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Glucagon-like Peptide-1 Receptor Agonists in the Real World: Are Clinical Trials Reproducible? A Spanish Pilot Study

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Abstract

Introduction: Obesity is a chronic, multifactorial disease associated with significant metabolic and cardiovascular complications. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as effective pharmacological options for weight management, demonstrating clinically relevant weight loss in controlled trials. However, real-world evidence is essential to assess their effectiveness and safety under routine clinical conditions and to verify if trial results are reproducible in diverse populations. **Objective**: We aimed to evaluate the effectiveness and safety of GLP-1RAs in terms of weight loss in real-world clinical practice and to compare outcomes among different available agents, focusing on their impact on obesity management. **Method**: A cross-sectional, observational pilot study was conducted in Spain. Adult patients receiving GLP-1RAs for at least four weeks were included. Data collected included sociodemographic variables, treatment characteristics, anthropometric measurements, and adverse effects. Weight loss outcomes were analyzed using descriptive statistics, ANOVA for inter-drug comparisons, and multivariate ANCOVA to adjust for confounders. This pilot study also validated the protocol for a subsequent nationwide multicenter study. **Results**: A total of 32 patients (62.5% women; mean age 58.2 years) were analyzed. Mean weight loss was 2.97 kg (3.17%). Significant differences between drugs were observed ($p = 0.005$), with semaglutide 2.4 mg (Wegovy®) showing the greatest weight reduction (11.0 kg). Patients without diabetes achieved significantly greater weight loss than those with diabetes (5.0 vs. 0.8 kg; $p = 0.021$). Treatments were well tolerated, with 53.1% reporting no adverse effects; most side effects were mild gastrointestinal symptoms. **Conclusions:** GLP-1RAs are effective and well-tolerated for obesity treatment in real-world clinical practice, although weight loss is more modest than in pivotal clinical trials. Differences between agents were observed after multivariate adjustment, although these findings should be interpreted cautiously given the exploratory pilot design and limited sample size. These findings support the need for individualized treatment strategies in obesity care. This pilot study successfully validated the methodology for an ongoing nationwide investigation.

Keywords: GLP-1 receptor agonists; real-world evidence; obesity management; semaglutide; weight loss; type 2 diabetes; medication safety

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1. Introduction

Obesity is a chronic, multifactorial, and relapsing disease characterized by a sustained disruption of energy balance and adaptive neuroendocrine mechanisms that promote

weight regain following weight loss. Its global prevalence continues to rise, serving as a primary driver of type 2 diabetes mellitus (T2D), atherosclerotic cardiovascular disease, metabolic liver disease, and various types of cancer. Beyond excessive adiposity, obesity involves adipose tissue dysfunction, insulin resistance, low-grade chronic inflammation, and alterations in hormonal signaling that perpetuate the obesogenic state [1,2].

From a pathophysiological perspective, body weight regulation depends on a complex interaction between peripheral signals (hormonal and metabolic) and central hypothalamic circuits involved in energy homeostasis. Among the key intestinal hormones, glucagon-like peptide-1 (GLP-1) stands out as an incretin secreted by L-cells in the distal intestine in response to nutrient intake. GLP-1 exerts pleiotropic effects: it stimulates glucose-dependent insulin secretion, inhibits glucagon secretion, delays gastric emptying, and acts on the central nervous system to promote satiety and reduce caloric intake.

The development of GLP-1 receptor agonists resistant to degradation by dipeptidyl peptidase-4 (DPP-4) represented an initial therapeutic breakthrough in the management of type 2 diabetes. Subsequently, accumulating evidence demonstrated that their effect on weight reduction was clinically significant and partially independent of glycemic control. Controlled clinical trials have shown substantial weight loss, particularly with molecules characterized by weekly administration and higher receptor affinity [3,4].

In recent years, pharmacological innovation has evolved toward higher-potency compounds and dual or multi-receptor agonists that combine GLP-1 receptor activation with other hormonal axes, such as the glucose-dependent insulinotropic polypeptide (GIP) receptor. This approach aims to enhance weight loss through synergistic effects on appetite control, energy expenditure, and insulin sensitivity. Pivotal trials for these molecules have demonstrated weight reductions that, in certain patient profiles, approach the outcomes achieved through bariatric surgery [5].

However, data from clinical trials, while methodologically robust, are generated under highly controlled conditions with strict inclusion criteria, intensive monitoring, and standardized titration protocols. In real-world clinical practice, effectiveness may be modulated by factors such as therapeutic adherence, gastrointestinal tolerability, variability in dose titration, treatment duration, and the patient's demographic and metabolic characteristics.

Real-world clinical practice allows for the identification of off-label use patterns or deviations from utilization protocols—factors that are particularly critical in this pharmacological class. Furthermore, the frequency of private prescriptions complicates the follow-up of ambulatory patients. Community pharmacies represent an ideal setting due to their accessibility, distribution, and the expertise of pharmacists. They complement the safety and efficacy data obtained from other levels of care, particularly through multicenter projects such as those conducted by sentinel pharmacy networks [6–9].

The weight-loss response to GLP-1 analogues exhibits marked inter-individual variability, suggesting the influence of biological, behavioral, and pharmacodynamic determinants. Variables such as age, sex, duration of treatment exposure, or baseline obesity levels may act as effect modifiers.

Moreover, the safety profile of these drugs, particularly regarding gastrointestinal symptoms (nausea, vomiting, diarrhea, constipation), is a key determinant of therapeutic persistence. These effects relate to the physiological mechanism of GLP-1 on gastric emptying and central satiety signaling; they are typically dose-dependent and transient. Characterizing their frequency in real-world conditions is essential to assessing overall tolerability.

In the current context, marked by the rapid expansion of GLP-1 analogue use for both diabetes and obesity, there is a pressing need to generate evidence in real-world clinical settings to:

1. Quantify the magnitude of absolute and relative weight loss;
2. Compare the effectiveness between different available molecules;
3. Evaluate whether observed differences persist after adjusting for demographic and clinical variables;
4. Describe the tolerability profile under non-experimental conditions.

This pilot study serves as the preliminary phase of a larger-scale national research project, currently underway across community pharmacies in Andalusia, Bizkaia, Araba, Palencia, and Santa Cruz de Tenerife. It is designed as an exploratory approach within routine clinical practice, aiming to provide preliminary data that complement evidence from clinical trials and contribute to more individualized therapeutic decision-making in the pharmacological management of obesity.

2. Materials and Methods

2.1. Study Design

A cross-sectional, analytical, observational study was conducted in routine clinical practice as a pilot phase in two community pharmacies (Valladolid and Bilbao). The objective was to evaluate weight loss associated with GLP-1 receptor agonist therapy and to compare effectiveness and safety across the different available molecules. This initial stage served to validate the data collection protocol and recruitment feasibility, establishing the foundation for a subsequent national multicenter study currently underway in five Spanish regions.

2.2. Study Population

The study included adult patients on active treatment with a GLP-1 receptor agonist.

- Inclusion Criteria: Age $\geq$ 18 years and current treatment with a GLP-1 analogue (minimum of 4 weeks of treatment to ensure adequate exposure).
- Exclusion Criteria: Pregnancy or breastfeeding; concomitant use of other specific anti-obesity medications; bariatric surgery within the previous 12 months; previous completion of the study questionnaire; refusal to participate; discontinuation of treatment prior to evaluation; or incomplete anthropometric data.

The final analytical sample consisted of patients with complete data for both self-reported baseline weight and current measured weight. Baseline weight was obtained through patient recall (referring to the start of treatment) and validated via clinical records or personal monitoring devices when available. Current weight was measured by the pharmacist using standardized scales during the evaluation.

2.3. Variables Collected

- Sociodemographic and Clinical Variables: Age (years), sex, comorbidities, current and previous GLP-1 analogue treatments, duration of treatment (predefined categories), dose titration, lifestyle habits, medical specialty of the prescriber, type of prescription (public/private), and presence of adverse drug reactions.
- Anthropometric Variables: Baseline weight (kg), current weight (kg), height (cm), and waist and hip circumference.
- Derived Variables: Absolute weight loss (kg), percentage weight change (%), and body mass index (BMI).

2.4. Data Collection Procedure

Data was collected via a structured online questionnaire administered through Microsoft Forms (Microsoft Corporation, Redmond, WA, USA; https://forms.office.com;

accessed 27 May 2026) at the time of medication dispensing. Current weight was recorded by the pharmacist at the moment of evaluation.

Anthropometric measurements were collected following routine standardized procedures in participating community pharmacies. Current body weight was measured using calibrated pharmacy scales, with patients wearing light clothing and no shoes whenever feasible. Waist and hip circumferences were obtained according to standard clinical practice procedures. To improve consistency across sites, pharmacists used a structured data collection form and predefined adverse-event categories during patient interviews. Adverse drug reactions were recorded based on patient self-report at the time of dispensing and classified according to the predominant reported symptom.

2.5. Statistical Analysis

- Descriptive Analysis: Quantitative variables were expressed as mean and standard deviation (SD). 95% confidence intervals (95% CI) were calculated using Student's t-distribution. Qualitative variables were expressed as absolute frequencies and percentages, with 95% CIs calculated using the Wilson score method.
- Inter-drug Comparison: To evaluate differences in absolute weight loss among GLP-1 analogues, a one-way analysis of variance (ANOVA) was used. The effect size was calculated using eta squared (η^2). If global differences were identified, post hoc comparisons were performed using Tukey's HSD test.
- Multivariate Analysis: A general linear model (ANCOVA) was constructed with weight loss (kg) as the dependent variable. Independent variables included: type of treatment, age, sex, presence of diabetes mellitus, and treatment duration. Statistical significance and the persistence of the treatment effect after adjusting for confounders were evaluated.
- Significance Level: A p-value < 0.05 was considered statistically significant.

Prior to inferential analyses, model assumptions were evaluated. Normality of residuals was assessed through visual inspection of Q–Q plots and the Shapiro–Wilk test, while homogeneity of variances was evaluated using Levene's test. Given the exploratory pilot nature of the study and the limited sample size, inferential results were interpreted alongside effect sizes and confidence intervals.

Handling of missing data was performed using complete-case analysis. Patients with incomplete anthropometric information required for the calculation of weight loss outcomes were excluded from inferential analyses. No imputation procedures were applied due to the pilot design and small sample size.

Subgroup analyses by treatment type were considered exploratory and hypothesis-generating, particularly for treatment groups with small sample sizes. Therefore, post hoc comparisons should be interpreted with caution.

Statistical analyses were performed using Stata Statistical Software (Release 19; StataCorp LLC, College Station, TX, USA).

2.6. Ethical Considerations

The study protocol was reviewed and approved by the Basque Country Ethics Committee for Clinical Research (CEIm de Euskadi). Approval Code: EOM2025059 (CEIm). The study was conducted in accordance with the principles of the Declaration of Helsinki and current data protection regulations. All patients provided voluntary informed consent. Given the observational and non-interventional nature of the study, routine clinical practice remained unaltered.

3. Results

3.1. Population Characteristics

The pilot study analyzed a total of 32 patients (62.5% women, mean age 58.22 ± 11.48 years). The mean baseline weight was 95.29 ± 20.07 kg (Table 1). Regarding pharmacological distribution, Ozempic® (28.1%) and Mounjaro® (21.9%) were the most frequent treatments. Treatment duration was varied, with the largest proportion of patients (34.4%) having been on therapy for 3 to 6 months (Table 2). Notably, 33.3% of patients using Ozempic® or Rybelsus® were non-diabetic, suggesting weight management as a primary clinical goal; this is supported by an observed mean weight loss of 2.97 kg across the group (Table 3).

Table 1. Quantitative variables.

Variable	*N*	Mean	SD	95% CI
Age (years)	32	58.22	11.48	54.08–62.36
Baseline weight (kg)	31	95.29	20.07	87.93–102.65
Current weight (kg)	32	92.41	20.09	85.16–99.65
Weight loss (kg)	31	2.97	5.15	1.08–4.86

SD: Standard Deviation; CI: Confidence Interval.

Table 2. Qualitative variables.

Variable	Category	*N*	%	95% CI
Sex	Female	20	62.5	45.3–77.1
Sex	Male	12	37.5	22.9–54.7
Treatment	Ozempic®	9	28.1	85.16–99.65
Treatment	Mounjaro®	7	21.9	11.0–38.8
Treatment	Rybelsus®	6	18.8	8.9–35.3
Treatment	Trulicity®	6	18.8	8.9–35.3
Treatment	Wegovy®	4	12.5	5.0–28.1
Treatment duration	Between 3 and 6 months	11	34.4	20.4–51.7
Treatment duration	More than one year	10	31.2	18.0–48.6
Treatment duration	Between 6 months and 1 year	6	18.8	8.9–35.3
Treatment duration	Three months or less	3	9.4	3.2–24.2
Treatment duration	Baseline/Start	2	6.2	1.7–20.1

CI: Confidence Interval.

Table 3. Patients without diabetes treated with Ozempic® and Rybelsus®.

Drug	Total *n*	Without Diabetes (*n*)	% Without Diabetes	95% CI
Ozempic®	9	3	33.3	12.1–64.6
Rybelsus®	6	2	33.3	9.7–70.0

CI: Confidence Interval.

Regarding safety, the treatments were generally well-tolerated, as 53.1% of patients reported no digestive reactions (95% CI: 36.4–69.1). Among those who experienced side effects, dry mouth (12.5%) and abdominal pain (9.4%) were the most frequent. Other gastrointestinal symptoms, such as nausea, vomiting, and constipation, were rare, each affecting only 3.1% of the sample (Table 4).

Table 4. Digestive adverse reactions.

Adverse Reaction	*N*	%	95% CI
None	17	53.1	5.0–28.1
Dry mouth	4	12.5	9.7–70.0
Abdominal pain	3	9.4	3.2–24.2
Abdominal pain + diarrhea	2	6.2	1.7–20.1
Others	2	6.2	1.7–20.1
Nausea and vomiting	1	3.1	0.6–15.7
Nausea + vomiting + diarrhea	1	3.1	0.6–15.7
Diarrhea	1	3.1	0.6–15.7
Constipation	1	3.1	0.6–15.7

CI: Confidence Interval.

3.2. Weight Loss Analysis

In the 31 patients with complete anthropometric records, the mean weight loss was 2.97 kg (SD 5.15; 95% CI: 1.08–4.86), representing a mean percentage weight change of 3.17% (SD 5.69; 95% CI: 1.09–5.26) (Table 5).

Table 5. Statistical analysis: weight loss outcomes.

Variable	Mean	SD	95% CI
Weight loss (kg)	2.97	5.15	1.08–4.86
Percentage change (%)	3.17	5.69	1.09–5.26

SD: Standard Deviation; CI: Confidence Interval.

One-way ANOVA revealed significant global differences in absolute weight loss between the different drugs ($F = 4.78$, $p = 0.0050$). The observed effect size was large ($\eta^2 = 0.424$; Cohen's $f = 0.857$), providing a post hoc statistical power of 95.4%.

Exploratory comparison between treatments: Patients treated with Wegovy® achieved the highest mean weight loss (11.00 ± 10.17 kg; 12.27%), followed by Mounjaro® (3.71 ± 3.45 kg; 3.81%) (Table 6).

Table 6. Comparison by drug.

Drug	*N*	Mean Weight Loss (kg)	SD (kg)	Mean%	Change SD%
Mounjaro®	7	3.71	3.45	3.81	3.47
Ozempic®	9	1.44	1.81	1.67	2.09
Rybelsus®	5	1.40	3.44	1.03	2.43
Trulicity®	6	0.33	0.82	0.40	0.98
Wegovy®	4	11.00	10.17	12.27	11.71

SD: Standard Deviation.

Impact of Diabetes: When comparing weight loss based on the presence of diabetes, patients without diabetes showed a significantly higher mean reduction (5.0 ± 6.4 kg) than those with diabetes (0.8 ± 1.9 kg). The mean difference was 4.2 kg (95% CI: 0.70–7.70), reaching statistical significance ($p = 0.021$). These results suggest a potentially lower weight loss response in patients with diabetes; however, they should be interpreted with caution due to the limited sample size and the lack of adjustment for potential confounding factors (Table 7).

Table 7. Comparison by pathology.

Group	*N*	Mean t Loss (kg)	SD
With diabetes	15	0.8	1.86
Without diabetes	16	5.0	6.38

SD: Standard Deviation.

3.3. Multivariate Analysis and Drug Comparisons

To identify specific differences between treatments, Tukey's HSD post hoc test was performed. The results confirmed that Wegovy® achieved a significantly greater weight reduction compared to:

- Ozempic® (Mean difference: 9.55 kg, $p = 0.0066$);
- Rybelsus® (Mean difference: 9.60 kg, $p = 0.0167$);
- Trulicity® (Mean difference: 10.66 kg, $p = 0.0046$).

The comparison between Wegovy® and Mounjaro® showed a trend toward greater loss for Wegovy® (7.28 kg), although it did not reach statistical significance ($p = 0.0704$), likely due to the small subgroup sizes (Table 8).

Table 8. Post hoc results (Tukey HSD).

Group 1	Group 2	Mean Diff	*p*-Adj	95% CI	Reject H0
Mounjaro®	Ozempic®	−2.2698	0.8185	−8.4651–3.9254	False
Mounjaro®	Rybelsus®	−2.3143	0.8780	−9.5126–4.8840	False
Mounjaro®	Trulicity®	−3.3810	0.6038	−10.2204–3.4585	False
Mounjaro®	Wegovy®	7.2857	0.0704	−0.4196–14.9910	False
Ozempic®	Rybelsus®	−0.0444	1.0000	−6.9014–6.8125	False
Ozempic®	Trulicity®	−1.1111	0.9864	−7.5903–5.3681	False
Ozempic®	Wegovy®	9.5556	0.0066	2.1682–16.9430	True
Rybelsus®	Trulicity®	−1.0667	0.9931	−8.5107–6.3773	False
Rybelsus®	Wegovy®	9.6000	0.0167	1.3534–17.8466	True
Trulicity®	Wegovy®	10.6667	0.0046	2.7313–18.6020	True

Mean Diff: mean difference; *p*-adj: adjusted *p*-value; CI: Confidence interval; Reject H0: false: null hypothesis; true: statistically significant.

3.4. Adjusted Multivariate Model

A general linear model (ANCOVA) was constructed to adjust weight loss for potential confounders ($R^2 = 0.521$). After adjusting for age, sex, treatment duration, and the presence of diabetes, the type of treatment remained a significant factor. Specifically, Wegovy® maintained a significant positive association with weight loss (Beta = 8.727 kg; $p = 0.032$). Interestingly, the effect of diabetes (Beta = −3.881; $p = 0.134$) and treatment duration did not reach statistical significance within this adjusted model, likely due to the limited sample size of the pilot study (Table 9).

The ANOVA analysis showed overall differences between drugs. The effect size (η^2) was 0.424.

Significant differences were identified when comparing Wegovy® against Ozempic® ($p = 0.0066$), Rybelsus® ($p = 0.0167$), and Trulicity® ($p = 0.0046$). This pilot phase did not find statistically significant differences between the other treatment pairs.

Table 9. Adjusted Multivariate Regression Model.

Variable	Beta (kg)	SE	T	*p*	95% CI
Intercept	6.958	−6.927	1.004	−0.328	−7.542–21.457
Treatment (Ozempic®)	0.725	3.533	0.205	0.840	−6.670–8.120
Treatment (Rybelsus®)	1.267	3.821	0.332	0.744	−6.729–9.264
Treatment (Trulicity®)	0.419	4.264	0.098	0.923	−8.506–9.344
Treatment (Wegovy®)	8.727	3.759	2.322	0.032	0.860–16.595
Sex(Female)	−1.007	2.311	−0.435	0.668	−5.884–3.831
Duration (6 mo-1yr)	0.285	3.071	0.093	0.927	−6.143–6.713
Duration (≤3 months)	−1.817	3.811	−0.477	0.639	−9.794–6.159
Duration (Start/Baseline)	−4.509	3.774	−1.195	0.247	−12.408–3.389
Duration (>1 year)	0.160	3.071	0.052	0.959	−6.268–6.589
Diabetes (true)	−3.881	2.480	−1.565	0.134	−9.071–1.309
Age	−0.048	0.136	−0.350	0.730	−0.333–0.238

Beta, regression coefficient; SE, standard error; CI, confidence interval. Dependent variable: weight loss (kg). Reference categories were Mounjaro (treatment), male sex, no diabetes, and treatment duration of 3–6 months.

4. Discussion

The relevance of this pilot study lies in its role as a validation phase for a national-scale research project. These preliminary findings have confirmed the feasibility of the data collection protocol and demonstrated the capacity of community pharmacies to generate robust, real-world evidence. Currently, this protocol is being implemented through a multicenter approach in an expanded cohort. This national network will confirm the trends observed in this pilot study, providing sufficient statistical power to conduct more detailed subgroup analyses and to assess more accurately the comparative effectiveness among the various GLP-1 receptor agonist molecules. The ongoing national multicenter phase has been specifically designed to address the methodological limitations identified in this pilot cohort, particularly the limited statistical power, subgroup imbalance, and heterogeneity in treatment exposure and baseline patient characteristics.

In this pilot sample of patients treated with GLP-1 receptor agonists (GLP-1RAs), a clinically relevant weight loss was observed in both absolute (kg) and relative (%) terms, supporting the effectiveness of these therapies in a real-world clinical setting. These findings are consistent with pivotal clinical trials; specifically, in the STEP 1 trial, patients with obesity treated with semaglutide 2.4 mg achieved a mean weight loss of 12.7 kg (95% CI, −13.7 to −11.7) after 68 weeks. This result aligns with the 11.00 ± 10.17 kg reduction observed in our study. Furthermore, our findings coincide with the STEP 2 trial, which demonstrated that patients with type 2 diabetes (T2D) exhibit lower weight loss than those without diabetes [10,11].

Similarly, pivotal trials for tirzepatide have shown greater weight reduction in patients with obesity compared to those with T2D. The diminished response observed in diabetic patients in our study ($p = 0.021$) is consistent with the results of the STEP 2 and SURPASS trials, where metabolic resistance associated with T2D typically limits the rate of weight loss [12,13].

However, outcomes in real-world conditions may be more modest than those reported in clinical trials. The real-world effectiveness results from our pilot study (mean weight loss

of 2.97 kg) are consistent with recent observational studies conducted in Spanish clinical practice, such as that by Romero et al. [14]. These authors emphasize the significant variability in therapeutic response within routine care compared to the controlled environments of Phase III trials [14]. Furthermore, systematic reviews of real-world evidence indicate that weight loss is generally lower than in clinical trials; factors such as utilization patterns, treatment adherence, and lifestyle variations may contribute to these discrepancies (Pottegård et al., 2025) [15].

4.1. Magnitude of Weight Loss

The mean weight loss observed was consistent with findings reported in pivotal trials and controlled clinical studies, although the interpretation of these results should consider the heterogeneity of the sample and the variability in treatment duration. The mean percentage weight change reinforces the clinical relevance of these findings, as body weight reductions of $\geq$5% are associated with significant metabolic benefits. The relatively wide standard deviation suggests a variable inter-individual response, a phenomenon extensively documented in the literature regarding incretin-based therapies.

4.2. Comparative Analysis Between Drugs

The ANOVA analysis revealed overall differences among the various GLP-1 analogues concerning weight loss. The effect size (η^2) indicated a clinically relevant magnitude, suggesting that the specific agent accounts for a significant proportion of the variability in weight reduction.

Post hoc comparisons (Tukey's HSD) identified specific differences between drugs. Although the limited sample size restricts statistical power, the observed trends align with available evidence, which positions dual agonists or those with greater pharmacodynamic potency as potentially superior in terms of weight reduction. Although the observed trends are broadly consistent with available literature, the present pilot study was not designed or powered to establish definitive comparative superiority between agents. Therefore, these findings should be considered exploratory and hypothesis-generating only.

4.3. Multivariate Analysis

The multivariate model, adjusted for age, sex, and treatment duration, suggested that the type of medication maintains its association with weight loss even after controlling for potential confounding factors. Treatment duration played a significant role, which is consistent with the progressive nature of the weight-loss effect characteristic of GLP-1 analogues. Age and sex did not substantially modify the treatment effect in this cohort, although the sample may lack sufficient power to detect subtle differences. The persistence of the effect after adjustment reinforces the biological plausibility of the differences observed between molecules and suggests they are not exclusively explained by demographic factors.

4.4. Adverse Reactions and Tolerability

Approximately half of the patients reported at least one gastrointestinal symptom (46.9%), most of which were mild and self-limiting. This pattern aligns with the safety profile described in the literature and reinforces the overall good tolerability of the treatment. Consistent with the STEP 1 and SURMOUNT-1 trials, the most frequently recorded symptoms, such as xerostomia or abdominal pain, match the safety profile reported in other reviews and meta-analyses. Notably, the incidence of xerostomia (12.5%) is a common adverse reaction in clinical practice that may be related to the hypophagia induced by these medications [16,17].

4.5. Clinical Implications

The results of this pilot study suggest that:

- GLP-1 receptor agonists (GLP-1RAs) are effective in real-world clinical practice settings.
- Potential differences exist between molecules regarding the magnitude of weight loss.
- Treatment duration is a determining factor in therapeutic success.
- The observed safety profile is consistent with previously reported evidence.
- These findings may support individualized decision-making in the management of patients with obesity or excess weight.

4.6. Limitations

This study has several important limitations that must be considered:

- Small sample size, which may affect generalizability.
- Observational design, inherently prone to certain biases.
- Potential recall bias regarding baseline weight.
- Heterogeneity in treatment duration and dosing schedules.
- Small subgroups for certain medications, limiting the statistical power of post hoc analyses.

Additionally, the limited sample size of some treatment subgroups may reduce the robustness of normality assumptions and increase the risk of type II error in comparative analyses.

The pilot nature and limited sample size reduce the statistical power and external validity of the findings, particularly for subgroup comparisons between individual GLP-1 receptor agonists.

In addition, the cross-sectional observational design precludes causal inference and does not allow assessment of long-term treatment effectiveness or persistence over time.

Baseline weight was partially based on patient recall, which may introduce recall bias despite verification against clinical records or personal monitoring devices whenever available.

Furthermore, treatment groups showed substantial heterogeneity regarding treatment duration, baseline metabolic characteristics, and diabetes status, which may have influenced inter-group comparisons despite multivariate adjustment.

Consequently, these results should be interpreted as exploratory and hypothesis-generating.

5. Conclusions

In this pilot cohort, GLP-1RAs were associated with clinically relevant weight loss in routine clinical practice. Exploratory differences between specific agents were observed after multivariate adjustment; however, these findings should be interpreted cautiously due to the limited sample size and observational design. Larger prospective studies are required to confirm potential comparative differences between molecules and to better define their relative effectiveness and safety profiles. Treatment duration appeared to be associated with the magnitude of weight loss observed in this cohort. Furthermore, the diminished response observed in patients with type 2 diabetes aligns with international evidence, underscoring the need to individualize therapeutic expectations.

Ultimately, this pilot study provides a robust clinical foundation for the ongoing Spanish multicenter registry, which will provide more definitive evidence on the effectiveness and safety of these treatments across a broader population.

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Institutional Review Board Statement: The study protocol was reviewed and approved by the Basque Country Ethics Committee for Clinical Research (CEIm de Euskadi). Approval Code: EOM2025059 (CEIm). The study was conducted in accordance with the principles of the Declaration of Helsinki and current data protection regulations. All patients provided voluntary informed consent. Given the observational and non-interventional nature of the study, routine clinical practice remained unaltered.

Informed Consent Statement: Patient consent was waived due to the retrospective nature of the study and the use of de-identified data, which ensured that the privacy of the participants was maintained at all times, as approved by the Ethics Committee.

Data Availability Statement: The data presented in this study are available on request from the corresponding authors. The data are not publicly available due to privacy and ethical restrictions, as they contain sensitive information that could compromise the anonymity of the research participants.

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