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ORIGINAL RESEARCH

Oral Nutritional Supplements and Body Composition Outcomes Among GLP-1 Receptor Agonist Users: Real-World Evidence

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Introduction: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are widely used for obesity and type 2 diabetes treatment, promoting glycemic management and substantial weight loss. However, rapid weight reduction may lead to loss of lean body mass (LBM), especially among malnourished or high-risk patients. Oral nutritional supplements (ONS), which provide protein and micronutrient support, may help preserve LBM and optimize weight-related outcomes during GLP-1RA therapy, but real-world evidence remains limited.

Research Design and Methods: We conducted a retrospective cohort study of 252 adult patients treated with GLP-1RAs for obesity and/or type 2 diabetes at an outpatient clinic from January 2018 to January 2025 who had complete data on body composition. Patients diagnosed with protein malnutrition were prescribed ONS. Coarsened Exact Matching (CEM) was used to balance age, sex, diabetes status and GLP-1RA exposure duration between ONS (n=88) and non-ONS (n=32) patients. Weight-related outcomes—body fat ratio, BMI, body fat, LBM, total body weight, and fat-to-LBM loss ratio—were assessed using difference-in-differences regression models. Subgroup analyses were conducted by age, sex, diabetes status, ONS compliance, and duration of GLP-1RA use.

Results: ONS use was associated with significantly greater reductions in BMI (−1.4 kg/m^2), body fat (−8.4 lbs), total weight (−10.1 lbs), and a 2-percentage-point decrease in body fat ratio (all $p<0.05$). While ONS users also lost 5.5 lbs of LBM ($p<0.01$), the fat-to-LBM loss ratio remained favorable (2.3, $p<0.01$). Subgroup analyses showed the strongest effects among patients younger than 50 years, ONS compliers, those treated with GLP-1RA for 181–365 days, and patients without diabetes (all $p<0.05$).

Conclusion: ONS use during GLP-1RA therapy was associated with improved weight loss outcomes and favorable shifts in body composition, particularly among subgroups at higher risk of muscle loss or prolonged treatment. Incorporating ONS into GLP-1RA–based weight management may enhance clinical outcomes while mitigating risks of muscle loss.

Keywords: GLP-1 receptor agonists, oral nutritional supplements, lean body mass, body composition, obesity, diabetes

Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have revolutionized the treatment of obesity and type 2 diabetes, demonstrating significant improvements in weight loss, glycemic management, and cardiometabolic outcomes.[1–3] Agents such as liraglutide, semaglutide, and tirzepatide are widely prescribed for chronic weight management and type 2 diabetes, and their effectiveness has been shown across clinical trials and real-world settings.[4,5] However, notable variation exists in patient responses, adherence, and the persistence of weight loss outcomes. Additionally, gastrointestinal adverse events (AEs)—including nausea, vomiting, diarrhea, constipation and gastroesophageal reflux—are common with GLP-1RA use and may impair nutritional intake or lead to early treatment discontinuation.[6,7]

Emerging evidence indicates that weight loss induced by GLP-1RAs, much like weight loss following metabolic and bariatric surgery (MBS), can be accompanied by clinically meaningful reductions in lean body mass, particularly among

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older adults and individuals with sarcopenia.[8] This parallel is biologically plausible, as both interventions induce rapid negative energy balance and substantial appetite suppression, conditions under which inadequate protein and micronutrient intake may exacerbate lean tissue loss.[9] These risks are especially relevant to patients with diabetes, who often face compounded nutritional challenges due to insulin resistance, low-grade chronic inflammation, and underlying metabolic dysfunction. Despite the central role of nutrition in diabetes care, relatively little attention has been given to dietary interventions that support nutritional adequacy during GLP-1RA treatment.[6]

Oral nutritional supplements (ONS), including protein-fortified beverages and micronutrient-enriched formulas, have been proposed as an adjunctive strategy to preserve lean mass, enhance adherence with GLP-1 RA use, and improve overall treatment response.[1,10] Recent studies have begun to characterize dietary intake among GLP-1RA users, revealing suboptimal consumption of key nutrients such as protein, iron, vitamin D and calcium.[6,11] Clinical guidelines increasingly call for proactive nutritional support to mitigate lean mass loss and support functional outcomes, yet no prior population-based study has evaluated whether ONS use enhances the effectiveness of GLP-1RA therapy for weight management.[12] Addressing this gap is critical, especially as these therapies expand in use across diverse populations.

This study examined the association between ONS and body composition outcomes among patients treated with GLP-1RAs at a large academic medical center in the West region of the United States. Using real-world data, we evaluated differences in weight loss and body composition between GLP-1RA users who did and did not use ONS. Findings from this study inform integrated clinical strategies to optimize pharmacologic weight loss therapy while safeguarding nutritional status and functional health in patients with or at risk for type 2 diabetes.

Methods

Study Design and Participants

This retrospective cohort study identified 920 adult patients treated with GLP-1RAs (liraglutide, semaglutide, and tirzepatide) for obesity or type 2 diabetes at a hospital-based outpatient clinic between January 1, 2018, and January 31, 2025. Of these, 252 patients with complete records, including baseline and follow-up measurements of body mass index (BMI) and body composition analysis, were included. Due to retrospective study design, data were extracted from electronic medical records of eligible patients and a waiver of informed consent was approved by the institutional review board. This study complies with the Declaration of Helsinki and was approved by the University of Southern California Institutional Review Board (#HS-24-00004).

ONS were prescribed for *daily* use to patients with a documented diagnosis of protein malnutrition. Protein malnutrition was diagnosed based on either the Global Leadership Initiative on Malnutrition (GLIM)[13] or the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition (AAIM) criteria.[14,15] These standardized frameworks consider both clinical presentation and underlying etiologies. According to the AAIM criteria, malnutrition is diagnosed when at least *two* of six indicators are present: (1) inadequate energy intake, (2) unintentional weight loss, (3) loss of muscle mass, (4) loss of subcutaneous fat, (5) fluid accumulation, or (6) diminished functional status (eg, impaired grip strength). Alternatively, the GLIM criteria require at least one phenotypic indicator (eg, low BMI, non-volitional weight loss, or reduced muscle mass) and one etiologic factor (eg, reduced intake or inflammation). Meeting the diagnostic threshold under *either* framework was sufficient for a clinical diagnosis of moderate protein malnutrition and supported the initiation of nutritional intervention.

The ONS recommended for patients without diabetes had a standardized formulation, providing approximately 150–180 kcal, 15–30 g of protein, and 1 g of sugar per serving (eg, Ensure® Max Protein). For patients with diabetes, ONS recommended were slow-release, low–glycemic index formulations (eg, Glucerna® Hunger Smart) to support more stable postprandial glucose control. At the initiation of GLP-1 therapy, all patients received low-calorie, high-protein, general or diabetes-specific ONS recommendation, regardless of baseline characteristics. Patients were advised to consume one to two servings daily, depending on whether individualized protein targets could be met through food intake alone. Daily protein targets were set at 1.0–1.2 g of protein per kilogram of body weight per day, inclusive of protein obtained from both food and ONS. The ONS was recommended primarily as a meal replacement to support protein adequacy during periods of reduced appetite, with flexibility to use it as a supplement when additional caloric or

protein support was needed. The ONS was not provided directly by the clinic but was recommended for over-the-counter purchase by patients. Importantly, ONS use was initiated concurrently with GLP-1 therapy to support nutritional adequacy during the early phase of pharmacologically induced weight loss.

As part of the comprehensive weight management program, all patients received ongoing nutrition and behavioral support. Registered dietitian nutritionist (RDN)–led dietary counseling was provided approximately every three months and included weight management counseling and, when applicable, diabetes self-management education and support (DSMES), consistent with Academy of Nutrition and Dietetics guidelines. RDN counseling also included education on resistance and weight training, using either resistance bands or circuit-based weight training with gym equipment. In addition, patients received Medical Nutrition Therapy (MNT) from a bariatric physician every three to six months as part of routine clinical care. Patients were also enrolled in the Lifestyle Redesign program at the academic medical center, a structured behavioral counseling intervention designed to promote sustainable dietary and lifestyle changes. Together, these components ensured that nutrition assessment, education, and behavioral support were integral elements of the weight management program.

Outcome Variables

We evaluated six body composition outcomes: (1) Body Fat Ratio, calculated as body fat (lbs) divided by total body weight (lbs); (2) BMI, calculated as weight (kg) divided by height squared (m^2); (3) total body fat (lbs); (4) lean body mass (LBM, lbs); (5) total body weight (lbs); and (6) fat-to-lean mass loss ratio, defined as body fat loss (lbs) divided by lean body mass loss (lbs). Given substantial biological differences in baseline muscle mass between sexes, we additionally express selected outcomes in percentage terms. To further account for sex-specific biological variation, we also report sex-standardized z-scores for total body fat, lean body mass, and total body weight. Body composition was measured at baseline and follow-up during routine office weigh-ins using bioimpedance analysis with the same device for all patients (InBody Model 570 Body Composition Analyzer).

Bioimpedance analysis (BIA) offers a practical, noninvasive method for assessing body composition in clinical and real-world settings. Compared with dual-energy X-ray absorptiometry (DXA), which is often considered a reference standard for body composition assessment, BIA is less accurate for estimating absolute fat and lean mass and is sensitive to hydration status and proprietary prediction equations.[16,17] However, multiple validation studies demonstrate that BIA performs reasonably well in tracking within-individual changes over time, particularly when the same device and standardized measurement conditions are used.[18,19] While DXA provides more precise absolute estimates, its cost, limited accessibility, and exposure to ionizing radiation make it less feasible for frequent repeated measurements. Given the longitudinal and observational nature of this study, the consistent use of a single BIA device supports reliable assessment of relative changes in fat and lean mass in routine clinical practice.

The primary explanatory variable was a binary indicator denoting whether the patient was recommended ONS during the period of GLP-1RA use. Additionally, we conducted stratified regression analyses to explore how ONS affected body compositions across different patient subgroups.

Statistical Analyses

To address potential selection bias—since only patients diagnosed with protein malnutrition were prescribed ONS—we used Coarsened Exact Matching (CEM).[20] Patients receiving ONS may differ systematically from non-ONS users, as they are often sicker or more prone to weight loss due to underlying conditions. CEM was applied to construct a comparable non-ONS control group by matching patients on key characteristics, thereby enhancing the balance of observable variables and ensuring that ONS status is the primary difference between the groups.

The CEM improves the study design by enhancing covariate balance and reducing model dependence compared to conventional matching methods like Propensity Score Matching (PSM). By matching units exactly within coarsened strata of covariates, CEM ensures better pre-processing of the data, thereby reducing the risk of post-matching imbalance and minimizing reliance on complex model specifications. This makes CEM more transparent, robust, and computationally efficient.[20,21]

Matching was based on age, gender, duration of GLP-1RA exposure and diabetes status. We then employed a difference-in-differences (DiD) approach, following Angrist and Pischke (2008),[22] to estimate the association between ONS and weight outcomes among GLP-1RA users by comparing changes in outcomes before and after ONS use between matched ONS and non-ONS groups.

The DiD approach was well-suited for this analysis because it helped control for unobserved, time-invariant differences between the ONS and non-ONS groups that could have biased the estimated effect of ONS on weight outcomes. While matching ensured that the two groups were similar on observable characteristics (eg, age, gender, diabetes status, and GLP-1RA exposure), unobserved differences—such as baseline health behaviors or metabolic profiles—could still have remained. The DiD method addressed this by examining how weight outcomes changed over time within each group and then comparing those changes between groups. This controlled for shared time trends and better identified the association between ONS and body composition outcomes.[23]

T-tests were conducted to assess the significance of variables, with a p-value of <0.05 considered statistically significant. All statistical analyses were performed using STATA version 16.

Results

Patient Baseline Characteristics

Table 1 presents summary statistics for the unmatched sample. ONS patients differed significantly from non-ONS patients across several characteristics: they were younger (54.7 vs. 59.0 years, $p = 0.009$), more likely to be female (84% vs. 59%, $p < 0.001$), and less likely to have diabetes (26% vs. 56%, $p < 0.001$). They also had shorter exposure to GLP-1RA therapy (684.7 vs. 875.8 days, $p = 0.002$), lower baseline lean body mass (115.0 vs. 127.7 lbs, $p = 0.002$), and lower baseline body weight (204.6 vs. 222.0 lbs, $p = 0.04$). Before matching, patients receiving ONS were more nutritionally compromised at baseline, as ONS was prescribed exclusively to individuals diagnosed with protein malnutrition.

Table 2 shows the characteristics of the matched sample, comprising 88 ONS patients and 32 non-ONS patients. Following CEM, no statistically significant differences were observed between the groups in age, gender, duration of GLP-1RA use, diabetes status, or baseline weight-related measures (all $p > 0.05$), indicating a well-balanced analytic sample. Although matching was conducted on age, gender, duration of GLP-1RA use, and diabetes status only, balance was also achieved for baseline weight-related measures. Notably, the matched population was at elevated risk for diabetes—with an average BMI of 33—or had already been diagnosed with the condition.

Weight Change

Table 3 presents the effects of ONS on absolute weight outcomes, with corresponding percentage changes in parentheses. Among ONS patients, the body fat ratio decreased by 2 percentage points (or 5.5% reduction from the baseline, both $p<0.01$), while no significant change was observed among non-ONS patients—indicating a net 2 percentage points reduction associated with ONS. Difference between the change in weight outcomes for ONS and non-ONS patients are

Table 1 Characteristics of Unmatched Sample by ONS

Variables	ONS Patients (n=182)	Non-ONS Patients (n=70)	*P-value*
Age, mean ± SD	54.7 ± 10.9	59.0 ± 13.8	0.009
Female, n (%)	153 (84%)	41 (59%)	<0.001
Days of GLP-1RA Exposure, mean ± SD	684.7 ± 409.1	875.8 ± 524.0	0.002
Diabetes, n (%)	47 (26%)	39 (56%)	<0.001
Baseline BMI, mean ± SD	33.7 ± 6.2	34.6 ± 7.4	0.35
Baseline Body Fat (lbs), mean ± SD	89.6 ± 31.2	92.3 ± 39.0	0.57
Baseline Lean Body Mass (lbs), mean ± SD	115.0 ± 26.1	127.7 ± 33.5	0.002
Baseline Body Weight (lbs), mean ± SD	204.6 ± 49.6	220.0 ± 61.8	0.04

Notes: The table presented unweighted averages and *t* test results for ONS and non-ONS patients.
Abbreviations: SD, Standard Deviation; ONS, Oral Nutritional Supplements; BMI, Body Mass Index.

Table 2 Characteristics of Matched Sample by ONS

Variables	ONS Patients (n=88)	Non-ONS Patients (n=32)	*P-value*
Age, mean ± SD	55.5 ± 8.5	55.2 ± 8.6	0.89
Female, n (%)	78 (89%)	28 (89%)	1.00
Days of GLP-1 Exposure, mean ± SD	688.5 ± 349.8	661.5 ± 381.8	0.72
Diabetes, n (%)	20 (23%)	7 (23%)	1.00
Baseline BMI, mean ± SD	33.4 ± 6.0	33.6 ± 8.1	0.87
Baseline Body Fat (lbs), mean ± SD	88.8 ± 30.3	91.1 ± 43.7	0.75
Baseline Lean Body Mass (lbs), mean ± SD	113.4 ± 24.8	116.7 ± 25.4	0.53
Baseline Body Weight (lbs), mean ± SD	202.3 ± 47.5	207.8 ± 60.1	0.60

Notes: The table presented *weighted* averages and *t* test results for ONS and non-ONS patients.
Abbreviations: SD, Standard Deviation; ONS, Oral Nutritional Supplements; GLP-1RA, Glucagon-like Peptide-1 Receptor Agonist; BMI, Body Mass Index.

shown in the Diff. row. Compared to non-ONS patients, those receiving ONS also experienced significantly greater reductions in BMI (−1.4 kg/m^2), body fat (−8.4 lbs), and total body weight (−10.1 lbs), all statistically significant at the $p<0.05$ level. In percentage terms, ONS use was associated with a 4.5% greater decline in BMI, 7.6% more fat loss, and a 4.6% larger reduction in total weight. Consistent with these findings, ONS use was also associated with significantly larger decreases in sex-standardized z-scores for body fat (−0.25, $p < 0.01$) and total body weight (−0.21, $p < 0.01$). Notably, ONS patients had a fat-to-LBM loss ratio of 2.2, whereas non-ONS patients had a ratio of –0.1, indicating a markedly more favorable body composition change among ONS users.

Subsample Analysis

Table 4 presents subgroup analyses of the impact of ONS on absolute weight outcomes, with percentage changes shown in parentheses. Among patients under age 50, ONS use was associated with a 3.0 fat to LBM loss ratio and a 3 percentage-point reduction in body fat ratio, while no significant associations were observed in those aged 50 and older. Among older adults, body fat decreased by 7.8 lbs (−6.4%; $p < 0.05$), but no significant changes were seen in overall weight—suggesting that ONS may be more effective at improving body composition in younger individuals.

ONS was associated with significant improvements in the fat-to-LBM loss ratio (2.5, $p<0.05$) and reductions in BMI (−2.1, $p<0.05$). In contrast, among patients with prediabetes or diabetes, ONS use was not associated with significant changes in either outcome. Notably, all patients with diabetes in the sample had type 2 diabetes.

Women receiving ONS experienced significant reductions in BMI (−1.4 kg/m^2, −4.6%; $p<0.05$) and body fat (−9 lbs, −8.1%; $p<0.01$), along with a favorable fat-to-LBM loss ratio (3.2; $p<0.05$), compared with women not receiving ONS. In contrast, ONS was not significantly associated with weight outcomes among male patients.

The associations between ONS and body composition outcomes varied by the duration of GLP-1RA therapy. Among patients treated for 181–365 days, ONS use was associated with a favorable fat-to-LBM loss ratio (2.4), a significant reduction in BMI (−1.8 kg/m^2, −5.4%; $p<0.01$), and a decrease in body weight (−14.5 lbs, −7.2%; $p<0.05$). No significant benefits were observed in patients with <181 days of GLP-1RA use. Among those treated for >1 year, ONS was associated with reduced body fat, but other weight-related outcomes did not differ between ONS users and non-users.

Finally, the association between ONS and the outcomes was stronger among participants with higher compliance, defined as consuming ONS at least four days per week. Compliant users achieved significantly greater reductions in body fat (−10.2 vs. −6.4 lbs; *z* scores: −0.31 vs −0.19) and body weight (−14.3 vs. −5.6 lbs; *z* scores: −0.30 vs. −0.12) compared to non-compliers. Although ONS use was associated with a favorable fat-to-LBM loss ratio among non-compliers (3.4; $p<0.05$), this ratio did not differ significantly between compliers and non-compliers.

Discussion

This study found that ONS use was associated with a 2.5-point improvement in the fat-to-LBM loss ratio. Compared to non-ONS patients, those receiving ONS also experienced significantly greater reductions in BMI (−1.4 kg/m^2), body fat (−8.4 lbs,

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Table 3 The Impact of ONS on Weight Outcomes

Variables	Body Fat Ratio Reduction	BMI Reduction (kg/m^2)	Body Fat Reduction (lbs)	Body Fat *Z* Score Reduction	Lean Body Mass (LBM) Reduction (lbs)	LBM *Z* Score Reduction	Weight Reduction (lbs)	Weight *Z* Score Reduction	Fat to LBM Loss Ratio
ONS Patients (n=88)	−0.02*** (−5.5%***)	−2.4*** (−6.8%***)	−12.3*** (−13.5%***)	−0.37***	−5.5*** (−4.7%***)	−0.27**	−17.8*** (−8.7%***)	−0.37***	2.3***
Non-ONS Patients (n=32)	−0.005 (−2.1%)	−0.95 (−2.4%)	−3.9** (−6.0%***)	−0.12**	−3.7 (−3.2%)	−0.19	−7.6** (−4.0%**)	−0.16	−0.1
Diff.	−0.02 (−3.4%)	−1.4** (−4.5%***)	−8.4*** (−7.6%**)	−0.25***	−1.7 (−1.5%)	−0.08	−10.1** (−4.6%)	−0.21**	2.5**

Notes: ** p<0.05, *** p<0.01. The percentage changes are in parentheses.
Abbreviations: ONS, Oral Nutritional Supplements; BMI, Body Mass Index; Diff, Difference.

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Table 4 Subsample Analysis - The Impact of ONS on Weight Outcomes

Variables	Body Fat Ratio Reduction	BMI Reduction (kg/m^2)	Body Fat Reduction (lbs)	Body Fat *Z* Score Reduction	LBM Reduction (lbs)	LBM *Z* Score Reduction	Weight Reduction (lbs)	Weight *Z* Score Reduction	Fat to LBM Loss Ratio
Age<50 (n=28)	−0.03*** (−6.8%**)	−0.08 (−1.4%)	−9.3 (−10.5%**)	−0.28	−1.1 (−0.7%)	−0.04	−10.4 (−5.3%**)	−0.22	2.98**
Age≥50 (n=92)	−0.01 (−2.2%)	−1.7** (−5.1%***)	−7.8** (−6.4%)	−0.23**	−2.0 (−1.8%)	−0.10	−9.8 (−4.3%)	−0.20	2.33
No diabetes (n=32)	−0.02 (−2.8%)	−2.1** (−6.5%***)	−6.6 (−5.0%)	−0.19	−0.4 (−0.6%)	−0.02	−7.0 (−3.0%)	−0.15	2.5**
Prediabetes (n=59)	−0.02 (−3.6%)	−1.1 (−3.8%)	−7.5 (−6.1%)	−0.23	−1.1 (−1.0%)	−0.05	−8.6 (−3.6%)	−0.18	1.7
Diabetes (n=29)	−0.03 (−3.8%)	−1.4 (−3.7%)	−12.3** (−13.6%**)	−0.37**	−4.8 (−3.8%)	−0.23	−17.1 (−8.9%)	−0.36	4.1
Male (n=19)	−0.01 (−1.1%)	−1.5 (−3.6%)	−4.0 (−3.5%)	−0.13	−4.1 (−1.7%)	−0.17	−8.1 (−2.6%)	−0.17	−3.0
Female (n=101)	−0.02 (−3.7%)	−1.4** (−4.6%**)	−9.0*** (−8.1%**)	−0.27***	−1.4 (−1.5%)	−0.07	−10.4 (−4.9%)	−0.22	3.2**
Days on GLP-1RA ≤180 (n=8)_	−0.03 (−3.4%)	−0.8 (−1.8%)	−7.2 (−2.0%)	−0.21	7.3 (5.8%)	0.37	0.1 (1.3%)	0.002	4.9
Days on GLP-1RA 181–365 (n=19)	−0.01 (−1.0%)	−1.8*** (−5.4%***)	−8.5 (−8.1%)	−0.25	−6.0*** (−5.1%***)	−0.29***	−14.5*** (−7.2%***)	−0.31***	2.4**
Days on GLP-1RA >365 (n=93)	−0.02 (−5.2%)	−1.4 (−4.7%**)	−8.9** (−9.6%**)	−0.26**	−3.2 (−2.8%)	−0.16	−12.1 (−6.0%**)	−0.25	2.5
ONS non-compliers (n=74)	−0.03 (−5.3%**)	−1.5 (−5.0%**)	−6.4 (−6.7%)	−0.19	0.8 (0.7%)	0.05	−5.6 (−2.9%)	−0.12	3.4**
ONS compliers (n=46)	−0.01 (−1.7%)	−1.3 (−4.0%**)	−10.2*** (−8.3%**)	−0.31***	−4.1 (−3.6%)	−0.20	−14.3** (−6.3%**)	−0.30**	1.6

Notes: ** p<0.05, *** p<0.01. The percentage changes are in parentheses.

Abbreviations: ONS, Oral Nutritional Supplements; BMI, Body Mass Index; LBM, Lean Body Mass; GLP-1RA, Glucagon-like Peptide-1 Receptor Agonist.

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7.6%, −0.37 z-scores), and total body weight (−10.1 lbs, −4.6%, −0.21 z-scores). These results suggest that ONS is associated with improved weight-related outcomes in patients treated with GLP-1RA. The findings align with prior evidence that high-protein ONS promote preferential fat loss while preserving lean mass during caloric restriction.[24,25] Protein-enriched ONS have been shown to enhance satiety, improve metabolic efficiency, and stimulate muscle protein synthesis, thereby contributing to improved body composition and more favorable fat-to-lean mass loss ratios.[26,27]

Our analysis revealed that among patients under 50, ONS was associated with a 3.0-point improvement in the fat-to-LBM loss ratio compared to non-ONS patients, whereas no significant associations were observed among those aged 50 and older. This suggests that ONS may be more effective at improving body composition in younger adults. Several mechanisms may explain this age-related differential effect. Younger individuals generally exhibit greater anabolic capacity, more efficient muscle protein synthesis, and stronger hormonal support (eg, higher growth hormone and IGF-1 levels), which enhance responsiveness to protein supplementation.[28] In contrast, older adults often experience anabolic resistance and reduced physical activity, which may attenuate the benefits of ONS unless paired with structured resistance training or higher protein intake. These findings highlight the need for age-specific nutritional strategies and underscore the importance of tailoring ONS interventions to maximize efficacy across different populations.

Exploratory sex-stratified analyses suggested that the association between ONS use and body composition outcomes may differ by sex. Among female patients, ONS use was associated with larger reductions in BMI (−1.4 kg/m^2; −4.6%), greater losses in body fat (−9 lbs; −8.1%; −0.27 *z* scores), and improvements in the fat-to–lean body mass (LBM) loss ratio (3.2) compared with female non-ONS users. In contrast, corresponding estimates among male patients were smaller and not statistically significant. However, these sex-stratified analyses were limited by small sample sizes—particularly among males (n = 19)—and the absence of formal interaction testing between ONS use and sex. As a result, the lack of statistically significant findings in men should not be interpreted as evidence of no benefit, and conclusions regarding sex-specific effectiveness should be viewed as hypothesis-generating rather than definitive.

ONS use was associated with greater lean mass preservation in patients without diabetes relative to those with prediabetes or type 2 diabetes. This likely reflects metabolic impairments in dysglycemia, including insulin resistance, chronic inflammation, and reduced muscle protein synthesis, which blunt the anabolic response to protein supplementation.[29] Patients with diabetes are more likely to have anabolic resistance, and the use of low–glycemic index ONS—while appropriate for glycemic management—may limit insulin-mediated anabolic signaling needed for lean mass preservation. In contrast, individuals without diabetes maintain stronger insulin signaling and anabolic capacity, allowing them to derive greater benefit from ONS. These findings suggest that ONS may be most effective in populations without serum evidence of insulin resistance and highlight the need for tailored nutritional strategies—such as higher protein dosing or combined resistance training—to optimize lean mass preservation in patients with diabetes.[30,31]

Our findings demonstrated that the effectiveness of ONS was strongly associated with patient compliance. Patients who consistently consumed ONS—defined as at least four days per week—experienced significantly greater reductions in both body fat (−10.2 vs. −6.4 lbs; *z* scores: −0.31 vs −0.19) and total body weight (−14.3 vs. −5.6 lbs; *z* scores: −0.30 vs. −0.12) compared to non-compliant users. This dose–response relationship underscores the importance of adherence in realizing the full therapeutic benefits of ONS. Prior studies have similarly shown that consistent intake of high-protein supplements enhances satiety, improves metabolic efficiency, and supports muscle protein synthesis during energy restriction.[24,25] The lack of significant improvements among non-compliers suggests that sporadic or insufficient intake may not be adequate to offset the muscle loss risk associated with rapid weight reduction or protein malnutrition. These findings highlight the need for structured counseling and monitoring to support adherence, particularly in high-risk populations.

The association between ONS and the outcomes varied by duration of GLP-1RA treatment. Among patients on therapy for 181–365 days, ONS was associated with improved the fat-to-LBM loss ratio (+2.4), reduced BMI (−1.8 kg/m^2, −5.4%), decreased LBM (−6 lbs, −5.1%), and lowered body weight (−14.5 lbs, −7.2%, −0.31 *z* scores). No significant associations were observed among patients treated for <181 days, while in those on therapy for >1 year, ONS was associated with lower body fat (−8.9 lbs, −9.6%, −0.26 *z* scores) but was not related to other outcomes. These findings suggest that ONS is most beneficial during the intermediate phase of GLP-1RA therapy, when weight loss plateaus and muscle preservation is critical. In contrast, early treatment effects of GLP-1RA may mask ONS benefits, and

longer-term use may involve metabolic adaptations that limit responsiveness. This highlights the need for time-sensitive nutritional strategies to optimize weight management and body composition.

These findings emphasize the importance of proactively addressing lean mass loss in patients undergoing GLP-1RA therapy. Because prolonged treatment is associated with sustained appetite suppression and potential protein deficits,[31,32] clinicians could consider introducing high-protein ONS early in the course of therapy to mitigate muscle loss and optimize body composition. Particular attention should be given to subgroups most likely to benefit, including younger adults, and patients without diabetes, as well as those on extended GLP-1RA regimens. Tailoring ONS use to individual patient characteristics—such as age, comorbidity status, and treatment duration—may enhance weight management outcomes, reduce functional decline, and lower the risk of weight regain.[33,34]

Despite the strengths of this study, several methodological limitations associated with non-randomized designs warrant consideration. The retrospective cohort design is subject to residual confounding, including unmeasured differences in physical activity and dietary intake, despite matching and subgroup analyses. Importantly, ONS prescribing was based on clinical assessment of protein malnutrition, which was available at baseline but not captured over time; therefore, matching on observed characteristics (eg, age, sex, BMI, and body composition) may not fully balance baseline nutritional status between the ONS and non-ONS groups. This creates potential confounding by indication, where the reason for receiving ONS is itself related to subsequent changes in lean and fat mass. Accordingly, these findings should be understood as descriptive comparisons between two clinically distinct groups, not as evidence of a causal treatment effect. Although ONS use was associated with changes in lean body mass, reductions in muscle mass do not necessarily imply declines in muscle strength or physical function. Evidence on functional impairment in individuals with metabolic dysfunction remains mixed, and the functional implications of muscle loss may be context dependent.[35,36] Some studies suggest that GLP-1 RAs–associated muscle loss may not result in clinically meaningful functional impairment, particularly with adequate nutritional support and resistance training.[37] However, because functional outcomes were not measured in this study, we cannot directly assess these implications. ONS adherence was self-reported and may be affected by recall bias. Finally, although our sample included adults aged 34–80 years, with GLP-1RAs also being utilized among children and adolescents, concerns among younger populations regarding lean mass preservation and nutritional adequacy merit attention.[38,39] Future studies incorporating dietary assessment, functional outcomes, and younger populations are needed to better characterize short and long-term implications across the life span.

Conclusion

Our findings suggest that targeted nutritional support may help preserve lean mass during weight loss in patients receiving GLP-1RA therapy. ONS use was associated with improved lean body mass preservation, with relatively greater benefits among younger adults, individuals without diabetes, those with longer durations of GLP-1RA use, and patients with higher adherence. Because GLP-1RAs can suppress appetite and make it challenging to meet protein needs, early use of high-protein ONS may support muscle preservation and healthier body composition. While observed findings in the study cohort may reflect differences in baseline nutritional status, aligning ONS use with individual protein goals, tracking adherence, and incorporating complementary strategies such as resistance training may help optimize long-term weight management outcomes.

Data Sharing Statement

Data will be made available on reasonable request by contacting the lead author (Kurt Hong; kurthong@med.usc.edu).

Author Contributions

K Hong, S Sulo, K Kerr, D Williams: Conceptualization, Methodology. W Wang, M Kim, L Hong: Data curation. W Wang, L Fan: Formal analysis, Writing – Original draft. K Hong, S Sulo, K Kerr, W Wang, M Kim, L Hong, D Williams: Writing – Review and editing. K Hong: Funding acquisition, Supervision. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

S Sulo, KW Kerr, DR Williams are employees and stockholders of Abbott Laboratories. The authors have no other conflicts of interest to declare.

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