The Role of Exercise in the Contemporary Era of Obesity Management Medications

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Abstract

Contemporary obesity management medications have been shown to be highly efficacious for weight loss and improvements in many related health outcomes. However, a potential concern is the reduction in lean body mass, and possibly muscle mass, that may accompany the weight loss that is achieved. Physical activity and structured exercise have been suggested as potential strategies for attenuating these reductions, yet there is a paucity of research to support that these benefits will be realized. The effects of exercise may be most effective for enhancing the quality of lean tissue and muscle tissue, suggesting a need to pivot to these as important outcomes for patients treated with an obesity management medication. Thus, the inclusion of exercise in the treatment of patients with obesity who are prescribed an obesity management medication should be primarily focused on the health benefits beyond weight loss, with programming focused on the individual health needs of the patient.

Introduction

Overweight and obesity, which results from the presence of excess weight and adiposity, continue to be significant public health problems due to the association with numerous chronic health conditions (1). These include, but are not limited to, cardiovascular disease, type 2 diabetes mellitus, and many forms of cancer, musculoskeletal disorders, reduced quality of life, and other negative health outcomes (1). Thus, while primary prevention of excess weight gain and the development of obesity remain an important public health focus, because of the high prevalence of overweight and obesity (2) and the associated high healthcare expenditures (3), there continues to be a need for effective treatments.

It has been long accepted that lifestyle factors are foundational to effective treatments of excess weight and adiposity that can be associated with increased risk of negative health consequences. These lifestyle factors have typically included things that can impact components of energy balance, which include energy intake (diet quantity and quality) and energy expenditure (physical activity and sedentary behavior). When these components of energy balance are coupled with a behavioral intervention, such as what was implemented in the Diabetes Prevention Program (4) and Look AHEAD (5), weight loss of approximately 7% to 10% of initial body weight is typically achieved within 6 to 12 months of initiating treatment within the context of a research environment. However, commercial behavioral weight loss programs have demonstrated less weight loss (6). Moreover, there is a high degree of weight loss variability observed in response to these types of behavioral interventions (7–9).

Recently, there has been an increase in the popularity of pharmacotherapy approaches for the treatment of obesity, which may be referred to as obesity management medications (OMMs). This increase in popularity is likely a result of contemporary OMMs being more effective than their earlier counterparts (10), and there are many additional OMMs in the developmental pipeline (11). This has very rapidly ushered in a new era of obesity treatment, and it is important that physical activity and exercise approaches adapt to this changing landscape.

Contemporary OMMs

The field of pharmacotherapy focused on OMMs has evolved since the 1960s, and this has been summarized by others (10). The main development that has influenced current OMMs has been the focus to mimic naturally occurring hormones that have been shown to regulate eating behavior and energy intake, with an additional focus on targeting the receptors that regulate eating behavior, energy intake, and appetite and hunger signaling. While many refer to these as GLP-1s, which refers to glucagon-like peptide 1, it is important to denote that this specific group of OMMs can be referred to as nutrient stimulated receptor agonists (NuSH-RAs). These medications were initially developed for the treatment of type 2 diabetes and, due to their observed effects on weight loss, are now further approved for the treatment of obesity. However,

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because not all currently approved NuSH-RAs only target GLP-1 receptor agonists (GLP-1RA), these should not all be referred to as a GLP-1 OMM.

Liraglutide

Liraglutide is an early generation of a NuSH-RA that targets GLP-1 receptors. Because of its half-life, it is prescribed as a once daily subcutaneous injection. While liraglutide is still available and in generic formats, more current OMMs have shown greater efficacy for weight loss (12).

Semaglutide

Semaglutide also is a GLP-1RA that was approved by the U.S. Food and Drug Administration (FDA) for the treatment of obesity in 2021. In contrast to liraglutide, because of its half-life, semaglutide is prescribed as a once weekly subcutaneous injection. In adults with obesity and without type 2 diabetes mellitus, weight loss was 14.9% versus 2.4% with placebo (13). This is consistent with the findings of a systematic review and meta-analysis that concluded weight loss with semaglutide exceeds placebo by 11.9% (14). However, the magnitude of weight loss in adults with type 2 diabetes may be less, with one study reporting 9.6% versus 3.4% weight loss with semaglutide and placebo, respectively (15). These magnitudes of weight loss are consistent with the results of other studies (12,16–18).

Tirzepatide

Tirzepatide is a dual-acting GLP-1RA and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist that was approved by the U.S. FDA for the treatment of obesity in 2023. In adults with overweight or obesity and without type 2 diabetes mellitus, tirzepatide has been shown to result in weight loss of 20.9% of baseline weight versus 3.1% with placebo (19). The magnitude of weight loss in adults with type 2 diabetes may be less (14.7% with tirzepatide vs 3.2% weight loss with placebo) (20). The effectiveness of tirzepatide for weight loss appears to be consistent across studies, with a systematic review reporting that weight loss with tirzepatide exceeded placebo by 9.8 kg (21). More recently, it has been reported that tirzepatide is more effective for weight loss than semaglutide (22,23).

Health Benefits beyond Weight Loss

There is a growing body of scientific literature on the health benefits, beyond weight loss and improved glycemic control, of GLP-1RA OMMs. A summary of many of these health benefits has recently been published (24). This demonstrates health benefits across many bodily systems that include cardiovascular, respiratory, digestive, genitourinary, nervous, musculoskeletal systems, and others (24). Additional benefits include reduced cardiovascular events, preserved ejection fraction, reduced progression of chronic kidney disease, and reduced symptoms of chronic obstructive sleep apnea (25). Thus, because many of these health conditions are associated with obesity, the health benefits of these OMMs appear to extend beyond their effects to reduce body weight.

Potential Concerns

Despite the effects of these NuSH-RA OMMs on weight loss and many obesity-related health conditions, there are some possible concerns, and these may have implications for physical activity and exercise considerations for patients receiving OMM therapies. One possible concern is the potential loss of lean body mass that may accompany weight loss with semaglutide and tirzepatide. While there have been few studies reporting on the changes in lean body mass with these OMMs, it has been estimated that this may account for approximately 25% to 40% of the weight loss that is achieved, with the reduction in lean body mass potentially being greater with semaglutide than with tirzepatide (10). This could be of concern because of the potential negative impact on metabolic rate, muscular strength and physical function, and other physiological processes that may be impacted with a reduction in lean body mass. However, physical function appears to improve with weight loss, which may indicate concerns regarding a decrease in physical function may not be warranted. Moreover, the concerns regarding the possible reduction in lean body mass should be viewed with caution for various reasons. Few studies have reported on the changes in body composition, and in those that have, there have been measures of fat-free mass or lean body mass, but most of these studies have not included direct measures of skeletal muscle mass. However, one exception is a very recent study that examined muscle mass and muscle fat infiltration in participants with type 2 diabetes who received tirzepatide, which showed a reduction in both outcomes (26). The change in muscle volume with weight loss followed the same pattern that was observed in a population comparison based on the UK Biobank (26), which might suggest that this change in muscle volume may not be of concern. Moreover, the change in fat infiltration exceeded what would be expected based on this comparison (26), which might suggest that this may result in even greater health benefits than expected. However, caution is warranted when interpreting these results because the measurement of muscle was limited to the thigh, which may not reflect what may be occurring to muscle in other body regions. Moreover, this study did not report on whether these changes in muscle were associated with changes in physical function, strength, or other metabolic outcomes.

The reduction in lean body mass with weight loss does not appear to be unique to OMMs, with this also being observed when weight loss is achieved through other treatment interventions. Behavioral interventions that reduced energy intake and increased physical activity to achieve weight loss of 8% to 10% also have shown that reduced lean body mass accounts for approximately 15% to 20% of the weight loss (10,27), and with more severe energy restriction, this may account for as much as approximately 25% of the weight loss (28).

Because of the potential impact on body composition, there has been a shift from solely monitoring body weight to an emphasis on potentially assessing changes in body composition for patients receiving OMM therapies. Thus, within a clinical or health-fitness setting, consideration should be given to appropriate methods for assessing body composition that may provide valuable information to inform patient/client care. While some methods of body composition may be less costly and feasible, these may create challenges that affect the measurement reliability and accuracy. Moreover, given the potential concerns with the reduction in lean body mass, and possibly muscle mass, with OMM therapy, measures of body composition should provide assessments of these components. However, these assessments of body composition should be coupled with measures of physical function and muscular strength to

allow for an indication of whether observed reductions in these components of body composition are negatively impacting additional important outcomes. A summary of these body composition assessment considerations is illustrated in Figure 1.

It also is important to emphasize that different terminology is used throughout the literature when describing the nonadipose aspects of body composition. These terms include fat-free mass, lean body mass, and muscle mass. Fat-free mass is typically referring to the nonadipose component of body weight that consists primarily of muscle, connective tissue, organ tissue, bone, and water. Lean body mass is typically referring to the weight that consists of muscle, connective tissue, organ tissue, and water, but does not include the weight of bone. What is important to recognize is that neither fat-free mass nor lean body mass provides a sole measurement of muscle mass, but rather, muscle mass is one of their components. Therefore, it cannot be assumed that any observed change in fat-free mass or lean body mass is reflective of specific changes to muscle mass.

Implications for Physical Activity and Exercise

Despite the demonstrated effectiveness of NuSH-RA OMMs for weight loss and obesity-related health conditions, physical activity and structured exercise remain important lifestyle behaviors for patients undergoing this method of treatment. However, there is a paucity of research studies focused on the effects of adding physical activity to current OMM therapies for the treatment of obesity. Therefore, guidance is needed to support reasonable approaches for physical activity and exercise, when combined with these OMM therapies, until results from studies that are known to be underway are available (*e.g.*, ClinicalTrials.gov NCT06645470).

As highlighted in the recent American College of Sports Medicine (ACSM) Consensus Statement and recommended by others, because current OMMs have shown very good efficacy for weight loss, the emphasis of physical activity does not need to be on enhancing weight loss beyond what is already being achieved with these OMMs (29,30). This would suggest that there is not a need to focus on maximizing energy expenditure to contribute to a large energy imbalance and deficit, but rather for physical activity to be recommended in a manner to target other benefits that may not be fully realized with weight loss alone (29,30). These benefits may include enhanced cardiorespiratory fitness, physical function improvements, muscular strength and endurance, kinesthetic awareness, balance, and others. However, within this context, it is important to recognize that patients seeking treatment for obesity should not be recommended physical activity and exercise in the same manner as an individual who is seeking to maximize physical performance, such as a recreational athlete. Rather, the emphasis should initially be on improving movement and function, encouraging engagement in a regular pattern of physical activity, and achieving and maintaining a dose of physical activity that can enhance aspects of health and well-being. Thus, there is not a need to emphasize high doses and higher intensities of physical activity until the individual is physically able to engage at this level and expresses a desire to progress to these higher levels. This concept is illustrated in Figure 2, which shows that a primary focus should be on emphasizing health and well-being with a secondary focus, when appropriate, on physical performance.

Within the context of physical activity, for an individual with obesity, mobility and current level of physical function may be a concern. It has been shown that higher levels of obesity are associated with reduced mobility and lower capacity for selective aspects of physical function (31). Thus, it is important to recognize that for individuals living with obesity

Measurement Technique	Adipose Mass	Fat-Free Mass	Lean Body Mass	Muscle Mass	Connective Tissue	Organ Tissue	Bone	Water	Distribution of Weight or Adiposity
Weight									
Body Mass Index (BMI)									
Circumference Measurements	☑	☑							☑
Skinfold Measurements	☑	☑							☑
Bioelectrical Impedance Analysis (BIA)	☑	☑		*				☑	
Hydrostatic Weighing	☑	☑							
Air Displacement Plethysmography	☑	☑							
Dual-Energy X-Ray Absorptiometry (DXA)	☑	☑	☑	*			☑		☑
Magnetic Resonance Imaging (MRI)	☑	☑	☑	☑	☑	☑	☑		☑
Computed Tomography (CT) Scan	☑	☑	☑	☑	☑	☑	☑		☑

*Indicates that muscle mass is estimated using these measure of body composition.

Figure 1: Components of body composition measured using various techniques.

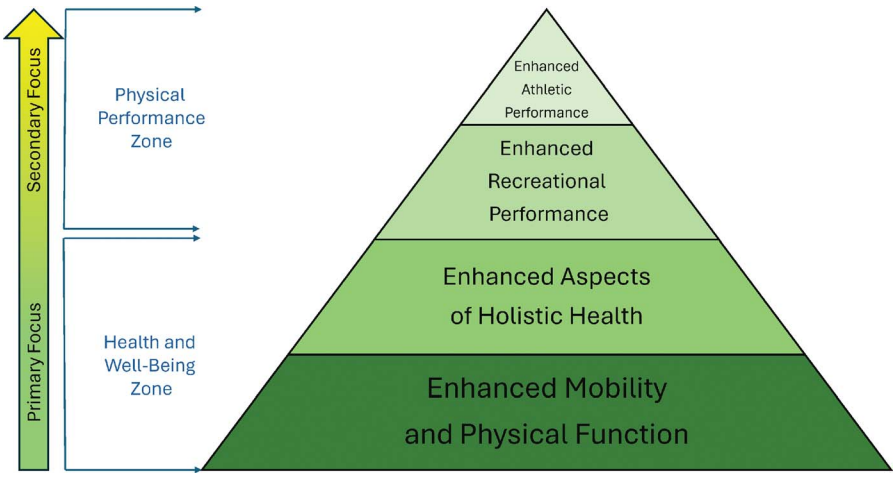

Figure 2: Prioritizing the focus of physical activity recommendations and programming for individuals with obesity receiving OMM as a treatment.

who have mobility or physical function limitations, progression directly to a traditional exercise program may not be an appropriate approach. Rather, as recommended previously, for individuals identified as having these limitations, initial treatment with a rehabilitation specialist (*e.g.*, physical or occupational therapist) may be warranted before being transitioned to an appropriately trained and certified exercise professional for guidance on further development of their physical activity and exercise program (32). It also is important to highlight that with intentional weight loss, mobility and physical function have been shown to improve (33), which may suggest that the recommended progression of physical activity and exercise may be facilitated as an individual reduces their weight and adiposity with OMM therapy.

As highlighted in the section above, there is some concern of the reduction in lean body mass, and possibly skeletal muscle mass, with NuSH-RA OMMs. Because of this, it has been suggested that exercise, and specifically resistance exercise, should be recommended to prevent decreases in these components of body composition with weight loss (34,35). However, to date, there is a paucity of published studies examining adults with overweight or obesity on the effects of exercise, which includes resistance exercise, on changes in body composition when implemented prior to weight loss and at onset of obesity treatment using a NuSH-RA OMM (*e.g.*, semaglutide, tirzepatide, etc.). Thus, the effects of exercise when coupled with these treatments are not clear and warrant further exploration (36,37). Therefore, the effects may only be hypothesized based on the results of other studies that have not included these OMMs.

The effects of exercise on body composition, and particularly lean body mass and muscle mass, may differ when not coupled with a reduced energy intake diet compared to when exercise is used in combination with a reduced energy intake diet. The results of a systematic review and meta-analysis concluded that resistance exercise alone or in combination with aerobic exercise would significantly increase lean body mass in adults with overweight or obesity when these were not coupled with an energy-reduced diet (38). However, these forms of exercise did not assist in preserving lean body mass when coupled with an energy-restricted diet compared to an energy-restricted diet without exercise. Similar conclusions have been reported by others based on their reviews of the scientific literature (39). However, simply considering changes in the volume of lean mass or muscle mass may not provide a complete perspective of the potential impact of changes in lean mass or muscle mass. Rather, it has been suggested that the focus may need to shift to whether exercise impacts the quality of tissue (*e.g.*, muscle quality) rather than volume (*e.g.*, muscle mass) (30). When considering this, even with a reduction in fat-free mass or lean body mass with diet-induced weight loss, the addition of aerobic exercise improves cardiorespiratory fitness and resistance exercise improves muscular strength (28). Moreover, when weight loss is induced with bariatric surgery, the addition of exercise further enhanced improvements in insulin sensitivity (40) and mitochondrial function (41). Extending beyond skeletal muscle, physical activity was shown to preserve cardiac tissue (left ventricular mass) when measured by cardiac magnetic resonance imaging with weight loss (27). Thus, it appears that there are unique benefits of physical activity and structured exercises based on measures of muscle quality, and these can be realized even in the presence of weight loss that may contribute to a reduction in lean body mass and potentially muscle mass.

There is a need for appropriately designed studies to thoroughly examine the effects of exercise across an array of outcomes for patients receiving OMM therapies. This research may need to focus on modality and varying doses and intensities of exercise. Moreover, there is a need also to examine how to best translate and implement exercise into nonresearch settings for patients receiving OMM therapies.

Additional Considerations for Implementing Physical Activity with OMM Therapies

Physical activity is an important lifestyle behavior for patients with obesity to realize the benefits of holistic health and well-being, which extend beyond the health benefits of weight loss alone. Many of these benefits have been highlighted in the recent (ACSM) Consensus Statement that focused on physical activity within the context of excess weight and adiposity (29). It also has been stated that these health benefits of physical activity can very likely be realized in adults with overweight or obesity who are receiving OMM treatment (30). Thus, clinicians should continue to recommend physical activity for patients receiving these treatments.

The importance of physical activity within the context of OMM treatments also has been highlighted by others. A recent perspective on the importance of lifestyle factors within the obesity treatment that implements OMMs provides a roadmap that can be applied to physical activity (42). Key elements of this perspective suggest that the approaches need to be around person-centered care, which considers individual needs and perspectives, and this also should be applied to physical activity. An example of how this can be applied is that rather than making the same general physical activity recommendation to all people living with obesity, the clinician considers the person's needs and perspectives, which may result in these recommendations being individualized.

The ACSM Consensus Statement also endorsed the need for equitable access to obesity treatment (29), which has been supported by others (30,42), and this applies to physical activity. Thus, access to appropriate and affordable physical activity programming and facilities for individuals living with obesity is needed. This should include consideration of how existing healthcare resources can be used to assist in these efforts, which requires assistance by employers and other payers to support these important initiatives.

It also is important that appropriately trained and certified physical activity and exercise professionals be included as members of comprehensive care teams for individuals receiving clinical treatments for obesity that include OMMs (29,32,42,43). This comprehensive care team is led by physicians who manage the overall care of patients with obesity. The inclusion of an exercise professional will complement the other members of the team that include dietitians to assist with nutrition and dietary needs, physical/occupational therapists to assist with rehabilitation needs, and behavior and health psychology professionals to facilitate behavior change.

Conclusions

Obesity continues to be a major public health concern. However, the treatment options for obesity have been rapidly changing with the approval of the current generation of OMMs that have demonstrated a high degree of efficacy for weight loss and other obesity-related health conditions. Despite their effectiveness, individuals living with obesity who receive an OMM treatment can realize additional benefits from physical activity and structured exercise. However, these benefits extend beyond facilitating additional weight loss and may contribute in other ways to the holistic health and well-being of individuals living with obesity. This requires physical activity and exercise recommendations and interventions to be tailored to the needs of individuals with obesity who receive OMM treatment.

Dr. Jakicic is on the Scientific Advisory Board for Wondr Health, Inc. Dr. Rogers serves as an educational consultant for Seca and is a consultant and instructor for Wondr Health, Inc.

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