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NUTRITIONAL CONSIDERATIONS DURING MAJOR WEIGHT LOSS THERAPY

SIMPLY GOOD

Contents

05 INTRODUCTION
- Purpose
- The Scope of the Obesity Problem
- Nutrition is Uniquely Different than Other Weight Loss Options

14 RELATIVE SUCCESS OF DIFFERENT WEIGHT LOSS APPROACHES
- Bariatric Surgery
- Pharmacotherapy
- Exercise
- Diet
- Holistic Approaches

14 NUTRITIONAL CONSIDERATIONS DURING MAJOR WEIGHT LOSS
- Dietary Protein
  - Fat Free Mass
  - Quantification of Fat Free Mass
  - Protein Requirements
  - Protein Quality
  - Protein Dosing and Distribution
- Low-Fat vs Low-Carbohydrate Diets
  - Effects on Weight Loss
  - Effects on Body Composition
- Potential Pitfalls and Concerns
  - Vitamin & Mineral Deficiencies

14 NUTRITIONAL CONSIDERATIONS DURING MAJOR WEIGHT LOSS
- Endurance Exercise Training
- Resistance Exercise Training

26 SUMMARY

28 REFERENCES

INTRODUCTION

PURPOSE

The primary objective of this review is to highlight the fundamental importance of nutrition during caloric restriction for promoting healthy weight loss. When calories are significantly restricted to induce major weight loss – which often occurs after bariatric surgery or with use of very low-calorie diets and glucagon-like peptide-1 (GLP1) analogues – maintaining muscle mass and consuming nutrient dense foods to ensure adequate essential micronutrient intakes is a high priority. In this review we examine the scientific evidence addressing nutritional considerations in maintaining lean tissue, functionality, and health during significant weight loss. This includes a focus on the optimal quantity and quality of protein necessary to achieve nitrogen balance and maximize lean tissue and health. We also review the unique role of low-carbohydrate and ketogenic dietary patterns on lean tissue, visceral adipose tissue, and other health markers during weight loss, as well as the role of exercise, including resistance training.

THE SCOPE OF THE OBESITY PROBLEM

The prevalence of obesity in the United States has more than tripled over the last half century and indicate that approximately 4 out of 10 adults are classified as obese (i.e., BMI ≥30 kg/m2) and an additional one-third are overweight (i.e., BMI 25 to <30 kg/m2) (Hales et al., 2020). Thus, about 3 out of 4 adults or more than 150 million people in the U.S. have a weight problem. Childhood obesity rates are increasing at an even greater rate. Given the close association between obesity and diabetes, it may not be surprising that half of U.S. adults (>100 million people) are either prediabetic or diabetic (Menke et al., 2015). Besides the stigma, personal suffering, and reduced health span associated with obesity and diabetes, these conditions also inflict an extraordinary financial burden on our economy with over $400 billion spent annually on managing diabetes alone, which reflects one-fifth of all healthcare expenditures and is more than all cancers combined. The obesity and diabetes epidemics are not isolated to the Unites States; it is a world-wide problem. Sadly, there are few signs of stemming the obesity crisis. By 2030 nearly 1 in 2 adults in the U.S. are projected to be obese (Ward et al., 2019). On a more promising note, the results of clinical trials indicate that bariatric surgery and the recently developed GLP1 receptor agonists have the most potent ability to produce substantial weight loss, but both requite proper attention to diet to be successful.

NUTRITION IS UNIQUELY DIFFERENT THAN OTHER WEIGHT LOSS OPTIONS

For many reasons, diet is a cornerstone for weight loss therapy. Notably, it is the only intervention that is essential (i.e., it is not optional). People with excess adiposity can choose to not have invasive surgery, engage in exercise, or take medications. But they must consume a diet and make decisions every day on what type of foods to consume. Moreover, just about every other weight loss approach, including surgery and medications, are viewed as an adjunct to nutritional counseling focused on caloric restriction.

Another unique aspect of nutrition is that it can interfere with or augment outcomes of other weight loss strategies. For example, a poorly formulated diet (e.g., deficient in protein, minerals, or some other essential nutrient) may attenuate or cancel out any positive effects of exercise or anti-obesity medications on weight loss. On the other hand, a well-formulated nutrition plan may synergize with an exercise regimen or maximize surgery and drug effects to facilitate long-term weight loss and health benefits.

The substantial weight loss achieved from bariatric surgery or GLP1 receptor agonists is often associated with significantly decreased energy intake, as is also the case with very low-calorie or semi-starvation diets (<800 kcal/day) in the medical management of obesity (Palgi et al., 1985; Vertes, 1984). The greater the degree of caloric restriction and weight loss, the more likely nutritional deficiencies occur. The new gastrointestinal physiology that accompanies bariatric surgery, and the common gastrointestinal reactions associated with GLP1 receptor agonists, also increase the likelihood of inadequate essential nutrient intake (Bettini et al., 2020).

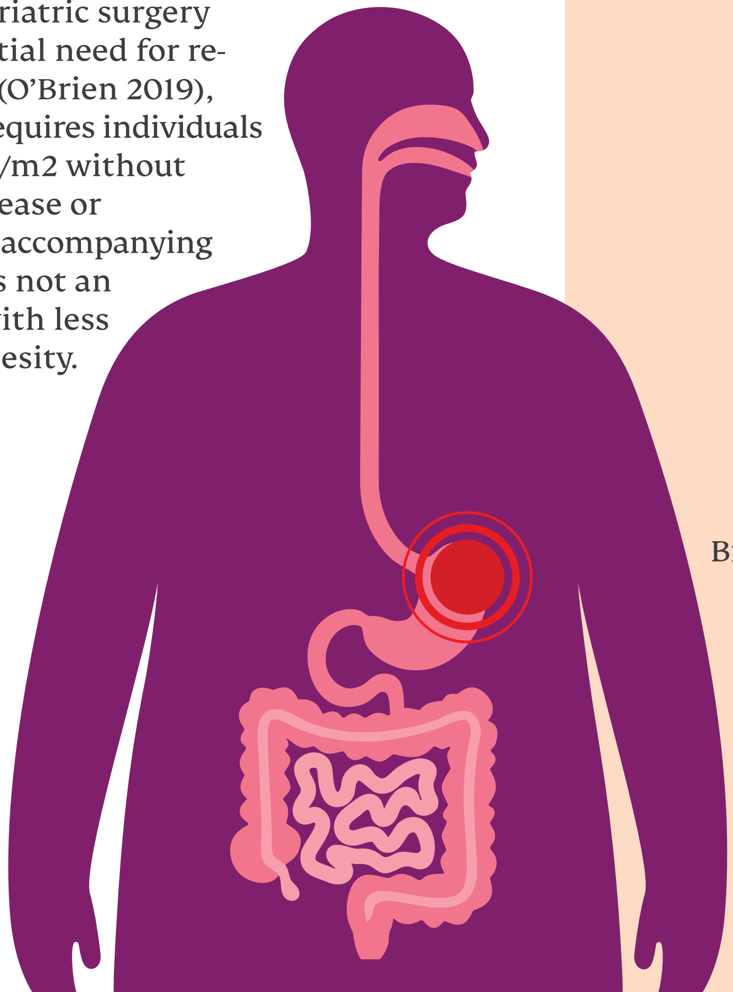
There is also the issue of weight regain, which happens frequently with all weight loss approaches, especially if individuals discontinue GLP1 receptor agonist therapy. For all these reasons, nutrition must be viewed as the foundation of safe, effective, and sustainable weight loss and maintenance. Traditional weight loss strategies span from lifestyle behavioral and metabolic interventions (exercise training and diet interventions) to medical approaches that include surgery and pharmacotherapy, and various combination of these approaches.

"the common gastrointestinal reactions associated with GLP1 receptor agonists, also increase the likelihood of inadequate essential nutrient intake (Bettini et al., 2020)."

RELATIVE SUCCESS OF DIFFERENT WEIGHT LOSS APPROACHES

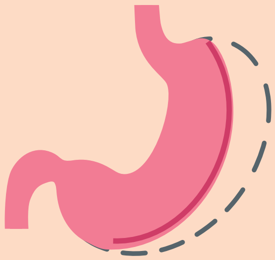
Bariatric Surgery

Bariatric surgery, which includes various invasive surgical procedures, has proven to be uniquely effective at promoting significant short-term and sustained (20-yr) weight loss (Gulinac 2023). According to one recent review, average weight loss at a single center at 1, 10, and 20-yr was 18, 20, and 22%, respectively (O'Brien 2019). In addition to the impressive durability of weight loss, there is accumulating evidence that bariatric surgery also improves obesity-related comorbidities including diabetes (Sheng 2017) and cardiovascular disease (van Veldhuisen 2022). Bariatric surgery is generally safe, but reporting of side effects lacks rigorous quality. Early problems include leaks, stenosis, bleeding, GERD, and thromboembolic events, whereas late-complications include band erosion, obstruction, gallstone disease, Dumping syndrome, ischemia, anemia, calcium loss, kidney stones, and osteoporosis (Gulinac 2023). Bariatric surgery also has a substantial need for re-operative surgery (O'Brien 2019), is expensive, and requires individuals have a BMI >40 kg/m2 without accompanying disease or ≥35 kg/m2 with an accompanying disease and thus is not an option for those with less severe forms of obesity.

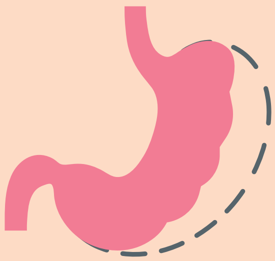


Types of Bariatric Surgery

VSG
Gastrectomy

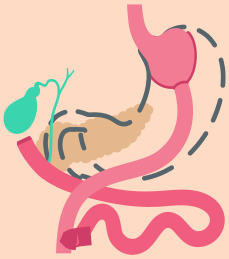


ESG
Gastroplasty



RYGB
Gastric bypass

BPD
Biliopancreatic diversion



Pharmacotherapy

The history of drugs for obesity has mostly been marked by failure. There are only a few currently FDA-approved anti-obesity medications and – except for GLP1-analogues – they produce only moderate weight loss (<10%) and have adverse side effect profiles (Chakhtoura 2023). In contradistinction, the recently FDA-approved GLP1 receptor agonists are associated with average weight loss similar to that of bariatric surgery (i.e., ~15 to 25%) (Chetty 2023) with fewer side effects and possibly many other benefits beyond obesity (Wilbon 2024). This degree of effectiveness represents a major advancement in the treatment of obesity, but it should be noted these drugs do not address the fundamental causes of obesity and they do require consumption of a properly formulated diet. If GLP1 receptor agonists are discontinued then weight regain occurs (Wilding 2022; Rubino 2021), emphasizing the need for properly formulated nutrition plans, such as carbohydrate restricted diets, that can maintain weight loss after GLP1 use (McKenzie 2024).

There is increasing anecdotal evidence that much of the weight loss with GLP1 receptor agonists may be derived from muscle mass, although direct evidence from most large trials do not include outcome measures of body composition to substantiate this concern. In a subset of obese participants (n = 95) in the STEP 1 semaglutide trial who had dual-energy X-ray absorptiometry (DXA) scans performed pre- and 68-wk post intervention, total soft tissue loss was 13.6 kg and lean mass loss was 5.3 kg, or 39% of the weight loss (Wilding 2022). This represents a significant loss of muscle, some of which would be expected considering the magnitude of weight loss, but clearly there were people who lost disproportionate lean mass. Pharmaceutical companies are looking at druggable targets to address this concern, but a more relevant question is why is muscle loss happening and what non-drug measures can be taken to optimize preservation of lean tissue during major weight loss? In this regard nutrition and exercise can be force multipliers when employed appropriately.

> "In the STEP 1 semaglutide trial at 68-wk post intervention, lean mass loss was 39% of the weight loss"

Diet and Exercise

Diet and exercise are considered first line approaches for weight management, but surprisingly the role of exercise alone in weight loss may be described as disappointing with minimal effects compared to other approaches (Franz et al., 2007), which often results in individual discouragement (Thomas et al., 2016). While frequent exercise training is associated with a wide range of health benefits, exercise interventions alone have a small role in weight loss (Cox, 2017; Donnelly et al., 2009; Swift et al., 2018). This may seem paradoxical based on the clear increase in energy expenditure elicited by physical activity, but there are compensatory responses to exercise training that limit weight loss (Church et al., 2009) such as increased caloric intake (Blundell et al., 2015; Thomas et al., 2012) and/or decreased energy expenditure (Heymsfield et al., 1989; Phinney et al., 1988). There is also wide variability in how individuals translate exercise-induced energy deficits into weight loss (Careau et al., 2021), which is highly dependent on genetics (Bouchard et al., 1994). Compared to endurance exercise, resistance training may offer unique benefits by increasing the proportion of fat loss while retaining lean tissue without altering total weight loss (Kraemer et al., 1999).

The role of diet in weight loss has a slightly better track record than exercise training, but there exists a high degree of nonconsensus related to the ideal macronutrient composition to promote healthy weight loss (Ludwig & Ebbeling, 2018). Most large-scale nutrition interventions for obesity have involved low-fat diets in line with the major tenets of the Dietary Guidelines for Americans and major professional medical organizations for the last four decades. The largest and longest low-fat diet study – the Women's Health Initiative – showed that postmenopausal women randomized to a low-fat diet intervention had minor weight loss at 1-yr that was not sustained after 7-yr (Howard et al., 2006) with similar lack of benefit on breast cancer (Prentice, 2006), type 2 diabetes (Tinker et al., 2008), and cardiovascular disease (Howard et al., 2006). In fact, there were plausibly harmful effects of the low-fat

dietary pattern on future risk of coronary heart disease in the subset of women with insulin resistance (Noakes, 2021; Shikany et al., 2011). Systematic analyses of long-term weight loss trials with low-fat diets have not shown a benefit over other dietary approaches (Tobias et al., 2015).

A large number of studies over the last two decades have compared low-fat to low-carbohydrate dietary patterns on weight loss. Summarizing this large body of literature, low-carbohydrate diets are at least as effective as low-fat diets for weight loss, and often outperform them in the short-term (Mansoor et al., 2016; Soltani et al., 2023). Low-carbohydrate diets appear to be especially superior to low-fat diets in individuals who are insulin resistant (Hjorth et al., 2018; McClain et al., 2013). Long-term weight loss beyond 1-yr generally shows less disparity between diets of any

composition, but this is likely driven by the relative high rate of noncompliance and attrition, which could be due to several factors.

Holistic Approaches

It is common to combine dietary and exercise interventions, which tend to produce better weight loss than either approach alone (Franz et al., 2007) and help preserve muscle mass during weight loss (Kraemer et al., 1999). However, long-term weight loss success is still moderate even when intensive behavioral strategies are employed. For example, the Look AHEAD trial randomized over 5,000 overweight individuals with type 2 diabetes to an intensive lifestyle intervention (ILI: low-fat diet, exercise, behavior modification, meal replacements, etc.) or standard diabetes support. Although there was nearly a 9% weight loss at 1-yr in the ILI group, weight regain occurred over the next several years with an average weight loss of ~5% in ILI compared to ~2% in the control group after 8-yr when the study was halted early due to lack of efficacy (Look A.R.G 2014).

The role of diet pattern prior to and after surgery has also been examined with some evidence pointing toward superior effects of a pre-bariatric surgery low-calorie ketogenic diet over a Mediterranean and other diet approaches (Erdem et al., 2022; Khalooeifard et al., 2020). A ketogenic diet may also have benefits post-bariatric surgery, especially in those who have a poor response or weight regain (Correa et al., 2021; Vinciguerra et al., 2023).

NUTRITIONAL CONSIDERATIONS DURING MAJOR WEIGHT LOSS

DIETARY PROTEIN

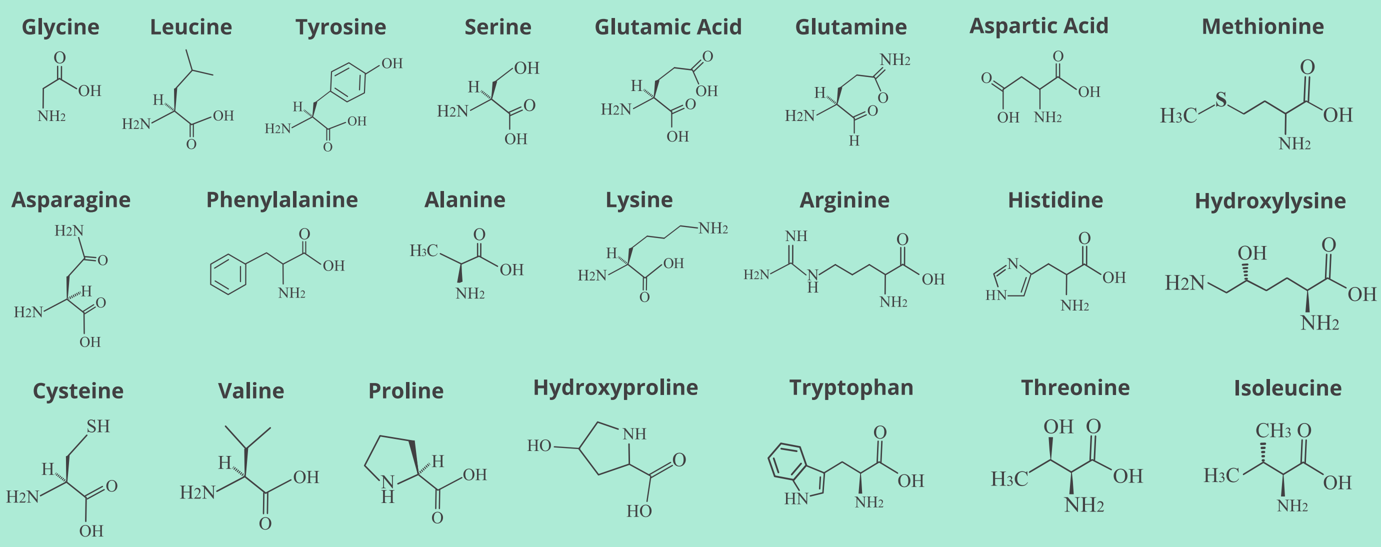
Protein is considered an “essential” nutrient because some of the constituents of protein, amino acids, must be obtained from the diet to prevent deficiency symptoms. In nature, there are nine essential amino acids, two essential fatty acids (linoleic acid and α-linoleic acid) and no essential carbohydrates. Resupplying the amino acid pool with an adequate quantity, and quality, of protein is necessary to prevent excess loss of lean mass during weight loss. Following is a brief discussion of issues relevant to determining the optimal quantity, quality, and timing of protein intake during major weight loss.

Fat-Free Mass

The fat-free mass (FFM) compartment comprises skeletal muscle, bones, organs, and extracellular fluid. Skeletal muscle constitutes ~40% of adult body weight and half of the physiological amino acid pool (Emery, 2003). Preserving, and in some cases augmenting, FFM in the context of major weight loss is a priority because it has a dominant role in determining total daily energy expenditure (Elia, 1992; Johnstone et al., 2005), physical strength (Celis-Morales et al., 2018; Reed et al., 1991), and lifespan (Bigaard et al., 2004), among many other bodily functions conducive to well-being.

FFM exists in a state of dynamic equilibrium whereby a fine balance of remodeling processes between protein synthesis and breakdown – together referred to as “protein turnover” – are required to maintain organ integrity, synthesize neurotransmitters and hormones, and produce glucose (i.e., gluconeogenesis) during prolonged fasting or to a lesser extent during a

Amino Acids



ketogenic diet (Wu, 2016). A healthy adult can turnover ~5.0 – 6.0 g protein/kg per day (Waterlow & Jackson, 1981), or in other words traffic nearly half a kilogram of protein per day between diet and FFM-stored amino acids to sustain homeostasis. These remodeling processes are thus protein intensive, and hence require adequate protein intake to modulate FFM positively.

There are two main physiological mechanisms that can augment FFM. De novo skeletal muscle tissue can be synthesized via satellite cell differentiation – a set of specialized cells located proximally to skeletal muscle basal lamina – that can develop into new muscle fibers (i.e., hyperplasia) in the presence of robust stimuli, such as resistance training or injury. Muscle fibers also increase in diameter (i.e., hypertrophy) and thereby increase their total cross-sectional area when exposed to the same stimuli, all whilst preserving the original number of fibers (Fleck & Kraemer, 1983). Whereas hyperplasia is largely influenced by epigenetic factors, hypertrophy can be rapidly modulated by resistance training and sustained by adequate protein manipulations, highlighting features that are warranted from lifestyle and pharmaceutical interventions.

Quantification of Fat-Free Mass

A gross estimate is that for every kilogram of body weight lost, approximately three-fourths originate from fat mass (FM) and one-fourth from FFM (3:1 ratio)(Webster et al., 1984). However, many modulating factors can affect this ratio such as diet, training status, concurrent resistance training, weight-loss magnitude, and body composition model assumptions (Heymsfield et al., 2014). To accurately evaluate the composition of weight loss, non-invasive imaging techniques have advantages due to their excellent sensitivity and accuracy over metabolite excretion and anthropometric measurements, including discerning discrete changes between tissue compartments (Nana et al., 2015; Shepherd et al., 2017).

Dual-energy X-ray absorptiometry (DXA) is often used as the gold standard to assess fat and lean mass, and bone density responses in many diet and training studies (Nana et al., 2015; Shepherd et al., 2017). Despite having advantages over other common body composition methods (e.g., underwater weighing, skin folds, bioelectrical impedance, air displacement plethysmography, etc.), an important limitation of DXA lies in its FFM algorithm, whereby fluid is calculated as lean tissue (Kerr et al., 2017). Thus, DXA underestimates lean mass under conditions where fluid may be lost (e.g., after profuse sweating, onset of a ketogenic diet, glycogen-depleting exercise, heavy diuretic use, etc.) or vice versa overestimated when fluid is retained (e.g., edema, carbohydrate loading, etc.). This limitation may be circumvented using other advanced imaging techniques less sensitive to fluid shifts, such as magnetic resonance imaging (MRI), but nevertheless problematic for studies comparing diets, especially ketogenic diets, expected to modulate fluid storage by altering carbohydrate intake, notably in the first few weeks of diet initiation (Buga et al., 2021; Phinney et al., 1983; Phinney et al., 1980; Yang & Van Itallie, 1976).

Protein Requirements

Dietary protein is the only nitrogen-containing macronutrient, and thus requirements for protein are often calculated using the nitrogen balance method, which calculates nitrogen ingested and subtracts nitrogen excretion (Allison, 1955; Hoffer, 2016). Assuming that ~16% of dietary protein is nitrogen by weight, daily nitrogen balance can be calculated mathematically by subtracting nitrogen measured in a 24-h urine collection plus nitrogen loss through sweat and feces as follows (Blackburn et al., 1977):
Positive nitrogen balance reflects greater protein synthesis than degradation and FFM preservation or gain, whereas negative nitrogen balance reflects greater protein breakdown than synthesis and net loss of FFM over time. The current recommended dietary allowance (RDA) for maintaining nitrogen balance is 0.8 g protein/kg/day, which translates to about 10%-15% of the total daily energy expenditure. This threshold value was determined by the USDA and WHO/FAO based on 24-h urinary nitrogen excretion patterns to achieve nitrogen balance in the majority of healthy sedentary adults (Organization & University, 2007; Trumbo et al., 2002). Extensive debates on the adequacy of 0.8 g/kg protein have permeated the literature due to concerns of poor ecological validity in athletes, older adults, or clinically ill patients, and inherent limitations in nitrogen excretion estimations owing to integumentary and fecal nitrogen loses (Matsumoto et al., 2023; Pencharz et al., 2016; Trumbo et al., 2002).

Nitrogen Balance =
Protein Intake (g/day)* 0.16
– [Urine Nitrogen Excretion
(g/day)+4]

Relevant to this review, the adequacy of the RDA for protein in the context of major weight loss is also dubious, as studies have indicated skeletal muscle protein synthesis is down-regulated and protein degradation accelerated during energy deficits (Pasiakos et al., 2015). A ~10% decrease in daily calories has been shown to increase protein requirements 50% (Rao et al., 1975). Complicating interpretation of protein requirements during weight loss is the fact that the mechanisms regulating protein turnover are modulated by the degree of energy deficit and time. It is well documented that the amount of protein required to maintain nitrogen balance during energy deficit is reduced over time as adaptive mechanisms act to preserve lean tissue (Pasiakos et al., 2014; Stein et al., 1991; Yang & Van Itallie, 1976).

Protein intake guidelines build on more robust evidence from detailed

amino acid oxidation methods (often involving a tracer amino acid; 13C-lysine/leucine or 2H5-phenylalanine) and dose-response clinical trials (Elango et al., 2012; Hayamizu et al., 2021; Humayun et al., 2007; Matsumoto et al., 2023; Pencharz et al., 2016; Poortmans et al., 2012; Young et al., 1989). Collectively, an optimal dietary protein intake for weight-loss is approximately two-fold higher than previously estimated; a range of ~1.2 to 2.0 g/kg/day is supported by large empirical evidence as an optimal dietary protein target that can offset untoward proteolytic turnover and promote protein synthesis, highlighting a substantial discrepancy from the prior guidelines (Campbell et al., 1994; Courtney-Martin et al., 2016; Dickerson et al., 2012; Humayun et al., 2007; Krieger et al., 2006; Layman, 2009; Meredith et al., 1989; C.H. Murphy et al., 2015" to: "Murphy et al., 2015; Poortmans et al., 2012; Tarnopolsky et al., 1988).

During major weight loss, the question of whether it is best to seek a protein intake that achieves a zero nitrogen balance (i.e., equal rates of protein synthesis and degradation) or a protein intake that achieves a high net positive nitrogen balance and gain in FFM is worth considering. It has also been postulated that high protein diets may have other beneficial outcomes, begging the question of what the minimum versus optimal protein level of protein is. A review of very high protein diets is beyond the scope of this review but has been done so by others (Moon & Koh, 2020).

Importantly, protein requirements should be calculated based on a reference or adjusted weight in people with excess adiposity. As shown in Table 1, a typical normal-weight male (Person A) may have an upper limit of reasonable protein intake of 150 g/day. But a similar height individual with obesity (Person B) would be prescribed protein up to 250 g/day using their actual weight, which is clearly excessive relative to requirements needed to maintain lean tissue and functionality.

Table 1 | Protein Adequacy vs. Over-Prescription

	Person A (Non-Obese)	Person B (Obese)
Weight (kg)	75	125
Height (inches/m)	68/1.73	68/1.73
BMI (kg/m2)	23.7	39.5
Protein Needs (g/day) Based on Actual Weight		
0.8 g/kg (RDA)	60	100
1.2 g/k (optimal low range)	90	150
2.0 g/kg (optimal high range)	150	250
Protein Needs (g/day) Based on Adjusted Weight (75 kg)		
0.8 g/kg (RDA)	60	60
1.2 g/k (optimal low range)	90	90
2.0 g/kg (optimal high range)	150	150

Note: the color gradient intensity is relative and anchored to the 60g dose.

Protein Quality

The biological value of proteins is influenced by the amount of nitrogen retained in the body; a reflection of individual amino acids being incorporated into FFM. Complete dietary protein sources contain 20 amino acids, 9 of which are essential amino acids (EEA): histidine, leucine, isoleucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine. Protein quality is directly related to the presence of EAA, especially leucine, the most robust activator of mTORC1 (Son et al., 2019; Symons et al., 2009; Young et al., 1975).

Protein sources that are limiting in EAAs are considered lower quality or incomplete proteins that can hinder the FFM growth and development in response to diet and exercise (Blomstrand et al., 2006; Volpi et al., 2003), an effect that becomes even more important during weight loss. When consumed as intact foods, EAAs are highly abundant in all animal-derived meats and byproducts (i.e., eggs, dairy), except collagen and gelatin, and several plant sources (Symons et al., 2009; Young et al., 1975). As a side note, the protein digestibility-corrected amino acid scale – a standardized range of amino acid absorption per unit of protein consumed; PDCAAS – uses eggs as the reference food for high-biological value determinations.

> "an optimal dietary protein intake for weight-loss is approximately two-fold higher than previously estimated"

It is well-established that omnivores achieve their total protein and EAA with greater ease than vegetarians/vegans. Plant-based approaches may often fail to provide adequate amounts of leucine lysine, methionine, and threonine because the amount of EAAs in plant foods is generally less compared animal foods, thereby compromising protein synthesis (Norton et al., 2017; Tang et al., 2009). Moreover, intact plant protein sources may lack the necessary digestibility relative to equal amounts of animal proteins because plant proteins often tend to integrate within the plant fiber matrix, creating an inaccessible mesh during digestion that provides less protein than what is advertised on the label, thus prompting supplementation.

With the advent of protein powder formulations and the ability to decouple plant proteins from their fiber matrix, protein supplements have been able to increase EAA availability to a point where animal and plant-based powders exhibit similar kinetics with respect to their protein synthesis potential (Scrimshaw et al., 1983; Tang et al., 2009), albeit in several instances still favoring whey (Norton et al., 2017). Whey protein is ~50% by weight EAAs and 11% leucine (Poortmans et al., 2012; Tang et al., 2009). A quality source of whey protein

will provide 25g of protein per serving, with ~3g of leucine. This guideline is often cited in the literature as a proxy against protein "spiking" (i.e., diluting the content with cheap, non-essential amino acids); therefore, supplementing a diet with whey during weight loss requires two major considerations: that the supplement received a reputable third-party purity certificate (i.e., NSF) and individual amino acids are listed in gram amounts on the label.

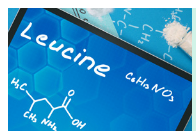
Collectively, protein quality is guided by EAA composition, especially leucine content. Although outside the scope of this review, some qualities of dairy proteins remain to be elucidated albeit relevant to carbohydrate-restriction. Of importance, whole-eggs – specifically egg yolks – may augment protein synthesis independent of total calories and protein content, in part explained by non-caloric compounds (e.g., miRNAs) contained within the yolk fraction (Abou Sawan et al., 2018; Baier et al., 2015; van Vliet et al., 2017). Similarly, full-fat milk (3.5%) appears to exert protein synthesis signaling properties that are beyond skim milk (0%) in the post-exercise window (Elliot et al., 2006). When viewed within a low-carbohydrate context, inclusion of full-fat dairy products is not only appropriate and encouraged but may strategically modulate protein synthesis signaling beyond fat-free items.

Protein Dosing and Distributions

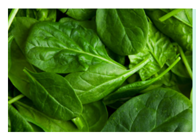
Beyond quantity and quality of protein, the optimal (grams per meal) and distribution (timing or frequency of intake over the day) has been a subject of research and debate over the last few decades, and in more recent discourse, the physiological upper-limit of protein digestion questioned (Trommelen et al., 2023). In general, a meal that provides ~25-30g of a high-biological value protein can adequately stimulate muscle protein synthesis due to the intrinsic connection between total protein dose and EAA content, specifically leucine, to surpass rate-limiting threshold for protein synthesis (Breen & Phillips, 2011; Katsanos et al., 2006; Paddon-Jones & Rasmussen, 2009; Son et al., 2019). Substituting incomplete protein sources for dairy products may lower the leucine-threshold requirement per meal (15-20g), in part owing to the insulinogenic amino acid profile and the unique dairy matrix properties discussed earlier and in greater detail elsewhere (Holt et al., 1997; Poortmans et al., 2012).

In regard to protein timing, evidence from both pre-clinical and clinical trials suggests that distributing total daily protein evenly across breakfast, lunch, and dinner can drive greater anabolic responses and FFM preservation relative to skewed intakes (Jespersen & Agergaard, 2021; Layman, 2009; Mamerow et al., 2011; Norton et al., 2017; Paddon-Jones & Rasmussen, 2009; Yasuda et al., 2020). In other words, when total daily protein is held constant, an individual who consumes at least 25-30g of protein per meal should expect a 25% greater protein synthesis response compared to an individual who consumes a low-protein breakfast (~10g) and a protein-rich dinner (~60g) (Mamerow et al., 2011). Collectively, it appears that overweight/obese individuals who undergo weight-loss may benefit from the protein distribution strategy presented herein (Murphy et al., 2015), albeit some evidence suggests no demonstrable effects of protein distribution (Hudson et al., 2017) in part explained by less sensitive changes in untrained individuals versus trained (Damas et al., 2015). A graphical summary of the main points discussed in this protein section is provided below.

Consuming 1.2-2.0 g of protein per kilogram of reference weight is a reasonable target for most adults undergoing weight loss therapy.



Leucine is the most robust protein synthesis "trigger" event.



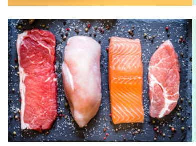
Plant-sources may provide less EAAs than advertised, whereas plant-powders may increase digestibility and availability.

Each meal should contain ~25-30 grams of high-biological value protein.

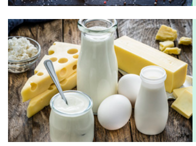
Muscle amino acid uptake increase significantly post-exercise.

Whey should comprise by weight 50% EAAs and 11% leucine.

Protein doses should be evenly distributed across the day versus skewed.



Whole-food animal sources are most likely to contain all EAAs.



Full-fat dairy may preferentially augment protein synthesis beyond fat-free products.

LOW-FAT VS LOW-CARBOHYDRATE DIETS

A comprehensive discussion on various dietary patterns is beyond the scope of this review, as the permutations of nutrient combinations even within low-carbohydrate diets are vast. With the focus of this review on low-carbohydrate dietary patterns, we provide a general overview comparing and contrasting the main differences between low-fat and low-carbohydrate diets.

For this review, we advocate definitions of dietary patterns as proposed in a recent expert consensus paper (Volek et al., 2021), where very-low carbohydrate/high-fat ketogenic diets consist of <10% carbohydrate or 20-50 g/day; low-carbohydrate diets consist of 10-25% carbohydrate or 50-129 g/day; and low-fat/high-carbohydrate diets consist of >45% carbohydrate or >225 g/day. Notably, not all low-carbohydrate dietary patterns are ketogenic, but all ketogenic diets are low in carbohydrate. The limited carbohydrates are primarily derived from non-starchy vegetables, nuts, seeds, low-sugar/high-water content fruits (berries, avocados, olives, tomatoes), with lower amounts from full-fat dairy, whole eggs, and other protein sources. Protein needs are estimated based on 1.2 to 2.0 g/kg reference weight, usually ranging between ~80-150 g/day. Fat is prescribed to satiety which can be consumed from meats, high-fat dairy (butter, cheese, sour cream, heavy cream), avocados, oils (olive, canola, avocado, coconut, etc.), nuts and seeds.

A low-fat dietary pattern is reduced in overall fat intake, especially saturated fat. Most low-fat approaches encourage the consumption of lean proteins, fruits, vegetables, and whole grains while limiting high-fat dairy products, fatty meats, and processed foods. Variations of low-fat diets may encourage primary replacement of saturated fat with carbohydrate and/or polyunsaturated fat. Most plant-based vegetarian patterns would be considered low-fat, but it is possible to also design plant-based low-carbohydrate diets. In contrast, the hallmark of a low-carbohydrate diet generally involves restricting many carbohydrate-dense foods while consuming moderate protein, and moderate- to high-fat (depending on the degree of caloric restriction). There is an emphasis on avoiding added sugars, limiting highly processed foods, and consuming nutrient-dense minimally-processed whole foods

Effects on Weight Loss

There are now several published comparative studies between low-fat and low-carbohydrate dietary patterns of less than 130 grams per day of carbohydrate ranging from a few weeks to 2-years in duration. It is clear that individuals can lose weight on a variety of diets varying in macronutrient composition. The results of multiple recent meta-analyses indicate that low-carbohydrate dietary patterns do at least as well, and often better, at promoting weight loss and certain risk markers for cardiovascular disease when compared with low-fat dietary patterns (Mansoor et al., 2016; McClain et al., 2013; Chawla et al., 2020; Sackner-Bernstein 2015; Silverii et al., 2022). A unique aspect of low-carbohydrate diets is that in many studies they were implemented ad libitum without prescribing an explicit caloric reduction, yet still elicited significant weight loss (Volek et al., 2009; Boden et al., 2005). Without going into detail on the many individual trials now published, there is generally less of a discrepancy in weight loss among diets of any macronutrient composition the longer the intervention duration (Ge et al., 2020), emphasizing the need for ongoing support and selecting the most appropriate diet that works for each person. In regard to this idea of personalized or precision nutrition, it is noteworthy that low-carbohydrate diets appear to be especially superior to low-fat diets in individuals who are insulin resistant or have high insulin secretion (McClain et al., 2013; Hjorth et al., 2018; Ebbeling et al., 2018; Hron et al., 2015; Pittas et al. 2005), which is common in people with obesity. In regards to the challenge of the high cost and poor persistence of GLP1 therapy, there is now evidence that a low-carbohydrate diet may enable deprescription with maintenance of weight loss and clinical improvements (McKenzie 2024).

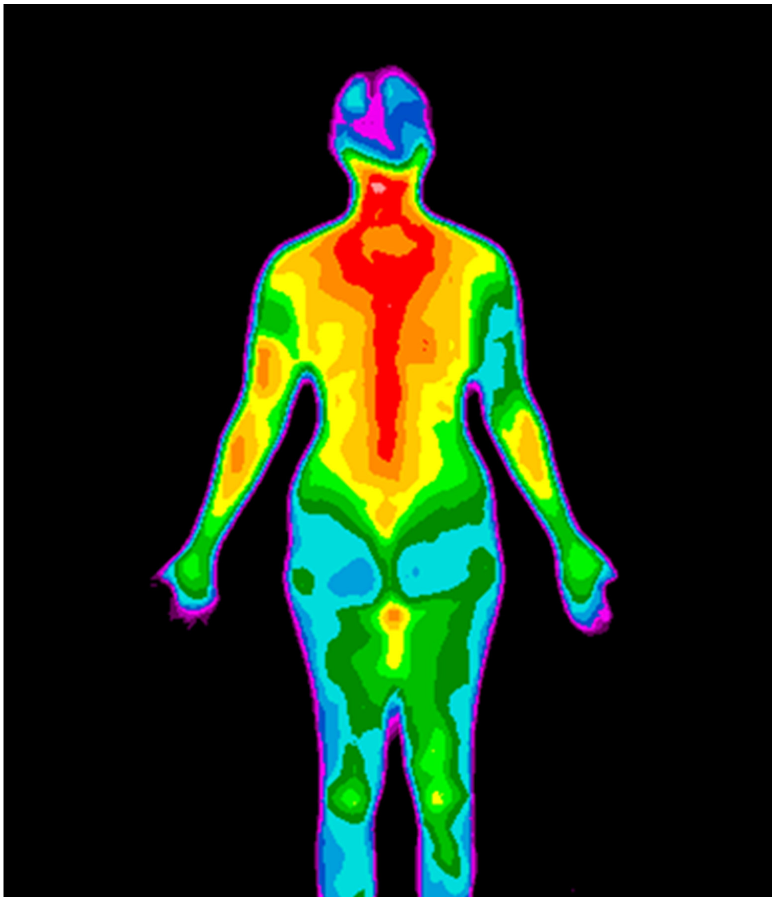
Effects on Body Composition

Considering both low-fat and low-carbohydrate dietary patterns can be used to achieve weight loss, a crucial question is whether the composition and distribution of weight loss is similar between diets. Ideally, weight loss strategies should target FM reduction, particularly in visceral adipose tissue (VAT), while preserving lean tissue. According to meta-analyses, low-carbohydrate diets compared with other weight loss interventions of the same duration demonstrate greater loss of total weight, fat mass, and waist circumference (Muscogiuri et al., 2021; Hashimoto et al., 2016; Di Rosa et al., 2020). Because total weight loss is often higher on a low-carbohydrate diet, there may also be a greater amount of lean mass lost, but this is an expected response and associated with an overall maintenance of physical function and decrease in percent body fat. Discrepancies between individual studies may be attributed to factors such as inadequate protein intake, limitations in common body composition assessment methods that misinterpret water loss as a decrease in lean tissue, and insufficient sodium compensation for the natriuretic effect of carbohydrate-restriction.

In a few short-term hypocaloric diet studies, a greater loss of nitrogen has been demonstrated with ketogenic diets compared to non-ketogenic diets (Vazquez 1992; Dietz 1985), but these diets were severely energy-restricted, very short-term, and more importantly did not provided inadequate sodium and potassium to account for the natriuretic effect of ketogenic diets, which has a key role in maintaining nitrogen (DeHaven et al., 1980). In contrast, there may be some instances where a ketogenic diet could lead to greater preservation of lean tissue during major weight loss, especially if combined with resistance training or exogenous ketones that have anticatabolic effects (Koutnik et al., 2020), but this area of investigation remains understudied and controversial.

There is evidence that ketone bodies may protect against muscle loss in catabolic conditions such as sarcopenia, cachexia, and excessive inflammation, potentially through mTORC1 signaling (Halle 2020). While still a hypothesis, these previous findings suggest it may be possible to augment preservation of lean tissue during major weight loss through oral ingestion of ketones. In support of this possibility we recently observed that ingestion of a modest does of BHB-salts (12g day; twice-daily) during a 6-wk ketogenic diet controlled-feeding intervention resulted in a modest reduction in urinary nitrogen excretion compared to placebo (-8%), although this did not translate into a detectable difference in lean body mass determined by DXA (Buga et al., 2021).

Accumulation of fat in VAT and the liver (NAFLD) are particularly problematic and strongly associate with higher risk for diabetes and cardiovascular disease. Only a few studies have assessed how low-carbohydrate dietary patterns affect VAT using precise imaging technologies. In one study, a 12-wk ad libitum ketogenic diet in military-affiliated healthy adults resulted in significant weight loss (7.7 kg) and a 44% reduction in VAT assessed by MRI (LaFountain et al., 2019). In another 12-wk study, patients with NAFLD assigned to a calorie restricted low-carbohydrate diet lost weight (-8.0 kg) and had a 18% reduction in VAT assessed by MRI (Lindqvist et al., 2023). Thus, a ketogenic diet may uniquely target VAT (Cunha et al., 2020).
NAFLD is a progressive liver disorder characterized by the accumulation of more than 5% fat in the liver. If left untreated, it can progress to non-alcoholic steatohepatitis, fibrosis, cirrhosis, and liver failure. Hypocaloric low-fat and low-carbohydrate dietary patterns have been demonstrated to reduce liver fat to a similar extent in relatively healthy overweight individuals (Crabtree et al., 2021), with more profound effects seen in patients with NAFLD (Haufe et al., 2011). Some evidence points to superior effects of ketogenic diets (Cunha et al., 2020; Browning et al., 2011; Kirk et al., 2009), likely attributed to both decreased de novo lipogenesis and increased metabolism of fatty acids into the ketogenic pathway (Mardinoglu et al., 2018; Luukkonen et al., 2020), both decreasing the availability of fatty acids to accumulate as triglycerides in the liver.



POTENTIAL PITFALLS AND CONCERNS

Vitamin & Mineral Deficiencies

Ensuring adequate essential vitamin and mineral intakes is a priority for all dietary patterns, especially during caloric restriction, but practically challenging for individuals to accomplish without professional support (Damms-Machado 2012; Gardner et al., 2010). Most individuals who qualify for bariatric surgery are micronutrient deficient in key areas (Parrott et al., 2017); remarkably ~99% of patients are vitamin-D-deficient (Ben-Porat et al., 2015) and women are twice as likely than men to be iron-deficient (Ben-Porat et al., 2015). Poor micronutrient status can, however, be reversed with proper supplementation (Sayadi Shahraki et al., 2019). Relevant to carbohydrate-restriction, the whole-food items proposed by the well-formulated ketogenic diet guidelines are congruent with the recommendations for reversing micronutrient malnutrition and meeting international DRI standards (Beal & Ortenzi 2022). Human trials further support the idea that a ketogenic diet can be micronutrient adequate in patient populations (Taylor et al., 2019), and when implemented over 4-weeks in pre-operative individuals (n = 27) it can favorably reverse micronutrient deficiencies during major weight loss (-10%) while simultaneously improving body composition (5:1 FM:FFM kg:kg losses) (Schiavo et al., 2018). Whereas the consensus is still extensively investigated (Gardner et al., 2010), or is obfuscated dietary assessment methods (Damms-Machado et al., 2012; Malik et al., 2020) and early clinical evidence (Christodoulides et al., 2012; Prudencio et al., 2021), there is recent promising data suggesting that carbohydrate-restriction is sensible to micronutrients with proper implementation and guidance.

Particularly noteworthy is the issue of sodium, which is an essential but controversial mineral. At the onset of a low-carbohydrate diet, especially a ketogenic diet, the kidneys switch from retaining sodium to rapidly excreting it (Spark et al., 1975). In many obese individuals, this natriuresis and diuresis is associated with positive effects (e.g., rapid weight loss, less swelling, reduced blood pressure), but once this excess fluid is cleared continued loss of sodium and fluid leads to what has been termed “keto-flu”. The contracted plasma volume can manifest in dizziness, fatigue, headache, and lethargy. It also triggers the adrenal glands to release aldosterone and cortisol to retain sodium, but this occurs at the expense of losing potassium in the urine. Thus, restriction of sodium on a ketogenic diet can disrupt metabolic and hormonal homeostasis compromising sustainability and effectiveness of a ketogenic diet. Careful attention to ensuring adequate sodium as well as potassium and other minerals is necessary, which can be accomplished with normal foods, but regular consumption of broth or dietary supplements are effective as well.

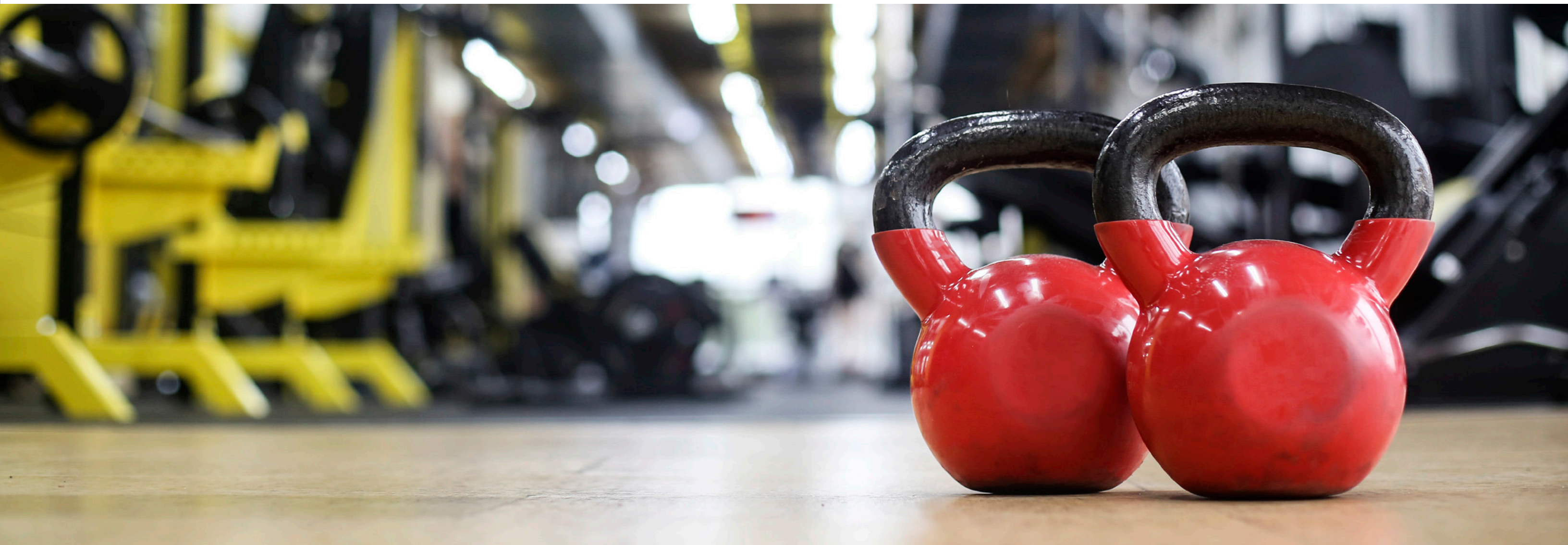
BENEFITS OF COMBINING EXERCISE WITH DIET

Exercise Considerations

As overviewed in the previous section, nutritional considerations are paramount in the context of major weight loss, but it is important to also consider the role of exercise. It seems reasonable to speculate that regular exercise may promote weight loss, but an equally plausible hypothesis is that a healthy weight enables people to be more active. There may be truth to both perspectives. Surprisingly, when a sedentary person performs an exercise training program the vast majority of studies indicate that regular physical activity, in the absence of dietary intervention, is not effective at promoting clinically significant weight loss in the majority of people (Franz et al., 2007; Swift et al., 2018; Cox 2017; ACSM 2009).

Why the caloric expenditure associated with performing structured exercise fails to translate into a predictable weight loss (i.e., assumes a 3,500 kcal deficit results in a 1-pound fat loss) remains unclear. There is likely a genetic component to how people with excess adiposity translate exercise into weight loss. For example, in a remarkable identical twin metabolic ward study, obese siblings lost a similar amount of weight but only ~20-30% of twin pairs lost the predicted amount of weight in response to a precisely monitored exercise dose (640 kcal/day), whereas some twin pairs lost almost no weight (Bouchard 1997). This is consistent with evidence supporting a restraint on human metabolic rate in individuals who are extremely active (Pontzer et al., 2015) and larger studies that show only about a quarter of participants exercising at a high dose do not compensate (i.e., they lose weight in response to exercise) (Church et al., 2009). Ironically, the "compensatory" responses to exercise that contribute to minimal weight loss appear to be more robust in people with greater adiposity (Careau et al., 2021), making weight loss even more challenging. The mechanisms underlying compensation likely involve an increase in appetite and subsequent caloric intake (Thomas et al., 2012; Blundell et al., 2015) as well as a decrease in resting energy expenditure (Phinney et al., 1988; Heymsfield et al., 1989).

Regardless of the poor effects of exercise alone on weight loss, incorporating regular physical activity into a weight loss plan may have other benefits such as assisting in weight maintenance and improving body composition and health outcomes. We briefly discuss the literature on both endurance/aerobic and resistance/strength training.



Endurance training alone is a weak weight loss tool for many, it has been shown to slightly augment fat loss and retention of lean mass (Garrow 1995) and is associated with a myriad of health benefits.

Similar to endurance exercise, resistance training alone is not advocated as a primary method of weight loss (Swift et al., 2018), but it does augment retention of lean mass during major weight loss, and thereby improves body composition (Kraemer et al., 1999) while also promoting numerous health benefits. Importantly, the majority of diet and resistance as well as endurance training studies examining weight loss were performed in the context of moderate-to-high carbohydrate and low-fat intakes, but a few low-carbohydrate diet interventions have been published recently.

In summary, endurance and resistance training are not effective primary methods of weight loss for most people, but research supports a consistent benefit of exercise when combined with diet, especially resistance training, on weight maintenance, lean mass and physical performance. Although there is more debate surrounding the optimal dietary macronutrient distribution, there is preliminary evidence supporting the combination of a low-carbohydrate diet with resistance training to maximize fat loss and retention of lean while improving many cardiometabolic risk factors.

SUMMARY

An impressive amount of scientific evidence now supports low-carbohydrate dietary patterns that contain moderate protein (1.2 to 2.0 g/kg reference weight) from food sources with high biological value as effective for promoting clinically meaningful decreases in adiposity without unwanted muscle mass loss. As the scientific community delves into these emerging areas, collaboration between researchers, healthcare practitioners, and policymakers is crucial to translate findings into accessible and effective interventions that promote individual and global well-being.

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