The physiological basis for weight recidivism following severe caloric restrictive diet therapies: a molecular rationale for exercise-and nutrition-based treatment optimization

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Medically prescribed very-low calorie diet (VLCD) programs have shown efficacy in producing clinically significant weight-loss in obese patients. This loss in bodyweight (BW), however, cannot be solely accounted for by reduced adiposity, but also significant deficits in lean tissue. With respect to these frequently reported weight-loss patterns for lean body mass (LBM), the potential for optimum weight-loss as well as sustainable weight-maintenance is adversely affected on a number of levels. Lowered resting metabolic rate (RMR), neuromuscular impediments, and poor physical function have been reported to occur as a result of reduced LBM. Any of these factors taken together with a dramatic loss of lean tissue would be a condition that is conducive to impeded fat reduction, weight-regain, and relapses of prior health complications. Therefore, the main purpose of this review is 3 fold: 1) to comprehensively discuss the molecular and morphological adaptations to VLCD treatment in lean and fat tissues, 2) to provide molecular- to practical-based rationale for systematic exercise and nutrition applications in VLCD treatments, and 3) to discuss current research limitations and future research implications.


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Introduction

Epidemiological findings from the recent National Health and Nutrition Examination Survey (NHANES 2009-2010) reported that 36% of U.S. adults are currently classified as obese, while 16% represent incidences of severe cases [1]. Obesity reflects a prevalence rate far exceeding the threshold of 15% set by the World Health Organization for epidemics needing intervention [1, 2]. Hence, national health initiatives have prompted the urgency for effective clinical treatments to
reconcile the global spread of obesity and subdue the heightened socioeconomic burdens directly attributable to this epidemic [3]. Despite the methodological advancement in treatment options, such as surgical- or pharmacological-based approaches, medically supervised weight-loss programs incorporating hypocaloric dietary modifications have remained the most prudent and pragmatic intervention for clinical obesity [4]. Amongst hypocaloric approaches, proprietary very low calorie diet (VLCD) programs (~800 kcal/day), e.g. Optifast® (Nestlé HealthCare Nutrition), have been medically prescribed as a viable option for high-risk patients whose body mass index (BMI) exceeds 30 kg/m², exhibit critical mortality risk, or have failed to respond favorably to conventional and unmonitored weight-loss programs.

VLCD prescriptions, which are based on meal replacement formulas, have been consistent with outcomes of revitalized health with significant body weight reductions ranging between 15-27% in obese subjects [4-7]. This loss in total body mass, however, cannot be solely accounted for by reduced adiposity, but also significant deficits in lean tissue, especially for skeletal muscle [7-12]. With respect to these frequently reported weight-loss patterns for lean body mass (LBM), the potential for optimum weight-loss as well as sustainable weight-maintenance is adversely affected on a number of levels. Lowered resting metabolic rate (RMR), neuromuscular deficiencies, undue fatigue, poor physical functioning, and increased risk for musculoskeletal injury have been reported to occur as a result of reduced LBM [4, 7, 13-17]. Any of these factors taken together with the dramatic loss of lean tissue would be a condition conducive to impeded fat reduction, weight-regain, and relapses of prior health complications [18].

While large-scale weight-loss yields important clinical benefits for the morbidly obese, the rate of recidivism remains inordinately high with contemporary VLCD programs. In fact, significant weight-regain has been reported in 77% to 100% of subjects who underwent a VLCD-based weight-loss intervention [5, 19-22]. Accordingly, previous findings indicated that VLCD-treated subjects initially lost 19.6% (-21.4 kg) of their entry weight; however maintained only 4.3% (-5.1 kg) after 4.5 years [4, 6]. Thus, a positive prognosis for acute and prolonged treatment success remains, at present, marginally supported with current VLCD-based therapeutics for obesity. When considering the public health relevance of these corollaries, a major unmet clinical need is a strategy that can be practically applied to current VLCD programs in efforts to optimize weight-loss composition while enhancing metabolic and functional outcomes. To address the burden imposed by severe hypocaloric diets on lean tissue morphometry, energy metabolism, and perhaps functionality, the integration of exercise countermeasures has been examined extensively [7, 10, 23-30]. However, an equivocal body of pertinent data has likely precluded the sophisticated integration of exercise training into clinical weight-management prescriptions using a VLCD system.

As a potent anabolic stimulus for muscle, resistance training would appear as the ideal countermeasure to the loss of lean mass during caloric restriction; yet, the majority of studies have employed relatively low-force activities in the form of aerobic exercise training [8, 27-28]. On the basis of previous whole-body outcomes [8, 29-31] and molecular rationale [32-33], aerobic training may be an ineffective strategy for lean mass retention during severe hypocaloric conditions. In fact, aerobic training has even demonstrated to extend lean tissue loss beyond the degree induced by caloric restriction alone, suggesting that prolonged, low-force activity can exacerbate the catabolic nature of energy deficiency in muscle [8, 29-31]. Because it is well established that high-force and high-load bearing activities function favorably to improve muscle mass and performance, resistance training may be the most effective means of optimizing VLCD treatments towards enhanced weight-loss composition, resting metabolism, and muscular function [34-36]. Of the limited pool of available evidence comparing modes of exercise during VLCD-induced weight-loss, resistance training demonstrated similar effects on fat reduction but greater efficiency in maintaining LBM and RMR [10, 37, 38]. Unfortunately, these previous attempts using resistance training to moderate the burden of severe hypocaloric diets lack sufficient support to be systematically integrated into current therapeutic procedures. This likely is attributable to the paucity of applicable clinical data that can properly guide medical weight-management programs towards an optimized hypocaloric treatment through a resistance exercise prescription.

There is undoubtedly a clinical need to further understand the physiological basis of weight-recidivism, and in so doing, identify molecular targets through which exercise- and nutrition-based interventions may systematically counteract these deleterious effects. Therefore, the purpose of this review is 3 fold: 1) to discuss, from cell to whole-body, the adaptive response to VLCD-based medical weight-loss therapies, 2) to provide molecular- to practical-based rationale for systematic exercise applications in VLCD treatments, and 3) to discuss limitations in the current body of pertinent findings and future research implications.

**Current Dietary Approach in Obesity Therapeutics**

The extent of morbidity and mortality related to obesity is quite substantial and has thereby imposed significant burden on the national socioeconomic status. Fortunately, there is mounting evidence that support the potential for reversing
these obesity-related health risks through a range of conventional to more clinical-based weight-management strategies. Regardless of therapeutic approach, the main principle for treating obesity is to achieve weight-loss that is clinically significant. Having said that, voluntary weight-loss has been consistent with reports of improved clinical health parameters, such as blood pressure, circulating lipid levels, and glucose tolerance, among overweight and obese cohorts [39-48]. Because of the progressively rising prevalence of obesity and related clinical and socioeconomic liabilities, the urgency for effective treatment strategies have been of utmost priority in the medical community. When defining the efficacy of weight-loss therapeutics for clinical obesity, it is important to look beyond short-term weight-loss achievements and bear in mind the propensity for sustaining healthy-weight status and minimizing the risk for recidivism. To promote the best opportunity for long-term weight-management success, the American College of Sports Medicine, the National Heart, Lung, and Blood Institute with the National Institute of Diabetes and Digestive and Kidney Diseases, and the Obesity Society have developed comprehensive lifestyle modules for diet, physical activity, and behavioral modifications [15, 36, 49]. However, such a lifestyle-centric approach to weight-management may be more applicable to subclinical or post-obese populations that do not necessarily exhibit a heightened level of comorbid conditions and risk for mortality. In the case for the more high-risk patient cohort in which rapid weight-loss is of highest priority, medical-based treatment options such as bariatric surgery, pharmacotherapy, or proprietary hypocaloric diet programs have been developed and established to address the most urgent clinical cases [50].

Treatment of Obesity through Proprietary Hypocaloric Diets

Despite the methodological advancement in treatment options, such as surgical or pharmacological approaches, medically supervised weight-loss programs incorporating strict dietary modifications have remained the most prudent and pragmatic prescription for clinical obesity [4]. Among the variety of dietary programs available, proprietary very low calorie diet (VLCD; 450-800 kcals/day) systems have been medically prescribed as a viable option especially for high-risk patients whose BMI exceeds 30 kg/m², exhibits critical mortality risk, or has failed to respond favorably to conventional and unmonitored weight-loss programs [4, 51, 52]. VLCD-based treatments are perhaps the most utilized yet most controversial among current dietary prescriptions for the management of clinical obesity. This appears to relate primarily to concerns over their safety, cost, or long-term efficacy. In that regard, a proprietary VLCD is typically prescribed and administered under strict medical supervision by a multidisciplinary team comprised of physicians, therapists, dieticians, and exercise physiologists to especially minimize physical complications, improve compliance, and monitor clinical parameters.

According to the international food standards documented by the CODEX Alimentarius [53], a VLCD is defined as a hypocaloric, meal-replacement diet with a daily caloric content of 450-800 kcal [50, 54]. The earliest form of VLCD programs utilized a more severe energy restriction of approximately 450 kcal/day, but research has demonstrated equivalent weight-loss efficacy across 12 to 16 weeks with a VLCD providing 800 kcal/day [55, 56]. Thus, contemporary VLCDs are designed in reference to an 800 kcal/day diet given the greater tendency for compliance and equal effectiveness with a less severe restriction of caloric intake. It must be noted, however, that VLCDs should not be defined entirely on the basis of caloric content. Instead, one should consider the following key features that are characteristic of most prescribed VLCD programs: 1) complete replacement of all usual food consumed through formulated products (usually liquid-based) [50]; 2) hypocaloric, relatively high protein content (70-100g/day), and permits appropriate metabolic adaptations [50, 57]; 3) provides a full complement of the Recommended Daily Allowance (RDA) for vitamins, minerals, electrolytes, and fatty acids [50, 53]; and 4) total treatment duration of 12-16 weeks with a subsequent transitional period to reintroduce solid food at a more sustainable caloric intake [58].

One of the more prominent medically monitored VLCD programs prescribed today is Optifast® (Nestlé HealthCare Nutrition), a comprehensive meal-replacement system administered through liquid-based and some solid-based (e.g. bars) formulas. Optifast® is one of the few proprietary diets that mandates medical supervision and requires proper documentation to obtain products. A standard Optifast® treatment offers a 4-phase approach to weight-loss administered in the following sequence: 1) 4 weeks of LCD (~1200-1500 kcal/day); 2) 12-week rapid weight-loss phase with full meal-replacement (~800 kcal/day); 3) 6-week transition period when solid foods are reintroduced with a more sustainable caloric intake; and 4) a variable maintenance phase to support weight-stabilization mainly through nutritional and behavioral counseling. Also, it is routine for physicians and/or clinical dieticians to circumstantially modify the patient’s VLCD program. For instance, a patient concurrently engaged in a rigorous exercise regimen or one who is of older age may be prescribed additional nutrient provision through high-quality protein supplementation.

Efficacy for Acute Weight-Loss and Long-Term Maintenance

In terms of the rate and amount of weight-loss achieved, a
VLCD treatment that is properly administered yields outcomes superior to low calorie diets (LCD; ~1200 kcals/day; non-meal replacement), at least in theory. In support, a previously studied VLCD treatment has shown efficacy in promoting short-term weight-loss of at least 10 kg over 12 to 24 weeks in 90% of the study cohort [59-61]. Contrastingly, only 60% of the subject pool exhibited a weight-loss of similar degree when utilizing a balanced LCD treatment [50, 62]. Moreover, a 12-week VLCD treatment resulted in a mean weight-loss of 20 kg at a rate of 1.5-2.0 kg/week for females and 2.0-2.5 kg/week for males [22], while previous LCD trials produced more moderated outcomes regardless of a longer timespan (~8.5 kg across 24 weeks at a rate of 0.4-0.5 kg/week) [21, 43, 50, 61]. Furthermore, Tsai et al. [63] recently conducted a controlled meta-analysis of six randomized trials that showed a significantly greater short-term weight loss with VLCDs (-16.1%) versus conventional LCDs (-9.7%). These corroborating findings were also suggested to be independent of compliance as attrition rates between VLCD and LCD treatments have been shown to be comparable (i.e. 15% vs. 20%, respectively) [50, 63]. Although there is a clear consensus on the advantages of VLCDs over LCDs in the stimulation of acute rapid weight-loss, its efficacy in the context of stabilizing post-treatment weight status is of significant debate.

Indeed, weight maintenance has remained the most challenging component with all obesity therapeutics, undoubtedly perpetuating the high rate of recidivism that has been reported both anecdotally and empirically. Hence, an important question with respect to VLCD efficacy is how sustainable the outcomes are once ideal weight-loss is achieved. Deriving a firm conclusion in that regard is rather difficult given the limited availability of follow-up data in VLCD-treated subjects. However, Saris [52] conducted an evaluation of weight-maintenance success following a VLCD treatment on the basis of nine randomized clinical trials. At the one-year follow-up mark, the percentage of initial weight lost that was regained demonstrated large variations ranging between -7% to 122%. This variation was marginalized to a range of 26% to 121% at a five-year follow-up time point. The Optifast® program, as described earlier, has also demonstrated to result in a considerable rate of weight-regain following a 26-week treatment period under medical supervision [6, 64]. For instance, Wadden et al. [64] conducted a multicenter evaluation of 517 obese patients who underwent the Optifast® treatment program. Among the 45% of the subject pool who completed the treatment, a weight-loss of 21.8% of initial body weight was observed. At one-year post-treatment, patients maintained only a 9% weight-loss from their pre-intervention weight. In a single-center evaluation of the Optifast® program, patients lost 20% of initial body weight after 26 weeks of treatment; however, after four years, only a 4.3% reduction was preserved [6].

Taken together, the available body of empirical evidence point towards a more significant initial weight-loss with VLCDs compared to LCDs. However, a number of follow-up evaluations suggest long-term maintenance of weight-loss to be relatively substandard with either modes of treatment [50]. Even when behavioral therapy was incorporated into VLCD programs, partial to full weight-regain was evident [50, 61, 65, 66]. It can be concluded that VLCD-based weight-loss programs demonstrate some level of futility as long-term success has been poorly supported. This suggests that practical and effective solutions to improve long-term efficacy are lacking in current VLCD-based treatment plans. Although, behavior therapy has shown some extent of effectiveness in promoting post-VLCD weight stability, it may be an insufficient approach as a high incidence of recidivism remains [59]. With that said, an important question to probe is whether the long-term efficacy of a VLCD treatment is determined solely by behavioral factors or if the physiological adaptations to the treatment per se are causal to weight-regain. In other words, could the weight-loss patterns in body composition and metabolic adaptations acutely resulting from a VLCD treatment predispose a patient to subsequent weight-regain? Previous evidence may be suggestive of such possibilities. To address this question, the effects of VLCD or severe hypocaloric conditions on body composition, energy metabolism, and function must be explored as these factors would conceivably influence the potential for not only efficient weight-loss but also success in sustaining these outcomes.

Hypocaloric Diets and Body Composition: Outcomes for Lean Tissue

As aforementioned, comprehensive VLCD interventions have been consistent with outcomes of significant body weight reductions ranging between 15-27% in obese subjects [4-7]. This loss in total body mass, however, cannot be solely accounted for by lowered adiposity, but also significant deficits in lean tissue, especially for skeletal muscle mass [7-12]. Because of the clinical significance of decreased lean tissue, weight-loss treatments incorporating VLCD or other modes of severe energy restriction remain controversial. The typical weight-loss composition with VLCDs is approximately 75% fat and 25% lean mass [50, 67]. Interestingly, these ratios are similar to those obtained with weight-loss following LCD interventions of similar dietary composition [50]. Chaston et al. [12] conducted a broad and systematic review of various weight-loss interventions and the proportion of weight reduction attributable to decreased LBM. Lean body mass herein encompassed muscle, bone, and internal organ tissues. Among 19 trials employing severely...
restrictive diets for at least 9 to 16 weeks, an average of 20.6% of total weight lost was accounted for by a reduction in LBM, with the greatest contribution reported at 37.4% [12]. To date, a quantitative classification scheme for severity of LBM loss has yet to be devised especially in the context of voluntary weight-loss. Therefore, the measurable extent to which LBM loss is clinically relevant remains to be determined. Nevertheless, a reduction in LBM has shown to have significant physiological consequences that may explain the relative ineffectiveness of VLCD programs with respect to long-term weight maintenance.

Metabolic and Functional Consequences of Rapid Weight-Loss

The significance of energy expenditure and its adaptive response to hypocaloric conditions has been somewhat confounded by issues pertaining to: 1) the methodology of normalizing data to the loss of metabolically active tissues; and 2) identifying compartments of body composition (fat, lean, or both) that are most contributory to basal energy requirements. Nevertheless, the most fundamental adaptation that can be firmly asserted is that total energy expenditure is suppressed with significant weight reduction. In support, Leib et al. [68] examined changes in energy expenditure and its components in response to experimental perturbations to body weight. Investigators concluded that a 10% reduction of body weight (induced by VLCD) was accompanied by a 15% decrease in 24-hour total energy expenditure. This general adaptive response has been demonstrated in a number of human [66-76] and polygenic [77-80] models of obesity and weight-loss. Moreover, it is suggested that all components of total energy expenditure, which include activity-related thermogenesis, postprandial thermogenesis, and RMR, are affected by weight-loss, at least to a general extent [68, 81]. The mechanistic underpinnings of these effects are directly associated to the loss of tissue mass, especially those with high basal energy requirements, e.g. skeletal muscle [68].

Weight-loss, and thereby reduced tissue mass, contributes to depressed energy expenditure through several distinct pathways. First of all, accompanying weight-loss is a reduced amount of body mass to be shifted during bodily movements, thus reducing the energy cost for any given workload of physical activity. Therefore, if the level of physical activity is unaltered pre- to post-weight-loss, activity-related thermogenesis, which accounts for 20-30% of total energy expenditure, would be conceivably lowered [75]. Secondly, suppression of total energy expenditure during dietary restriction may occur in response to the reduced quantity of food being consumed. Resulting from decreased nutrient intake would be a blunted thermic effect of food which contributes to nearly 10% of total energy expenditure. Postprandial thermogenesis can be compartmentalized into two energy-expending components, one that is obligatory and the other, facultative [82, 83]. The obligatory component is simply described to be the metabolic demand, and thereby energy cost, of food digestion, which also comprises processes of nutrient absorption and storage [83]. Energy expenditure that occurs beyond these obligatory, postprandial processes is suggested to be due to heightened sympathetic nervous tone, protein turnover, and substrate cycling in response to nutrient consumption [83-85]. Thus, because these processes are subdued during dietary restriction, the absolute energy expended from the thermic effect of food is diminished [86].

Lastly and perhaps most causal to the suppression of energy expenditure during weight-loss is the adaptive response for resting metabolism [69]. Resting metabolism, which is typically reflected as RMR (kcais/day), accounts for approximately 60-70% of total energy expenditure and therefore plays a significant role in the regulation of energy balance especially during weight-loss situations [13, 18, 74]. Participants that received either a VLCD or LCD treatment exhibited a significant decrease in energy expenditure predominately through diminished resting metabolism [16, 27, 74, 76, 87-89]. Total body mass appears to be a direct determinant of RMR in both healthy-weight and obese individuals, particularly the lean compartment (i.e. LBM) which comprises of more metabolically active tissues than fat, i.e. skeletal muscle [14, 17, 68, 87, 90, 91]. Correspondingly, LBM has been significantly correlated to not only total energy expenditure ($r^2= 0.74; p< 0.001$), but also RMR ($r^2= 0.44; p= 0.004$) among subjects studied at their initial weight and after a 10% and 20% weight-loss [68]. In the same study cohort, obese subjects who lost 10% of their initial weight exhibited significant declines for total energy expenditure (-17.7%) and RMR (-14.0%). Thus, the majority of the total energy expenditure reduced was attributable to lowered resting metabolism (~80% accountable). These effects were also observed in parallel to a significant decrease in LBM. Therefore, deficits observed for total and resting energy expenditure, may likely be explained by the significant loss of lean tissue. Perhaps because of this relationship, rapid weight-loss situations where LBM is reduced have shown consistently to be accompanied by a decrease in RMR [10, 27, 68, 76-79, 92, 93]. In support, Wang et al. [94] conducted an evaluation of tissue-specific metabolic rates and demonstrated 1kg of skeletal muscle to be associated with an energy expenditure of approximately 13 kcal/day while the per-kg energy cost for adipose is nearly 4.5 kcal/day. Because RMR is a major component of daily energy expenditure and therefore energy balance, maximizing resting metabolism during a rapid weight-loss scenario would be advantageous in terms of facilitating fat loss while supporting long-term...
weight-management. With respect to potential strategies to counter RMR suppression during severe hypocaloric conditions, maintaining lean tissue emerges as an imperative weight-loss objective. In so doing, one may prevent the dramatic decline in energy expenditure with weight-loss. This would have significant long-term implications to weight-management as reduced energy expenditure has shown to be evidentially predictive of recidivism [68, 95].

In addition to metabolic deficits, there are concerns that a reduction in LBM during weight-loss could impose negative functional consequences. This contention is partly supported by data indicating a positive correlation between LBM and functional strength in subclinical populations [96-98]. Further, according to the work of Donnelly et al. [7], subjects undergoing 90 days of severe energy restriction exhibited a 13.3% decline in absolute strength output from pre- to post-treatment while also demonstrating a significant reduction in LBM. However, muscular strength relative to LBM remained unchanged from baseline. These results suggest that the absolute loss of strength may be most accounted for by decreased lean tissue. Correspondingly, a 5-week, 800 kcal/day VLCD was shown to accompany significant declines in muscular strength relative to both body weight and LBM [29]. In terms of contractile kinetics during VLCD conditions, results from Eston et al. [9] and Krotkiewski et al. [99] reported a significant decline in isokinetic torque output across a spectrum of constant angular velocities. In fact, the latter study suggested the changes in muscular torque production to be significantly correlated (r=0.49; p< 0.05) to the negative changes in LBM following the VLCD. Although this does not imply causation, it can certainly support the argument that declines in muscle contractility during a VLCD is due to decreased LBM. To date, limited evidence substantiates the quantitative relationship between the changes in LBM and muscular strength especially during weight-loss conditions. Therefore, it cannot be completely ascertained whether strength loss observed during energy restriction is on the account of decreased LBM. Regardless of whether any correlation exists, hypocaloric interventions have shown to be detrimental to muscular strength. The potential clinical implications of these effects could be a reduced capacity to perform physical work and functional movements. Given that most clinically obese patients exhibit some heightened degree of functional limitations, any additional deficits to contractile force and muscular function accompanying weight-loss could be of significant disadvantage.

It can be speculated that one would be able to maintain or perhaps improve muscular strength during voluntary weight-loss even in the presence of reduced LBM. To elaborate, muscular strength is not exclusively governed by morphological phenotype but also largely through a neurological capacity to stimulate force production [33]. Neural factors contributing to force productivity include motor unit recruitment, firing frequency, and synchronization of motor unit activation. These factors are enhanced as an adaptive response to serialized neuromuscular overloading, and would result in positive strength manifestations [32, 33]. Therefore, strength development can be achieved independently of morphometric responses in muscle (i.e. hypertrophy or atrophy) if provided sufficient and appropriate stimuli [100]. Certainly, the most potent stimulus for strength development would be persistent, mechanically-overloaded muscle contractions, which are most prudently afforded through exercise [33, 100]. Thus, an exercise provision that is tailored towards both lean mass and strength development may act in favor of enhanced weight-loss patterns and functional outcomes when applied to hypocaloric treatments. Considering the causative nature of LBM loss to negative metabolic and functional outcomes, evidence certainly supports the need for strategies to effectively mitigate the physiological processes that drive the loss of lean tissue during hypocaloric/energy deficient states. To identify targets for intervention, prominent pathways of lean tissue catabolism and therefore atrophy must be examined.

Physiological Basis for Lean Tissue Loss during Energy Restriction

The metabolism of myocellular proteins is a key determinant for the morphometric fate of skeletal muscle (i.e. hypertrophy, atrophy, or stasis) during adaptive periods. During a prolonged energy deficient state, a metabolic shift conducive to both protein catabolism and hypoanabolism drives the muscle phenotype towards the atrophic end of the adaptation continuum [11,101-104]. This shift in muscle protein metabolism, often described as a negative protein turnover, reflects the body’s need to mobilize fuel substrate, such as amino acids, to contend with a deficiency in cellular energy and to reestablish energy homeostasis. Distinct molecular signaling pathways and upstream effectors, such as hormones, have been identified to delineate the mechanisms controlling the degradation and synthesis of myocellular proteins in the presence of metabolic perturbations [104]. Under homeostatic conditions, regulators of protein degradation and synthesis orchestrate in a fashion that maintains muscle protein balance, and therefore, myofiber size remains relatively unchanged [104]. With a negative energy balance that is sustained, protein degradation predominates while anabolic processes are repressed, ultimately coercing an adaptive response towards myocellular atrophy (Figure 1). This being a hallmark of most hypocaloric weight-loss conditions, protein turnover and the mechanisms underlying hypercatabolic and hypoanabolic responses is of clinical relevance.
This adaptive response in protein metabolism is partly mediated by high circulating levels of catabolic hormones, in particular glucocorticoids [105-108]. Endogenous cortisol is the most important human glucocorticoid as it is a key homeostatic regulator of systemic energy metabolism. For instance, its release from the adrenal cortex is elevated in response to hypoglycemic conditions, such as in prolonged energy restriction or expenditure [105-108]. In so doing, cortisol stimulates catabolism of large molecules, such as protein, to generate a substrate pool to support hepatic gluconeogenesis [106-111]. It is well documented that glucocorticoids induce a catabolic response in skeletal muscle to liberate amino acids into circulation by the degradation of intact myofibril proteins, i.e. proteolysis [106, 112]. The catabolic signals conferred by glucocorticoids are stimulatory to the ubiquitin-proteasome pathway (UbP), one of the most prominent proteolytic mechanisms proposed to induce the atrophic phenotype in skeletal muscle [113-115]. The role of UbP in skeletal muscle atrophy has been well established as so is the altered expression patterns of genes with a regulatory function in UbP-dependent proteolysis [103, 104, 115-117]. These genes, collectively termed “atrogens”, induce two skeletal muscle-specific E3 ubiquitin ligases: muscle ring finger1 (MuRF1) and atrogin-1. Increased atrogen expression is reflective of increased protein degradation via UbP and initially requires the dephosphorylation and nuclear translocation of the forkhead box O (FoxO) transcription factor [102, 116, 118, 119]. Evidence indicates that activation of FoxO by glucocorticoid administration stimulates an atrogen transcriptional program responsible for inducing UbP-proteolysis and myofiber atrophy [102, 120]. It is through this mechanism that cortisol disseminates its catabolic effects on skeletal muscle and may be pivotal in the loss of LBM during energy restriction.

A divergent pathway implicated as a catalyst to myocellular atrophy involves the activation of 5’ adenosine monophosphate (AMP)-activated protein kinase (AMPK), a
prominent energy sensing enzyme in skeletal muscle cells [121]. AMPK is a ubiquitously expressed protein kinase that is considered by most as the cell’s principal molecular regulator of energy homeostasis [122]. In brief, AMPK is directly activated by elevated levels of cytosolic AMP and is accordingly sensitive to an enhanced AMP to adenosine triphosphate (ATP) ratio, a distinct mark of depleted cellular energy [123-125]. Acute activation of AMPK in response to energy depriving conditions, e.g. nutrient starvation or prolonged exercise, initiates molecular events to mutually conserve as well as generate ATP. With that regard, AMPK inhibits anabolic processes that consume cellular energy while stimulating catabolic processes that would generate energy [122, 125]. Protein synthesis, an energy-costly event, is the major anabolic process inhibited upon AMPK activation [122]. The mammalian target of rapamycin (mTOR) signaling pathway is central in the control of protein synthesis and is cues in response to a multiplex of anabolic stimuli, including growth factors (e.g. insulin like growth factor-1 or IGF-1), insulin, or intramyocellular amino acids (e.g. leucine) [104, 126]. AMPK suppresses anabolism largely through the inhibition of mTOR signaling by two mechanisms: 1) inactivation of mTOR itself and/or 2) activation of its upstream inhibitor, tuberous sclerosis complex 2 (TSC2) [127, 128]. AMPK has also shown to exert catabolic effects on muscle protein in efforts to derive cellular energy, i.e. ATP, from freed amino acids. This process is regulated through a pathway similar to that involved in cortisol-induced protein degradation. Evidence reveals a link between AMPK activation and FoxO-induced transcription of atrogenes, which again is indicative of proteolysis induction and heightened atrophic potential. Romanella et al. [129] investigated a model of energy deprivation in which AMPK activation led to FoxO dephosphorylation and subsequent epigenetic up-regulation of atrogin-1 and MuRF1. Activation of AMPK activity, therefore, appears to constitute changes at the protein level preceding the development of the atrophic phenotype during energy deficiency.

The loss of muscle mass induced by extended energy deficits might also involve the insulin/IGF-1 signaling pathway. This pathway incorporates many of the molecular events essential to our current understanding of protein metabolism and its regulation of morphometric adaptations in skeletal muscle. Insulin and IGF-1, in particular, are potent anabolic and anti-catabolic stimuli for skeletal muscle through distinct molecular pathways mediated by protein kinase B (Akt) [130-132]. Akt is an important signaling hub activated upon growth factor ligation and has multiple substrate targets commensurate with its many molecular functions. These include those affecting protein synthesis as well as proteolysis [103]. In contrast to AMPK function in protein metabolism, substantial evidence supports the role of Akt as a key activator of mTOR and therefore is highly linked to the biosynthetic pathways responsible for cellular growth [130, 131, 133]. Akt also appears to counteract atrophic adaptations through the inhibition of FoxO translocation which in turn would suppress the expression of proteolytic atrogenes [103, 120]. Collectively, Akt appears to have a central function in integrating anabolic and anti-catabolic signals derived from growth factors (i.e. IGF-1) and insulin. Hence, limiting the bioavailability of these circulating factors would conceivably preclude cellular growth potential and promote tissue catabolism.

Nutritional status is a major effector for circulating IGF-1 concentrations and may take part in the molecular events preceding the course for muscle atrophy during hypocaloric interventions [134-137]. Significantly decreased serum IGF-1 levels were previously demonstrated during prolonged and short-term calorie restriction, delimiting the capacity for protein synthesis and muscle growth [138-141]. Henning et al. [137] characterized the temporal response of the circulating IGF-1 system to acute caloric restriction over a 48-hour period. Free IGF-1 decreased 43% with severe caloric restriction while remaining stable during a eucaloric state. Interestingly, caloric restriction yielded a dramatic 445% increase in circulating IGF-1 binding protein-3 (IGFBP-3). Because IGFBP-3 is inhibitory to the actions of free circulating IGF-1, these results suggest that severe caloric restriction obstructs ligation of IGF-1 to membrane receptors, thereby repressing downstream, Akt-mediated pathways. Consequently, both mTOR activation and FoxO/atrogenic inhibition would be withdrawn.

Hypocaloric intake often depletes muscle of ample nutrient supply, which may consequently compound the catabolic effects of blunted growth factor activity. As mentioned earlier, mTOR is a key integrator of environmental cues, including nutrient availability and growth factors, and ensures that cellular growth manifests when conditions are permissible [130]. In fact, several findings demonstrated the importance of amino acid sufficiency in mTOR signaling, as growth factors are unable to effectively activate mTOR under an inadequate amino acid reserve [142-144]. Under nutrient-rich conditions in which an abundance of amino acids are present, mTOR signaling is permitted, thus allowing stimulation of biosynthetic pathways while inhibiting molecular catabolism [144]. The fundamental role of amino acid availability in the context of muscle anabolism is to provide an ample substrate supply to support the manufacturing of myofiber proteins. However, beyond this basic function, evidence has specified unique amino acids to be stimulatory of mTOR activation and the initiation of ribosomal translation (i.e. protein synthesis) [142-146]. Among these amino acids, the branched chain amino acid (BCAA) leucine appears to be distinguished in the nutrient-stimulation of mTOR signaling [147-149]. Atherton et
al.\textsuperscript{[150]} evaluated the response of anabolic signaling mechanisms in cultured skeletal myocytes inoculated with a spectrum of amino acids, including BCAAs. Among all amino acids administered, leucine alone stimulated a robust increase in the phosphorylation/activation of mTOR and its downstream substrate targets, including eukaryotic initiation factor 4E-binding protein (4E-BP1), p70 ribosomal protein S6 kinase (p70S6K), and ribosomal protein S6 (rpS6). Several other investigations support this distinct pro-anabolic effect of leucine in skeletal muscle by mTOR-dependent mechanisms \textsuperscript{[151-154]}. In the context of hypocaloric treatments, diets lacking sufficient amino acid provision would be detrimental to the retention of muscle tissue due to: 1) limited substrate pool for synthesizing new proteins, and/or 2) withdrawal of nutrient stimulation of anabolic pathways (i.e. leucine and mTOR signaling).

For this reason, supplementary protein and/or amino acids have been explored as a potentially effective nutrient provision for lean mass during hypocaloric intake \textsuperscript{[25, 155-157]}. Hypocaloric diets with relatively higher protein content (30-50% of total kcal) have resulted in greater reduction in body weight and fat, while better preserving LBM compared to diets lower in protein content (~18% of total kcal) \textsuperscript{[24, 158, 159]}. Therefore, when considering the importance of optimizing weight-loss patterns, a relatively high-protein hypocaloric treatment (protein accounting for ~50% of total kcal) would be the most ideal dietary approach. A contemporary VLCD system, i.e. Optifast®, provides a standard 800 kcals per day of which 35%, 50%, and 15% derive from protein, carbohydrate, and fat, respectively. This would provide 70 g of high-quality protein daily and would elicit approximately 0.7 g/kg of bodyweight/day based on a reference bodyweight of 100 kg. In fact, the mean bodyweight at baseline for a single-center cohort of 32 patients who underwent the Optifast\textsuperscript{®} program was approximately 130 kg. Thus, the relative protein intake for this particular cohort was nearly 0.5 g/kg/day. While the RDA for protein intake is currently 0.8 g/kg/day, meta-analyses suggested that higher-protein consumption (~1.20 g/kg/day) promotes greater LBM maintenance than diets lower in protein (<0.7 g/kg/day) under weight-loss circumstances, particularly when combined with resistance training \textsuperscript{[67, 160]}. Furthermore, Pasiakos et al.\textsuperscript{[161]} conducted a randomized controlled trial comparing the effects of varying levels of dietary protein (i.e. RDA vs. 2x-RDA vs. 3x-RDA) on body composition and muscle protein synthesis (MPS) during energy restriction and a subsequent weight maintenance phase. Participants, regardless of protein intake, exhibited a 3-kg weight-loss. However, weight-loss composition differed among conditions as a reduction in LBM was less and fat loss was greater in those receiving 2x-RDA and 3x-RDA compared to just the RDA treatment. Also, the post-absorptive anabolic response was blunted during energy restriction when compared to what was demonstrated within the weight-maintenance phase. Higher protein intake, however, maintained an elevated and consistent post-meal-MPS across both energy restrictive and weight maintenance phases. Thus, it remains reasonable to suggest the RDA for protein intake, and thereby customary Optifast\textsuperscript{®} protein content, to be inadequate for the preservation of LBM, especially for the average 100-130 kg patient. Based on this reference bodyweight range and the aforementioned protein recommendation (1.20 g/kg/day), approximately 150 g of protein per day would be required to facilitate the sparing of LBM during hypocaloric weight-loss treatments, especially when coupled with resistance training. From a practical perspective, given that VLCD systems comprise of proprietary meal-replacement formulas with fixed nutrient composition, increasing protein content to 150 g/day would be most prudently achieved via addition of an 80 g/day supplement of high-quality protein, such as whey. Although additional calories would result from supplementing 80 g of protein (~320 kcal/day more), it would be clinically discouraged to substitute VLCD meal products with a protein supplement as other necessary nutrients afforded through the formulas would be compromised. Indeed, some may also be apprehensive to the idea of additional caloric intake from protein supplementation as it may be perceived to compromise the weight-loss efficacy of the VLCD program.

In efforts to provide rationale for the added protein calories, Bray et al.\textsuperscript{[162]} concluded that excess caloric intake derived from moderate (15% of total kcal; 1.8 g/kg/day) to high (25% of total kcal; 3.0 g/kg/day) proportions of dietary protein leads to greater lean mass accretion while preventing further fat gain as compared to conditions in which carbohydrates and fat constituted the excess calories. Therefore, additional calories to a VLCD that is primarily derived from protein may act in favor of lean mass retention without compromising the rate of fat loss.

Undoubtedly there is much debate regarding the ideal source of supplementary protein within the context of lean tissue growth or maintenance, especially during hypocaloric weight-loss endeavors. In efforts to elucidate the optimum protein source, the role, as well as benefits, of dairy foods during energy restrictive weight-loss have been examined via meta-analysis of randomized controlled trials \textsuperscript{[163]}. The report suggested that hypocaloric diets higher in dairy content result in superior weight-loss composition characterized by enhanced total weight-loss, fat loss, and LBM retention. This is most likely attributable to the type of protein that is derived from milk (i.e. whey and casein). Based on the molecular rationale presented above, a protein source rich in essential amino acids (EAA), and therefore BCAA content, and thereby leucine, would supply appropriate nutrient support for muscular growth as well as stimulation of MPS (i.e. mTOR
signaling), provided that a sufficient quantity is consumed. In that specific regard, two of the most prominent supplementary forms of protein are in fact whey and casein, which comprise of an amino acid profile high in EAA, BCAA, and leucine according to the USDA Food Composition Tables. Whey may be considered as the higher-quality protein compared to casein due to its relatively greater concentration of BCAA and leucine (12% vs. 9.3% of total protein), which to reiterate, is a unique nutrient stimulator of MPS \[147\]. This may likely explain the reported advantages of whey over casein supplementation in enhancing the changes in body composition and strength that accompany resistance training \[164\]. Although very limited evidence demonstrates the role of supplementary protein in clinical VLCD interventions, whey protein supplementation, in its appropriate dosages, may be the most effective dietary means of sparing lean tissue \[26, 164-166\].

**Exercise Training Application in Hypocaloric Weight-Loss Treatments**

An important question emerges regarding the capacity through which exercise training can elicit a hypertrophic or anti-atrophic response in skeletal muscle under the catabolic strain imposed by hypocaloric intake. This morphometric adaptation in muscle is one likely to act in favor of enhanced total LBM during energy restrictive weight-loss endeavors. With that said, it would be of significant value to further evaluate the extent to which the specific adaptations from divergent exercise modes would either protect against or facilitate lean mass reduction during rapid weight-loss. Advances in molecular physiology have considerably enhanced our understanding of the specificity of adaptations to different modes of training, i.e. endurance and resistance type, and may provide rationale for appropriate exercise programming during hypocaloric dietary treatments.

**Specificity of Training Adaptation in Skeletal Muscle: Rationale for Resistance Exercise.**

Many features of training adaptation in skeletal muscle are unique to the type of stimulus that is applied, namely contractile activity \[32, 33, 167\]. Contractile activity can generally be defined as low muscular force development across an extended duration, or high force generation of limited duration, features characteristic of endurance and resistance exercise, respectively. Training-induced adaptations at the whole-body, cellular, and molecular levels demonstrate specificity to the mode of exercise performed \[168\]. For instance, increased muscle cross-sectional area (hypertrophy)
and enhanced motor unit recruitment patterns constitute the fundamental adaptations to repeated bouts of high-force activity, i.e. resistance exercise. In contrast, prolonged endurance/aerobic training elicits a variety of metabolic and morphological reformation, including enhanced maximal oxygen consumption, oxidative metabolism, and mitochondrial content concomitant with a fast-to-slow shift in muscle fiber type. Each mode of exercise training induces divergent signaling pathways and mechanisms that when chronically activated, direct muscle adaptation towards either an aerobic or hypertrophic phenotype (Figure 2).

First, myofiber hypertrophy results from proper resistance training, which provides a recurrent overloading stimulus conducive to intracellular protein synthesis and blunted proteolytic activity in muscle. Activation of signaling mechanisms associated with muscle growth have also been exhibited, composing changes at the protein level preceding the advancement towards a hypertrophic phenotype. For instance, the Akt-mTOR pathway has been considered by most as an integral component of the hypertrophic process since it coordinates the molecular basis for myocellular protein synthesis. Among the various stimuli that subsequently lead to Akt-mTOR activation, studies support IGF-1 as a potent anabolic agent for skeletal muscle. Resistance exercise increases circulating and muscle-derived expression of IGF-1 which may transiently increase Akt-mTOR activity and ensuing activation of translational machinery (i.e. 4E-BP1, p70S6K, and rpS6 phosphorylation). In the context of chronic adaptations in the circulating IGF-1 system, work from Borst et al. and Marx et al. reported elevated resting concentrations of serum IGF-1 following resistance training (~25-week protocol). These systemic shifts in IGF-1 levels may explain the heightened activation of muscle-specific mTOR previously demonstrated following 8 weeks of resistance training in human subjects. An alternative agonist to constituents of the Akt-mTOR pathway is derived from the mechanical deformation of muscle fibers during resistance exercise, i.e. mechanotransduction. Mechanotransduction, a process converting mechanical signals from contractile activity into molecular events, plays a key role in inducing protein synthesis through an mTOR-dependent mechanism autonomous from growth factors or hormones. Further, while a degree of protein degradation is required for muscle remodeling during adaptive periods, resistance training may also decrease chronic activation of catabolic processes through a diminished expression of MuRF1 and atrogin-1. Results from others suggest these effects to be mediated by the actions of Akt and its inhibition of FoxO-induced modulation of atrogene transcription. Overall, resistance training induces a sequential cascade of: 1) neuromuscular activation, 2) signaling events (i.e. Akt-mTOR pathway) stemming from mechanotransduction and circulating factors (e.g. IGF-1), 3) protein synthesis due to altered gene expression and increased translation, 4) myofiber hypertrophy, and 5) muscular growth and enhanced contractile force capacity.

Indeed, it is reasonable to suggest that the specific adaptations to the diverse exercise modes demonstrate a broad degree of incompatibility, at least at the cellular and molecular levels. For instance, high-load resistance training fails to elicit any marked improvements in mitochondrial biogenesis and is therefore, a suboptimal approach to induce adaptations conducive to muscle oxidative capacity and endurance performance. Likewise, endurance training is an inefficient promoter of myofiber hypertrophy and may negatively affect muscle protein synthesis and turnover. Consequently, training with prolonged, low-force exercise fails to generate an adaptive response favorable for muscular growth and enhanced contractile force capacity. Endurance and resistance training, therefore, represent opposite extremes of an adaptation continuum characterized by their respective phenotypic and functional manifestations. Key regulators of muscle adaptation are continually being identified, and are likely to elucidate the specificity of training responses leading to differentiated muscle phenotypes. The work of Vissing et al. investigated the effects of AMPK vs. Akt-mTOR signaling mechanisms on converting divergent exercise modes into training specific adaptations in human subjects. Participants initially underwent either endurance or resistance training for 10 weeks thereby being accustomed to a distinct mode of exercise. As expected, differentiated adaptations occurred with each exercise mode as endurance training enhanced maximal oxygen uptake while resistance training increased muscle size and strength. Following the training period, data were collected before and after a single bout of exercise that was specific to the mode the subject was previously accustomed to. The results indicated that Akt-mTOR signaling is preferentially stimulated through resistance training, while AMPK was activated exclusively in endurance trained subjects. A substantial body of evidence supports the key homeostatic role of AMPK in energy metabolism during acute bouts of exercise, especially modes that deplete intracellular energy level and raise cytosolic AMP content, e.g. endurance exercise. Similar to the function of AMPK during hypocaloric conditions, its exercise-induced activation is also an effort to conserve energy by inhibiting anabolic processes, e.g. protein synthesis, while restoring ATP through catabolism of molecules, such as myofibrillar proteins. Although chronic activation of AMPK is an important component of the adaptive response in muscle to endurance training (i.e. mitochondrial biogenesis), this occurs at the expense of myofiber size and muscle mass due to the continuous inhibition of anabolic pathways (i.e. mTOR).
and stimulation of catabolic events (i.e. proteolysis) \cite{32, 33, 123, 189}.

Since the hypercatabolic and hypoanabolic nature of endurance training parallels that of caloric restriction, such an exercise mode may be an ineffective means of preserving lean mass during energy restrictive weight-loss endeavors, despite its putative advantages for fat loss. Although resistance training appears as the ideal countermeasure to the loss of lean mass during hypocaloric intake, the question remains whether an anabolic, and thereby hypertrophic, response would manifest in muscle in a highly energy deficient state. From a clinical perspective, obese patients undergoing hypocaloric interventions, such as VLCDs, may benefit most from a resistance training prescription provided that the stimulus suffices to overcome the catabolic strain imposed by the diet and elicits an adaptive response in lean tissue concomitant with growth. Recent findings have revealed a fresh perspective on resistance training as an integrative component of dietary weight-loss treatments. When considering the major role of LBM, RMR, and physical function as key elements of successful weight-loss, it is important to review and dissect previous experimental resistance training paradigms and its impact during hypocaloric weight-loss interventions.

Effects of Resistance Training on Weight-Loss Composition, Metabolic Rate and Function during VLCD Treatment

The preferred outcome for most clinical weight-loss interventions is three-fold: 1) to reduce total body adiposity to an extent that is clinically meaningful; 2) to minimize substantial declines in LBM; and 3) to maintain metabolic and functional capacities. Taken together, these factors emerge as a fundamental clinical objective which is to optimize weight-loss patterns in favor of long-term success. As outlined earlier, obesity therapeutics incorporating proprietary hypocaloric systems, such as Optifast\textsuperscript{®}, have shown efficacy in clinical weight-management, however has failed to successfully resolve important issues pertaining to the maintenance of LBM, resting energy expenditure, and muscular function \cite{4-10, 12}. To address the burden imposed by severe hypocaloric diets on lean tissue morphometry and metabolism, the integration of exercise countermeasures has been examined extensively \cite{7, 10, 23-30}. However, an equivocal body of pertinent data has likely precluded the sophisticated integration of exercise training into clinical weight-management prescriptions using a VLCD system.

Based on the information previously discussed, resistance training would appear as the more rational exercise provision to counteract the loss of lean mass during caloric restriction; yet, the majority of studies have employed relatively low-force activities in the form of endurance/aerobic training \cite{8, 27, 28}. On the basis of previous whole-body outcomes \cite{8, 29-31}, endurance training may be an ineffective strategy for lean mass retention during severe hypocaloric conditions. In fact, endurance training has even demonstrated to extend lean tissue loss beyond the degree induced by caloric restriction alone, suggesting that prolonged, low-force activity can exacerbate the catabolic nature of VLCD treatments in muscle \cite{8, 29-31}. Because it is well established that high-force and high-load bearing activities function favorably to improve muscle mass and performance, resistance training may be the most efficient means of enhancing VLCD treatments towards enhanced weight-loss composition, resting metabolism, and muscular function \cite{34-36}. However, previous attempts to improve weight-loss composition with resistance training paradigms have demonstrated promising yet mixed outcomes, thereby impeding the progress towards clinical applicability.

An early investigation on obese female participants undergoing a 12-week, 800kcal/day VLCD examined the effects of resistance training on various morphometric variables \cite{7}. Based on histological analysis of quadriceps muscle fibers, resistance trained participants exhibited a significant increase in fiber cross-sectional area compared to pre-treatment measures, whereas the sedentary control group demonstrated no longitudinal changes. These results suggest that, at least on the cellular level, resistance training can produce significant muscle hypertrophy during severe hypocaloric and rapid weight-loss conditions. However, these cellular adaptations failed to manifest at the whole-body level as each group exhibited paralleled weight-loss composition from pre- to post-VLCD. Both groups, regardless of exercise, demonstrated a 16-kg weight-loss, of which 76% was attributable to fat loss while reduced fat-free mass accounted for about 24%. On the contrary, resistance training showed efficacy in improving muscular strength by 17.6% and completely reversing the functional detriments evidenced in the sedentary control group. Inconsistencies in the outcomes for LBM and function, however, do not appear surprising as muscular strength gains have been well known to precede any measurable signs of whole-muscle growth during novice resistance training \cite{169, 190}. These results collectively lead to speculation that the protocols employed lacked in areas that would likely explain the failure of resistance training in maintaining lean tissue despite inducing muscle fiber hypertrophy. One possibility may be the insufficiency of the resistance training protocol in stimulating a hypertrophic response robust enough to elicit marked gains in LBM, especially when compared to a sedentary control. Exercise volume, intensity, and type performed within the allotted training period may be particular variables of interest. The employed training protocol offered limited manipulations in
these exercise variables across the entire 12-week period. For instance, a change in intensity, as measured by a percentage of pre-training one-repetition maximum (1RM), was implemented once starting week 5 (i.e. 70% 1RM from weeks 1-4 and 80% 1RM from weeks 5-12). The issue here is that the load prescription beginning week 5 was relative to 1RM values obtained at week 1 and thus fails to account for probable strength gains achieved during the prior weeks of training (i.e. weeks 1-4). Given the dramatic overall strength improvements exhibited by the resistance trained subjects, it is reasonable to suggest that 1RM would have increased by week 5, a contention well-supported by previous literature \[190\]. Thus, the 80% 1RM prescription from weeks 5-12 was likely a crucial misrepresentation of “high” relative intensity and may have precluded conditions optimal for muscle growth to manifest, at least to a measurable extent. Furthermore, training volume (i.e. sets and reps) also lacked variation across the 12-week period as the only modification employed was a 1-set addition starting week 5. Modern innovations in exercise programming illustrate the significance of training variations especially for intensity and volume \[191-193\]. Periodization is a training concept defined as the systematic manipulation of exercise variables, e.g. intensity and volume, with the intent to avoid stagnation and promote continual adaptations/improvements \[191-193\]. Therefore, when considering the advantages of periodization modeling in resistance training adaptations, an experimental exercise protocol should implement appropriate and timely variations while choosing proper load and volume prescriptions to produce the optimum condition for adaptation and progression. A subsequent investigation in a similar study cohort partly addressed these limitations as a more progressive training protocol was implemented\[10\].

A notable study by Bryner et al. \[10\] revealed the potential therapeutic value of resistance training with respect to its application during severe hypocaloric interventions. In this study, twenty obese middle-age participants underwent 12 weeks of VLCD consisting of liquid meal-replacement formulas with a daily caloric intake of 800 kcais. During the treatment period, participants performed either a resistance or aerobic exercise regimen. One group performed resistance training 3 days/week with bouts consisting of 10 exercises performed 8-15 repetitions and gradually progressing from 2 to 4 sets across 12 weeks. A separate control group performed aerobic type exercise 1 hour/day, 4 days/week by walking, biking, or stair climbing. Results for weight-loss composition were promising with resistance training. The control group exhibited a significantly greater weight-loss than the resistance trained group (-19.4% vs. -14.7%) with similar reduction in body fat, body fat percentage, and BMI. The difference in weight-loss was explained by a significant decline in LBM for the control (~4kg) while resistance training protected against any detectable loss. In addition, resistance training preserved RMR while the control group demonstrated a significant decrease from pre- to post-treatment. Although previous results show promise for resistance training in moderating the burden of severe hypocaloric diets, they lack sufficient support to be confidently integrated into routine treatment protocols. This is likely attributed to the paucity of applicable clinical data that can properly guide medical weight-management programs towards an optimized hypocaloric treatment through a resistance exercise prescription.

Research Limitations to be Addressed

To achieve a vertical step in that regard, several important issues must be addressed. First, an experimental approach examining VLCD-treated subjects should closely represent clinical situations in which: 1) VLCDs are prescribed to patients who are severely obese and exhibit comorbid conditions, 2) VLCD-based treatments are medically monitored by a multifaceted team of physicians, dieticians, and exercise physiologists, 3) duration of VLCD treatment is 12 weeks with regular behavioral counseling, and 4) exercise is not specifically prescribed; rather general physical activity is recommended and typically unsupervised. Secondly, an experimental resistance training intervention should be: 1) formatted based on empirical innovations in training programming, i.e. periodization, to optimize protocols towards enhanced lean mass and muscular strength \[170, 191-196\], 2) combined with sufficient nutrient support through high-quality protein intake for lean tissue maintenance or growth, and 3) integrated into the standard clinical care of the VLCD-treated patient to enhance the understanding of its practical application. A trial taking into account for these limitations may be an effective means to evaluate the clinical effectiveness of resistance training in enhancing standard VLCD-based treatments towards improved weight-loss composition, metabolic rate, and muscular function. An applied approach integrating sophisticated measurements of morphometric, metabolic, and functional parameters with relevant biochemical indices such as hormones, growth factors, and metabolites would be especially insightful.

Summary and Implications for Future Research

In summary, the obesity epidemic represents an enormous challenge for the medical community to develop and implement weight-management programs that are both acutely and chronically effective. Proprietary VLCD systems have been the most prudent and pragmatic approach for urgent weight-loss circumstances due to its immediate benefits for a number of clinical parameters, i.e. blood pressure, metabolic and lipid profile, etc. However, current clinical strategies have
yet to address critical issues pertaining to the long-term stability of these positive treatment outcomes. This is reflected by the extreme rate of weight recidivism that is evident within the first 4 years after completing a VLCD treatment. Beyond behavioral factors, research point towards addressing the physiological adaptations to VLCD interventions that act in favor of weight-regain. Specifically, the dramatic loss of LBM and RMR resulting from hypocaloric treatments is conducive to the regaining of body fat and probable relapses of prior health complications. Thus, a present unmet clinical need is a practical strategy that can be applied to medical VLCD-based treatments to optimize rapid weight-loss patterns for lean tissue while enhancing RMR and physical functionality. Resistance training may be the most effective means of achieving these outcomes. Unfortunately, previous attempts using resistance training to moderate the burden of severe hypocaloric diets lack sufficient support to be systematically integrated into current therapeutic procedures. This is likely attributable to the limited availability of applicable clinical data that can efficiently guide medical weight-management programs towards an optimized hypocaloric treatment through a resistance exercise provision. To achieve progress in that regard, experimental approaches should implement a more sophisticated and systematic resistance training prescription in VLCD-treated patients under real clinical scenarios and with sufficient nutrient (i.e. protein) support. This approach coupled with the implementation of more refined analyses of body composition, energy metabolism, and neuromuscular function with relevant biochemical parameters would be of great value.

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