 21% for the female population [2]. Evidence shows that obesity commonly generates adipose tissue dysfunction [3,4]. The excessive accumulation of fat in adipocytes can result in a decrease in mitochondrial metabolism, and an increase in the release of pro-inflammatory adipokines, such as TNF-α and IL-6 [4]. Additionally, this chronic low-grade systemic inflammation can act as an underlying risk factor for developing many chronic diseases, including type II diabetes, cardiovascular disease, hypertension, and cancer [4]. Adipose tissue also synthesizes and secretes certain hormones, such as leptin and adiponectin, which play essential roles in appetite regulation [5].

Recent epidemiological studies show that dietary strategies involving intermittent energy restriction (IER) are beneficial therapeutic interventions for the prevention or treatment of inflammatory disease [6,7]. IER diets restrict energy intake from one day to a few days a week, followed by intervals of refeeding in the remainder of the week. Various versions of IER diets restrict energy from 75% to as low as 10% of the total energy intake required to maintain body weight. IER diets have been demonstrated to improve metabolic performance and cellular modifications that contribute to reversing oxidative damage and inflammation [8,9]. These diets may also be effective at regulating blood glucose levels and enhancing metabolic outcomes [9]. In addition, recent evidence indicates that IER diets can serve as an alternative to continued energy restricted (CER) diets for weight loss and to improve health indicators like decreasing pro-inflammatory markers. For example, a recent randomized controlled trial compared an IER strategy to a CER diet in adults aged between 18 and 45 years with a BMI of 22.0–35.0 kg/m^2. They reported similar benefits in terms of hunger and health markers such as total cholesterol and low-density lipoprotein cholesterol over the 12 weeks, although some indicators suggested that the IER diet may be more beneficial [10]. A systemic review that compared the effect of IER to CER diets on weight loss also reported that both have similar effects on weight loss [11]. Giving further credence to the efficacy of an IER diet, a recent systematic review, which included 27 randomized controlled trials on women and men who were overweight or obese, found that IER diets reduced both body weight and fat mass [12].

Many versions of IER diets are purported to be beneficial. Some of these alternate the intervals of energy restriction versus normal energy intake; currently, the optimal protocol for an IER diet is unclear. A study using an animal model has demonstrated that three consecutive days of energy restriction were associated with greater improvements in insulin sensitivity, inflammation, and even the regeneration of failed pancreatic cells [13]. Nevertheless, the benefits and feasibility of such diets for human subjects have not been adequately identified and investigated. Interestingly, a recent study demonstrated that an IER diet modified the hypothalamic expression of critical genes that are involved in lipid metabolism, inflammation, and the regulation of the insulin and leptin pathways [14]

Non-adherence is a common issue with human dietary interventions designed for weight loss, especially in diets that depend on restricted energy intake [15]. For instance, a systematic review and meta-analysis involving 45 randomized controlled trials that examined the effects of energy restriction interventions in obese individuals reported that nearly 28% of subjects dropped out due to non-adherence to their dietary interventions [16]. Accordingly, increasing the ability to adhere to an IER diet is an important factor for its success [15,17]. One of the critical elements for adherence may be increased satiety. Thus, including foods that increase the satiety in energy restricted diets, such as foods with higher protein content, may increase adherence [18].

An IER diet that increases the protein content of the diet while restricting the fat and carbohydrate proportions will result in a higher calculated total energy intake than a diet that decreases the intake of all three macronutrients. However, this difference in protein intake is unlikely to profoundly impact total energy availability because protein is used by the body sparsely as a primary source of energy [19], yet it is the macronutrient that provides the greatest satiety [20]. Therefore, in the current study, our primary hypothesis was that a higher protein content combined with an IER diet will facilitate adherence to the diet because protein intake enhances satiety. Secondly, we hypothesized that an IER diet will reduce inflammation independent of protein content. Since this is a feasibility study, we examined the feasibility, effectiveness, and acceptability of an IER diet at low- versus high-protein content to improve health indicators such as CRP, body weight, waist circumference, and fasting glucose.

2. Materials and Methods

2.1. Participants

In the summer of 2018, we posted the study poster in LISTSERVs for recruiting participants in Halifax, Nova Scotia, Canada. We recruited six women between the ages of 33 and 55 years with a body mass index of 27–33 kg/m^2. Only women were included in order to increase the homogeneity of the participants in the study considering the small sample size [21]. An additional reason for selecting only women was that clinical trials have shown differences between men and women in appetite sensations and appetite responses to macronutrient content changes in diets [22,23]. We also narrowed the age range of participants because evidence has demonstrated physiological differences in sensory satiety among age groups (i.e., adolescent, middle age, and elderly) [24,25]. We also selected participants who were in a discrete range of overweight or obese measures. For the purpose of this study, overweight and obese criteria were determined by a body mass index (BMI) between 27 and 33 kg/m^2. By excluding obese individuals who have a BMI greater than 33 kg/m^2, we excluded those who were more likely to have undiagnosed obesity-related chronic disease [26]. Additionally excluded from this study were pregnant or breastfeeding women because of their greater nutritional needs, as well as individuals predisposed to or with serious diagnosed health conditions. Participants taking prescribed medications that could affect their metabolism and possibly their immune function, such as those with special dietary requirements for a health condition (collected by self-assessed report), were also excluded. All participants were non-smokers who did not consume more than one alcoholic beverage per day or drink more than two cups of coffee per day, as both can alter metabolism levels. All participants were willing to eat the food used in this study, either the regular (meat included) meal options or the vegetarian meal options, and they were capable of preparing their own food during the study period.

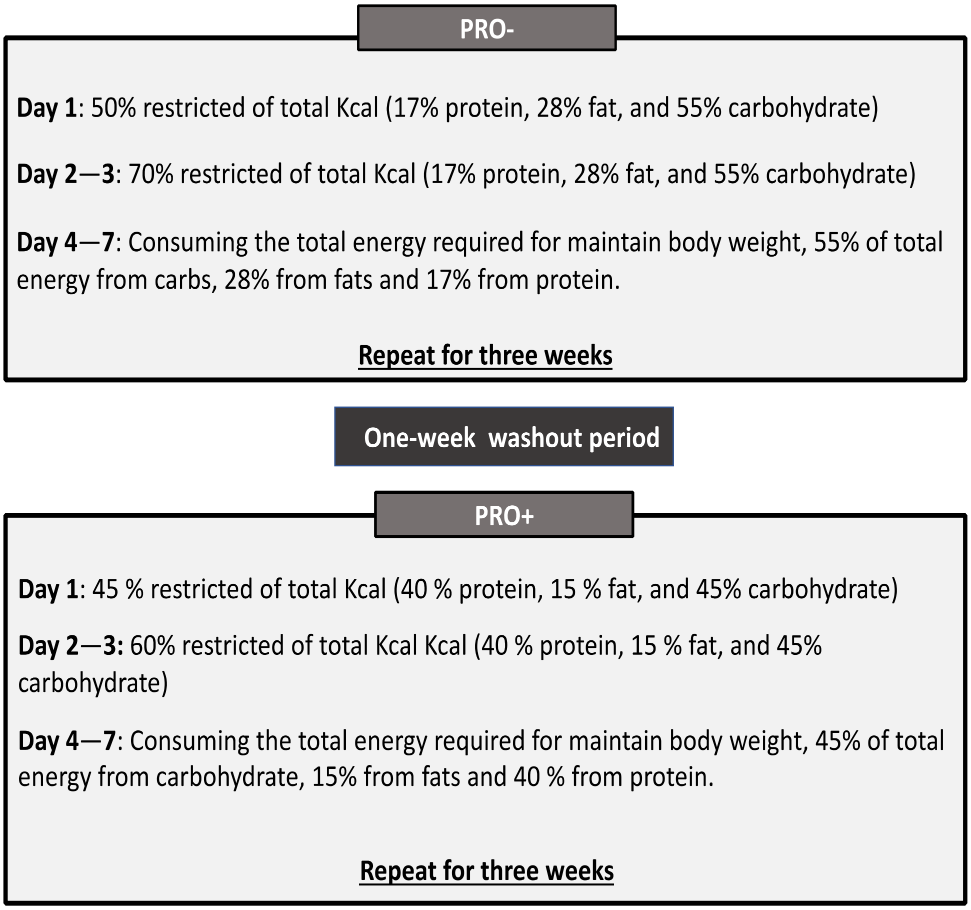
For the individuals who were interested in participating, we set up individual interviews for identity protection. This initial interview consisted of a brief description of the study, objectives, methodology, inclusion and exclusion criteria of the participants, and their answers to a prepared oral questionnaire, which provided the necessary information to ascertain a participant's understanding of the study before starting further screening eligibility. The researcher then measured the waist circumference, weight, and height of the volunteer and calculated their BMI; if the BMI measurement met the criterion, then the interview was conducted with each prospective participant. The main purpose of the interview was to go through the self-screening questions that were already been filled by participants. The researcher did not retain a participant's name until the researcher was certain of their eligibility and they agreed to participate. If eligibility was confirmed, and the volunteer fully understood the study and their role, they were asked to sign the consent form. Participant identification numbers rather than names were used on all materials, and this information was kept with consent forms in a separate locked cabinet. The study protocol was approved by the Dalhousie University Research Ethics Board (protocol number 2018-4477).

2.2. Study Design

The study utilized a cross-over design consisting of two three-week treatment periods with a one-week washout period with no dietary restrictions between treatment periods. The participants were randomized to begin with either the low- or high-protein IER diet. See Figure 1 and Section 2.3 for dietary details.

2.3. Dietary Interventions

The dietary plan consisted of three low-energy intake days followed by four days of consuming the amount of energy calculated to maintain body weight; this cycle was repeated for three weeks. The two treatment periods differed by protein content in days 1–3, which were designated as PRO− and PRO+ as shown in Figure 1. Between dietary periods, the participants had one week off so that the effects of the previous diet would wear off. Doing so helped us assess the effects of each diet separately. Since these are novel diets, this pilot study was used to inform us on the design of a future, larger study. For study purposes, we developed quick recipes, which use similar ingredients to those used in the classic Mediterranean diet, which is generally considered to be a healthy diet [27]. The primary source of protein was a variety of animal- and plant-based proteins based on each participant's preferences. The recipes were same for both interventions and only differed by the macronutrient content as described in following section.



PRO-

Day 1: 50% restricted of total Kcal (17% protein, 28% fat, and 55% carbohydrate)

Day 2—3: 70% restricted of total Kcal (17% protein, 28% fat, and 55% carbohydrate)

Day 4—7: Consuming the total energy required for maintain body weight, 55% of total energy from carbs, 28% from fats and 17% from protein.

Repeat for three weeks

One-week washout period

PRO+

Day 1: 45 % restricted of total Kcal (40 % protein, 15 % fat, and 45% carbohydrate)

Day 2—3: 60% restricted of total Kcal Kcal (40 % protein, 15 % fat, and 45% carbohydrate)

Day 4—7: Consuming the total energy required for maintain body weight, 45% of total energy from carbohydrate, 15% from fats and 40 % from protein.

Repeat for three weeks

Figure 1. Study design. CHO = carbohydrate; FAT = fat; PRO = protein.

2.3.1. PRO− Diet

The PRO− diet consisted of a 7-day cyclical diet. On the first day of the PRO− diet, the participants' dietary energy intake was restricted to 50% of the total energy required to maintain their current body weight. On days 2 and 3, energy intake was restricted to 70% of the total required energy. The proportion of energy intake from macronutrients remained at 17% protein, 28% fat, and 55% carbohydrates. The total energy on day one was approximately 1000–1300 kcal, and on days 2 to 3, it was approximately 700 to 800 calorie kcal. During days 4 to 7, the participants consumed a diet that maintained the same proportion of macronutrients (17% protein, 28% fat, and 55% carbohydrates) but in amounts calculated to maintain their body weight.

2.3.2. PRO+ Diet

The PRO+ diet, the experimental diet we developed for this study, differed substantially from the PRO− diet only in protein content on days 1–3 of each treatment week. The participants' dietary energy intake was restricted to 45% of the total energy required to maintain their current body weight. On days 2 and 3, energy intake was restricted to 60% of the total required energy. The proportion of energy intake from macronutrients remained at 40% protein, 15% fat, and 45% carbohydrates. The total energy in day 1 was approximately 1200–1500 kcal, and on days 2–3, it was 900 to 1300 kcal. During days 4 to 7, the participants consumed a diet that maintained the same proportion of macronutrients (40% protein, 15% fat, and 45% carbohydrate) but in amounts calculated to maintain their body weight.

2.4. Anthropometric Measures

The anthropometric measurements were obtained on the first day of the diet (baseline) and at the end of the third week (the end of treatment) of each treatment period. These measurements included weight, height, and waist circumference, all of which were measured according to standardized procedures. To measure height, the participants were required to remove their shoes and anything on their heads and then stand upright on the central point of a stadiometer platform with their backs against the wall and their feet together while looking straight ahead with their backs and shoulders touching the wall. Their BMI was then calculated. Waist circumference was measured while the participants were in an upright but relaxed position using the World Health Organization method, which posits the location as "at the mid-point between the highest point of the iliac crest and the last floating rib" [28].

2.5. Blood Tests

Blood samples were collected via finger stick after a minimum of 12 h of fasting and tested for glucose and a hs-CRP test at baseline and at the end of each of the two treatment periods. The CRP high-sensitivity rapid test (CRP-K10, Schwerin, Germany) was used, which has a reference range for CRP as follows: negative, less than 10 mg/L; positive, which is divided into three levels: low, 10 mg/L or less than 30 mg/L; medium, 30 mg/L; and high, greater than 30 mg/L. These reference ranges were provided by the manufacturer of the test kits. Additionally, based on the manufacturer of the test kits, the relative sensitivity of the CRP-K10 kit depends on the CRP level. Specifically, for CRP values of 10 mg/L, the relative sensitivity is 99.4%; 94.3% for a CRP range of 10 mg/L to less than 30 mg/L; and 99.1% for CRP values of 30 mg/L or greater. For the measurement of blood glucose from serum, the One Touch Ultra (USA) was used, which has been demonstrated to have sufficient validity and reliability [29].

2.6. Hunger, Satisfaction, and Fullness

A visual analogue scale is a self-assessment tool that dietary researchers often use to assess the magnitude of hunger, satisfaction, and fullness. The visual analogue scales used in this study provide a continuum of values in ascending order from 0 to 10, where 0 is the lowest level, and 10 is the highest level represented. These values are classified into specific categories, with each category representing the level of a participant's experience of hunger, satisfaction, and fullness. In the current study, the participants indicated their value of each category on the scale, as illustrated in Figure 2. Each participant completed the visual analogue scale by marking the point on the scale that best represented the level of their feelings of fullness, satisfaction, and hunger during the energy-restricted days.

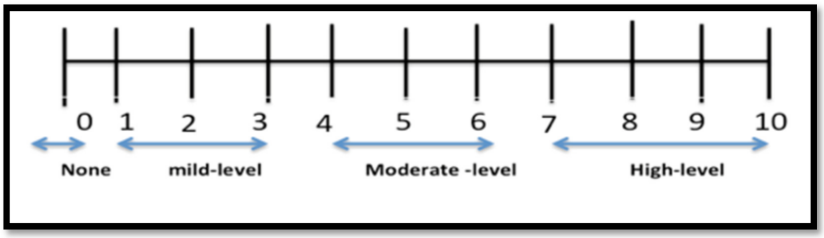


Figure 2. The categories for hunger, satisfaction, and fullness on the visual analogue scale.

2.7. Adherence

Subject behavior was our greatest concern when considering enhanced adherence to the diet. Tactics used in this study to avoid high withdrawal rates included the use of whole foods rather than liquids, because solid foods offer greater prolonged satiety than liquid meals. Additionally, our study did not require specific times for food consumption; thus, the participants could consume meals based on their individual schedules.

Adherence is also enhanced by self-monitoring [15]. Therefore, all participants were given a food journal and asked to record their food consumption on fasting days and then bring their journal to each lab visit. To further encourage compliance, each participant was contacted at least twice a week by phone or in person. During these communications and the lab visits, the participants were asked questions that gathered more information about how they were managing their diet, and to determine if they were experiencing any difficulties. Based on ongoing feedback, a researcher also customized the foods to the preferences of the participants to enhance adherence. All participants were also encouraged to use the Lifesum app for self-monitoring during non-restricted days. Additionally, each participant was provided with an individualized cookbook with recipes for days one to three of the PRO− and PRO+ diets; these recipes considered the participants' food choices but remained commensurate with the dietary plan of the study.

2.8. Statistical Analysis

Each numerical parameter (weight, waist circumference, BMI, and glucose) of pre-diet values was subtracted from post-diet values using SPSS (Version 24). All data were expressed as mean ± SD. Considering that the current study used a single case study design that involved a small sample size, the data were also presented descriptively and graphically.

3. Results

3.1. Participants

Six participants completed both phases of the study. An additional participant completed only a single treatment and was not included in the results. See Table 1.

Table 1. Baseline characteristics of study participants.

Participant ID	Age (y)	Body Weight (kg)	WC (cm)	BMI (kg/m^2)
Case 1	49	78.2	93	28.9
Case 2	47	79.8	91	29.5
Case 3	37	79.9	80	29.2
Case 4	54	90.0	105	33.9
Case 5	51	71.9	84	29.4
Case 6	44	81.0	88	31.5

3.2. Body Weight

Weight loss occurred in 9 out of the 12 interventions, with an overall average loss of 2.40 kg on the IER diets. Similar losses occurred on both the PRO+ (2.45 kg) and PRO− (2.35 kg) diets (see Figure 3). The dietary records of Case 5, who showed a slight gain in body weight on both diets, indicated that she consumed an excessive amount of energy on the non-restricted days 4 to 7 compared to her isocaloric needs. Similarly, Case 3 reported that she ate unhealthy food during the restricted days of her PRO− diet, which may be the cause of her lack of weight loss.

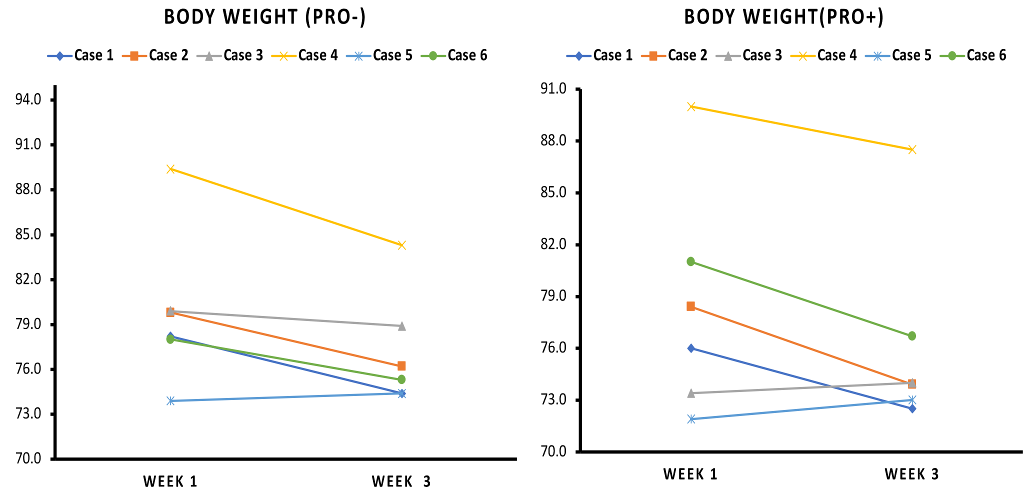


Figure 3. Body weight changes on three weeks of the PRO+ and PRO− diets.

3.3. Waist Circumference

Changes in waist circumference varied considerably among the cases, ranging from 0 to 4 cm, with an average loss of 1.88 cm over each of the 12 periods (see Figure 4). A plausible reason that Case 5 did not experience a reduction in her waist circumference from her PRO− intervention is that she consumed more than the total energy required to main body weight on some non-restricted days.

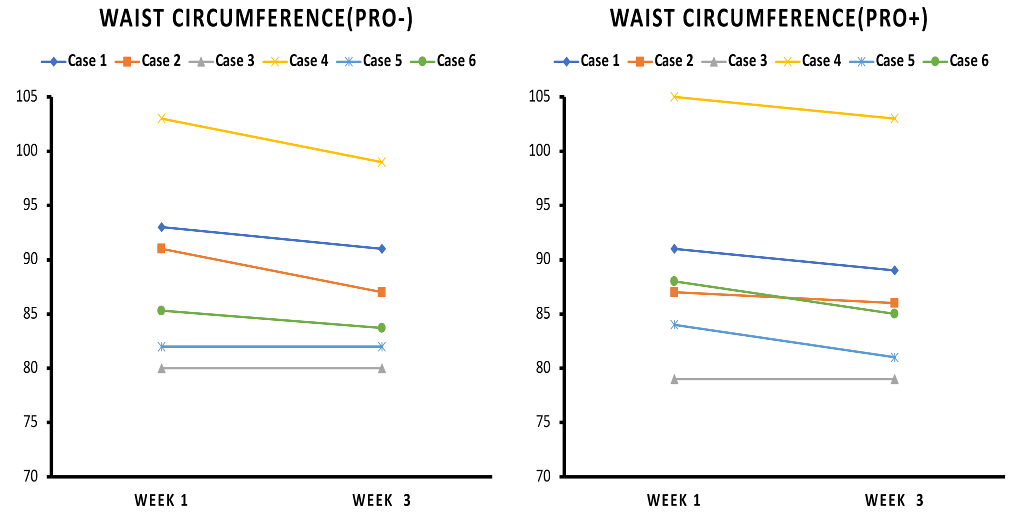


Figure 4. Waist circumference changes on three weeks of the PRO+ and PRO− diets.

3.4. CRP

Most participants showed reductions in CRP levels from the baseline value measured at their initial rotation (see Table 2). Three participants with a low level of CRP at the beginning of the first phase of intervention dropped to negative at the end of week three and maintained this negative status through their subsequent dietary rotation.

Table 2. CRP at baseline and the end of each intervention period.

	CRP		CRP	
	Baseline (PRO−)	**Week 3 (PRO−)**	**Baseline (PRO+)**	**End Week 7 (PRO+)**
Case 1	Negative	Negative	Negative	Negative
Case 2	Moderate	Negative	Negative	Negative
Case 3	Moderate	Negative	Negative	Negative
Case 4	Moderate	Moderate	High	Moderate
Case 5	Negative	Negative	Moderate	Negative
Case 6	Moderate	Moderate	Moderate	Moderate

Negative: CRP concentration of less than 10 mg/L; moderate inflammation: CRP concentration 10 mg/L or less than 30 mg/L; high inflammation: CRP concentration > 30 mg/L.

3.5. Fasting Glucose

There were no discernible trends in fasting glucose levels throughout the intervention period (see Figure 5). This might have been because the participants' fasting glucose levels were within normal blood glucose levels both at baseline and at the end of the interventions. One participant, who had a higher than normal glucose level at baseline, decreased in fasting glucose from baseline to the final measurements in the second phase of the interventions.

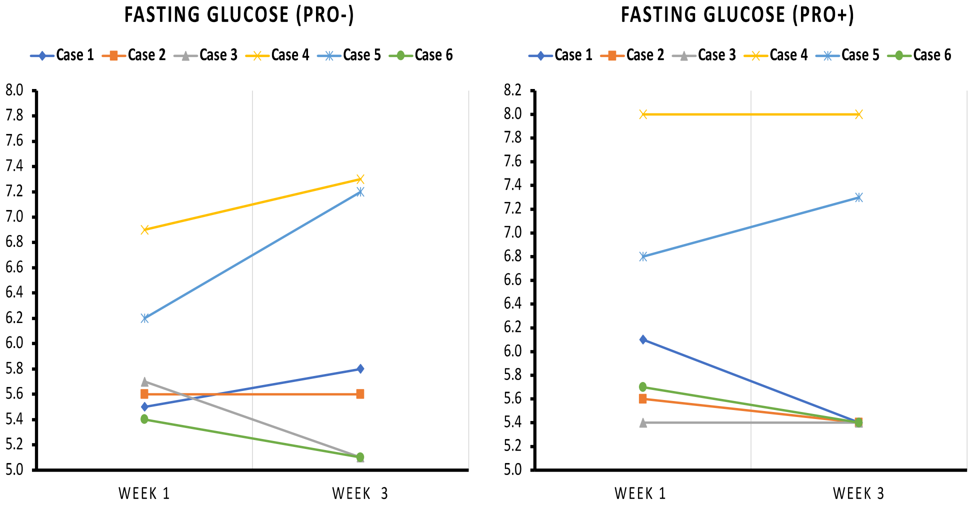


Figure 5. Glucose changed after following the dietary interventions.

3.6. Satiety

The participants reported greater satiety on the PRO+ diet than on the PRO− diet (see Figure 6). The participants indicated that they were successfully adhering to both diets (PRO+ and PRO−) but found the PRO+ diet easier to adhere to because it produced less hunger. All participants reported that, on the PRO+ diet, they felt more fullness than on the PRO− diet. Two participants in the PRO− diet group mentioned that on the third day of the restricted portion of the diet, they had an increased desire to eat, whereas two participants in the PRO+ diet group reported feeling full before finishing their meals.

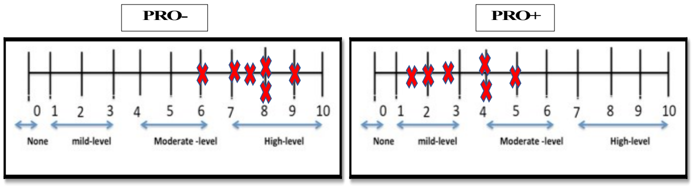


Figure 6. Participants' responses to a visual analog scale questionnaire for comparing the difficulties in adherence to PRO- and PRO+ diets.

3.7. Effect of Order of Rotation on Results

Participants who started with the PRO- diet achieved greater reduction in body weight and waist circumference than those who started with the PRO+ diet. There was no effect of the order of rotation of dietary intervention on fasting glucose and CRP results.

3.8. Additional Observations

Six participants completed the entire set of interventions. Only one participant did not complete the second phase of the intervention for reasons unrelated to the study. None of the participants reported adverse events during the PRO+ or PRO- diets. While following the PRO- diet, one participant reported slight headaches on days one and two of the restricted intake portion. No other adverse conditions were reported. Some of the participants found the Lifesum app was useful in teaching them how to select healthy food. All participants mentioned that they were committed to consuming the total recommended energy.

4. Discussion

4.1. Weight Loss and Waist Circumference

In this study, both diets induced a reduction in body weight and waist circumference, even though the high-protein diet contained higher energy density than the low-protein diet. These findings support a previous study that found that positive losses of waist circumference did not differ between two levels of moderate protein intake in participants on a low calorie diet [30]. Similarly, others have tested the effects of protein level while energy intake is restricted and reported similar results in weight loss [26]. Interestingly, the higher protein intakes result in increased retention of muscle mass at the expense of fat mass [26]. However, a very high-protein diet may have no further benefit, as increasing the protein content above the normal level of protein requirement has not produced a further reduction in body weight, although it helped maintain a higher level of free fat mass [31].

4.2. CRP

This pilot study suggests that three days of an energy restricted diet, whether it is high- or low-protein, can result in improvement in CRP for OW/OB women. Previous studies have used anti-inflammatory diets to investigate the effects of macronutrient proportions on inflammatory processes [32,33]. However, to our knowledge, no study has tested the effect of protein content on hs-CRP. Instead, various studies have investigated aspects of carbohydrate and fat intake on inflammation. Thus, previous studies have failed to fully inform guidelines for people with significantly high levels of hs-CRP.

Aspects of dietary carbohydrate content seem to exert effects on hs-CRP. For example, a study using 29 overweight women with an average BMI of 32.1 ± 5.4 kg/m^2 found more benefits for reducing hs-CRP using a low-carbohydrate diet compared to a low-fat diet [34]. Interestingly, many of these studies found that macronutrient content is likely a more critical factor in reducing inflammation markers than weight loss. For example, a study with OW/OB patients aged 18–40 years reported that low glycemic load diets more effectively reduced the level of hs-CRP than a low-fat diet, although both diets similarly impacted weight loss [35]. These findings are consistent with those of a 12 month randomized trial that found that a low glycemic diet was more effective in reducing high levels of hs-CRP than a low-fat diet, despite the similarities in weight loss outcomes in both groups [36]. Another study compared the two versions of Mediterranean diets to a low-fat diet, and reported that the Mediterranean diets reduced hs-CRP without weight loss more effectively than the low-fat diet [37]. Similarly, in the current study, most of the participants demonstrated decreases in their hs-CRP levels, although some of them showed slight weight increases. However, this is inconsistent with a 2007 systematic review that concluded that weight loss led to a reduction in CRP regardless of which intervention approach was used [38]. It is important to mention that this review excluded the interventions that did not have weight loss as an objective. Further studies are required to obtain a clear conclusion about the role of the dietary intervention type, especially from protein level and weight loss on CRP levels.

4.3. Glucose

There was no significant reduction in fasting blood glucose for most of the participants. A possible reason for this finding is that most of the participants began this study at a normal level of the fasting blood glucose. Indeed, the beneficial effects of energy restriction interventions are more likely to manifest in individuals with insulin resistance than in healthy individuals [39]. Additionally, the apparent lack of correlation between weight loss and decreasing fasting glucose in our findings could also be attributed to the short study length, which may have been inadequate to show the effects of weight loss on enhancing fasting glucose. Most energy restricting studies that have demonstrated that the capacity to be effective for controlling glucose levels and enhancing metabolic outcomes were conducted over periods of seven weeks or more [40–42]. Lim et al., for instance, reported that, after eight weeks of restricted energy intake by type 2 diabetic patients, there was an enhancement in the function of beta cells [43], which has a curvilinear relationship with fasting blood glucose level [44]. Similarly, one large diabetes prevention study with middle-aged overweight women and men with impaired glucose tolerance used intensive lifestyle interventions for eight weeks, including reducing fat consumption to less than 30%, saturated fat intake to no more than 10% of the total energy consumed, and total body weight by at least 5% [45]. The study found that this dietary intervention prevented the progression to diabetes by 58% [45]. Thus, it is probable that a longer study than ours and one with participants with higher baseline glycemic values would be needed to test the effects of protein level on fasting glucose levels while on an IER diet.

In the current study, Case 4 initially had a glucose level that was stable at 8 mg/dL in week one and remained unchanged at the end of week three (during the PRO + diet intervention), although with a slight body weight loss. During the subsequent PRO- diet intervention, though, she lost 5% of her body weight, and her glucose level decreased to 6.8 in the fifth week even though she did not take medication to regulate blood glucose. These findings correspond to evidence suggesting that 5% weight loss in OW/OB individuals induces improved metabolic function and the diminution of metabolic, disease-associated risk factors such as fasting blood glucose [46,47]. Similarly, several studies have revealed that weight loss contributes to a decrease in visceral fat and improves markers of glucose metabolism [13,25,26]. These results match those observed in an earlier study, which concluded that OW/OB people can reduce their risk for diabetes with every kilogram of body fat they lose [48].

4.4. Adherence

The participants in this study completed both phases of the diet without exception, and only one participant withdrew by the end of Phase 1 for reasons unrelated to the study. We therefore assume that our methodology provides the ability to adhere to an energy-restricted diet. The participants reported that they experienced more fullness and satiety on the PRO+ diet than on the PRO- diet. The reason for this may be the role of protein in increasing satiety. Several studies have investigated the association between macronutrients and satiety, with the majority indicating that protein increases satiety and suppresses energy intake more than other macronutrients [20,49], likely because protein contributes to an increase in the release of gastrointestinal appetite hormones, such as PYY, and also increases concentrations of ghrelin [20]. A previously published systematic review recommended a high-protein diet for controlling appetite [50].

4.5. Limitations

There were certain limitations to this study, such as the small sample size. This study included only women who have a BMI between 27 and 33 kg/m^2 and were aged 33–55 years in order to increase the homogeneity of the samples. The reason for selecting the age group is that evidence has demonstrated physiological differences in sensory satiety among age groups (i.e., adolescent, middle age, and elderly) [24,25]. Further research is needed to investigate the effects of IER diets on obese men because the clinical trials have shown differences between men and women in appetite sensations and appetite responses to changes in macronutrient content in diets [22,23].

5. Conclusions

This pilot study demonstrated that an IER diet, whether the protein content is low or high, is a feasible strategy for obese women. Most participants lost weight and reduced their waist circumference. Additionally, most of them improved their CRP. Although both PRO+ and PRO- diets reduced CRP levels among the participants, the IER PRO+ diet resulted in greater satiety than did the IER PRO- diet and was preferred by the participants. This suggests that a higher protein content while consuming a IER diet may lead to greater long-term adherence. These positive findings hold promise for potentially similar exciting advances in larger and longer studies that involve an IER high-protein diet. To provide more data, a large study should investigate the effects of intermittent fasting combined with a high-protein diet on satiety, weight loss, and various health indicators, such as blood glucose, lipid profile, and pro-inflammatory markers, in overweight and obese adults.

Author Contributions: Conceptualization, J.B. and N.A.; methodology, N.A. and J.B.; formal analysis, N.A.; investigation, N.A.; resources, J.B. and N.A.; writing—original draft preparation, N.A.; writing—review and editing, J.B. and N.A.; supervision, J.B.; project administration, J.B. All authors have read and agreed to the published version of the manuscript."

Funding: This research received no external funding.

Institutional Review Board Statement: The ethical approval for this study was granted by Dalhousie University Research Ethics Board (protocol number 2018-4477 on April 19, 2018).

Informed Consent Statement: All participants signed written informed consent forms for participation, and the Dalhousie University Research Ethics Board approved the study. Written informed consent has been obtained from the participants to publish this paper.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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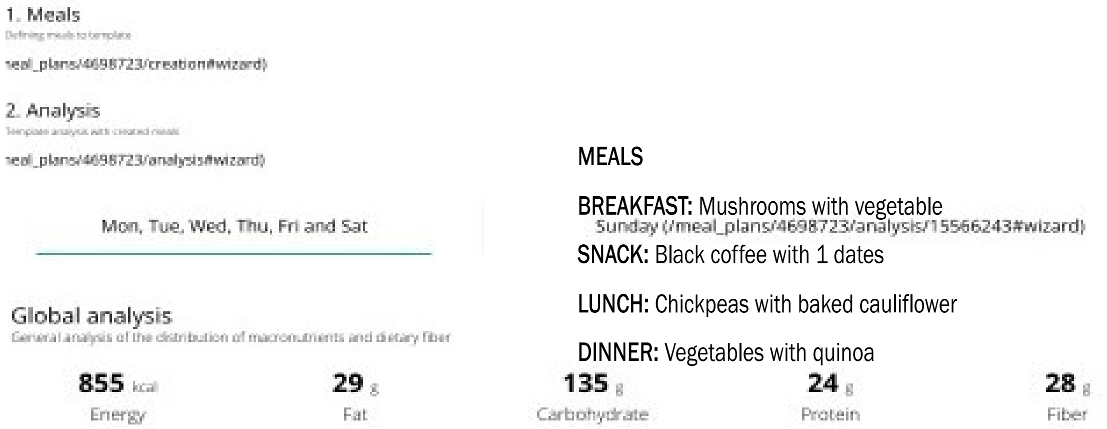
Example for Recipes for one restricted- day on the LP diet

The total energy required to maintain body weight is: 2100 kcal which restricted by 60%



1. Meals

Defining meals to template

neal_plans/4698723/creation#wizard)

2. Analysis

Template analysis with created meals

neal_plans/4698723/analysis#wizard)

Mon, Tue, Wed, Thu, Fri and Sat

Sunday (/meal_plans/4698723/analysis/15566243#wizard)

Global analysis

General analysis of the distribution of macronutrients and dietary fiber

Energy	Fat	Carbohydrate	Protein	Fiber
855 kcal	29 g	135 g	24 g	28 g

MEALS

BREAKFAST: Mushrooms with vegetable

SNACK: Black coffee with 1 dates

LUNCH: Chickpeas with baked cauliflower

DINNER: Vegetables with quinoa

Mushrooms with vegetable

INGREDIENTS

- 15 grams of squash, summer, zucchini, includes skin, raw
- 20 grams of peppers, green, raw
- 1 tbsp chopped of onions, raw (10 g)
- 35 grams of sweet potato, raw, unprepared
- 2 medium slices of tomatoes, red, ripe, raw, (40 g)
- 8 grams of oil, olive,
- 1 regular slice of bread, multi-grain (24 g)
- 1/2 cup, pieces or slices of mushrooms, white, raw (35 g)
- 40 grams of potatoes, white, flesh and skin, raw

COOKING METHOD

- Chop all mushrooms and vegetables into small-sized pieces.
- Now heat oil in a non-stick pan, add onions and vegetables to it and sauté for 2-5 minutes on medium heat until slightly changed their color.
- Add the mushrooms and sauté for another 5 minutes on medium heat. The mushrooms should start getting browned.
- Serve it with bread.

SNACK

Black coffee with 1 unit, pitted of dates, medjool (24 g)

Chickpeas with baked cauliflower

INGREDIENTS

- 80 grams of chickpeas, canned, drained solids
- 20 grams of tahini
- 3 grams of lemon juice, raw
- 1/4 clove of garlic, raw (1 g)
- 1/4 cup of kale, raw (5 g)
- 1 chopped cup (1/2" pieces) of cauliflower, raw (107 g)
- 15 grams of beans, kidney, canned
- Salt and pepper to taste
- 1.25 medium units of apples, raw, gala, with skin (215 g)

COOKING METHOD

- In a bowl combine cauliflower with oil, cumin and salt. Then put them in a tray baking dish; bake it for 5 to 8 minutes or until the cauliflower is tender.
- In a small bowl. whisk 3 tbsps of water, tahini, lemon juice, garlic, cumin and zaatar(optional) . For the serving, put kale, beans, and baked cauliflower and chickpeas and then drizzle with tahini.
- Serve it with apple

Calories 186; total fat 11.6g; saturated fat 1.6g; cholesterol 5.6mg; sodium 483mg; total carbohydrate 418.6g; dietary fiber 5.5g; protein 5.6g

Vegetables with quinoa

INGREDIENTS

- 1/4 cup of quinoa, cooked (46 g)
- 5 grams of lemon juice, raw
- 1.25 tsps of oil, olive, salad or cooking (6 g)
- 5 grams of coriander (cilantro) leaves, raw
- 35 grams of peppers, sweet, red, raw
- 1/4 cup chopped of broccoli, raw (23 g)
- 45 grams of sweet potato, raw, unprepared
- spices, cumin, black paper, salt and paprika for test.

COOKING METHOD

- Mix the pepper, olive oil, cumin, paprika, garlic and coriander together. Place the vegetables and lemon on a baking tray pour the mixture over top and then add then put them to the skillet and cook for about 5 to 8 minutes flipping.

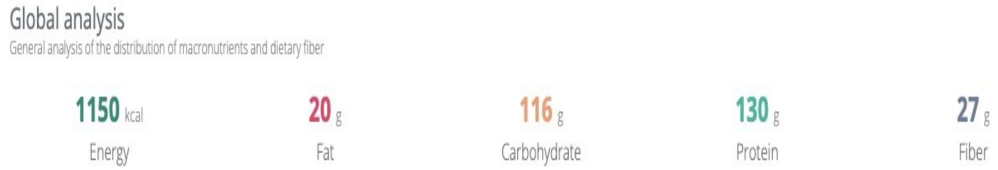
- Mix the vegetable with the quinoa and add the lemon juice and salt

Calories approx. 670-790; total fat 35g; saturated fat 2.6g; cholesterol 2.5mg; sodium 310mg; total carbohydrate 55-65g; dietary fiber 5.5g; protein 12g

4

Example for Recipes for one restricted- day on the HP diet

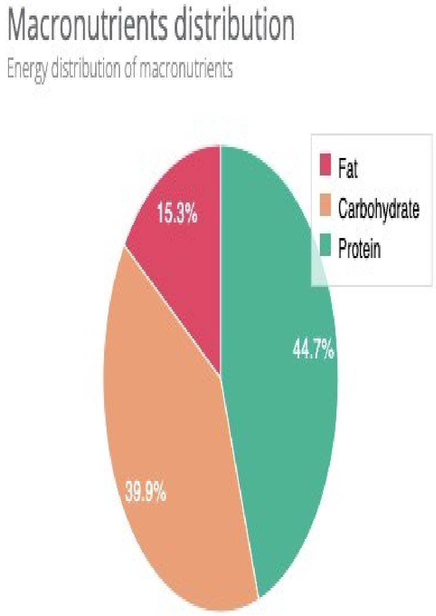
The total energy required to maintain body weight is: 2100 kcal which restricted by 60%



Global analysis

General analysis of the distribution of macronutrients and dietary fiber

Energy	Fat	Carbohydrate	Protein	Fiber
1150 kcal	20 g	116 g	130 g	27 g



Macronutrients distribution

Energy distribution of macronutrients

MEALS

BREAKFAST: egg with vegetables and mushrooms

SNACK: apple

LUNCH: breast chicken with asparagus

DINNER: banana, raspberries smoothie

Egg with vegetables and mushrooms

INGREDIENTS

- 15 grams of zucchini, includes skin, raw
- 15 grams of peppers, raw
- 1 tbsp chopped of onions, raw (10 g)
- 2 medium slices (1/4" thick) of tomatoes, red, ripe, raw(40 g)
- 4 large units of egg, white, raw, fresh (132 g)
- 1/2 cup, pieces or slices of mushrooms, white, raw (35 g)
- 1/2 slice of bread, whole-wheat, commercially prepared (16 g)

COOKING METHOD

- In a medium bowl combine egg whites with pepper and salt and whisk together until mixed.
- In a small, non-stick skillet, on low heat. Add vegetables, and mushroom, and cover with foil or any suitable cover for 5-7 minutes.
- Scatter the egg whites over the top of the vegetables without stirring and cover it again. Let the mixture cook for about 4 minutes over low heat. Serving with sliced cucumber

6

SNACK

1.25 medium units of apples, raw, gala, with skin (215 g)

Banana, raspberries smoothie

INGREDIENTS

- 150 grams of raspberries, frozen, red, unsweetened
- 25 grams of avocados, raw.
- 250 grams of yogurt, Greek, plain, nonfat

COOKING METHOD

- In a blender, add the avocados and raspberries. Cover and blend on low speed until smooth. Pour into glasses and mix it with yogurt.

Chicken with asparagus

INGREDIENTS

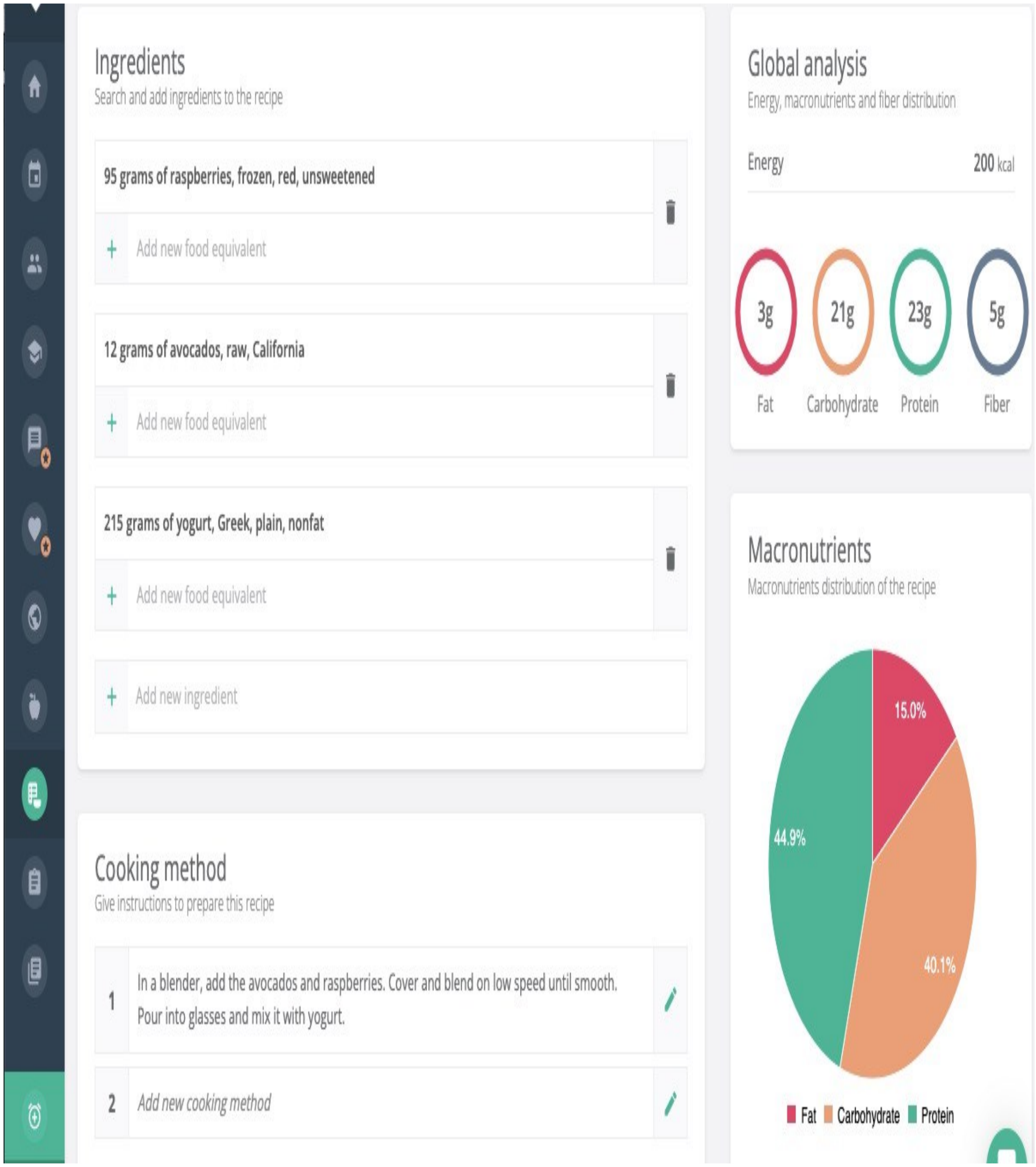
- 50 grams of tomato, red.
- 1.5 cups of asparagus, raw (201 g)
- 280 grams of chicken, breast, skinless, boneless, meat only, raw
- 1 clove of garlic, raw (3 g)
- 2 slices of bread, whole-wheat, commercially prepared (64 g)

COOKING METHOD

- Toss chicken, and tomato into a medium bowl and mix together.
- Place the chicken on a tray and cover with tomato, asparagus, garlic, salt and your favourite spices.
- Cover the tray with tinfoil and bake for 15-20 minutes at medium heat. Served with the bread.

8

TEST MEAL-HP GRPUP



Ingredients

Search and add ingredients to the recipe

95 grams of raspberries, frozen, red, unsweetened

12 grams of avocados, raw, California

215 grams of yogurt, Greek, plain, nonfat

Cooking method

Give instructions to prepare this recipe

1 In a blender, add the avocados and raspberries. Cover and blend on low speed until smooth. Pour into glasses and mix it with yogurt.

2 *Add new cooking method*

Global analysis

Energy, macronutrients and fiber distribution

Energy 200 kcal

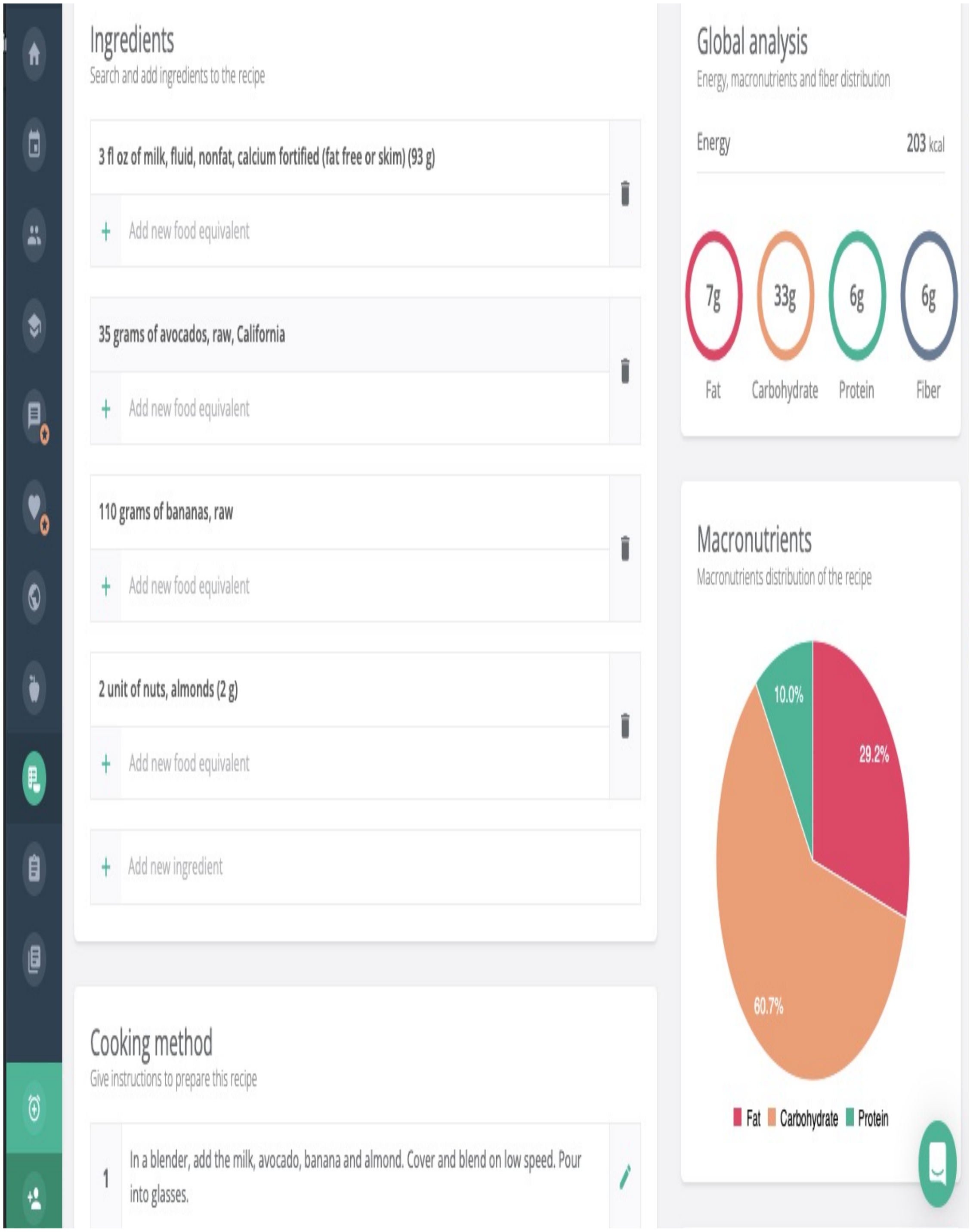
Fat	Carbohydrate	Protein	Fiber
3g	21g	23g	5g

Macronutrients

Macronutrients distribution of the recipe

+ Add new food equivalent
+ Add new food equivalent
+ Add new food equivalent
+ Add new ingredient
15.0%
40.1%
44.9%
🟥 Fat 🟧 Carbohydrate 🟩 Protein

TEST MEAL-LP GRPUP



Ingredients

Search and add ingredients to the recipe

3 fl oz of milk, fluid, nonfat, calcium fortified (fat free or skim) (93 g)

+ Add new food equivalent

35 grams of avocados, raw, California

+ Add new food equivalent

110 grams of bananas, raw

+ Add new food equivalent

2 unit of nuts, almonds (2 g)

+ Add new food equivalent

+ Add new ingredient

Cooking method

Give instructions to prepare this recipe

1 In a blender, add the milk, avocado, banana and almond. Cover and blend on low speed. Pour into glasses.

Global analysis

Energy, macronutrients and fiber distribution

Energy 203 kcal

Fat	Carbohydrate	Protein	Fiber
7g	33g	6g	6g

Macronutrients

Macronutrients distribution of the recipe

Crossover-study (First study)

Example of the food contents of first restricted day on the LP diet using iProfile software

Breakfast:

- 3.0 slices Cucumbers
- 0.5 items Squash, Summer, Zucchini
- 0.5 cups Cauliflower
- 0.75 cups Potatoes, Sweet
- 5.0 items Tomatoes, Cherry, Fresh
- 2.5 tsp Oil, Olive

Lunch:

- 1.0 pieces Tuna, Fresh
- 1.0 cups Cauliflower
- 0.5 cups Tomatoes, Peeled
- 0.3 cups Lentils, Dry
- 1.75 cups Lettuce, Romaine, Shredded

Dinner:

- 0.25 cups Quinoa, Cooked
- 75.0 g Haddock, Raw
- 1.0 tsp Cumin, Ground
- 1.0 cups Peppers, Bell or Sweet, Green
- 1.0 items Garlic Clove
- 1.0 tsp Paprika
- 2.0 tsp Oil, Olive
- 0.5 items Lemon, with Peel

Snacks:

- 1.0 items Apple, Medium
- 9.0 items Almonds, Shelled

Nutrient	My DRI	My Intakes	0% 50% 100%
Kilocalories	1830 Kcal	907 Kcal	
Fat, Total	20-35%	259 Kcal	🟩 27.9
Carbohydrate	45-65%	492 Kcal	🟩 54.3
Protein	10-35%	161 Kcal	🟩 17.8

Nutrient	Intake amount
Fat	30 g
Carbohydrate	132 g
Protein	43 g

Example of the food contents on days 2 and 3 on restricted days on the LP diet using iProfile software

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Breakfast:

- *0.5 items Banana*
- *0.25 cups Milk, Non Fat, Skim or Fat Free*

Lunch:

- *0.25 tsp Oregano, Ground*
- *2.0 tsp Yogurt, Plain, Non Fat (13 grams protein per 8 ounces)*
- *0.25 cups Carrots*
- *2.0 tsp Juice, Lemon*
- *1.0 tsp Parsley*
- *0.25 cups Beets*
- *0.25 items Garlic Clove*
- *0.25 cups Pepper, Bell or Sweet, Red*
- *0.25 cups Quinoa, Cooked*

Dinner:

- *0.25 cups Tomatoes, Red*
- *1.0 tsp Oil, Olive*
- *40.0 g Chicken, Breast, Meat Only, Boneless, Skinless, Roaste*
- *7.0 items Asparagus*
- *0.25 cups Carrots*
- *0.5 items Onions*
- *0.5 slices Bread, Mixed Grain*
- *1.0 cups Celery*

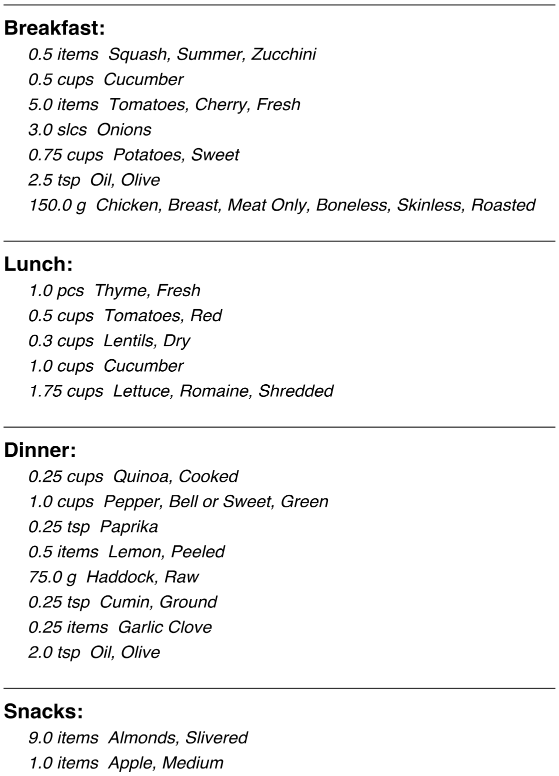
Snacks:

- *1.0 items Apple, with Skin*

Nutrient	My DRI	My Intakes	0% 50% 100%
Kilocalories	1833 Kcal	544 Kcal	
Fat, Total	20-35%	150 Kcal	🟩 27.6
Carbohydrate	45-65%	298 Kcal	🟩 54.8
Protein	10-35%	96 Kcal	🟩 17.7

Nutrient	Intake amount
Fat	18g
Carbohydrate	78 g
Protein	25 g

Example of the food contents of first restricted day on the HP diet using iProfile software



Breakfast:

0.5 items Squash, Summer, Zucchini
0.5 cups Cucumber
5.0 items Tomatoes, Cherry, Fresh
3.0 slcs Onions
0.75 cups Potatoes, Sweet
2.5 tsp Oil, Olive
150.0 g Chicken, Breast, Meat Only, Boneless, Skinless, Roasted

Lunch:

1.0 pcs Thyme, Fresh
0.5 cups Tomatoes, Red
0.3 cups Lentils, Dry
1.0 cups Cucumber
1.75 cups Lettuce, Romaine, Shredded

Dinner:

0.25 cups Quinoa, Cooked
1.0 cups Pepper, Bell or Sweet, Green
0.25 tsp Paprika
0.5 items Lemon, Peeled
75.0 g Haddock, Raw
0.25 tsp Cumin, Ground
0.25 items Garlic Clove
2.0 tsp Oil, Olive

Snacks:

9.0 items Almonds, Slivered
1.0 items Apple, Medium

Nutrient	Intake amount
Fat	35 g
Carbohydrate	127 g
Protein	97 g

Example of the food contents on days 2 and 3 on restricted days on the HP diet using iProfile software

---

Breakfast:

0.25 cups Milk, Non Fat Skim or Fat Free

0.5 items Banana

Lunch:

0.25 tsp Oregano, Ground

0.25 cups Carrots

1.0 tsp Parsley

0.25 items Garlic Clove

0.25 cups Quinoa, Cooked

2.0 tsp Yogurt, Plain, Non Fat (13 grams protein per 8 ounces)

2.0 tsp Juice, Lemon

0.25 cups Beets

0.25 cups Pepper, Bell or Sweet, Red

Dinner:

1.0 tbsp Oil, Olive

250.0 g Chicken, Breast, Meat Only, Boneless, Skinless, Roasted

0.25 cups Carrots

0.5 slcs Bread, Mixed Grain

0.25 items Tomatoes, Red

7.0 items Asparagus

0.5 items Onions

1.0 cups Celery

Snacks:

1.0 items Apple, with Skin

Nutrient	Intake amount
Fat	25 g
Carbohydrate	78 g
Protein	90 g