Communication

Effectiveness of Oral versus Injectable Semaglutide in Adults with Type 2 Diabetes: Results from a Retrospective Observational Study in Croatia

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Abstract: Background: The number of people with type 2 diabetes is increasing daily, and therefore, effective therapy is needed to successfully regulate glycemia and reduce the risk of associated complications. Recently, an oral formulation of the glucagon-like peptide-1 receptor agonist (GLP-1 RA) semaglutide has become available. Therefore, the aim of our study was to compare the effectiveness of the new oral formulation and the existing injectable formulation of semaglutide in terms of glycemic and body weight control in a real-world setting. Patients and methods: This was a single-center retrospective observational study conducted at the Rijeka Clinical Hospital Centre. A total of 106 patients with inadequately controlled type 2 diabetes (HbA1c $\geq$ 7%) on different oral or basal insulin supported oral therapy were enrolled in the study, and data from electronic medical records were retrospectively collected and analyzed from May 2021 to November 2022. All subjects were GLP-1 RA-naive and consequently prescribed 0.5 or 1.0 mg of once weekly injectable semaglutide (IS) or 7 mg or 14 mg of once daily oral semaglutide (OS) for at least 6 months. Glycated hemoglobin (HbA1c), body weight, and body mass index (BMI) were assessed prior to semaglutide administration and after a 6-month follow-up period. The primary endpoint was the change from baseline in HbA1c, and secondary endpoints were the change in body weight and the proportion of participants with a reduction in body weight of $\geq$5% and $\geq$10%, respectively, 6 months after the initiation of semaglutide treatment. Results: At the 6-month follow-up, no significant difference was observed between the two formulations in terms of HbA1c reduction (IS −1.1% vs. OS −1.4%, $p = 0.126$) and weight loss (IS −6.50 kg vs. OS −5.90 kg, $p = 0.714$). Exactly the same proportion of participants in both groups achieved a weight loss of $\geq$5% (56.7%, n = 30). A weight loss $\geq$ 10% was observed in 20.7% (n = 11) of participants administered IS and 15.1% (n = 8) of participants administered OS, respectively ($p = 0.454$). Conclusion: In a real-world setting, oral semaglutide as an add-on therapy to ongoing antihyperglycemic treatment in patients with inadequately controlled type 2 diabetes who had not previously received GLP-1 RA demonstrated a similar effectiveness as injectable semaglutide in terms of glycemic control and weight loss after 6 months of treatment.

Keywords: glucagon-like peptide-1; semaglutide; type 2 diabetes

1. Introduction

According to International Diabetes Federation, it is estimated that 537 million people worldwide have diabetes, and the vast majority of cases are type 2 diabetes (T2D). In addition, there are around 541 million people who have impaired glucose tolerance. It is predicted that by 2045, the number of diabetes cases will reach 783 million. By all accounts, diabetes is certainly one of the fastest-growing global health issues of the 21st century [1].

According to a recent systematic review, the leading cause of mortality and comorbidity in people with diabetes is cardiovascular disease (CVD), which accounts for 50.3% of all deaths [2]. It is assessed that in the U.S., around USD 37.3 billion per year is spent on treating cardiovascular-related complications associated with diabetes [3]. A great number of people with type 2 diabetes have cardiometabolic risk factors that can be modified, such as diet, smoking, sedentary lifestyle, dyslipidemia, hypertension, and obesity.

Clinical guidelines recommend an approach to the management of type 2 diabetes that goes beyond simply lowering glucose levels to reduce modifiable cardiometabolic risk factors [4–8]. Treatment should be guided by a person-centered, holistic, multifactorial approach that takes into account individual goals related to glycemic control, body weight, and cardiovascular risk factor management to maintain and improve patient well-being. It is well established that obesity significantly increases the risk of developing type 2 diabetes and is associated with numerous other psychosocial and medical complications [9,10].

According to the American Diabetes Association (ADA), overweight patients with T2D may benefit from modest weight loss (3–7% of baseline weight) in terms of improved glycemic management and cardiovascular risk factor improvement. Greater benefit, including improvement in long-term cardiovascular outcomes and possible remission of disease, results from sustained weight loss of greater than 10% of body weight. It is recommended that the potential beneficial effects on body weight be considered when choosing an anti-hyperglycemic drug. Pharmacological therapy for obesity in these patients is considered effective if the patient loses $\geq$ 5% of body weight after 3 months of therapy [9].

Over the past decade, a number of clinical trials have been published with results showing that modern therapies, including glucagon-like peptide-1 receptor agonists (GLP-1 RA) and SGLT-2 inhibitors, achieve significant and consistent cardiometabolic benefits [11]. GLP-1 RAs have been shown to be an effective treatment for patients with type 2 diabetes. Remarkable clinical benefits of GLP-1 RAs have been demonstrated, not only in maintaining glycemic control and protecting against hypoglycemia, but also in significant weight loss, lowering blood pressure, and improving lipid profiles [12]. Moreover, their use has been associated with a reduced risk of major cardiovascular events (MACE), cardiovascular death, nonfatal myocardial infarction, and nonfatal ischemic stroke in patients with T2D [13].

Semaglutide is the only GLP-1 RA available in both injectable and oral formulation. Impaired absorption of orally administered peptides has been overcome by co-formulation with the absorption enhancer sodium N-(8-[2 hydroxybenzoyl]amino)caprylate (SNAC) which protects semaglutide through local buffering and leads to facilitated absorption across the gastric epithelium [14,15]. The first oral formulation of GLP-1 RA semaglutide (Rybelsus) was approved by the U.S. Food and Drug Administration (FDA) in September 2019 and by European Medicines Agency (EMA) in April 2020 [16,17]. Due to the lower bioavailability of oral semaglutide compared to the subcutaneous formulation, a higher dose of 7 mg to 14 mg/day versus 1 mg to 2 mg/week of the subcutaneous formulation is required [18].

The efficacy of once-weekly subcutaneously administered semaglutide and once-daily oral semaglutide has been evaluated in the comprehensive clinical trial programs SUSTAIN and PIONEER. Both formulations of semaglutide have been shown to be nearly equally effective in achieving and maintaining glycemic targets, with 66–80% of participants administered semaglutide 1.0 mg subcutaneously achieving an HbA1c < 7% in SUSTAIN trials, compared with 55–77% of participants treated with oral semaglutide 14 mg throughout the PIONEER study program [19]. Moreover, the safety profile of both formulations is highly

similar, and they have also been associated with significant weight loss and low risk of hypoglycemia [19].

However, to date, no direct comparative studies between injectable and oral semaglutide formulations have been performed evaluating their effects on glycemic control and body weight. Therefore, the aim of our study was to compare the effectiveness of the two semaglutide formulations in terms of glycemic and body weight control in a real-world setting.

2. Materials and Methods

2.1. Study Design and Population

This was a single-center retrospective observational study conducted at the Rijeka Clinical Hospital Centre. A total of 106 adult (>18 years of age) patients with inadequately controlled type 2 diabetes (HbA1c $\geq$ 7%) on different oral or basal insulin supported oral therapy were enrolled in the study. All subjects were GLP-1 RA-naive and consequently prescribed 0.5 or 1.0 mg of once weekly injectable semaglutide (IS) or 7 mg or 14 mg of once daily oral semaglutide (OS) for at least 6 months. Glycated hemoglobin (HbA1c), body weight, and body mass index (BMI) were assessed prior to semaglutide administration and after a 6-month follow-up period. The primary endpoint was the change from baseline in HbA1c, and secondary endpoints were the change in body weight and the proportion of participants with a reduction in body weight of $\geq$5% and $\geq$10%, respectively, 6 months after the initiation of semaglutide treatment. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Clinical Hospital Center Rijeka (No: 003-05/20-1/54).

2.2. Data Collection

Data from electronic medical records were retrospectively collected and analyzed from May 2021 to November 2022. Demographic (age, gender) and relevant clinical data [body weight, body height, BMI, HbA1c, comorbidities (arterial hypertension, dyslipidemia, cardio/cerebrovascular disease)] were collected.

2.3. Statistical Analysis

Statistical analysis was performed using Microsoft Excel 2016 for Windows, version is 1.0 (Microsoft Office) and MedCalc v12.1.3 (MedCalc Software bvba, Ostend, Belgium). Absolute and relative frequencies, measures of central tendency, and measures of spread were used to present the data. The Mann–Whitney test and the χ^2-test were used to compare outcomes between groups. Criterion for statistical significance was estimated on $p < 0.05$. All tests were run under 95% confidence interval (CI).

3. Results

The group of patients administered injectable semaglutide consisted of a total of 53 participants, 30 of whom were men and 23 women, aged 38–78 years. In this group, 10 (18.9%) patients received 0.5 mg of injectable semaglutide, and 43 (81.1%) of them received 1.0 mg. In addition, 12 (22.6%) patients were found to have cardiovascular disease (CVD). In addition to injectable semaglutide, patients also received previously prescribed concomitant therapy, including 48 (90.6%) metformin, 21 (39.6%) SGLT-2i, 11 (20.8%) a sulfonylurea, 3 (5.7%) pioglitazone, and 16 (30.2%) insulin.

The other group of patients who received oral semaglutide consisted of a total of 53 patients, 30 men and 23 women, aged 46–79 years. In this group, 20 (37.7%) patients received an oral semaglutide dose of 7 mg and 14 (62.3%) of them received a dose of 14 mg. CVD was confirmed in nine (17%) participants in this group. In addition to oral semaglutide, patients in this group also received previously prescribed concomitant therapy, 52 (98.1%) of them metformin, 24 (45.2%) patients SGLT-2i, 13 (24.5%) patients in therapy had a sulfonylurea, 2 (3.8%) patients pioglitazone, and 12 (22.6%) of them insulin.

The demographic and clinical characteristics of the patients (n = 106; 56.6% female), who were divided into two groups based on the therapy administered, are shown in Table 1. There were no significant differences between the oral semaglutide group and the injectable semaglutide group in age and confirmed cardiovascular disease (CVD). There was a difference between the doses of the investigational drugs (lower vs. upper dose) between the groups, in favor of the IS group (*p* = 0.014).

Table 1. Demographic and clinical characteristics of patients.

Variables	Injectable Semaglutide	Oral Semaglutide	*p*-Value
Number of patients (n)	53	53	
Male	56.6% (n = 30)	56.6% (n = 30)	
Female	43.4% (n = 23)	43.4% (n = 23)	
Age (years) *	63 (38–78)	59 (46–79)	0.552
Dosage (mg)	0.5 mg 18.9% (n = 10) 1.0 mg 81.1% (n = 43)	7 mg 37.7% (n = 20) 14 mg 62.3% (n = 33)	0.014 [a]
Confirmed CVD	22.6% (n = 12)	17% (n = 9)	0.095
Background therapy			
metformin	90.6% (n = 48)	98.1% (n = 52)	
SGLT-2i	39.6% (n = 21)	45.2% (n = 24)	
sulfonylurea	20.8% (n = 11)	24.5% (n = 13)	
pioglitazone	5.7% (n = 3)	3.8% (n = 2)	
insulin	30.2% (n = 16)	22.6% (n = 12)	

* Data are reported as median and interquartile range. [a] Categorical variables are analyzed with the Chi-Square (χ^2) test; $p < 0.05$.

Baseline HbA1c levels are shown in Figure 1. There was a difference in baseline HbA1c values between the injectable semaglutide group and the oral semaglutide group [median 8.0 (5.5–12.7 range) versus 8.80 (6.2–14.2)%, *p* = 0.039].
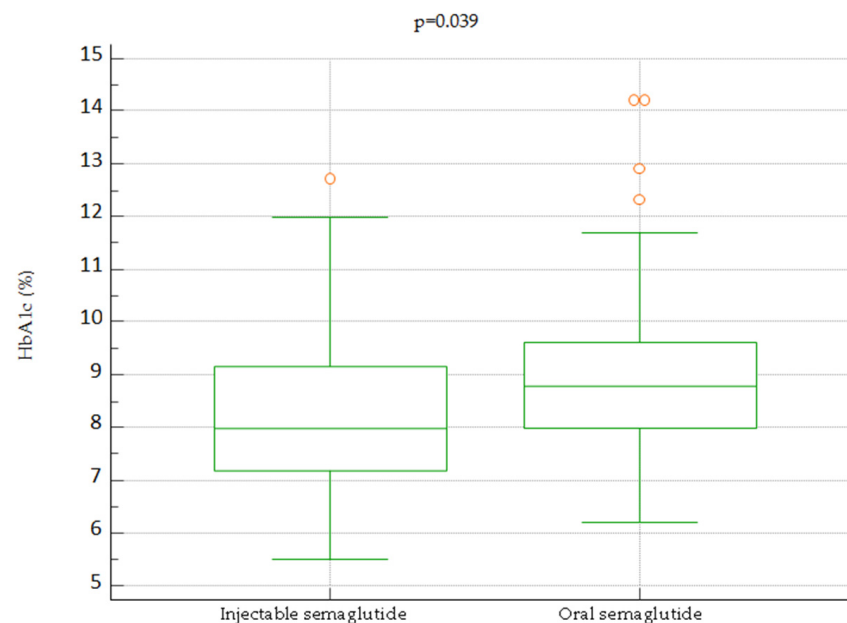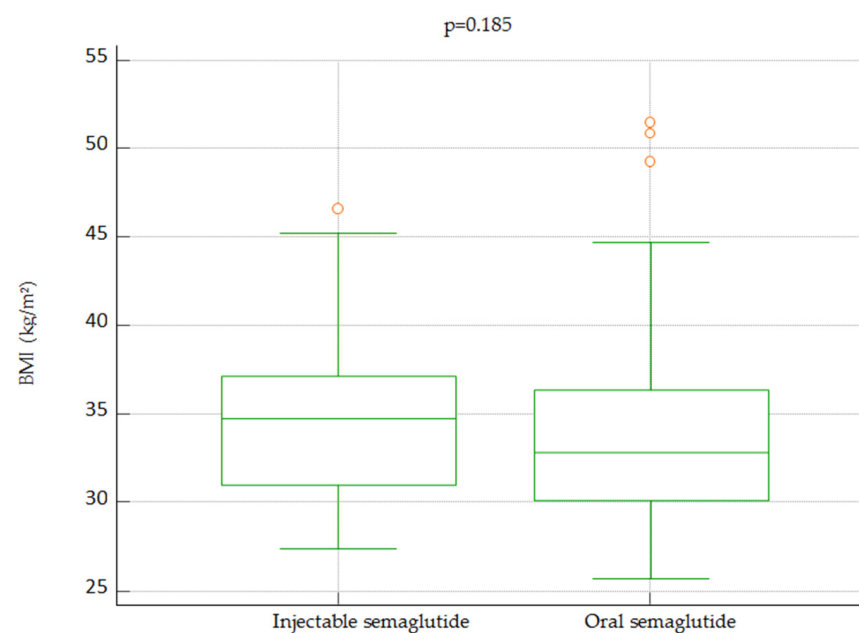

Figure 1. Box plot with comparisons of baseline HbA1c between IS and OS group.

There was no difference in terms of baseline body weight between the groups [mean 102.0 ± 5.1 kg standard deviation vs. 97.3 ± 5.9 kg (*p* = 0.081)] (Figure 2).

p=0.081
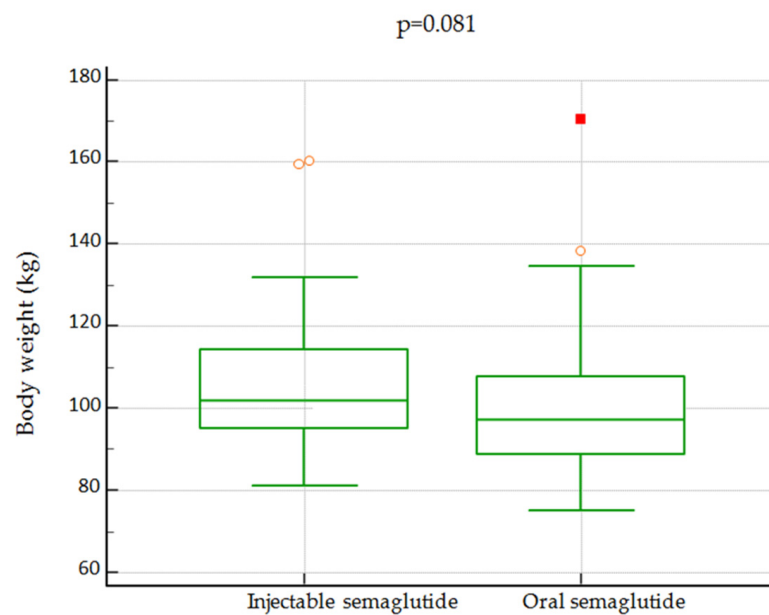
Figure 2. Box plot with comparisons of baseline body weight between IS and OS group.

In addition, no difference was found between groups in baseline BMI [median 34.72 (27.41–46.61 range) vs. 32.87 (25.73–51.45) kg/m^2, p = 0.185] (Figure 3).

p=0.185

Figure 3. Box plot with comparisons of baseline body mass index between IS and OS group.

When comparing the efficacy of IS and OS in lowering blood glucose (using HbA1c as a surrogate), no difference was observed between the two formulations at 6 months [-median 1.10 (−7.10–4.60 range) vs. −1.40 (−8.0–0.70)%, p = 0.126] (Figure 4).
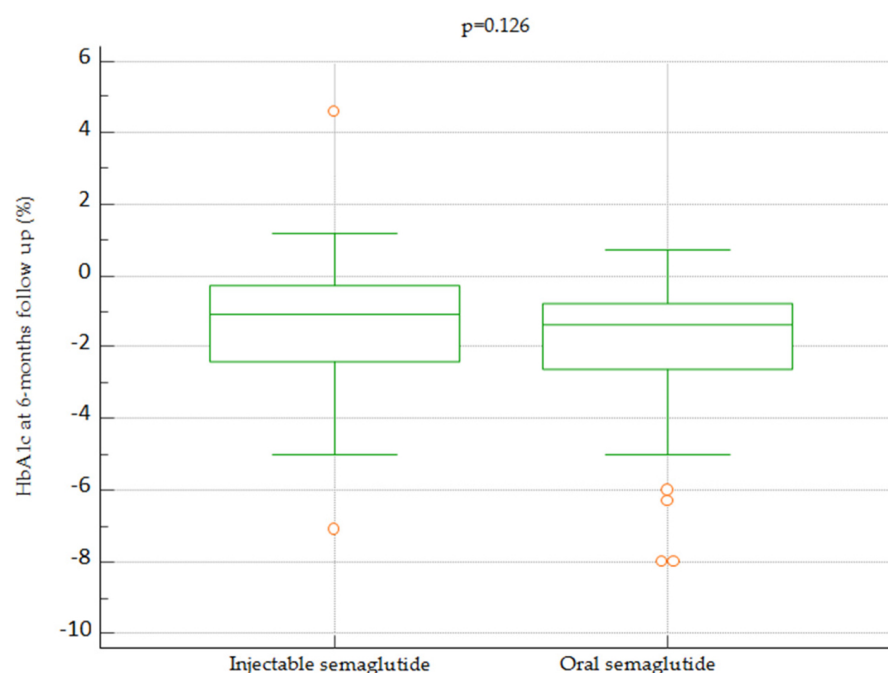
Figure 4. Change in HbA1c after 6 month of treatment with IS vs. OS.

At 6-month follow-up, no difference in body weight was observed between the injectable semaglutide group and the oral semaglutide group [median −6.50 (−28.0–10.0 range) vs. −5.90 (−45.3–0.2) kg, *p* = 0.714], as shown in Figure 5.
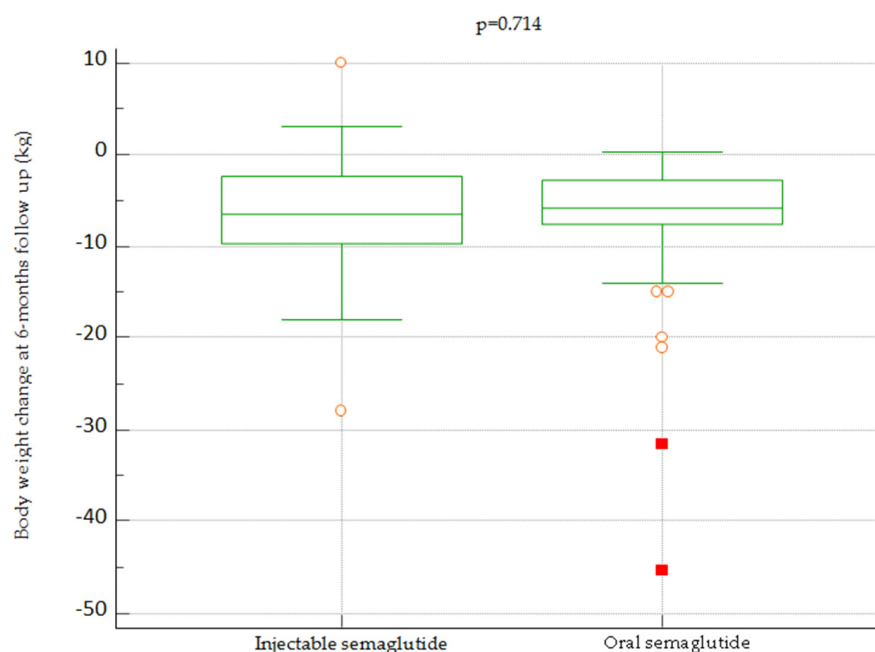
Figure 5. Change in body weight after 6 month of treatment with IS vs. OS.

Participants in both groups, 56.7% in total (n = 30), achieved a loss of body mass of >5% with no difference between groups. Weight loss of > 10% was observed in 20.7% (n = 11) of patients on injectable semaglutide and in 15.1% (n = 8) of patients on oral semaglutide, with no difference between the groups.

The most common adverse side effect was nausea, which was generally mild to moderate and transient, occurring in 20% of patients (n = 10) treated with oral semaglutide

and 22% (n = 12) of patients treated with injectable semaglutide. Overall, 14% (n = 7) of patients taking oral semaglutide and none taking the injectable form complained of excessive belching. None of the participants discontinued the medication due to these side effects.

4. Discussion

Our study is the first direct comparison between the two semaglutide formulations in a real-world setting as add-on therapy to ongoing antihyperglycemic treatment in patients with inadequately controlled type 2 diabetes who had not previously received GLP-1 RA. Both formulations of semaglutide have been shown to be nearly equally effective in achieving HbA1c reduction (IS −1.1% vs. OS −1.4%) and weight loss (IS −6.5 kg vs. OS −5.9 kg).

Across the SUSTAIN program, once-weekly subcutaneous semaglutide 1.0 mg reduced HbA1c by 1.5–1.8% after 30–56 weeks, while once-daily oral semaglutide 14 mg reduced HbA1c by 1.0–1.4% across the PIONEER program [19,20]. In addition, subcutaneous semaglutide reduced body weight by 4.5 kg to 6.5 kg, significantly more than all active comparators tested, while oral semaglutide reduced body weight more than sitagliptin and liraglutide and to a similar extent as empagliflozin, namely between 2.6 kg and 4.4 kg. In a clinical trial conducted by Gibbons et al., people with a BMI of 20–38 kg/m^2 had less food cravings, had greater control over their diet, and consumed less food at each meal of the day with oral formulation of semaglutide versus the placebo [18]. Overall, after 12 weeks of treatment, the mean body weight decreased by 2.7 kg with oral semaglutide and 0.1 kg with placebo, mostly attributable to body fat mass loss [18].

Our results suggest that the antihyperglycemic potential of oral semaglutide in a real-world setting is consistent with that demonstrated in randomized clinical trials. However, the potential for weight reduction was more pronounced than in the PIONEER program. On the other hand, the HbA1c reduction achieved with the injectable form was slightly weaker than expected, but with body weight loss consistent with that in the SUSTAIN program. Moreover, the safety profile of the two formulations was similar. As commonly observed with GLP-1 Ras, the most common adverse side effect was nausea, which was generally mild to moderate and transient. Excessive belching was reported by 14% of patients taking oral semaglutide and by none of the patients taking the injectable form.

Given the generally similar efficacy and safety profiles of the two formulations, further considerations may need to be made in selecting the most appropriate formulation. Many patients are reluctant to initiate treatment with injectable medications due to fear of pain during injection and a sense of failure related to disease progression. A possible disadvantage of taking semaglutide orally is that the tablet must be taken on an empty stomach 30 min before a meal, drink, or taking other medications to ensure unimpeded absorption [17]. On the other hand, for injectable semaglutide, it does not matter whether food or liquid has been consumed before or after the injection. Therefore, selection of the most appropriate formulation needs to be made on an individual basis to best suit the patient's preferences and needs.

Our study suggests that semaglutide offers the benefits of a highly effective GLP-1 RA in both injectable and oral formulations. However, since this is a single-center retrospective observational study, the findings should be interpreted accordingly. It was conducted on a relatively small sample of respondents. Furthermore, due to the study design, the researchers had no control over exposures and interventions or absolute medication adherence. Likewise, there is the possibility of various confounding effects, such as background therapy and comorbidities. Nonetheless, our results have shown that orally administered semaglutide may be as effective an option for improving glycemic target attainment and supporting weight loss in adults with T2D as the injectable formulation, particularly in patients who are reluctant to take injectable medications.

5. Conclusions

In a real-world setting, oral semaglutide as an add-on therapy to ongoing antihyperglycemic treatment in patients with inadequately controlled type 2 diabetes who had not previously received GLP-1 RA demonstrated the same effectiveness as injectable semaglutide in terms of glycemic control and weight loss after 6 months of treatment. Considering the almost equal effect, the oral formulation of semaglutide could make it easier for patients to use since there is no injection burden.

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