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Efficacy and Safety of Oral Semaglutide in Managing Type 2 Diabetes in India: A Real-World Study

ABSTRACT

Objective: To examine the effectiveness, safety, and tolerability of oral semaglutide, the only tablet that delivers glucagon-like peptide-1 (GLP-1) receptor agonists (RA) orally, in a real-world setting, for Indian patients with type 2 diabetes (T2D).

Materials and methods: Medical data were included for patients with uncontrolled T2D. Glycated hemoglobin (HbA1c) in the laboratory was the main outcome measure. Hypoglycemia, weight, and fasting plasma glucose (FPG) were used as secondary metrics. Results: The weight reduction was significant during the first 6 months, then it was in a plateau phase, and again it went up from 12 months until the end of the study period. The mean FPG dropped from 156.4 mg/dL to 103.8 mg/dL, and the mean postprandial blood glucose (PPPG) changed from 248.9 mg/dL to 169.8 mg/dL over the treatment period. Similarly, the HbA1c level changed from 8.6% to 7.0%. A small percentage of patients had hypoglycemia: 0.5% of patients at T6, 1.1% at T12, and 1.4% reported having a moderate episode (54–70 mg/dL); one incident of severe hypoglycemia was observed at T12.

Conclusions: For people with T2D, oral semaglutide therapy significantly reduced blood sugar levels and helped them lose weight. (Clin Diabetol 2024; 13, 6: 323–330)

Keywords: GLP-1 RA, oral semaglutide, type 2 diabetes, real world

Introduction

Diabetes mellitus is a very common disorder affecting more than 70 million people in India [1]. Most of these belong to the type 2 diabetes (T2D) category, which is considered a lifestyle disease. Moreover, India has the highest number of people with diabetes still undiagnosed, and by 2045 the number of diabetics is expected to reach 134.3 million (103.4–165.2) [2]. The steady migration of people from rural to urban areas, the economic boom, and corresponding changes in lifestyle all affect the level of diabetes [3]. While managing Indian patients with diabetes, it is imperative to recognize that, due to associated obesity and inadequate lifestyle modifications, metformin and lifestyle management alone may not be enough in the initial

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management of some patients. While choosing oral antidiabetic agents (ADAs), apart of the risk of hypoglycemia, it is important to also look into their impact on weight, renal safety, cardiac safety, and possible beta cell prevention. Awareness of the disease and its aggressive management are considered the cornerstone to control the disease in India.

During previous decades, management was primarily "beta cell" centric with the use of sulfonylureas and insulin. With the advent of newer therapies and a greater understanding of T2D, it has come to our understanding that it is important to address as many pathophysiological defects as possible to achieve better glycemic control. Glucagon-like peptide 1 (GLP-1) receptor agonists (RA) stimulate glucose-dependent insulin release from the beta cell. They also slow down gastric emptying, reduce appetite, improve satiety, and reduce glucagon levels. In animal models, GLP-1RAs have resulted in proliferation and regeneration of beta cells. The mechanism of action of GLP-1RAs is complex and involves multiple systems and pathways. The pathological approach to treatment favors the use of GLP-1RAs because they address several defects of T2D.

The first palatable GLP-1RA is semaglutide, which depends on cutting-edge pharmaceutical technology to guarantee absorption and efficacy upon ingestion: sodium N-[8-(2-hydroxybenzoyl) amino] caprylate (SNAC) is mixed with semaglutide to enhance absorption and shield the peptide from stomach enzyme degradation [4]. The oral formulation of GLP-1RAs has the advantage of greater patient acceptability and convenience than injectable GLP-1RAs [5].

In several clinical trials, despite receiving glucose-lowering medication, study participants' glucose control was suboptimal (mean baseline HbA1c 8.0–8.4%, 64–68 mmol/mol). Semaglutide substantially reduced HbA1c in a dose-dependent manner compared to all other comparators, including other GLP-1 analogues [6–10]. The highest HbA1c decrease was seen after 16–30 weeks, and semaglutide helped more patients reach HbA1c < 7% (53 mmol/mol) than placebo or other comparators. However, there have only been a small number of published studies on the practical application of this medication [11, 12]. As a result, the effects of this medication in routine clinical practice — both when oral semaglutide is added to other medications and when patients switch to it from glucose-lowering agents — remain to be fully established. As is well known, real-world research enables evaluation of the generalizability of experimental study findings to larger patient populations under standard clinical practice [13]. Thus, the current study's goal was to evaluate its efficacy and tolerability in the context of T2D treatment as an adjunctive therapy.

Materials and methods

Study procedure

This research was retrospective and observational. Through the use of electronic medical data, adult Indian patients (over the age of 18 years) with T2D who were receiving oral semaglutide and being monitored at the outpatient Diabetes Clinic were identified between January 2023 and August 2024. The concepts of T2D care and treatment advised by national Indian Council of Medical Research (ICMR) guideline, Research Society for the Study of Diabetes in India — Endocrine Society of India (RSSDI-ESI) clinical practice recommendations for the management of T2D [14, 15], and worldwide recommendations served as the foundation for the prescription of oral semaglutide. For this audit, a pre-made structured proforma was utilized to gather data from the participating doctors regarding the effectiveness of oral semaglutide when used in conjunction with other antidiabetic medications.

Primary and secondary endpoints

The change in mean HbA1c levels from baseline to 6 months was the primary endpoint. The following were continuous secondary endpoints: changes in mean fasting plasma glucose (FPG) levels and weight/ /body mass index from baseline to T6, T12, and T18 months; changes in mean HbA1c levels from baseline to T6, T12, and T18 months.

Categorical secondary endpoints were changes in serum urea and serum creatinine from baseline to T6, T12, and T18 months, patients discontinuing semaglutide, and reasons for discontinuation.

Therapy selection

The maintenance dose of semaglutide and any subsequently adjusted dosage were decided by the treating physician. The dose of oral semaglutide is as follows: a starting dose of 3 mg in empty stomach with 120 mL of water, then no food for the next 30 minutes. If the patient tolerated the 3 mg dose, we increased the dose to 7 mg after one month, and to 14 mg after another month. The therapy selection was based on the judgment of the physicians in charge and the agreement of the subject. No monitoring or diagnostic treatments beyond standard clinical practice were performed on the patients. A case-by-case determination of the maintenance semaglutide dosage was made after a 12-week semaglutide treatment, considering both the drug's cost and clinical response. Baseline was defined as the appointment (T0) at which the

patient was initially prescribed semaglutide; follow-up appointments were scheduled 6, 12, and 18 months after baseline. When semaglutide was started, each person received counselling on regular exercise and diet. One National Accreditation Board for Testing and Calibration Laboratories (NABL)-accredited lab was used for all pathology and biochemistry laboratory tests, and it was attached to each participating clinic. A self-monitoring blood glucose gadget was used at home to measure blood glucose on a regular basis. Hypoglycemia was defined as a blood sugar level of less than 70 mg/dL.

Patient data collection

The participating doctors' pre-existing hospital records provided the data, and an audit of the data was carried out to assess real-world efficacy in the past. Electronic health records were used to gather data, which was then compiled in a Microsoft Excel sheet. Demographic details, the length of the disease, the medication (withdrawn and/or associated, if any), the last oral semaglutide dose, the length of follow-up (from the start of the medication until the last visit), HbA1c, body weight, serum urea and creatinine levels, the frequency and reason for stopping the drug, and the frequency and kind of adverse events were all included.

Inclusion and exclusion criteria

Men and women over the age of 18 years, a diagnosis of T2D as defined by the American Diabetes Association (ADA) for at least 3 months, a minimum of 3 months of stable antihyperglycemic therapy using insulin or oral hypoglycemic agents (OHA), a prescription for oral semaglutide based on standard clinical practice, and signed informed consent were the requirements for inclusion.

The following conditions were excluded: other kinds of diabetes, any condition preventing the patient from understanding informed consent, and the patient's past or present involvement in interventional clinical trials.

Ethical approval

The Declaration of Helsinki and the norms for good clinical practice were followed in the retrospective evaluation of the patient files. Because it was a clinical audit intended to record the clinical results of patients started on semaglutide within the parameters of its legal use for weight reduction, and all the treatments were standard care, it was exempted from the need for ethical clearance. Therefore, this trial did not receive ethical approval.

Population size

Assuming a baseline standard deviation of HbA1c of 2.0% [larger than that reported in randomized clinical trials (RCTs)] due to the greater variability expected in an observational setting), and with a significance level (alpha error) of 0.05%, a minimum sample size of 80 subjects allowed detection with a statistical power of 80% and a minimum reduction of HbA1c of 0.6% at T6 (slightly lower than that obtained in RCTs but reflecting the greater variability of results derived from "real life" clinical experience, taking into account also the variability of associated therapies).

Statistical analysis

Data analysis was done using Microsoft Excel and SPSS (v.20). For continuous variables, descriptive data were summarized as mean and standard deviation; for categorical variables, they were summarized as percentage. Mixed models for repeated data were used to evaluate changes in the continuous study outcomes. The estimated mean or estimated mean difference from T0, together with its 95% confidence interval (95% CI), was used to express the results. For pre-post comparisons within groups, the paired t-test that was generated from linear mixed models for repeated measures was used. The trend of changes in categorical study endpoints was evaluated using the chi-square test. A p-value of less than 0.05 was used to indicate statistical significance.

Results

In our study, a total of 80 subjects were included. All the patients were on oral GLP-1 analogue. Out of these, the data of 20 patients were not included in efficacy analysis due to discontinuation for various reasons. For safety analysis and adherence all the patient data were included (Tab. 1). The participants' average age was 46.6 ± 8.1 years, with 70% of them being male. The mean duration of diabetes was 5.8 ± 3.9 years. At the time of semaglutide beginning (T0), the average weight was 82.27 ± 22.2 kg and the average HbA1c was 8.67 ± 1.3%. All patients received treatment with one or more OHAs, whereas 92.5% patients were on metformin and 22.5% had treatment with basal insulin plus OHAs. Approximately 65% of the individuals received treatment with antihypertensive and lipid-lowering medications, and around half (52.4%) of the subjects reported problems related to diabetes (Tab. 1). Dosages of oral semaglutide were adjusted by the attending physicians during treatment, resulting in 8 subjects treated with 3 mg/day, 33 with 7 mg/day, and 19 with 14 mg/day at 6 months. The highest dose of oral semaglutide was selected in sub-

Table 1. Patients' Baseline Characteristics

Baseline criteria	Value (N = 80)
M:F (%)	70:30
Age [years]	46.6 ± 8.1
Height [cm]	171.01 ± 8.4
Weight [kg]	82.27 ± 22.2
Waist circumference [cm]	94.68 ± 8.1
Duration of diabetes [years]	5.8 ± 3.9
FPG [mg/dL]	156.42 ± 21.6
PPPG [mg/dL]	248.95 ± 56.8
HbA1c [%]	8.67 ± 1.3
SBP [mmHg]	131.4 ± 13.6
DBP [mmHg]	79.4 ± 7.4
Creatinine [mg/dL]	0.844 ± 0.1
Urea [mg/dl]	31.6 ± 10.2
LDL cholesterol [mg/dL]	92.3 ± 28.2
HDL cholesterol [mg/dL]	46.2 ± 10.8
Triglycerides [mg/dL]	165.7 ± 90.4
Heart rate [bpm]	76.0 ± 10.9
Presence of co-morbidities (%)	
Hypertension	52 (65%)
Dyslipidemia	41 (51%)
CV Events	21 (26%)
Oral hypoglycemic agents before starting semaglutide (%)	
Sulfonylureas (%)	14 (22.5%)
SGLT2-i (%)	66 (82.5%)
Metformin (%)	74 (92.5%)
Pioglitazone	9 (11%)
DPP4i	12 (15%)
Basal insulin (%)	18 (22.5%)
Short-acting insulin (%)	5 (6%)

Data presented as mean ± SD or number (%)
CV — cardiovascular; DBP — diastolic blood pressure; F — female; FPG — fasting plasma glucose; HbA1c — glycated hemoglobin; HDL — high-density lipoprotein; LDL — low-density lipoprotein; PPPG — postprandial plasma glucose; SBP — systolic blood pressure; SD — standard deviation; SGLT2i — sodium-glucose cotransporter-2 inhibitors

jects with higher body weight and/or those treated with other GLP-1RAs.

The mean changes in body weight, FPG, and HbA1c at 6 and 12 months were clinically meaningful and statistically significant (Tab. 2).

The weight reduction was significant during the first 6 months, then it was in a plateau phase, and again it went up from 12 months until the end of the study period (Fig. 1A). There was no significant change in waist circumference (Fig. 1B)

There was a significant reduction in all blood glucose parameters. The mean FPG dropped from 156.4 mg/dL to 103.8 mg/dL (Fig. 1C), and the mean postprandial blood glucose (PPPG) changed from 248.9 mg/dL to 169.8 mg/dL over the treatment period (Fig. 1D). Similarly, the HbA1c level changed from 8.6% to 7.0% (Fig. 1E).

Analysis of variance (ANOVA) for HbA1c reduction throughout the treatment at T0, T6, T12, and T18 revealed an f-ratio value of 157.75878 with a p value of < 0.0001. The result is significant at $p < 0.05$.

Among the study participants, 74% continued their treatment. Out of the 26% patients who discontinued their treatment, in 14% this was due to adverse effects and in 12% it was due to the high cost of the therapy.

All the adverse effects noted in the study were non-serious in nature. The common adverse effects observed in the study were nausea (10 pts), vomiting (9 pts), belching (2 pts), and reflux (7 pts).

A small percentage of patients had hypoglycemia (0.5% of patients at T6, 1.1% at T12, and 1.4% at T18) reported having a moderate episode (54–70 mg/dL); one incident of severe hypoglycemia was observed at T12. During the 18-month period, no significant changes in concurrent glucose-lowering, antihypertensive, and lipid-lowering medications were seen.

Discussion

We found that oral semaglutide was a safe and effective therapy for uncontrolled T2D, independent of the patient's background, in this real-world observational retrospective cohort trial conducted in India. The research also demonstrated the safety and tolerability of oral semaglutide because all the side effects were mild and did not cause the medication to cease working; moreover, at the conclusion of the trial, there was a decrease in the number of hypoglycemic episodes.

We found that our patient subpopulation with HbA1c ≥ 8% showed a similar decrease in HbA1c at 6 months (−1.8%) as that reported in the IGNITE (−1.4%), PIONEER REAL Canada (−1.1%), and Japanese population (−1.2%) studies, despite the challenge of comparing our results with those of available real-world studies due to the significant baseline differences [11, 16, 17].

This is the longest real-world oral semaglutide trial to date. Our study's follow-up period was longer than that of the IGNITE worldwide observational study (about 6 months) [11], but further observational research will be required to evaluate the oral long-term effects and persistence of semaglutide in relation to body weight and glycemic control. The pattern of the HbA1c and body weight curves over time, which tended to plateau between 6 and 9 months and then rise further after 12 months, provides further evidence of the significance of dosage optimization.

Table 2. Changes in Estimated Mean Levels of Continuous Clinical Endpoints over Time

Change in	Visit	Estimated mean and 95% CI	Estimated mean difference from baseline and 95% CI	Within-group p-value
HbA1c [%]	T0	8.67 ± 1.3		
	T6	6.80 ± 1.2 (6.537; 7.063)	1.87 ± 0.7 (1.717; 2.023)	< 0.0001
	T12	6.85 ± 1.5 (6.521; 7.179)	1.82 ± 0.6 (1.689; 1.951)	< 0.0001
	T18	7.07 ± 1.1 (6.829; 7.311)	1.6 ± 0.3 (1.534; 1.666)	< 0.0001
FPG [mg/dL]	T0	156.42 ± 21.6		
	T6	91.64 ± 24.1 (86.359; 96.921)	64.78 ± 12.1 (62.129; 67.431)	< 0.0001
	T12	94.38 ± 23.2 (89.296; 99.464)	62.04 ± 10.2 (59.805; 64.275)	< 0.0001
	T18	103.8 ± 20.5 (99.308; 108.292)	52.62 ± 9.4 (50.560; 54.680)	< 0.0001
PPPG [mg/dL]	T0	248.95 ± 56.8		
	T6	156.46 ± 49.3 (145.657; 167.263)	92.49 ± 24.7 (87.077; 97.903)	< 0.0001
	T12	157.88 ± 51.6 (146.573; 169.187)	91.07 ± 21.3 (86.403; 95.737)	< 0.0001
	T18	168.86 ± 38.5 (160.423; 177.297)	80.09 ± 18.6 (76.014; 84.166)	< 0.0001
Body weight [kg]	T0	82.27 ± 22.2		
	T6	76.24 ± 20.3 (71.792; 80.688)	6.03 ± 2.8 (5.416; 6.644)	< 0.0001
	T12	76.12 ± 18.6 (72.044; 80.196)	6.15 ± 2.4 (5.624; 6.676)	< 0.0001
	T18	77.61 ± 15.2 (74.279 – 80.941)	4.66 ± 1.7 (4.287; 5.033)	< 0.0001
Waist circumference [cm]	T0	94.68 ± 8.1		
	T6	91.07 ± 7.3 (89.470; 92.670)	3.61 ± 1.1 (3.369–3.851)	< 0.0001
	T12	91 ± 6.4 (89.598; 92.402)	3.68 ± 0.9 (3.483–3.877)	< 0.0001
	T18	91.15 ± 5.8 (89.879; 92.421)	3.53 ± 0.4 (3.442–3.618)	< 0.0001
Serum urea	T0	31.6 ± 10.2		
	T6	30.8 ± 8.9 (28.850; 32.750)	0.8 ± 0.1 (0.778–0.822)	0.02
	T12	29.7 ± 7.4 (28.078; 31.322)	1.7 ± 0.8 (1.525; 1.875)	< 0.0001
	T18	28.6 ± 6.2 (27.241; 29.959)	3 ± 0.5 (2.890–3.110)	< 0.0001
Serum creatinine	T0	0.844 ± 0.1		
	T6	0.813 ± 0.1 (0.791; 0.835)	0.031 ± 0.03 (0.0244–0.0376)	0.06
	T12	0.792 ± 0.1 (0.770; 0.814)	0.052 ± 0.02 (0.0476–0.0564)	0.04
	T18	0.782 ± 0.1 (0.760; 0.804)	0.062 ± 0.01 (0.0598–0.0642)	0.05

Data presented as mean ± SD or number (%)
CI — confidence interval; HbA1c — glycated hemoglobin; FPG — fasting plasma glucose; PPPG — postprandial plasma glucose

The effects of GLP-1RAs on body weight reduction are therapeutically significant, given the rising incidence of obesity. Patients in our sample lost around 6.03 kg (6.03 ± 2.8 kg) after 6 months and 6.15 kg (6.15 ± 2.4 kg) at 12 months, and the weight reduction remained stable even after 18 months. Therefore, this research can serve as a first step in proving that semaglutide is beneficial for people who want to reduce weight. A significant difference in body weight was also seen in earlier semaglutide experiments and in other investigations, in which people with T2D lost less weight than comparable individuals without the condition [18, 19]. One reason for this might be that people with T2D have a larger reduction in energy expenditure when compared to those without the condition. Additionally, losing weight improves glucose regulation, which lowers glycosuria. As a result, there is a positive calorie balance, which makes it harder to lose weight. Another cause is the use of other anti-diabetic drugs such glipizide and insulin, which are linked to weight gain.

Additionally, the study showed that significant improvements in HbA1c were seen in both GLP-1RA--naive and GLP-1RA-experienced people, as expected. Although the safety profile is consistent with previous GLP-1RA reports, the information that is now available indicates that semaglutide may be more efficacious than its equivalents [20]. What exactly is causing semaglutide to be more successful than other GLP-1RAs is yet unknown. However, it is possible that liraglutide and semaglutide vary in this regard, and the acyl moiety found in acylated medications such as semaglutide may facilitate penetration into different parts of the central

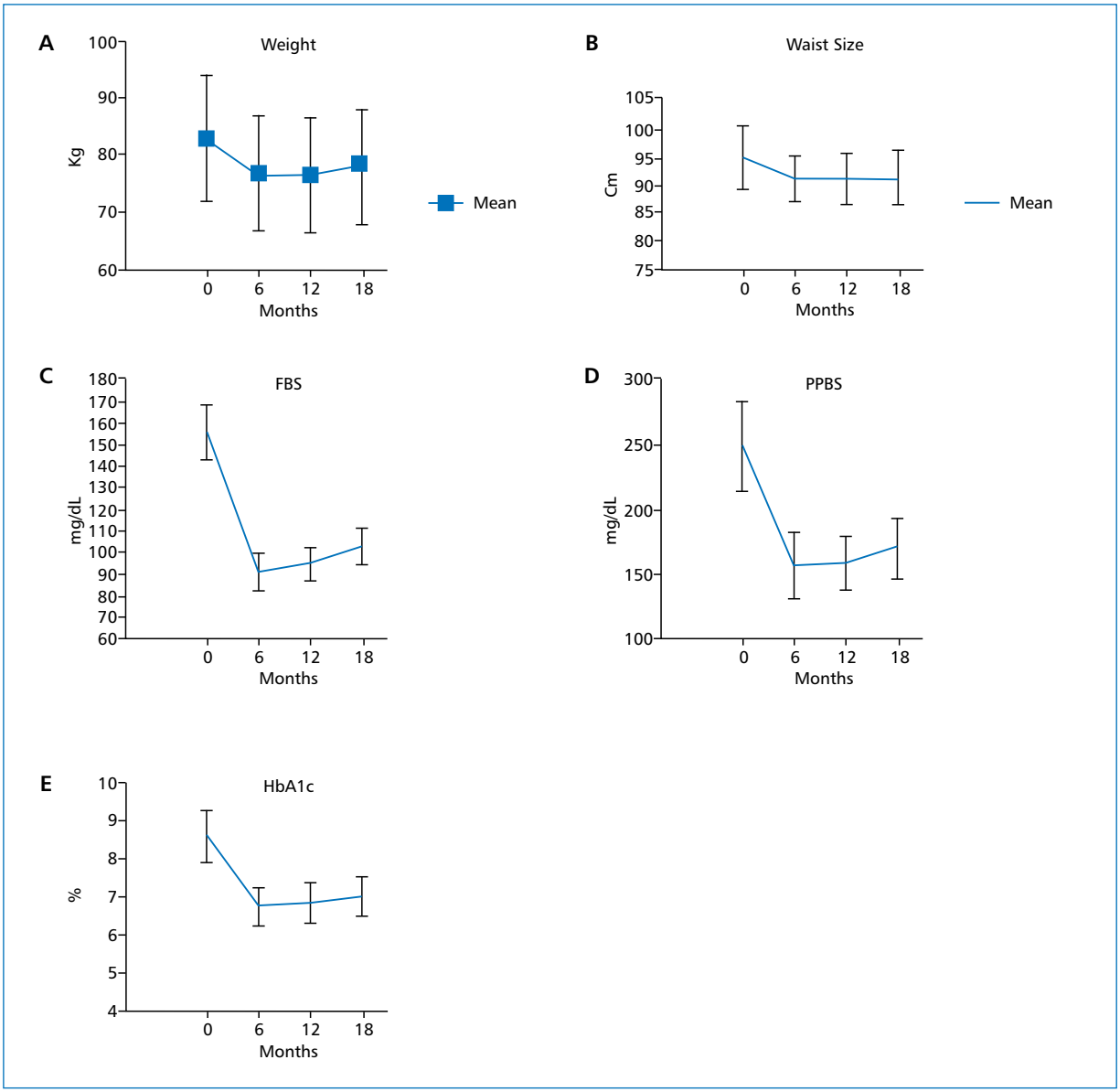

Figure 1. A. Weight change in overall population (N = 80); **B.** Change in waist circumference in overall population (N = 80); **C.** Change in fasting blood sugar (FBS) in overall population (N = 80); **D.** Change in postprandial blood sugar (PPBS) in overall population (N = 80) **E.** Change in glycated hemoglobin (HbA1c) in overall population (N = 80)

nervous system (CNS). Because of the way semaglutide is chemically structured, there is a theory that its effect on weight is mediated via CNS receptors that provide access to different parts of the nervous system [21].

GLP-1RAs, such as semaglutide, have been shown in cardiovascular (CV) outcome trials to lower CV risk and delay the deterioration of renal function. While improvements in glycemic management may play a role, these advantages are probably also mediated by additional effects, including decreased body weight, blood pressure, and albuminuria, enhanced endothelial function, and suppression of proinflammatory mediators [22]. In patients with diabetes kidney disease and moderate renal impairment (estimated glomerular filtration rate [eGFR]: 30–59 mL/min/1.73 m^2), the PIONEER-5 study demonstrated the safety and efficacy of oral semaglutide. Both the oral semaglutide and placebo groups' renal function did not change during the study period, but the oral semaglutide group's albumin-to-creatinine ratio dropped relative to the placebo group [23]. GLP1 can inhibit the expression of vascular cell adhesion molecule-1 and tumor necrosis factor-α in glomerular endothelial cells. GLP1 has been shown to increase nitric oxide synthesis, which may improve glomerular endothelial function [24]. The complete results of the FLOW study show that semaglutide sig-

nificantly lowers the risk of major renal disease events, major adverse cardiac events, and all-cause death in individuals with T2D and chronic kidney disease. It also slows down the decline of kidney function [25]. Furthermore, regardless of whether serum creatinine, cystatin C, or both were used to compute the eGFR, the effect of semaglutide was independent of changes in body weight [26, 27]. As a result, even in our trial, long-term use of oral semaglutide has a significant effect on the reduction of serum urea and creatinine.

Gastrointestinal events were the most common adverse events (AEs) with oral semaglutide that were recorded, and the ones that most commonly led to an early termination, as would be anticipated for a GLP-1RA and consistent with previous studies [28, 29]. However, most of these adverse events (AEs) happened early in the main phase, and no patient stopped because of an AE later in the durability phase. This suggests that discontinuations from oral semaglutide because of gastrointestinal AEs are more likely to happen early in treatment (during the initial dose-escalation phase) rather than with long-term use.

The study had merits and weaknesses. Our work is notable for being the first long-term observational retrospective research study in India to describe the effects of semaglutide in real-world settings. Extensive data on blood pressure, lipid profile, FPG, PPPG, side effects, and hypoglycemia further enhance its strength. However, there are many restrictions on the research. First, the absence of control groups makes it hard to separate the role that oral semaglutide played in lowering body weight and glycemic index from the role that lifestyle modifications may have played concurrently. Second, the data had to be forced into 6-month intervals to predict changes in body weight and HbA1c. This was because not every patient had the same observation duration and follow-up routine. Third, we had very little knowledge on the tolerability, adherence, or causes for stopping oral semaglutide, which left us with few options for enhancing persistence. Nevertheless, the retrospective design of the research and the lack of prearranged subgroup analysis according to age group, obesity, diabetes, or severity are drawbacks that make it impossible to draw firm conclusions about outcomes in these subgroups. More investigation is needed to determine the long-term efficacy and safety of semaglutide and implications on other endpoints (such the fatty liver index).

Conclusions

To sum up, this research represents the biggest multicenter real-world investigation of uncontrolled T2D patients in India receiving oral semaglutide as part of standard clinical practice. In an unselected group, oral semaglutide was safe and effective; almost two-thirds achieved a HbA1c of less than 7%, and one-third reported weight reduction of more than 10%. There were no signs of a safety hazard. Considering the worldwide supply chain challenges associated with subcutaneous GLP-1 RAs, the results of this investigation may aid in supporting clinical judgment.

Article information

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

Saswati Ray: conceptualization, formal analysis, methodology, writing — original draft, data collection. Aparajita Ray: conceptualization, supervision, data collection, writing — review and editing. Siddhartha Goutam: investigation, resources, formal analysis, data collection. Asis Mitra: methodology, formal analysis, writing — review and editing.

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Conflict of interests

The authors declare no conflict of interest.

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