

The Integration of Lifestyle Modification Advice and Diet and Physical Exercise Interventions: Cornerstones in the Management of Obesity with Incretin Mimetics

Marianna Minnetti^{a, b} Rocco Barazzoni^c John A. Batsis^d Luca Busetto^e
Volkan Yumuk^f Eleonora Poggiogalle^a Peter J.M. Weijs^{g, h}
Lorenzo M. Donini^a

^aDepartment of Experimental Medicine, Sapienza University, Rome, Italy; ^bUNESCO Chair on Urban Health Education and Research for Improved Health and Wellbeing in the Cities, Sapienza University, Rome, Italy; ^cDepartment of Medical, Surgical and Health Sciences, University of Trieste, Trieste, Italy; ^dDivision of Geriatric Medicine, School of Medicine, Department of Nutrition, The Gillings School of Global Public Health, Chapel Hill, NC, USA; ^eDepartment of Medicine, University of Padova, Padova, Italy; ^fDivision of Endocrinology, Metabolism and Diabetes, Istanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty, Istanbul, Turkey; ^gDepartment of Nutrition and Dietetics, Faculty of Health, Sport and Physical Activity, Amsterdam University of Applied Sciences, Amsterdam, The Netherlands; ^hDepartment of Nutrition and Dietetics, Amsterdam University Medical Centers, Vrije Universiteit, Amsterdam, The Netherlands

Keywords

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Abstract

Background: The introduction of incretin mimetics (IMs), including glucagon-like peptide-1 receptor agonists (GLP-1 RAs) such as liraglutide and semaglutide, as well as dual GLP-1/glucose-dependent insulinotropic polypeptide receptor co-agonists (GLP-1/GIP RAs) like tirzepatide, has revolutionized obesity treatment. These obesity management medications promote significant weight loss with metabolic and cardiovascular improvements. However, pharmacotherapy alone seems insufficient to address the multifactorial nature of obesity. While IMs suppress appetite and reduce caloric

intake, they do not prevent potential nutrient deficiencies and possible loss of skeletal muscle mass, nor do they guarantee lasting behavioral changes necessary for long-term weight management, particularly in the absence of other complementary interventions. **Summary:** In this context, a clear distinction must be made between general lifestyle modification advice (Ls-M) and personalized and structured dietetic and physical exercise interventions (D-PE-Is). Ls-M, including a balanced diet and regular physical activity, is essential for preventing obesity and reducing the risk of weight gain and associated metabolic disorders. However, once obesity is established, D-PE-I becomes necessary. Unlike Ls-M, D-PE-I integrates personalized nutritional strategies with structured exercise to maximize fat loss, preserve skeletal muscle mass and function, and enhance metabolic health. This narrative and concept-driven review aimed to delineate key areas for future clinical trials and meta-analyses. **Key Messages:** IMs have

brought important progress in the management of obesity, contributing meaningfully to current therapeutic approaches. However, pharmacotherapy alone is not sufficient to ensure long-term success. While lifestyle advice may aid in prevention, structured and personalized dietetic and physical exercise interventions are essential once obesity is established. Their integration with IMs is crucial to support long-term weight maintenance and improve overall health and quality of life.

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Introduction

The advent of incretin mimetics (IMs), such as glucagon-like peptide-1 (GLP-1) receptor agonists liraglutide and semaglutide, and dual GLP-1/glucose-dependent insulintropic polypeptide (GIP) agonists, like tirzepatide, has revolutionized obesity management by mimicking incretin hormones, enhancing satiety and appetite regulation through central and peripheral pathways, leading to significant weight loss and improvement in obesity-related comorbidities [1–3]. Despite their efficacy, obesity remains a multifactorial condition that extends beyond pharmacological weight loss [4]. IMs act through both physiological and behavioral pathways, including central appetite regulation and reduced energy intake, and do influence eating behaviors. However, these pharmacologically mediated effects do not fully replace the need for comprehensive approaches targeting nutritional adequacy, promoting structured behavioral interventions, and enhancing physical function [5–7].

On the other hand, general lifestyle modification advice (Ls-M), which applies to the entire population, remains a fundamental component of both obesity prevention and treatment. Adopting a healthy lifestyle is central to preventing nutritional deficiencies, avoiding overreliance on pharmacologic intervention, counteracting the harmful effects of sedentarism, and improving metabolic flexibility, a key factor in maintaining long-term metabolic homeostasis [8, 9]. A healthy lifestyle is variably defined worldwide and has elements of cultural sensitivity, yet from a public health standpoint, it is often associated with favorable outcomes, longevity, and high quality of life [10].

However, Ls-M alone may be insufficient for the management of obesity, even in individuals undergoing pharmacological treatment [11]. A structured dietetic and physical exercise intervention (D-PE-I) may be essential, as IMs alone do not directly address different

components of obesity management. Importantly, such a comprehensive individualized approach with D-PE-I may minimize the fat-free mass reduction inevitably associated with any weight-loss treatment, mitigate the potential gastrointestinal side effects associated with IMs, and enhance therapeutic outcomes by integrating structured protein intake and physical exercise as a metabolic enhancer [12, 13].

Given these considerations, this narrative and conceptual review examines the role of Ls-M and D-PE-I in obesity management in the era of IMs, advocating for a comprehensive and integrative approach that bridges pharmacotherapy with personalized strategies focused on diet and physical exercise.

Healthy Ls-M vs. Dietetic and Physical Exercise Interventions

A fundamental distinction must be made between healthy general Ls-M and structured dietetic and exercise interventions (D-PE-Is) in the management of obesity (shown in Fig. 1). While both significantly improve long-term health outcomes, they serve different purposes and target different aspects of metabolic health and weight management. Healthcare professionals (HCPs), clinicians, and researchers must be aware of these fundamental differences in order to provide tailored patient care.

Healthy lifestyle modification advice refers to broad, population-wide recommendations that are designed to promote general health and prevent disease [14]. This includes adopting a sustainable dietary model such as the Mediterranean diet [15]. Such diet includes a high intake of monounsaturated fats, generally found in extra virgin olive oil, an adequate balance of polyunsaturated fatty acids, mainly through consumption of fish, shellfish, legumes, and nuts, and a low intake of protein and saturated fats from animal sources, associated with a high intake of antioxidants found in particular in fruits, and vegetables [16]. Regular physical activity (PA) is another essential component, helping counteract sedentary behavior. PA refers to any bodily movement produced by skeletal muscles requiring energy expenditure. This includes a wide range of activities such as walking, household chores, occupational tasks, and recreational movements. Some lifestyle habits, such as walking at least 10,000 steps per day, can contribute to long-term metabolic benefits and cardiovascular protection [17, 18].

In contrast, a D-PE-I is an individualized, structured intervention designed for patients who require targeted

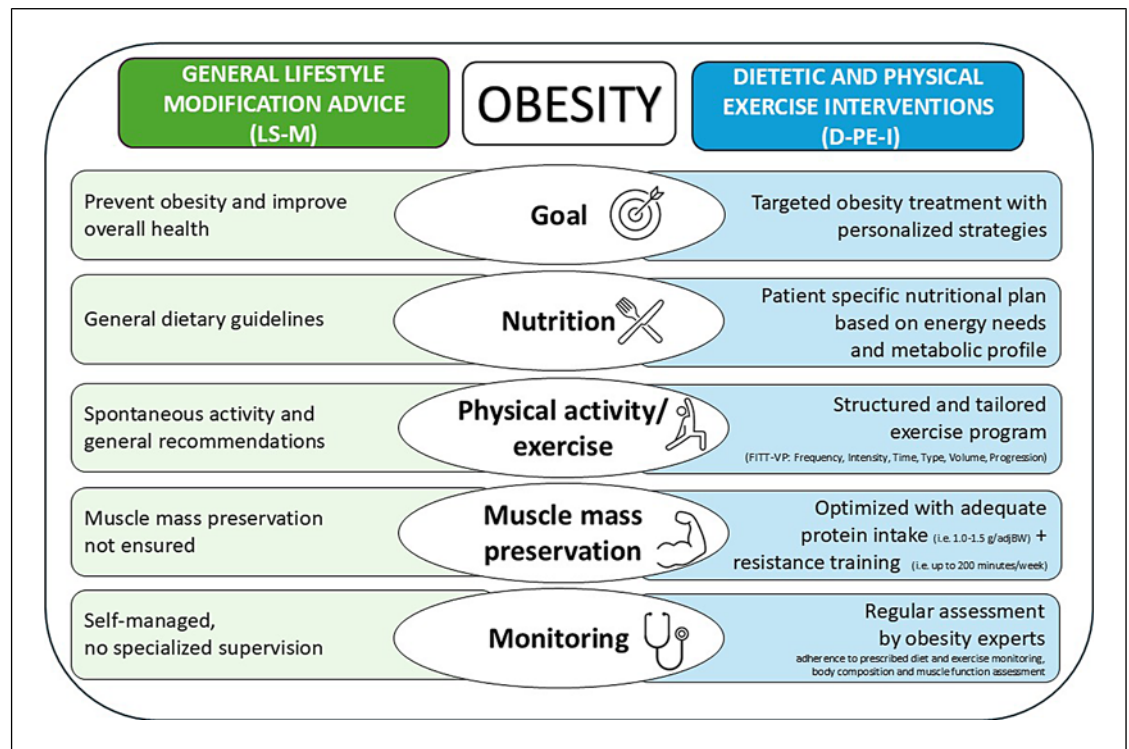


Fig. 1. Comparison between general lifestyle modification advice (LS-M) and dietetic and physical exercise interventions (D-PE-I) in obesity management. adjBW, adjusted body weight.

weight loss and metabolic improvements. Unlike LS-M, a D-PE-I involves the precise estimation of energy and nutrient intake based on individual metabolic needs and clinical goals [4]. A structured and personalized D-PE-I differs from LS-M and plays a crucial role in obesity treatment, especially in conjunction with pharmacotherapy. Unlike general lifestyle guidelines, a D-PE-I includes a personalized nutritional plan based on energy requirements, macronutrient distribution, and clinical conditions. Structured physical exercise follows a framework, which involves planned, systematic workouts designed to improve fitness. A combination of aerobic exercise for cardiovascular conditioning and resistance exercise to preserve muscle performance, when paired with personalized caloric restriction (CR), is essential for improving cardiovascular health, promoting fat loss, preserving muscle mass, and optimizing metabolic outcomes [19–22]. Additionally, structured exercise programs following the FITT-VP model (frequency, intensity, time, type, volume, and progression) will ensure that physical exercise is tailored to the individual's capabilities and goals [23].

A clear distinction between these two approaches is essential to design effective obesity interventions. While

healthy lifestyle changes are critical for disease prevention and general well-being, structured dietetic-physical treatments are necessary for targeted weight loss, metabolic regulation, and functional improvements in individuals undergoing obesity treatment (Fig. 2). Given the high prevalence of obesity, it is important that not only HCPs directly involved in obesity management but also those in general clinical practice understand the distinction between general lifestyle modifications and structured interventions on diet and exercise in patients living with obesity.

Why Should Individuals with Obesity Adopt a Healthy Lifestyle?

Improve Poor Nutritional Status and Malnutrition in Obesity

Risk of Micronutrient Deficiencies in Obesity

The paradoxical coexistence of obesity and malnutrition represents a critical public health challenge, with emerging evidence highlighting the complex interplay between excessive caloric intake and micronutrient deficiencies [24–26]. While obesity is traditionally

Fig. 2. Rationale for healthy lifestyle adoption and the role of dietetic and physical exercise interventions in the era of obesity pharmacotherapy.

Why should individuals with obesity adopt a HEALTHY LIFESTYLE ?			What is the utility of DIET AND PHYSICAL EXERCISE INTERVENTIONS (D-PE-I) in association with incretin mimetics?		
1	Improve or prevent malnutrition		1	Prevent associated gastrointestinal side effects	
2	Counteract the harmful effects of sedentary behaviour		2	Mitigate weight regain following treatment withdrawal	
3	Avoid over-reliance on pharmacological interventions alone		3	Preserve skeletal muscle mass and function during weight loss	
4	Enhance metabolic flexibility				

associated with overnutrition, individuals with obesity frequently exhibit deficiencies in essential vitamins and minerals, which are only partly explained by poor dietary quality [27]. Mechanisms underlying these deficiencies are complex and not yet fully understood, involving potential roles for chronic low-grade inflammation and altered absorption [28].

Ultra-processed foods and dietary patterns characterized by high energy density but low micronutrient content are strongly linked to insufficient intake of vitamin D, vitamin B12, folate, iron, and zinc [26, 29]. Obesity-related chronic low-grade inflammation exacerbates these deficiencies by altering nutrient absorption, distribution, and metabolism. Pro-inflammatory cytokines can disrupt intestinal barrier integrity and reduce the bioavailability of fat-soluble vitamins (A, D, E, and K), which are vital for antioxidant defense and immune homeostasis [25, 26]. This is particularly evident in vitamin D deficiency, where adipose tissue sequestration and inflammation-driven downregulation of hepatic 25-hydroxylase activity contribute to suboptimal serum levels [30, 31]. Moreover, recent advances in metabolomics have uncovered mechanisms linking obesity-associated dysbiosis to malnutrition [32, 33]. Gut microbiota alterations reduce the production of short-chain fatty acids, compromising colonic absorption of micronutrients, while simultaneously promoting systemic inflammation [32, 34]. This bidirectional relationship between gut health and nutrient metabolism underscores the need for personalized dietary strategies that address both microbial diversity and micronutrient adequacy.

Risk of Micronutrient Deficiencies in Patients Treated for Obesity

Restrictive weight-loss interventions, if not carefully managed, may worsen malnutrition by exacerbating micronutrient deficits [24]. Significant CR without adequate nutrient monitoring has been shown to deplete iron stores and B vitamins, increasing risks of anemia and neurological complications [25]. The risk of micronutrient deficiencies is particularly relevant when patients initiate strict dietary regimens such as low-carbohydrate, ketogenic, intermittent fasting, or very low-calorie diets [25]. Without proper medical supervision and supplementation, such diets may compromise patients' health by increasing the likelihood of deficiencies in iron, folate, vitamin B12, vitamin D, and other essential micronutrients, potentially affecting metabolic, neurological, and immune functions [25].

Patients treated with bariatric surgery require lifelong supplementation due to malabsorptive mechanisms that impair vitamins and minerals uptake, highlighting the necessity of structured nutritional support in obesity management [35, 36]. Malabsorptive procedures, such as Roux-en-Y gastric bypass and biliopancreatic diversion, are particularly associated with long-term deficiencies in iron, vitamin B12, folate, calcium, and fat-soluble vitamins, due to altered gastrointestinal anatomy. In contrast, restrictive procedures like sleeve gastrectomy tend to have a lower, though still significant, impact on micronutrient absorption [36, 37]. However, nutritional risk is not solely determined by surgical technique. Behavioral factors, including poor adherence to

supplementation, limited dietary diversity, and lack of ongoing clinical support, may exacerbate or even precipitate deficiencies, especially in patients with inadequate follow-up [37, 38].

The risk of micronutrient deficiencies may also be relevant in patients treated with IMs, which reduce appetite and overall energy intake. Therapy with IMs is not only associated with appetite suppression but also with temporary food aversion and changes in taste preferences, which can further impact dietary patterns and food variety [39, 40]. If dietary quality is not adequately addressed, this reduction in food consumption may contribute to insufficient intake of essential micronutrients, potentially increasing the risk of deficiencies despite overall weight-loss success [40].

Addressing these nutritional gaps through targeted interventions improves metabolic outcomes. Greater adherence to the Mediterranean diet pattern and inclusion of its typical foods are associated with a better nutritional profile in adults, resulting in a lower prevalence of individuals showing inadequate micronutrient intakes [41]. In fact, higher adherence to the Mediterranean diet has been associated with a significantly lower risk of micronutrient deficiencies and improved serum levels of vitamin D, folate, and zinc [16]. This dietary pattern leverages the synergistic effects of monounsaturated fats, fiber, and phytochemicals to counteract obesity-related dysbiosis and nutrient malabsorption, offering a comprehensive approach to mitigating malnutrition in obesity [42].

Harmful Effects of Sedentariness and Low PA

The inability to preserve muscle mass and function is an important and emerging complication of obesity, leading to malnutrition and sarcopenic obesity, particularly in older adults and in the presence of comorbidities [43, 44]. Metabolic derangements associated with excess adipose tissue may directly contribute to sarcopenia [43]. Besides aging and comorbidities, unhealthy diet and physical inactivity are also major risk factors [43]. Prolonged sedentary behavior may directly lead to reduced insulin sensitivity, impaired mitochondrial function, and loss of muscle mass [43, 45]. Emerging evidence also links sedentariness to elevated levels of circulating pro-inflammatory markers, which directly impair muscle protein anabolism and adipose tissue lipolysis, and promote ectopic fat deposition in the liver and skeletal muscle [46–48]. Further evidence suggests that breaking up prolonged sitting time and engaging in regular PA significantly reduces these risks [49]. Additionally, sedentary behavior has been linked to

increased visceral fat accumulation and therefore to systemic inflammation, further exacerbating obesity-related complications [50].

In general, sedentariness is also a major contributor to global mortality, with estimates suggesting that it is responsible for approximately 9% of all premature deaths worldwide, equating to more than 5.3 million deaths annually [51]. Given these detrimental effects, incorporating PA as a fundamental component of obesity prevention and treatment is crucial. When pharmacological interventions such as IMs are used, the promotion of regular exercise becomes even more essential to counteract muscle loss, which accompanies any weight-loss strategy, and maintains metabolic adaptations.

Over-Reliance on Pharmacological Intervention

To maximize the benefits of pharmacotherapy, it is essential to reinforce the importance of Ls-M as a foundation of obesity management, rather than viewing medications as a replacement for behavioral changes. The reliance on pharmacotherapy without nutritional support can create an unjustified sense of security, leading individuals to neglect lifestyle modifications.

Comparable patterns have indeed been observed in other chronic diseases [52–55]. Studies on cholesterol management have shown that individuals may initially improve their dietary pattern upon diagnosis, but once medications are prescribed (usually statins), many increase their intake of total and saturated fats, paradoxically undermining the intended benefits of pharmacological treatment [52, 53]. A similar trend has been observed in type 2 diabetes. Research indicates that individuals on intensive glucose-lowering therapies often have worse dietary habits compared to those managing their condition primarily through lifestyle changes [54]. This substitution effect, where medication use replaces lifestyle improvements instead of bringing synergistic clinical benefits, could potentially diminish long-term health outcomes [55, 56].

A similar issue might, therefore, potentially extend to IMs in obesity treatment. While these medications effectively reduce appetite and promote weight loss, they do not inherently encourage the adoption of healthier eating habits or sustained behavioral change [11, 57]. That said, some studies have reported short-term shifts in food preferences, such as reduced cravings for high-fat and high-sugar foods and decreased hedonic eating during treatment with semaglutide or tirzepatide [40, 58–60]. These findings suggest that pharmacotherapy may facilitate behavioral change under certain conditions. However, the durability and nutritional quality of

these changes remain uncertain; they often lack formal dietary guidance or objective long-term measurement and likely remain dependent on continued drug use with no sustained behavioral change to ensure a healthy eating pattern.

Enhancing Metabolic Flexibility

Metabolic flexibility refers to the capacity of biological systems to dynamically adjust fuel utilization in response to environmental or physiological demands, such as transitions between fasting and feeding or shifts in energy substrate availability [61]. This adaptive process involves coordinated regulation of glucose, fatty acid, and amino acid oxidation across tissues, particularly skeletal muscle, liver, and adipose tissue, to maintain energy homeostasis [62]. In obesity, chronic overnutrition disrupts this equilibrium, leading to metabolic inflexibility characterized by impaired switching between carbohydrate and lipid oxidation [61, 63, 64]. Visceral adipose tissue becomes a critical site of dysfunction, as mitochondrial inefficiency and oxidative stress reduce lipid buffering capacity, promoting ectopic fat deposition and systemic insulin resistance [63]. Although no information is available on the impact of medication-induced weight loss on metabolic inflexibility, it is reasonable to hypothesize that added metabolic benefits may be induced by lifestyle modifications during pharmacological obesity treatment.

What Is the Utility of Diet and Physical Exercise Interventions in the Era of Obesity Management Medications?

Preventing Side Effects Associated with IMs

Gastrointestinal adverse events are common during IMs, primarily due to delayed gastric emptying and central appetite modulation [1, 24]. Avoiding ultra-processed foods and carbonated beverages is critical, as these exacerbate delayed gastric emptying and dyspepsia [65]. Progressive fiber intake and adequate water consumption improve colonic motility and reduce constipation. Gradual dose titration paired with these dietary strategies lowers gastrointestinal side effects [1, 66]. Ensuring patients understand how to adjust their eating habits and manage sensations of satiety after starting IMs is crucial for optimizing adherence and reducing drop-out [67]. A multidisciplinary consensus has outlined practical recommendations to improve drug tolerability, including eating slowly, consuming smaller portions, avoiding sweet meals, and choosing

easy-to-digest, low-fat foods such as bland diets [66]. These dietary adjustments can help mitigate gastrointestinal side effects and enhance treatment adherence.

Weight Regain after Treatment Withdrawal Evidence of Weight Regain Post-IMs Discontinuation

As implied above, while obesity management medications (OMMs) significantly aid weight reduction, they improve but do not normalize the behavioral and physiological components of obesity that contribute to making it a chronic and relapsing disease [68]. Obesity is driven by persistent interactions between genetic susceptibility and an obesogenic environment, requiring lifelong management akin to other chronic diseases, such as arterial hypertension or diabetes [4, 69]. Similar to any nonsurgical obesity management strategy, treatment discontinuation also with IMs leads to progressive weight regain.

In the STEP-1 trial, discontinuation of semaglutide after 68 weeks led to regain of two-thirds of lost weight (11.6%) within 1 year, reversing cardiometabolic benefits [11]. STEP 4 showed that switching to placebo after 20 weeks of semaglutide resulted in a 6.9% weight regain over 48 weeks, while continued treatment maintained and further enhanced weight loss [70]. Similarly, in the SURMOUNT-4 trial, after an initial 36-week lead-in period with tirzepatide yielding a 20.9% mean weight loss, participants who discontinued treatment and switched to placebo regained an average of 14.0% of body weight over the following year, while those who continued tirzepatide maintained and further improved weight loss (total -25.3% from baseline) [71].

Body Composition Changes after Weight Loss

Achieving significant weight loss and a marked reduction in visceral fat, as indicated by large reductions in waist circumference in all STEP (investigating semaglutide) and SURMOUNT (investigating tirzepatide) trials, will substantially reduce cardiometabolic and many other health risks, representing a breakthrough in obesity management. However, it should be also underlined that a large number of treated patients remains above obesity thresholds both in terms of body mass index and in those of body fat (see, for example, Wilding et al.'s [1] (2021) paper supplementary material), making the implementation of synergistic management strategies a still relevant clinical issue. Since IMs, like other obesity treatments, do not normalize body mass index in all patients, the combination with individualized D-PE-I may represent an effective strategy to synergistically improve the final results [72, 73].

It is finally important to recognize that weight regain predominantly consists of fat mass, as consistently observed in studies on behavioral- and lifestyle-induced weight loss [74, 75]. This shift in body composition not only reverses previous metabolic benefits but may also worsen long-term health outcomes by increasing fat mass while reducing or failing to restore lean mass [75–77]. Repeated cycles of weight loss and regain, commonly seen in obesity management, have been associated with unfavorable changes in body composition, including reduced muscle mass and strength, potentially leading to sarcopenic obesity [77].

Based on the above observations, despite the impressive weight-loss outcomes for IMs, the long-term effectiveness of pharmacotherapy depends not only on the initial response but also on strategies to prevent weight regain and on multimodal approaches to optimize clinical results. This reinforces the need to integrate pharmacological treatment with a sustained lifestyle/behavioral approach and D-PE-I. In a broader approach, much like other chronic diseases, obesity treatment with OMMs should be theoretically taken as a lifelong treatment. In this perspective, IMs administration may be adapted to individual needs, with personalized adjustments in dosage, interval, and formulation to optimize long-term adherence and efficacy.

Preservation of Muscle Mass and Potential Role of Muscle Function

Preservation of Muscle Mass

The preservation of lean mass is a critical, yet often overlooked, challenge in obesity treatment, since all approaches inevitably lead to parallel reductions in fat and lean mass [78]. A major challenge in weight-loss interventions is preserving skeletal muscle mass, which is critical for metabolic health, physical function, and long-term weight-loss maintenance, through modulation of basal metabolic rate. CR without adequate protein intake and resistance training can lead to more pronounced muscle loss, primarily driven by increased muscle protein breakdown rather than reduced synthesis [79].

Interpretation of muscle mass loss in phase 3 trials of IMs also requires careful attention to body composition terminology. By definition, lean mass includes lean soft tissues but excludes bone, whereas fat-free mass comprises both lean mass and bone mass. These terms are often used interchangeably, despite representing distinct compartments, which may confuse interpretation of actual extent of muscle loss. Importantly, dual-energy X-ray absorptiometry (DXA)-derived lean mass includes multiple non-muscle components (e.g., organ tissue),

making it difficult to quantify the precise contribution of skeletal muscle to observed reductions [80]. Based on these considerations, it is not surprising that IMs induce substantial weight loss with a significant contribution from lean mass. This has raised concerns about potential metabolic and functional consequences [81].

Liraglutide. In patients treated with liraglutide, real-world data indicate concurrent reductions in absolute lean mass alongside fat mass, with approximately 25% of the weight lost attributed to the lean compartment [82]. In a randomized trial comparing liraglutide and CR, the fat-to-lean mass ratio decreased more substantially in the CR group (–6.5%) than in the liraglutide group (–2.2%), indicating a more favorable body composition change with CR [83]. The study protocol included recommending 150 min per week of moderate-intensity PA and dietary counseling focused on protein intake, yet adherence to these recommendations was not objectively measured.

Semaglutide. In the DXA substudy of the STEP-1 trial, participants treated with semaglutide 2.4 mg lost an average of 5 kg of lean body mass, corresponding to approximately 39% of the total weight lost, as assessed under the treatment policy estimand [1]. Participants in STEP 1 received monthly behavioral counseling sessions, a dietary plan targeting a 500 kcal/day deficit, and PA recommendations encouraging at least 150 min of moderate-intensity physical exercise per week. However, the study did not assess adherence to these interventions nor evaluate specific resistance training or protein intake, both of which are key factors in preserving lean mass.

Tirzepatide. In the SURMOUNT-1 trial, investigating tirzepatide effects, DXA data from a subset of participants showed a lean mass reduction of 10.9%, with improved body composition due to substantially higher fat loss [3]. Participants were also enrolled in a structured lifestyle intervention with CR and PA counseling, yet, as in most other trials, the study did not investigate the potential role of resistance training or protein intake in mitigating lean mass loss. Additional studies on tirzepatide effects on body composition have been conducted exclusively in patients with type 2 diabetes, further emphasizing the need for dedicated research in nondiabetic populations [84].

Overall, the above observations indicate the need for further studies to identify and implement strategies to optimize body composition changes and to minimize inevitable lean mass loss during treatment with IMs. Lifestyle modifications are obvious components of such strategies.

The Role of Muscle Function

Notably, both the STEP and SURMOUNT studies observed that weight loss was associated with an improvement in self-reported physical functioning [1, 3]. Observations of improved muscle function and physical performance despite inevitable lean mass loss are common in studies of obesity management, particularly but not limited to those implementing physical exercise protocols [21]. In agreement with this view, a seminal study by Villareal et al. [85] demonstrated improved muscle strength and physical performance in older adults undergoing weight loss programs based on calorie restriction, despite significant lean mass loss accounting for approximately one-third of the total weight lost. These findings indicate the need for more comprehensive evaluation of skeletal muscle mass and function during obesity treatment, as reduction of metabolic abnormalities such as inflammation and insulin resistance, as well as muscle fat deposition, may improve muscle metabolism, with enhanced muscle quality despite muscle mass reduction [86]. As mentioned above, indeed also in the STEP and SURMOUNT studies, physical function questionnaires indicated improvements in the presence of reduced metabolic abnormalities potentially improving muscle energy metabolism and function [1, 3]. Further studies are needed to investigate these issues. It is reasonable to hypothesize that rigorous implementation of nutritional and physical exercise programs during pharmacological obesity treatment may minimize muscle loss and further improve muscle function, thereby leading to optimal metabolic and health benefits.

The Need for Integration of Structured Physical Exercise and Protein Intake with IMs

Physical exercise. Even beyond the preservation of muscle mass and function, physical exercise is a cornerstone of obesity management. Structured physical exercise, which includes aerobic and resistance workouts, may contribute to clinically significant weight loss and long-term weight maintenance beyond general PA [22, 87]. While moderate PA improves cardiovascular health, dedicated physical exercise programs, especially when combined with CR, effectively preserve muscle mass and enhance metabolic outcomes [88–90].

Liraglutide. In the S-LiTE trial, which was double-blind and placebo-controlled for liraglutide treatment, combining 3.0 mg/day liraglutide with supervised aerobic/resistance exercise (150 min/week) resulted in significantly greater improvements in metabolic syndrome se-

verity, abdominal obesity, and inflammation compared to liraglutide monotherapy [73]. In a randomized, placebo-controlled trial, the combination of 3.0 mg/day liraglutide and structured exercise led to the greatest improvements in weight loss maintenance and metabolic health. After 1 year, participants in the combination group lost an average of 9.5 kg, compared to 4.1 kg with exercise alone and 6.8 kg with liraglutide alone. Only the combined strategy significantly enhanced insulin sensitivity, glycated hemoglobin levels, and cardiorespiratory fitness. The exercise regimen, based on individualized planning by exercise physiologists, included supervised high-intensity interval cycling, circuit training, and independent moderate-to-vigorous activities, emphasizing the critical role of structured physical exercise in sustaining weight loss and improving health outcomes [91].

Semaglutide and tirzepatide. Both the STEP trials (1, 2, and 4) investigating semaglutide and the SURMOUNT trials (1, 2, and 4) evaluating tirzepatide included lifestyle interventions as part of the treatment protocol. They include a 500 kcal/day caloric deficit and recommend at least 150 min per week of moderate-intensity PA, with adherence self-monitored and reviewed during scheduled counseling sessions [1, 3, 70, 71, 92, 93]. In contrast, STEP 3 included a substantially more intensive intervention: participants followed a structured 8-week low-calorie diet (1,000–1,200 kcal/day) with meal replacements, transitioned to a personalized hypocaloric diet (1,200–1,800 kcal/day), and progressively increased PA up to 200 min/week. They also received 30 individual behavioral therapy sessions over 68 weeks, which likely contributed to the greater weight loss observed (~16%) [94]. Notably, SURMOUNT 3, evaluating tirzepatide, also included structured exercise during its 12-week lead-in phase. This study design underscores the value of combining pharmacotherapy with supervised physical exercise rather than relying on general activity recommendations alone [95], although weight loss results did not appear to be enhanced by PE per se in the presence of substantial tirzepatide-induced reductions in body weight. Of interest, a 6-week intervention combining tirzepatide with a multimodal exercise program, including hypertrophy-, strength-, and power-oriented resistance training followed by aerobic exercise, led to greater improvements in fasting glucose, waist circumference, and body fat compared to tirzepatide monotherapy. Notably, exercise alone outperformed tirzepatide in improving cardiorespiratory fitness and muscle strength, reinforcing the indispensable role of structured exercise training in optimizing both metabolic and functional outcomes [96].

For the newer, second-generation IMs, further studies are needed to investigate the potential synergistic

impacts of exercise interventions not only on weight loss but also on key metabolic parameters. In general, while taking IMs, 150 min of aerobic exercise per week, along with 30 min of strength training two to three times per week, have been recently suggested (Fig. 1) [97]. However, it is important to underline that physical exercise should always be personalized by qualified professionals, based on the patient's clinical condition, physical capabilities, and treatment goals.

Protein intake. In general, in patients undergoing CR, protein intake is often insufficient and should be carefully monitored [75]. It has been recently suggested to increase protein intake during treatment with IMs, typically in the range of 1.0–1.5 g/body weight/day, and >1.5 g/body weight/day in older adults or post-bariatric surgery patients [97]. During weight loss, particularly in older individuals, the rebuilding of body tissues likely requires at least 1.2 g/kg body weight/day, with a maximum reference body weight corresponding to a BMI of 30 [98]. However, in patients with obesity, calculating protein requirements based solely on actual body weight may lead to overestimation. To address this, adjusted body weight (adjBW) is often used in clinical nutrition [98, 99]. A pragmatic approach is to calculate adjBW as ideal body weight plus 25% of the excess weight, using the formula: $\text{adjBW} = \text{IBW} + 0.25 \times (\text{actual body weight} - \text{IBW})$ [99, 100]. Nevertheless, dedicated studies are needed to validate the use of this approach in the context of obesity treatment with pharmacological therapies [97]. Protein intake should be personalized based on age, body composition, and clinical context, with attention to both quantity and quality to support muscle preservation [75]. While structured ET can reduce muscle mass loss during weight loss, especially in older adults, the co-administration of high-quality protein may further enhance this effect [85]. Although specific data on this combination in the context of IMs are still lacking, studies have demonstrated that such nutritional strategies can effectively support lean mass preservation during moderate weight loss when combined with structured exercise [101, 102]. Furthermore, evidence suggests that these beneficial effects on body composition, including fat mass reduction and lean mass maintenance, can be sustained even several months after the end of the intervention [103].

Strategies for the Implementation of Diet and Physical Exercise Interventions

Given the importance of integrating diet, physical exercise, and pharmacotherapy in the treatment of obesity, several strategies have been suggested to optimize

their implementation [7, 75]. The MEAL mnemonic (Muscle maintenance, Energy balance, Avoid side effects, Liquid intake) [7] has been proposed as a guide for dietary management in patients receiving therapy. It remains essential to individualize both dietary and exercise interventions (Fig. 1), ensuring they are appropriately adapted to each patient's specific clinical profile and needs. Possible scalable strategies to implement diet and physical exercise interventions are proposed in Table 1.

Considerations in Specific Populations

Certain populations require individualized attention due to specific physiological, behavioral, or clinical characteristics that may influence treatment efficacy and safety.

Older Adults

In elderly individuals, the risk of sarcopenia is significantly increased. This phenomenon is exacerbated by the physiological increase in fat mass and reduction in lean body mass associated with aging. Skeletal muscle begins to decline between the ages of 45 and 55, with an estimated loss of 12–15% per decade thereafter, reaching critical thresholds around the age of 80 [104–106]. These changes, when combined with obesity, contribute to sarcopenic obesity, a condition linked to frailty, reduced mobility, and increased morbidity [43].

In addition, older adults often show enhanced gastrointestinal sensitivity, including greater stimulation of phasic pyloric pressure waves and elevated fasting and postprandial concentrations of gastrointestinal hormones such as cholecystokinin and GLP-1, which slow gastric emptying and increase satiety [107–110]. These modifications may contribute to the “anorexia of aging,” a frequent condition in individuals over the age of 75, characterized by a spontaneous reduction in food intake and increased risk of malnutrition [109].

While these physiological changes do not contraindicate the use of OMMs in older adults, they necessitate careful clinical management. In this population, treatment must be accompanied by strategies aimed at preserving lean mass, including adequate protein intake and regular PA integrated with structured resistance-based exercise.

Individuals with Feeding and Eating Disorders

Obesity is frequently associated with feeding and eating disorders (FEDs). Among these, binge eating disorder (BED) is the most prevalent FED in individuals with excess weight. The prevalence of FEDs in patients

Table 1. Scalable procedures for implementing diet and physical exercise interventions

Procedures	Descriptions	Benefits	Challenges
Telemedicine and virtual consultations	Remote delivery of personalized nutrition and physical exercise counseling via secure digital platforms	Increases accessibility, especially in underserved or rural areas; flexible for patients and providers	Requires a stable internet connection; digital literacy barriers
Mobile apps and wearable integration	Use of smartphone apps and wearable devices to track dietary intake, PA, and progress	Scalable; enables self-monitoring and real-time feedback; allows personalization	Variable user engagement, concerns about data privacy, and digital inequality
Asynchronous digital platforms	On-demand access to structured content (e.g., video lessons, workouts, cooking tutorials, behavioral modules)	Flexible, cost-effective, and scalable; accessible at users' convenience	Limited interaction; lower accountability and support compared to live formats
Community-based programs	Implementation of diet and exercise interventions through local facilities such as gyms, community health centers, or municipal programs	Promotes cultural tailoring and local engagement; suitable for low-resource settings; Can be adapted for specific populations, including culturally sensitive approaches targeting underserved populations	Unequal distribution of services; dependent on local infrastructure and funding
Group-based interventions (including group medical visits)	Structured group sessions or group medical visits combining lifestyle education, clinical care, and peer support	Cost-effective; facilitates motivation and adherence through shared experience	May lack individualization; requires coordination and trained facilitators
School and workplace interventions	Health promotion programs embedded within school curricula or employee wellness initiatives	Supports early prevention; scalable within structured environments	Requires institutional commitment; variable implementation across settings
Exercise prescription	Formal prescription of physical exercise by HCPs, tailored to clinical status and capacity	Enhances adherence by medicalizing exercise; supports structured follow-up	Requires provider training and availability of referral pathways (e.g., to exercise professionals)

Overview of delivery mechanisms, benefits, and challenges for implementing diet and physical exercise interventions across clinical, digital, and community settings.

with obesity ranges from 19% to 48%, significantly higher than the 2–5% observed in the general population [111]. Additionally, diagnostic migration among FEDs is common, with individuals transitioning from BED to bulimia nervosa or other specified feeding or eating disorders over time. Recent literature suggests that GLP-1 receptor agonists may offer therapeutic benefits in managing FEDs such as BED, owing to their effects on appetite regulation and reward pathways [112, 113]. However, by enhancing satiety and reducing hunger, these medications may also increase the risk of reinforcing dietary restriction and cognitive restraint, potentially encouraging extreme and rigid eating behaviors such as skipping meals, eating minimal portions, or developing food avoidance patterns [114]. Therefore,

while IMs may represent a useful tool in the treatment of FEDs, they must be integrated into a broader lifestyle and behavioral framework. This should include regular and consistent eating patterns, attention to hunger and satiety cues, promotion of body acceptance, reduction of weight stigma, and psychological support. A multidisciplinary team with expertise in both obesity and eating disorders is essential to monitor patient progress, ensure safety, and maximize long-term outcomes [115, 116].

Women Planning Pregnancy

IMs are currently contraindicated during both pregnancy and lactation. Preclinical animal studies have demonstrated teratogenic effects, such as fetal growth restriction and skeletal anomalies [117, 118]. Although

the available human data are limited and do not indicate a clear increase in congenital anomalies, manufacturers currently recommend drug discontinuation before conception. Specifically, semaglutide should be stopped at least 2 months before conception, whereas tirzepatide requires a 1-month washout period [117, 118]. In this context, dietetic and physical exercise interventions become particularly important. Because the cessation of IMs has been associated with substantial weight regain, this is particularly relevant given that excessive gestational weight gain and pre-pregnancy obesity are well-known risk factors for adverse maternal and fetal outcomes, including gestational diabetes, hypertensive disorders, and miscarriage [119].

Conclusion

The present paper highlights the critical role of a healthy lifestyle and of dietetic-physical interventions in the era of pharmacological treatments for obesity, particularly GLP-1 receptor agonists and dual GLP-1/GIP receptor co-agonists [1–3]. While these medications have revolutionized obesity management by promoting significant weight loss, as well as cardiometabolic and renal improvements partially independent of weight loss, key factors such as nutritional adequacy, lean mass preservation, metabolic flexibility, and long-term behavioral adaptations still need to be considered and addressed [4, 5, 120].

A crucial distinction must be made between general lifestyle modifications and structured dietetic-physical interventions. While lifestyle changes, such as a balanced diet and PA, are essential for obesity prevention and for promoting overall health and well-being [14], once obesity is established, a structured and individualized approach is necessary. Dietetic-physical interventions involve personalized nutritional plans and exercise regimens designed to maximize fat loss while preserving muscle mass and nutritional status [19, 20].

In the era of second-generation OMMs, reshaping obesity management should be the paradigm shift. The dietitian's role has expanded from merely prescribing a hypocaloric diet to developing a balanced nutrition plan tailored to individual needs, ensuring adequate micronutrient intake and preventing malnutrition. Increased protein intake is emphasized to preserve muscle performance, while medical nutrition therapy is integrated to address obesity-related complications and comorbidities. Similarly, the role of the exercise spe-

cialist has become more structured, incorporating both aerobic training for cardiovascular conditioning and resistance training to maintain muscle function and performance.

This paper also addresses the potential risks associated with relying solely on pharmacotherapy, including the false sense of security it may create, leading to neglect of essential dietary and exercise interventions [53, 54]. Furthermore, it highlights the issue of lean mass loss associated with pharmacological weight loss and the importance of structured lifestyle intervention, particularly exercise, in mitigating this effect [1, 82]. As a narrative and conceptual synthesis, rather than a systematic or quantitative review, it may be subject to selection bias. Although no meta-analytic pooling was conducted, this narrative review highlights key areas that warrant future systematic and quantitative investigation on this important topic.

It is crucial to note that in pivotal registration trials, participants received structured dietary and PA counseling provided by trained HCPs [1, 3, 94, 95]. However, in real-world settings, such structured support may not always be available or consistently implemented, potentially limiting the full therapeutic potential of OMMs and increasing the risk of suboptimal outcomes.

To date, the access to both OMMs and structured interventions (D-PE-I) is shaped by healthcare disparities, including limited insurance coverage, geographic barriers, and socioeconomic constraints [121, 122]. Lack of consistent and equitable health plan reimbursement and high out-of-pocket costs reduce access and adherence and disproportionately impact vulnerable populations [123]. The individual financial burden of living with obesity adds further risk, particularly in low-income groups [124]. These inequities limit treatment uptake and outcomes, underscoring the need for policy solutions to improve equitable access to both pharmacological- and lifestyle-based obesity care. As an example, culturally sensitive programs developed for specific populations (such as non-Western migrant older adults) highlight how tailored interventions can expand reach and help reduce health disparities [125]. Therefore, policy efforts should not only ensure equitable access to OMMs but also invest in the implementation of personalized lifestyle strategies and structured dietetic-physical interventions that are broadly available, whose integration with pharmacotherapy is essential to improve metabolic health, enhance overall well-being, and optimize long-term obesity treatment outcomes.

Conflict of Interest Statement

V.Y. has received funding for providing educational sessions or attending advisory boards from Novo Nordisk, Eli Lilly, Regeneron, and Rhythm. J.A.B. is a consultant for Regeneron Pharmaceuticals and MEDACorp. Prof. Dr. V.Y. was a member of the journal's Editorial Board at the time of submission. The other authors have no conflicts of interest to declare.

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Author Contributions

L.M.D: conceptualization, writing, review, and editing. M.M.: investigation, writing, and editing. R.B., J.A.B., L.B., V.D.Y., E.P., and P.W.: review and editing.

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