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Dietary supplement considerations during glucagon-like Peptide-1 receptor agonist treatment: A narrative review

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ABSTRACT

Background: Recent advancements with Glucagon-like Peptide-1 Receptor Agonists (GLP-1RA) result in approximately 15 % or more weight reduction. Scientific research addressing specific nutritional concerns with GLP-1RA are still emerging. While some guidelines currently exist for nutritional considerations, they are largely focused on side effect management and providing basic dietary guidance during GLP-1RA.

Methods: This narrative review aims to provide practical evidence-based considerations for dietary supplementation to help optimize health outcomes while using GLP-1RA. We reviewed available literature of dietary supplementation interventions among individuals with obesity, weight loss clinical trials, and adiposity-related complications to help guide clinicians on potentially advantageous supplementation.

Results: Robust data from meta-analyses provides justification for a variety of dietary supplements that can support the unintended consequences of GLP-1RA treatments. Multivitamins are recommended to address micronutrient insufficiencies as determined by individual deficiencies and suboptimal intake. Protein supplements can help individuals meet daily protein intake recommendations of 1.2–2.0 g/kg/d. When combined with resistance training, whey protein can help preserve lean body mass during weight loss, with additional strength benefits from creatine monohydrate and β-Hydroxy β-Methylbutyrate supplementation. Antioxidants and anti-inflammatory nutrients can mitigate oxidative stress and inflammation. Fiber and probiotics can improve bowel regularity and mitigate side effects.

Conclusion: Healthcare providers play an active role in supporting their patients with comprehensive obesity treatment. Guidance should focus on improving their long-term health and potentially mitigating unintended consequences. Optimizing nutrient intakes with therapeutic doses of dietary supplements may enhance outcomes when used alongside GLP-1RA, such as increasing nutrient status, retaining lean mass, reducing oxidative stress and inflammation, and improving gastrointestinal health.

1. Introduction

Recent pharmaceutical developments with Glucagon-like Peptide-1 Receptor Agonist (GLP-1RA), such as incretin-based and glucagon-like peptide-1 receptor agonists, have significantly advanced medical treatments for obesity [1]. A once-weekly GLP-1RA injection provides approximately 14.9–20 % weight loss compared to an average of 5–7 % using traditional diet and lifestyle modifications [2,3]. Despite the proven weight loss efficacy of GLP-1RAs, addressing specific nutritional concerns are still emerging. Glucagon-like Peptide-1 Receptor Agonist can slow the transit time of the gastrointestinal tract and may suppress appetite. This potentially displaces nutrient intake and could lead to vitamin and mineral deficiencies. Further, side effects, such as nausea and vomiting can interfere with food choices, leading to suboptimal intakes of certain food groups. More concerning is the amount of skeletal muscle loss from significant weight loss [4]. Achieving optimal health outcomes with GLP-1RA requires a multifaceted approach that extends beyond pharmacological interventions. Lifestyle modifications, such as exercise, dietary habits, and complementary dietary supplementation can promote optimal health outcomes during and possibly after GLP-1RA treatment.

The need for more clinical trials that combine GLP-1RAs with targeted diet and lifestyle modifications to enhance patient outcomes is a growing call to action. Practicing Registered Dietitian Nutritionists (RDN) have highlighted a lack of quality nutrition education for patients using GLP-1RAs, noting similarities to the early stages of bariatric

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surgery when comprehensive dietary guidance was also insufficient [5]. A recent publication found within a 6-month window, bariatric surgery declined 8.7 % and GLP-1RA prescriptions increased 105.6 % [6]. The significant increase in GLP-1RA adoption further highlights the need to provide evidence-based recommendations for GLP-1RA treatment. Current clinical guidance focuses primarily on managing gastrointestinal side effects during GLP-1RA treatment, with some nutrition considerations recommended based on previous literature in weight loss science [7–11]. Fitzpatrick et al. provided a "5 A's" model (Assess, Advise, Agree, Assist, Arrange) for obesity treatment as a clinical interaction guide for patients. Within this model, behavioral weight loss counseling and referrals to RDN and MNT as part of a comprehensive treatment plan are emphasized [12]. Volek et al. [11] provides guidelines for dietary patterns during weight loss therapy and Almandoz et al. [8] offers comprehensive evidence-based nutritional considerations for advising patients using GLP-1RA based on previous weight loss research. A joint advisory from four U.S. health agencies provides guidance on nutrient adequacy from fruits, vegetables, whole grains, lean proteins, and legumes while limiting refined carbohydrates, sugary beverages, and processed foods with GLP-1RA treatment [13]. The guidelines mention that dietary supplements can be considered to mitigate nutrient, manage GI side effects, and preserve muscle mass. While these are initial steps in synthesizing relevant data to guide patients using GLP-1RAs, they lack comprehensive guidance for considering dietary supplementation to help optimize outcomes.

Nutritional intake from whole-food sources should be the first line of defense for improving health outcomes and mitigating side effects. However, a focus solely on food intake misses opportunities to advance and optimize health outcomes during weight loss, especially with lower appetites and reduced food intake (See Fig. 1). Pharmaceutical and dietary supplementation interventions are often viewed as competing or mutually exclusive [14]. Dietary supplements can offer beneficial ingredients that enhance or even counter the negative side effects of the pharmaceutical intervention. The combination of antibiotic treatments and probiotic supplementation illustrates this synergy. A meta-analysis found co-administration of probiotics with antibiotics reduced the risk of antibiotic-associated diarrhea by 37 % [15]. Complementary GLP-1RA and dietary supplement interventions could benefit the patient and help prevent unintended consequences of GLP-1RA treatment. This requires a paradigm shift in the development of education, research, and protocols on dietary supplementation in conjunction with GLP-1RAs.

Clinical studies investigating dietary intake while using GLP-1RA has been lacking and often do not report actual diet composition [16]. Based on available research, individuals report a 16–39 % reduction in total caloric intake during GLP-1RA treatment. A recent publication found suboptimal nutrient intake in community-dwelling individuals while using an GLP-1RA for several key vitamins and minerals [17]. The secondary analysis on dietary analysis is consistent with the general American population where individuals are not meeting key dietary intake for healthy eating [18]. With the available evidence, we can hypothesize there is room for improving dietary intake and a need for dietary supplementation to fill nutrient gaps. Consumer survey data report 96 % of individuals currently on GLP-1RAs are using dietary supplements [19]. However, in a cross-sectional study measuring dietary supplement intake in a cohort of individuals using GLP-1RA, only 43 % of subjects reported using dietary supplements and only 12 % were provided with recommendations from their healthcare provider [20]. This underscores the lack of understanding on both sides of the aisle on the important role of dietary supplements to support healthier weight loss.

While additional research is needed to address knowledge gaps with dietary supplementation in this population, current recommendations can be provided based on evidence from the populations with obesity, traditional dieting and weight loss, bariatric surgery interventions, and adiposity-related complications. Suboptimal obesity treatments can increase the risk of weight cycling, sarcopenia with aging, compromised quality of life, and reduced functional health [21]. With the rapid evolution of GLP-1RAs, nutritional interventions alongside GLP-1RA treatments are in their infancy. Therefore, a review of literature provides evidence-based considerations for dietary supplementation to build upon the current body of knowledge and provide practical guidelines as we wait for more rigorous research to be published. The purpose of this narrative review is to provide evidence-based dietary supplement considerations and recommendations for patients using GLP-1RAs.

2. Methods

Evidence for this review were identified through scientific databases include Cochrane Library, EMBASE, PubMed, and SCOPUS using keywords "dietary", "supplementation", "dietary supplements", "nutrition", "weight loss", "obesity", "diets", "adiposity", "glucagon-like-peptide-1", "bariatric", "weight loss", "muscle" and reviewed references for selected inclusion from March–December 2024. Position papers from professional committees, such as the Academy of Nutrition and Dietetics, were also explored. Meta-analyses, systematic reviews, and randomized clinical trials were primary sources included in the review analysis. High-quality dietary supplement interventions among individuals with obesity, weight loss clinical trials, and adiposity-related complications were used to develop the recommended doses. Open-label studies, case reports, and studies based solely on correlation data were excluded to ensure recommendations were grounded in robust clinical evidence. Publications helped answer the question, what considerations should be understood for weight loss and physiological changes? What evidence is available on nutritional needs during weight loss? What dietary supplements have been used to support related physiological changes from weight loss? This evidence was critically evaluated and analyzed to

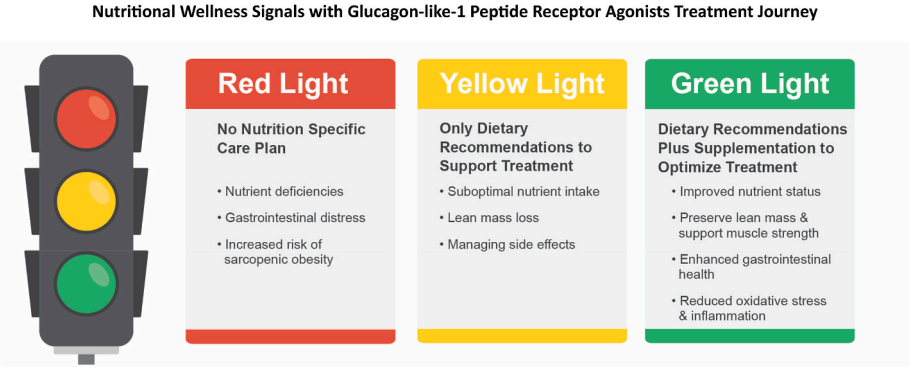

Fig. 1. Potential outcomes of obesity treatment care plans with and without nutritional and dietary supplementation interventions during glucagon-like-1 peptide receptor agonists treatment.
Note: The stoplight analogy reflects the authors' perspective and is not based on established criteria and should not be interpreted as a standardized framework.

provide recommendations for dietary supplementation, making necessary modifications from general population recommendations based on the available evidence. There are large gaps in research with GLP-1RA, noting future large-scale clinical trials are needed for dietary supplement interventions.

3. Discussion

With the rapidly evolving advancements of GLP-1RA, limited nutritional guidance is currently available for the needs of this specific population. Therefore, existing research across the spectrum of obesity and weight loss offers evidence-based approaches to guide dietary intake and nutrient optimization for individuals using an GLP-1RA. From previous weight loss studies, key areas of unintended consequences appear to be poor nutrient status, losing significant amounts of muscle mass, slowing metabolic rates, and metabolic dysfunction [22–25]. Further, managing nausea, vomiting, and diarrhea side effects, associated with GLP-1RA use should be considered as part of the MNT patient-centered care. Previous practice guidelines provide a comprehensive review of nutritional considerations for individuals using GLP-1RA [8,13]. This review expands upon those existing guidelines by presenting data on dietary supplementation that may help prevent unintended consequences associated with significant weight loss.

3.1. General dietary and nutrient considerations

Dietary patterns should focus on adequate energy balance, appropriate macronutrient distribution, nutrient-dense foods, and adequate hydration. The use of dietary supplements can be considered as supplementary, not meant to replace healthful diets. Several guidelines are provided from the United States Department of Agriculture (USDA) to promote well-balanced meals and nutrition guidelines, such as the Dietary Guidelines for Americans (DGA) and MyPlate recommendations [26]. However, these guidelines are for the general public and may not be appropriate for specialized populations, such as individuals with obesity using GLP-1RAs. Expert panels and committees from the Food and Nutrition Board of the Institute of Medicine developed DRIs based on gender and age to promote health and prevent chronic disease. However, there are no specific DRIs developed for medical weight loss, limiting our understanding of nutrient requirements while using GLP-1RAs. Previous studies investigating the nutritional status of individuals with obesity or overweight find higher prevalences of micronutrient deficiencies compared to individuals of normal weight [27]. Studies from adults with extreme obesity undergoing bariatric surgery have identified a wider array of pre-existing nutritional deficiencies prior to surgery [28]. Further, a reduced calorie intake is correlated with lower vitamin and mineral consumption [25]. It is unclear whether individuals taking GLP-1RA have inadequate nutritional status or if their nutrient needs exceed the DRI standards.

Thus, key considerations for nutritional intake require a paradigm shift from adequate intake to optimal intake. Adequate nutrient intake represents the level required to prevent deficiencies and chronic disease. Whereas optimal nutrient intake extends beyond those requirements and considers levels necessary to achieve peak physiological function, provide health benefits, and further disease prevention. Relying solely on standard DRIs may be outdated, as some research finds higher therapeutic doses support better health outcomes. For example, there are certain recommended levels for vitamins and minerals that only address adequate intake, yet robust data demonstrates higher levels are more optimal. A recent meta-analysis on vitamin D supplementation in those with type 2 diabetes found positive improvements in lowering hemoglobin A1C and fasting blood glucose (FBG) with high doses of 50,000 IU vitamin D per week (~7100 IU/day) [29]. This emphasizes that the Recommended Dietary Allowance (RDA) for vitamin D of 600–800 IU/day is not aligned with therapeutic doses in randomized clinical trials (RCT), which are significantly above the RDA. This demonstrates the need to focus on optimal intake rather than adequate intake for nutrients. Individuals using GLP-1RA represent a specialized population where general guidelines may be insufficient to support unique physiological changes and concerns. Further, there are non-vitamin and mineral nutrients with significant research supporting health benefits, which would be otherwise unattainable from diet only, emphasizing the importance of dietary supplementation.

3.2. Multivitamin supplementation

Previous research with individuals using GLP-1RA found diets fall short of critical micronutrients and poor diet quality [17,18]. Dietary supplements can serve as a tool in addressing nutrient shortfalls, especially in a society where dietary habits have remained largely unchanged, despite decades of public health initiatives. Multivitamins have typically been recommended to address nutrient gaps and support the increased nutritional needs of specific populations. For example, prenatal multivitamins are usually prescribed by healthcare providers to meet the higher nutritional needs of the mother and baby. To our knowledge, there is currently no intervention study assessing multivitamin use during GLP-1RA treatment. To optimize GLP-1RA treatment and long-term health afterwards, clinicians must be aware of pre-existing nutritional deficiencies. When biomarker serum levels are not available, there is preliminary evidence in this population that micronutrient supplementation should be considered for calcium, iron, magnesium, potassium, vitamin A, C, D, and E, and choline since dietary intake was significantly below the DRI from food alone [17]. For recommended micronutrient supplementation dosing based on average inadequate dietary intakes of those using GLP-1RA, see Appendix A. Given the reduction in food intake associated with GLP-1RA and safety of multivitamin interventions [30], multivitamins should be prescribed with GLP-1RAs to help fill nutrient gaps. It is worth noting that nutritional inadequacies are less common among those who take multivitamin supplements, not only because of the nutrients they provide, but also possibly because supplement users may eat more nutrient-rich foods and have healthier lifestyles overall [31]. While multivitamin supplements cannot replace eating adequate amounts of a variety of foods, they may be particularly beneficial to people who have poor nutrition or increased nutrients needs.

3.2.1. Vitamin D

Vitamin D is a fat-soluble vitamin that has garnered significant attention in dietary supplementation, as naturally occurring food sources are scarce. While our bodies can synthesize vitamin D endogenously, subclinical vitamin D deficiencies remain prevalent worldwide [32]. Individuals with obesity are 35 % more likely to be deficient in vitamin D compared to those with a normal body weight [33], highlighting the importance of vitamin D supplementation with GLP-1RAs as many are likely starting at a deficient level. A meta-analysis found vitamin D3 was more advantageous in raising serum 25-hydroxyvitamin D (25(OH)D) levels compared to vitamin D2 [34]. As aforementioned, clinical studies investigating vitamin D find therapeutic benefits above the RDA level. Pre-clinical studies have shown that vitamin D plays a role in regulating insulin secretion and therefore could affect insulin sensitivity [35]. In human studies, a meta-analysis with 20 RCTs in patients with type 2 diabetes found vitamin D supplementation significantly improved serum 25(OH)D levels and homeostasis model assessment of insulin resistance [36]. Additional meta-analyses show that vitamin D supplementation may reduce chronic low-grade inflammation in patients with type 2 diabetes [37]. Obesity is a multi-faceted disease and vitamin D supplementation may be advantageous with GLP-1RA treatment, especially to address potentially deficient serum 25(OH)D levels.

3.3. Omega-3 fatty acids

Fish oil supplements are rich in omega-3 fatty acids Eicosapentaenoic

acid (EPA) and Docosahexaenoic acid (DHA). Numerous health benefits have been associated with fish oil supplementation, including improved heart health, enhanced joint health, reduced inflammation, and emerging research on muscle health [38–42]. Metabolic syndrome, cardiovascular disease, and inflammation are highly correlated with people living with obesity [43]. Fish oil supplementation has been shown to have some positive impact on fasting blood sugars and insulin resistance. In populations with diabetes, a meta-analysis found fish oil supplementation beneficial for insulin sensitivity with at least one symptom of metabolic disorders compared to placebo [44]. Fish oil supplementation has also been shown to be correlated with reduced cardiovascular disease risk in a linear dose-response relationship in clinical trials [45]. Furthermore, emerging research with fish oil supplementation finds positive impacts on muscle quality. Smith et al. found fish oil slowed the normal decline in muscle mass and function in older adults after 6 months of supplementation [46]. Additionally, compared to a placebo control group, 4 g/d of fish oil supplementation significantly increased thigh muscle volume, handgrip strength, and 1-repetition maximum muscle strength. Another study supplementing 1020 mg of omega-3 fatty acids in conjunction with a weight loss program found that abdominal fat mass and percentage decreased more in the omega-3 fatty acid group than the control group. This data provides additional insights into omega-3 fatty acids for weight loss. However, other studies did not find a significant impact on weight loss with omega-3 fatty acid supplementation [47,48]. Theories suggest that omega-3 fatty acid supplementation supports muscle mass, muscle strength, and muscle performance through its anti-inflammatory pathways, promoting skeletal muscle protection [49]. While weight loss is not anticipated as a direct outcome of fish oil supplementation, its potential mechanism in protecting muscle, along with its well-documented metabolic and cardiovascular benefits, provides justification for fish oil supplementation during GLP-1RA treatment. Based on the available

Table 1
Summary of dietary supplement clinical guidelines for Glucagon-like-1 Peptide Receptor Agonists treatments, including recommended doses, intervention considerations, and level of evidence.

GLP-1RA Concern	Dietary Component	Primary Benefit	Recommended Dose	Intervention Considerations	Level of Evidence [References]
General Dietary Guidance	**Multivitamins, Vitamins, and Minerals**	Fill nutrient gaps from lower food intake	• Use a patient-centered approach • Suggested dosing for key nutrients in Appendix A	Complete a nutrition assessment based on average dietary intakes to better guide missing nutrients for individuals. If available, use biomarkers to assess nutrient status.	⊕⊕ [29–31]
	Vitamin D	Improve A1C, support muscle quality, heart health, low-grade inflammation	• High doses of 50,000 IU per week • ~7100 IU/day to normalize serum levels	Measure serum 25(OH)D levels before prescribing dose to determine level of deficiency. If prescribing a multivitamin in combination with a vitamin D supplement, consider the total vitamin D dose across supplementation + dietary intake.	⊕⊕⊕ [34,35,37]
	Omega-3 Fatty Acids	Support muscle quality, heart health, and anti-inflammation	• At least 1 g/d of fish oil	Choose an omega-3 supplement higher in EPA and DHA levels	⊕⊕⊕ [38–42,44–46]
Muscle Mass Protection	**Protein Supplements**	Help meet higher protein needs during hypocaloric dietary intake	• Total protein intake from food and supplements:1.2–2.0 g/kg/d	Use adjusted body weight when greater than 115 % ideal body weight and recalculate protein needs as body size reduces. Consider protein powders/drinks and meal replacements.	⊕⊕⊕ [50–55]
	Whey Protein	Preserve lean body mass during weight loss and optimize body composition	• 20–40 g/d	Distribute protein intake throughout the day, recommend whey protein in the morning to fill protein gaps at breakfast.	⊕⊕ [58,59]
	HMB	Stimulates mTOR pathways and inhibits ubiquitin-proteasome system	• 3 g/d	Combine with exercise for additional benefits	⊕ [61,62,64]
	Creatine	Increase muscle mass and strength	• 5 g/d	Combine with 3 d/week resistance training	⊕⊕ [67–72]
Metabolic Health	**Thermogenic**	Increase energy expenditure and fat oxidation	• 0.02 g/mg catechin-caffeine mixtures • 0.01 g/mg caffeine-only	Be aware of caffeine limits and patient's total daily caffeine intake	⊕ [75–79]
	Antioxidants & Anti-inflammatory Compounds	Neutralize free radicals, reduce inflammation, potent antioxidant	• Antioxidants: Dose-not specific • Curcumin 500–1500 mg/d	Antioxidants to consider: Polyphenols, CoQ10, garlic, or vitamin A, C, and E. Anti-inflammatory ingredients: polyphenols, EPA and DHA, garlic, anthocyanins, and lycopene.	⊕⊕ [84,86,88–90]
Gastrointestinal Side Effects	**Fiber**	Reduce constipation and improve stool consistency	• >10 g/d and treatment durations of at least 4 weeks	Increase water intake with fiber supplementation.	⊕⊕⊕ [93,94]
	Probiotics	Improve bowel movements, feed gut microbiome, and support body composition	• Medium dose 1–30 × 10^9 CFUs • High dose >30 × 10^9 CFUs	Look for probiotic strains that include *Lactobacillus* or *Bifidobacterium* species.	⊕⊕ [97–100]

KEY: kg = kilog
rams; g = grams; mg = milligrams; d = day; IU = International units; CFU: colony forming units.
⊕⊕⊕ **Strong Evidence:** Substantial clinical data available demonstrating the ingredient's effectiveness in conjunction with weight loss interventions or in populations with overweight, obesity, or diabetes.
⊕⊕ **Moderate Evidence:** Significant clinical data supporting the ingredient's mechanism of action or benefits related to symptoms or side effects of weight loss, but limited number of studies directly combining it with weight loss protocols.
⊕ **Emerging Evidence:** Limited clinical data specifically in weight loss or obesity populations. However, available evidence or mechanistic rationale suggests potential, warranting further investigation.

evidence, fish oil supplementation rich in omega-3 fatty acids can serve as a valuable adjunct to GLP-1RA treatment (see Table 1), with more research needed in the population.

3.4. Nutrient considerations for muscle mass

Preventing loss of muscle mass during GLP-1RA treatment is critical for long-term weight management and metabolic health [11]. Individuals using GLP-1RAs lose around 20–50 % of lean body mass, which is much higher than weight loss through traditional diet and exercise [50]. The degree of muscle mass decline during weight loss varies based on the intervention, however, the specific amount of skeletal muscle mass is largely not reported. Experts have noted that a 10 % muscle mass loss in 68 weeks using an GLP-1RA is similar to two decades of age-related muscle mass loss [21]. Long-term health and weight management are highly correlated with the retention of lean body mass since it plays a role in total energy expenditure, strength, activities of daily living, and lifespan [11]. Therefore, dietary supplementation considerations for preserving and promoting muscle mass should be part of the patient-centered care plan. This section will review the evidence on dietary supplements that have robust evidence for preserving and increasing lean body mass and muscular strength.

3.4.1. Protein supplements

Proper nutrition, such as higher protein diets, and exercise interventions are needed along with GLP-1RA treatments to minimize loss of muscle mass [50–52]. Muscle loss can impair metabolic function, decrease resting metabolic rate, reduce physical performance, and lead to a decline in overall health. While emerging research explores nutrition and resistance training (RT) interventions with GLP-1RAs, robust evidence shows that higher protein intake preserves lean mass during weight loss [53–55]. Daily protein goals should be 1.2–2.0 g/kg based on adjusted body weight. In previous research, GLP-1RA users, only 43 % consumed at least 1.2 g/kg of protein, 10 % consumed at least 1.6 g/kg, and 5 % consumed at least 2.0 g/kg, calculated based on adjusted body weight [56]. In a 12-week preliminary RCT, patients with obesity on GLP-1RA following a diet consisting of 1.3 g/kg protein successfully promoted fat mass reduction while preserving fat free mass, muscle strength, and resting metabolic rate compared to those following a traditional isocaloric diet [57]. This further indicates the importance of high protein intake during GLP-1RA-associated weight loss.

Reaching higher daily protein needs can be challenging with reduced food intake and protein supplements can help fill those gaps. Whey protein is a high-quality source of protein due to its high leucine content, the primary branched-chain amino acid responsible for muscle protein synthesis. Whey protein supplementation is shown to improve body composition in individuals with overweight and obesity by reducing body weight and total fat mass [58]. In previous clinical studies, higher protein intake has been documented to improve body composition during weight loss. Further, protein is also necessary as part of a dietary strategy for weight loss maintenance and the prevention of weight regain [59]. There are currently large gaps in understanding optimal protein dosing and timing for specific GLP-1RA needs. Future research is needed combining protein supplementation, resistance training, and GLP-1RA in randomized clinical trials to attenuate muscle mass loss.

3.4.2. Beta-hydroxy-beta-methylbutyrate (HMB)

Beta-Hydroxy-Beta-Methylbutyrate (HMB) is a metabolite of the amino acid leucine, however, only about 5 % of leucine is converted into HMB, with the majority being metabolized into isovaleryl-CoA. Due to poor endogenous synthesis, exogenous HMB supplementation is required to achieve the clinically meaningful dose of 3 g per day. HMB activates the mammalian target of rapamycin (mTOR) signaling pathway, which promotes muscle protein synthesis, while concurrently inhibiting proteolytic processes through the ubiquitin-proteasome pathway. This dual action suggests HMB's unique capability to stimulate protein synthesis and help prevent muscle degradation pathways simultaneously [60]. Stimulating the mTOR pathway is important during weight loss because mTOR plays a central role in regulating muscle protein synthesis, growth, and repair. During weight loss, caloric restriction can reduce the signals that normally promote muscle growth, increasing the risk of muscle breakdown. By stimulating the mTOR pathway, HMB may help to preserve lean muscle mass, even in a calorie-deficient state. Additionally, HMB exerts muscle-preserving effects by modulating the ubiquitin-proteasome pathway. The ubiquitin-proteasome system is the primary mechanism by which cells degrade and recycle damaged or unnecessary proteins. In muscle tissue, this system becomes particularly active during periods of muscle atrophy, inflammation, or stress, leading to the breakdown of muscle proteins. By modulating this pathway, HMB has an anticatabolic effect, creating a favorable environment for muscle protein turnover.

HMB has shown some promise for preserving and increasing lean body mass across elderly populations and novice exercisers. In a meta-analysis of older adults, HMB supplementation significantly increased muscle mass by 0.352 kg with no change in fat mass compared to the control groups [61]. These findings indicate a positive effect of HMB on muscle mass during aging. In a more recent publication, Lin et al. found similar results regarding HMB supplementation on improving lean body mass with significant increases in fat-free mass in older adults compared to control groups [62]. Further sub-analyses found HMB combined with exercise had no additional impact on fat-free mass. This suggests HMB supplementation alone can be an effective intervention for improving muscle mass in older individuals. While older adults are not the exact population sample of all individuals using GLP-1RA, previous research has correlated muscle loss during 68–72 week GLP-1RA treatment to two decades of age-related muscle loss [21].

In women with overweight and obesity, two clinical trials have been performed. A pilot study examined a supplement containing arginine, glutamine, and HMB on body composition in postmenopausal women with obesity. Fat-free mass (FFM) was maintained significantly in the supplemented group. However, it is challenging to conclude a direct benefit of HMB for body composition changes since it was combined with other ingredients [63]. Another study found six weeks of HMB supplementation improved upper and lower body strength compared to placebo in sedentary women with obesity [64]. However, no significant changes in body composition between groups were observed. These findings suggest that HMB may help preserve lean body mass and support muscle strength during weight loss. Based on the existing evidence, the definitive benefits of HMB within a weight management program remain inconclusive, however there is initial evidence suggesting positive results. The mechanistic basis for this potential benefit is strong to help preserve muscle mass during such rapid and substantial weight loss, although this has not yet been studied. Future research should investigate whether HMB supplementation during weight loss induced by GLP-1RA can mitigate the loss of lean muscle mass. For now, based on the available evidence, 3 g/d of HMB supplementation is warranted as a recommendation to help support pathways related to protein turnover.

3.4.3. Creatine

Creatine is a naturally occurring nitrogen-containing compound found primarily in myocytes. Creatine supplementation is well established for its ability to enhance exercise performance, improve body composition, and increase muscular strength. Creatine has only been briefly studied for benefits related to weight management. In preclinical data, creatine appears to play some role in browning adipose tissue, and a human study found creatine increased resting metabolic rate, indicating potential weight management benefits [65,66]. While there is limited data on creatine supplementation combined with weight loss interventions, sport performance studies provide evidence for its role in muscle mass and strength. A comprehensive analysis of 35 RCTs found creatine supplementation significantly increased lean body mass with a mean difference of 0.68 kg across a variety of populations with and

without exercise [67]. When combined with RT, lean body mass was more pronounced, averaging an increase of 1.1 kg across various demographics. Further, long-term studies investigating creatine supplementation find significant gains in muscle strength. Two large meta-analyses with 60 RCTs found improvements in lower body strength and 53 RCTs found improvements in upper body strength [68,69]. Dosing protocols varied across clinical trials, with a daily 5-g dose predominantly administered, typically combined with 3 d/week of resistance training.

Creatine exhibits similar muscle health benefits in older adults. Meta-analyses in adults 50–80 years old show significant gains in muscle mass when creatine is combined with RT compared to placebo and RT only [70,71]. The creatine group increased lean body mass by an average of 1.32 kg compared to placebo, adding almost three more pounds of lean mass. Even more compelling was the statistically significant increase in lean tissue when creatine was only consumed on training days rather than every day of the week; concluding creatine is still effective for improving lean tissue when taken on training days only [16]. Creatine supplementation is also widely regarded as safe to consume with little to no side effects across various age groups [72]. While creatine supplementation has not been studied in a GLP-1RA population, from the previous evidence, it's clear daily creatine supplementation with RT should be considered for an GLP-1RA care plan. Muscle mass and strength gains may not be as pronounced due to a hypocaloric diet; however, it's hypothesized it could help preserve lean body mass and strength greater than no creatine supplementation. Based on creatine's available evidence, creatine supplementation combined with RT could be advantageous during GLP-1RA weight loss (See Table 1 for specific dosing protocols).

3.5. Nutrient considerations for metabolic health

Obesity is associated with metabolic disturbances, chronic stress, and low-grade inflammation. Chronic stress and low-grade inflammation within the body can dysregulate metabolic health and lead to oxidative stress. Oxidative stress and inflammation can both lead to chronic disease and have a negative impact on weight loss efforts. Focusing on lifestyles to help manage metabolic stress and improving metabolic rate during weight loss are essential for overall health and weight maintenance. Maintaining higher metabolic rates and supporting cellular health through decreasing oxidative stress and inflammation may promote longer-term health outcomes. Several dietary supplement ingredients have been shown to improve resting energy expenditure and various aspects of cellular health by reducing oxidative stress and inflammation.

3.5.1. Thermogenic ingredients

The majority of clinical studies have not reported participants' resting metabolic rate before, during, and after GLP-1RA treatment. This is a significant gap in understanding how these drugs impact metabolic rate and daily calorie expenditure, which is a key aspect of long-term weight management. Weight loss results in a smaller body mass, which naturally lowers energy expenditure. This effect can be further compounded by the rate and degree of weight loss, dramatically impacting metabolic rates. The best available data comparing metabolic rate changes during rapid weight loss is a longitudinal study with participants of "The Biggest Loser" competition [73]. After a six-year follow-up, participants regained 70 % of their original weight loss, and their resting metabolic rate was nearly 700 calories lower than their baseline body weight. In contrast, their predicted resting metabolic rate was overestimated by approximately 500 calories, as calculated based on body composition changes. Clinically, this presents a challenge, as metabolic rate is typically calculated indirectly in practice and overestimated by approximately 26 % [73]. Preserving muscle mass is the primary target for maintaining a higher metabolic rate, however, potential ingredients with a thermogenic effect may provide additional support during weight loss [74].

Thermogenic dietary supplements can provide functional benefits through various biological pathways, such as activating uncoupling proteins, inhibiting phosphodiesterase, or targeting β_2-adrenergic receptor agonists to increase energy expenditure and activate brown adipose tissue [75]. Dietary supplement ingredients like caffeine, green tea extracts, capsaicin, and other herbal ingredient blends have been shown to increase energy expenditure in clinical studies [76]. A meta-analysis of catechin-caffeine mixtures and caffeine-only supplements significantly increased energy expenditure over a 24-h period by 4.7–4.8 % with a dose-dependent response by 0.4–0.5 kj/mg administered [77]. Few studies have examined thermogenic ingredients over extended periods. However, a handful of research studies provide evidence that the increase in metabolic rate persists for up to 8 weeks [78,79]. As previously mentioned, the metabolic rate remains low after significant weight loss and appears to remain low even with weight regain. Therefore, thermogenic supplementation during weight loss and post-weight loss may potentially support more optimal metabolic rates. This is a potential area of research to explore with adjunct diet and lifestyle weight loss modification and GLP-1RA use.

Thermogenic ingredients are not intended to promote significant weight loss but rather support the pathways of energy expenditure and browning of white adipose tissue. There is also evidence that activation of thermogenesis has other positive impacts on metabolic functions, such as insulin resistance, hyperglycemia, and elevated blood lipids, which may provide other benefits to those on GLP-1RA [80]. While there is no evidence of thermogenic supplements during GLP-1RA treatment, the mechanism warrants further exploration, especially post-GLP-1RA treatment (See Table 1 for specific dosing protocols).

3.5.2. Antioxidants & anti-inflammation

Oxidative stress, marked by reactive oxygen species (ROS), is another potential target for supplementation during GLP-1RA treatment. Obesity can induce oxidative stress, while the co-morbidities associated with obesity can further exacerbate it, such as hyperglycemia, nutrient deficiencies, and impaired mitochondrial function [81]. Accumulation of ROS may alter the nature of lipids and proteins, causing cellular dysfunction [82]. Therefore, increasing the intake of antioxidants that help neutralize free radicals may be beneficial for obesity. Dietary intake of antioxidant compounds is primarily through fruits and vegetables. Previous research indicates that those on GLP-1RA are not consuming adequate daily servings of fruits, vegetables, and antioxidant nutrients such as vitamins C and E [17]. Therefore, individuals using GLP-1RA may benefit from dietary supplementation with antioxidants.

Antioxidants are a broad class of dietary supplements comprised of several ingredients [83]. A meta-analysis of antioxidant supplementation in individuals with obesity has shown beneficial effects on reducing body mass index (BMI), waist circumference (WC), fasting blood glucose, and improving markers of oxidative stress and inflammation compared to placebo [84]. During GLP-1RA, antioxidant supplementation may support cellular health and help to prevent the long-term negative health consequences of uncontrolled oxidative stress. However, a patient-centered approach needs to be considered as not all antioxidant supplementation supports disease outcomes. For example, supplementation with beta carotene, vitamin A, and Vitamin E may increase mortality [85]. To our knowledge, there have been no published studies with antioxidant supplementation in conjunction with GLP-1RA. Further research is needed to determine the optimal antioxidant ingredient and dose needed in this population for optimal health outcomes.

Many nutrients and botanicals have anti-inflammatory properties, such as antioxidants and fish oil, as previously mentioned. A highly studied supplement is curcumin, which has been clinically studied in several RCTs for its anti-inflammatory properties. A large meta-analysis of 66 RCTs found curcumin/turmeric supplementation significantly reduced levels of inflammatory markers, including C-reactive protein,

tumor necrosis factor, and interleukin-6, and improved antioxidant activity compared to placebo [86]. In clinical applications, numerous studies have demonstrated beneficial effects on arthritis, depression, atherosclerosis, and metabolic syndrome [87,88]. In a meta-analysis of 50 RCTs, curcumin supplementation significantly reduced BMI, BW, and WC, however the daily doses varied widely from 50mg to 3,000 mg [89]. Other novel dietary supplement ingredients show promise in reducing inflammation, include polyphenols (such as resveratrol), EPA and DHA, garlic, anthocyanins, and lycopene [88,90]. Several studies indicate that polyphenol supplementation reduces markers of central adiposity (body fat percentage, fat mass, waist circumference) and visceral adipose tissue, however there is no consensus on dosage or form [91]. Since obesity and weight loss are associated with inflammation, dietary supplements with these anti-inflammatory ingredients may help reduce inflammation (See Table 1 for specific dosing protocols). More research is needed to understand the effect of different types of anti-inflammatory ingredients in combination with GLP-1RA treatment.

3.6. Nutrient considerations for gastrointestinal health

Gastrointestinal side effects, such as constipation and diarrhea, have been documented with some GLP-1RA treatments [10]. Due to increased nausea and vomiting, dehydration is a major area of concern with GLP-1RA treatments. Therefore, ongoing monitoring and follow-up should include regular reassessment of hydration status [13]. Dietary supplements, such as fiber and probiotics, can help mitigate these issues and should be considered for patients experiencing these side effects.

3.6.1. Fiber

Due to slowing gastric transit time, constipation is a primary side effect with GLP-1RA. Fiber-rich foods are well-documented to provide digestive support and promote regular bowel movements, yet average fiber intakes remain consistently low in American diets [92]. Fiber consumption while using GLP-1RA from food sources averaged 14.5 g, significantly below the daily recommendations of 25–38 g per day [18]. While it's important to emphasize fiber-rich food choices from fruits, vegetables, and whole grains, meeting daily fiber needs can be a challenge, especially with lower calorie intake. Some patients may be able to obtain daily fiber goals from food alone, whereas others may need to supplement their nutritional intake. There is evidence from a large dataset of human clinical trials for fiber supplementation reducing constipation [93]. Similarly, Christodoulides et al. found fiber supplements, including prebiotics, significantly increased stool frequency and softening stool consistency compared to placebo [94]. Adequate fiber intake can help promote digestive health if individuals are unable to meet their daily fiber intake from food alone and suffering from constipation. Therefore, fiber supplements may be beneficial for GLP-1RA patients on a case-by-case basis (See Table 1 for specific dosing protocols).

3.6.2. Probiotics

The role of the microbiome in weight management has garnered significant interest within the scientific community and among health professionals [95,96]. Probiotics, defined as live microorganisms, have been shown to positively influence the gut microbiome, metabolic function, and overall health [97]. This is particularly relevant as emerging research suggests that the gut microbiome plays a critical role in regulating body weight. Emerging research reports gut microbiome differences between individuals with obesity compared to individuals of normal weight [98]. Intervention studies find prebiotics, probiotics, and synbiotics significantly reduce body weight, BMI, and fat mass compared to placebo [99]. Therefore, probiotics could contribute to improved body composition. Most strikingly, these studies demonstrate that probiotics can significantly promote weight loss independent of dietary modifications. This provides compelling evidence for the role of gut health in weight management and highlights the synergy of nourishing the gut microbiome as a complementary approach for obesity treatment. Probiotics have also been shown to improve the efficacy of bowel movements in adults with constipation [97,100]. Supplementation with products containing *Lactobacillus* or *Bifidobacterium* species increase stool frequency and reduces transit time-related constipation in some studies [100]. Probiotics could be part of a complementary therapy alongside GLP-1RA treatment to improve unwanted GI side effects and promote a diverse microbiome (See Table 1 for specific dosing protocols).

4. Clinical practice framework

This review examined the existing evidence to assess the potential role of dietary supplementation as an adjunct to GLP-1RA treatments. Table 1 summarizes practical clinical recommendations based on the efficacy of select ingredients shown to support physiological adaptations during weight loss, drawing from prior clinical trials across populations with obesity and adiposity-related complications. These recommendations offer a preliminary framework for clinicians to consider during obesity management, while ongoing research continues to inform the development of customized medical nutrition therapy guidelines for GLP-1RA treatments.

Given the vast dietary supplement market, healthcare practitioners may face challenges in identifying and recommending products. Fig. 2 provides a recommended step-by-step process for incorporating dietary supplements into patient care and a checklist for evaluating supplement products.

4.1. Scientific organizations

The current guidance from professional organizations regarding dietary supplementation with GLP1-RA are provided in a joint advisory position paper from the American College of Lifestyle Medicine, the American Society for Nutrition, the Obesity Medicine Association, and The Obesity Society [13]. The guidelines mention vitamin D, calcium, B12, and a multivitamin supplement can be considered to reduce nutrient deficiencies. Additionally, recommendations for fiber and magnesium supplements are included to help manage GI side effects protein shakes to preserve muscle mass.

5. Limitations

To our knowledge, no clinical trials have directly evaluated the use of dietary supplementation in conjunction with GLP-1RA treatments, representing a key limitation of this review. As such, the clinical relevance of the active ingredients reviewed remains unclear for specific populations using GLP-1RA. There is evidence available to support the role of dietary supplementation across clinical trials in individuals with obesity, including weight loss interventions and adiposity-related complications. In the absence of GLP-1RA-specific data, clinicians must rely on existing literature, expert clinical judgement, and a patient-centered approach regarding dietary supplementation while using a GLP-1RA. The majority of recommendations cited were derived from meta-analyses identifying efficacious dosages for targeted health benefits. Nutrition is inherently individualized, influenced by genetics, epigenetics, and lifestyle factors, which should all be taken into consideration. Additionally, there is an absence of safety data on these ingredients in combination with GLP-1RA, including unknown drug–nutrient interactions. Future large scale, randomized-clinical trials are warranted to assess the efficacy and safety of dietary supplements as adjuncts to GLP-1RA therapy for improving and optimizing health outcomes.

6. Conclusion

Patients using GLP-1RA to treat obesity should receive individualized, evidence-based care focused on optimizing health outcomes and

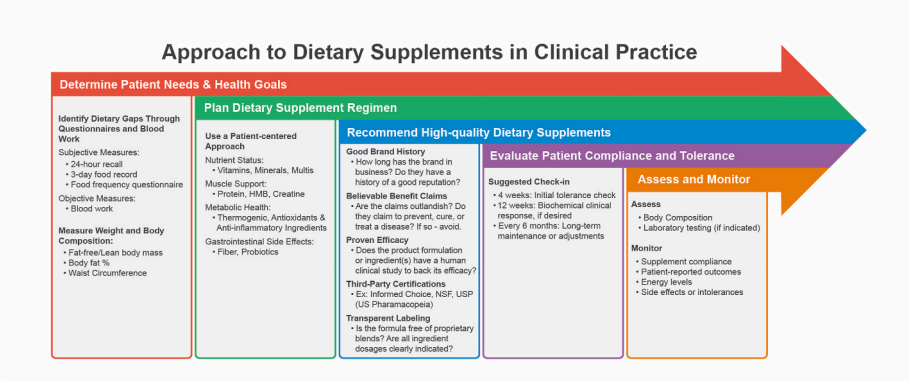

Fig. 2. Step-by-step process for incorporating dietary supplements into patient care and a checklist for evaluating dietary supplementation during glucagon-like-1 peptide receptor agonists treatments.
Note: This guide for implementing dietary supplementation reflects the authors' perspective.

mitigating unintended consequences of significant weight reduction. Based on this review, there is prior knowledge and data supporting considerations for dietary supplementation with GLP-1RA treatment. This review provides an initial guide for clinical practice and patient education for optimizing nutrient status, preserving lean mass and muscle strength, supporting metabolic health, and reducing gastrointestinal side effects. Future randomized clinical trials are needed to examine the health effects of combining dietary supplements with GLP-1RA treatments.

Key takeaways

- Multivitamins, vitamin D, and omega-3 or fish oil supplements can fill nutrient gaps from dietary intake, increase suboptimal serum nutrient levels, and potentially offer long term health benefits.
- Protein, whey, creatine, and HMB supplementation can preserve lean mass while building muscle strength during weight loss.
- Thermogenic, antioxidants, and anti-inflammatory dietary supplements can support metabolic function and reduce oxidative stress and inflammatory markers.
- Fiber and probiotic supplements can reduce constipation and improve stool consistency, a common side effect of GLP-1RA.

Author contribution

Conceptualization: BJ, MM, RK, RJ. Methodology: BJ. Validation: BJ, MM, RK, RJ. Investigation: BJ, MM. Data Curation: BJ, MM. Writing – Original Draft: BJ, Writing – Review & Editing: MM, Editing: RK, RJ. All authors reviewed and approved the final version of the manuscript for submission and publication. Visualization: BJ, MM.

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Appendix A. Supplementary data

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