Original Article

Effectiveness of Oral Semaglutide in Management of Type 2 Diabetes: A Real-World Study from India

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Abstract

Introduction: Oral Semaglutide (Sema-o) is the first oral glucagon like peptide-1 receptor analogue (GLP-1RA) commercially available for the treatment of type 2 diabetes (T2D). This study aimed to evaluate the efficacy of Sema-o in patients with T2D when added to the existing therapy. **Methods:** This retrospective real-world study enrolled adult patients with diabetes taking Sema-o, with at least one follow-up (from February 2022 till October 2023). A proforma recorded baseline and follow-up date, medications, body composition, laboratory and clinical parameters. Data is presented as median (interquartile range) and was analysed using SPSS. **Results:** A total of 351 patients followed up once, while 56 patients had 4 follow-up visits. Baseline parameters were as follows: age 53 years (43–61), duration of diabetes 10 years (5–16), weight 91 kg (79–103), body mass index (BMI) 32.7 kg/m^2 (29.3–36.6) and HbA1c 7.9% (6.9–9). The addition of Sema-o in the existing therapy for diabetes resulted in a significant reduction in HbA1c {follow-up: 1st 0.5%, 2nd 0.9%, 3rd 1.1% and 4th 1.1% (all, $P < 0.001$)} and % weight reduction {follow-up: 1st 2%, 2nd 3.3%, 3rd 4.1% and 4th 4.3% (all, $P < 0.001$)} from baseline. Reductions in BMI, glucose (fasting/post-prandial), lipids, liver enzymes and body composition parameters were significant. Gastro-intestinal side-effects (299 events in 52.4% of patients) were frequent. A total of 34/9.7% patients discontinued Sema-o. **Conclusion:** Intensification of existing therapy with Sema-o in obese patients with moderately uncontrolled diabetes proved to be an effective and relatively safe strategy. Achieving normoglycemia and reductions in weight, lipids and body fat/visceral fat with Sema-o may confer a much needed cardiometabolic benefit in these patients.

Keywords: HbA1c, oral semaglutide, type 2 diabetes, weight loss

Introduction

Oral semaglutide (Sema-o) is the first oral glucagon like peptide-1 receptor analogue (GLP-1RA) rolled out for the treatment of type 2 diabetes (T2D). The Peptide InnOvatioN for Early diabEtes tReatment (PIONEER) randomised controlled trials (RCTs) have comprehensively demonstrated the efficacy, safety, tolerability and cardiovascular safety of Sema-o when added in existing treatment of moderate to long-standing T2D.[1–7] In these trials, whether initiated as an early therapy, or added to existing treatment, Sema-o resulted in significant reductions in blood glucose and weight versus (individual) comparator arms.

India has an expanding population of people with diabetes. The most recent figures suggest that the prevalence of diabetes/prediabetes in India is 11.4%/15.3%, respectively.[8] Amongst these people, treatment intensification and/or cardiovascular risk mitigation remain unmet challenges. For example, the LANDMARC study evaluated T2D management in India over one year. Of 5,654 participants, mean HbA1c improved by 0.5%, with only 20% achieving HbA1c < 7%.[9] Asian–Indian phenotype in diabetes has previously been described,[10] where for any given level of body mass index (BMI), there is greater total body fat, visceral fat, central obesity, thin peripheries, insulin resistance and a diminished beta-cell reserve. These factors along with uncontrolled diabetes increase the cardiovascular risk in the Indian population,[11] wherein GLP-1RAs can play an important role. They improve

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beta-cell mass, insulin resistance (IR), glycemic control and reduce cardiovascular risk (dyslipidemia, hypertension and weight) in people with diabetes. A meta-analysis has shown that Asians obtain superior major adverse cardiovascular events benefit from GLP1RAs as compared to Whites.[12]

While injectable GLP-1RAs have been available in India for nearly two decades, Sema-o was recently launched in January 2022. It is not an unknown fact that clinicians in India struggle with patients to initiate injectable anti-diabetic drugs (ADAs).[9] The oral GLP-1RA has usurped the injectable GLP-1RAs in prescriptions, likely as a result of the ease of administration. The launch of Sema-o provided a pedestal for extending the clinical benefit of GLP-1RAs to the Indian population with diabetes. Hence, this study was initiated to observe and collect data on the effectiveness (glycemic parameters, weight, body composition, lipid profile), safety (side-effects) and tolerability (discontinuation, effect on other medications) in the Indian real-world scenario.

Materials and Methods

We conducted a real-world retrospective observational study. Participants were consecutive patients (≥18 years) with prediabetes or T2D initiated on Sema-o at the outpatient department of Endocrinology, Max Super Speciality Hospital, New Delhi, India between February 2022 and October 2023. During this period, Sema-o (3 mg) was prescribed to 756 patients out of which 351 had at least one follow-up visit and were included in this study. The study was designed to compare follow-up data from the baseline in the cohort. Outcomes included effectiveness (glycemic metrics, weight, body composition), safety (side-effects) and tolerability (discontinuation, effect on other medications) of Sema-o in this retrospective cohort.

Medication initiation and up-titration

Sema-o was initiated at a dose of 3 mg/day, in accordance with the package insert instructions for intensifying diabetes treatment. The dose was increased to 7 mg/day after four or more weeks. It was further escalated to 14 mg/day after another four or more weeks (as tolerated). Sema-o was to be taken empty stomach early morning with 120 mL water, while keeping a gap of at least 45 min with other medicines, beverage or food. Dipeptidyl peptidase-4 inhibitors (DPP4i) were discontinued at baseline. All patients were informed regarding the anticipated side-effects. Existing medications were modified/discontinued, and newer medications were added as required, with the goal of normalising glycemic control as per current American Diabetes Association guidelines.[13] Patients were instructed to follow-up in 4–6 weeks with investigations.

Data collection

A proforma recorded baseline and follow-up parameters for each individual. Parameters registered were as follows: name, registration, age, sex, duration of diabetes, weight, systolic/diastolic blood pressure (SBP/DBP), pulse rate, baseline medications for diabetes (type and dose), comorbidities, laboratory parameters such as fasting plasma glucose (FPG), post-prandial plasma glucose (PPPG), glycated haemoglobin (HbA1c), creatinine (Cr), aspartate aminotransferase/alanine aminotransferase (AST/ALT), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG) and body composition analysis (BCA). At follow-up, the visit date, weight and other biochemical/clinical parameters were recorded in the proforma. Changes in existing medications {insulin and anti-diabetic drugs (ADAs)}, side-effects and tolerability were recorded at each follow-up.

BCA was performed by Inbody 570, using bioelectric impedance to measure – waist-hip ratio (WHR), BMI, total body fat (TBF), fat mass (FM), fat-free mass (FFM), skeletal muscle mass (SMM), appendicular lean mass (ALM), and visceral fat (VF).

Statistical analysis

SPSS version 26 was utilised for analysis. Continuous variables were tested for normality using Shapiro-Wilk test. They were found to be not normally distributed ($P < 0.05$). These variables were represented as median and interquartile range (IQR). Intra-group paired analysis of continuous variables was conducted using Wilcoxon Signed Ranks test. Categorical variables were represented as number/%. Intra-group paired analysis of categorical variables was conducted using Fischer's exact test.

Ethical aspects

A waiver of consent was taken from the institutional ethics committee as retrospective patient data was used. The study was conducted in accordance with the declaration of Helsinki (1964).

Results

Demographics

The baseline sample consisted of 351 patients. Of these, 334/95.2% had T2D, while remaining had prediabetes (17/4.8%). The median (IQR) age was 53 years (43–61); 48.7% of patients were female ($n = 171$). The median (IQR) duration of diabetes was 10 (5–16) years, weight was 91 kg (79–103), and BMI was 32.7 kg/m^2 (29.3–36.6). At baseline, males had higher weight and WHR, whereas females had greater BMI and TBF. Other anthropometry is mentioned in Table 1. Comorbidities were as follows: dyslipidemia (284/80.9%), hypertension (219/62.4%), non-alcoholic fatty liver disease (NAFLD; 132/37.6%), obstructive sleep apnoea (OSA; 40/11.4%), coronary artery disease (CAD; 42/11.9%) and polycystic ovary syndrome (PCOS; 25/171; 14.6%).

At the initiation of Sema-o, median (IQR) FPG was 144 mg/dL (120–174), PPPG was 199 mg/dL (159–236), and HbA1c was 7.9% (6.9–9). Other baseline laboratory and BCA parameters are mentioned in Table 1. Baseline usage of ADAs {insulin secretagogues, metformin, DPP4i, sodium–glucose co-transporter type 2 inhibitors (SGLT2i), thiazolidinediones, alpha-glucosidase inhibitors (AGi)} and insulin/injectable GLP1RAs is represented in Supplementary Table 1.

Follow-up visits and medicine up-titration

We recorded data till 4 follow-up visits. Number of patients/median (IQR) days per visit (from baseline) were as follows: 1st follow-up – 351/38 days (31–68), 2nd follow-up – 198/89 days (69–133), 3rd follow-up – 108/160 days (110–231) and 4th follow-up – 56/270 days (201–351). Dose was escalated from 3 mg to 7 mg at a median (IQR) duration of 5 weeks (4–9) and from 7 mg to 14 mg at 12 weeks (9–23.5). A total of 301 and 167 patients were prescribed 7 mg and 14 mg doses, respectively.

Changes in glycaemic metrics and medications

Sema-o resulted in improvements in FPG, PPPG and HbA1c. While median FPG was normalised at the 1st follow-up (144 vs. 125 mg/dL, $P < 0.001$), PPPG (199 vs. 156 mg/dL, $P < 0.001$) and HbA1c (7.9 vs. 7%, $P < 0.001$) improved to near normal by the 2nd follow-up. Although glycemic metrics (at each follow-up) were significantly improved as compared to the baseline, the significance was lost when compared to the previous value by 3rd and 4th follow-up for FPG and PPPG/HbA1c, respectively [Table 2].

HbA1c reduction per follow-up was as follows: 1st 0.5% (0.1–1.2), 2nd 0.9% (0.3–1.7%), 3rd 1.1% (0.4–2) and 4th 1.1% (0.4–2.1). HbA1c at baseline and follow-ups was subdivided into tertiles of < 7%, 7–9%, ≥9%. During follow-up, the percentage of individuals in former two tertiles climbed steadily [Figure 1].

When compared to baseline, there was a significant reduction in doses of insulin secretagogues ($P < 0.001$) and metformin ($P = 0.031$) but not of insulin. Insulin secretagogues, metformin and SGLT2i were frequently discontinued during follow-up ($P < 0.001$, $P = 0.05$ and

Table 1: Baseline parameters

Parameter	Median (IQR)
Anthropometry	
Age (years, *n*=351)	53 (43–61)
Sex (male/female)	180/171
Diabetes duration (years, *n*=318)	10 (5–16)
Weight (kg, *n*=351)	91 (79.2–103)
Height (cm, *n*=351)	165 (158–174)
Body mass index (kg/m^2, *n*=351)	32.74 (29.34–36.64)
Waist-hip ratio (*n*=257)	1.03 (0.97–1.08)
Systolic BP (mmHg, *n*=342)	120 (120–135.8)
Diastolic BP (mmHg, *n*=342)	80 (80–80)
Pulse (/min, *n*=342)	88 (80–96)
Investigations	
FPG (mg/dL, *n*=334)	144 (120–174)
PPPG (mg/dL, *n*=318)	198.5 (159–235.8)
HbA1c (%, *n*=339)	7.9 (6.9–9)
Creatinine (mg/dL, *n*=312)	0.8 (0.6–0.9)
AST (IU/mL, *n*=286)	25 (20–36)
ALT (IU/mL, *n*=289)	31 (20–46)
LDL-C (mg/dL, *n*=299)	87 (64–114)
HDL-C (mg/dL, *n*=273)	42 (36–50)
TG (mg/dL, *n*=294)	151 (117–210.8)
Liver stiffness/E (kPa, *n*=146)	7.1 (5.2–10.7)
Body composition analysis	
Total body fat (%, *n*=212)	45 (38.1–50.4)
Fat mass (kg, *n*=212)	39.4 (32.1–49)
Fat-free mass (kg, *n*=212)	51.4 (42.7–59.8)
Skeletal muscle mass (kg, *n*=212)	28.1 (23.3–33.5)
Appendicular lean mass (kg, *n*=212)	21.5 (17.2–25.6)
Visceral fat level (*n*=212)	20 (16–20)

Gender differences	Males	Females
Weight (kg, *n*=351)	96.1 (84.8–108)	84 (74–95.5)
Body mass index (kg/m^2, *n*=351)	31.7 (28.9–35.9)	33.4 (30.4–37.9)
Waist-hip ratio (*n*=257)	1.06 (1.01–1.11)	0.99 (0.94–1.05)
Total body fat (%, *n*=212)	39.3 (34.4–44.1)	49.7 (45.1–51.8)

Legend: fasting plasma glucose (FPG), post-prandial plasma glucose (PPPG), glycated haemoglobin (HbA1c), aspartate aminotransferase (AST), alanine aminotransferase (ALT), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG)

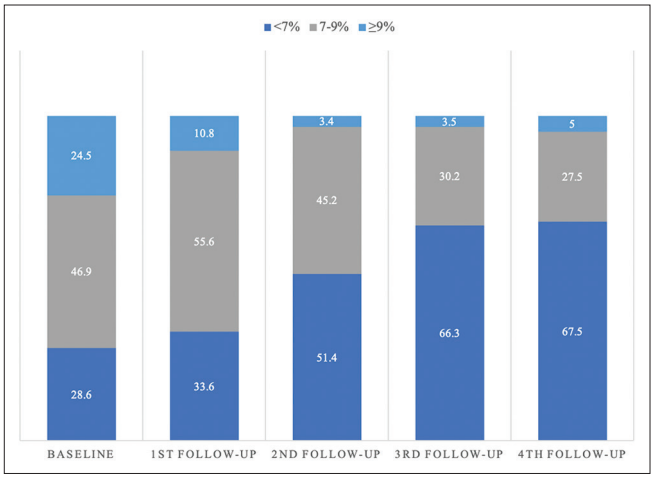

Figure 1: HbA1c levels after adding oral semaglutide

Table 2: Changes in glycaemic metrics

Follow-up	Value	*P* (baseline)	*P* (previous)
FPG (mg/dL)			
Baseline (*n*=334)	144 (120–174)		
1st (*n*=311)	125 (110–145)	<0.001	
2nd (*n*=189)	116 (99–131)	<0.001	<0.001
3rd (*n*=92)	115 (103–124)	<0.001	0.089
4th (*n*=42)	110 (99–122)	<0.001	0.106
PPPG (mg/dL)			
Baseline (*n*=318)	199 (159–236)		
1st (*n*=298)	171 (150–198)	<0.001	
2nd (*n*=182)	156 (135–176)	<0.001	<0.001
3rd (*n*=82)	154 (133–170)	<0.001	0.025
4th (*n*=36)	142 (123–161)	<0.001	0.086
HbA1c (%)			
Baseline (*n*=339)	7.9 (6.9–9)		
1st (*n*=286)	7.5 (6.7–8.2)	<0.001	
2nd (*n*=177)	7 (6.4–7.6)	<0.001	<0.001
3rd (*n*=86)	6.8 (6.1–7.3)	<0.001	<0.001
4th (*n*=40)	6.6 (5.9–7.1)	<0.001	0.547

Legend: fasting plasma glucose (FPG), post-prandial plasma glucose (PPPG), glycated haemoglobin (HbA1c)

$P = 0.023$, respectively). SGLT2i and insulin (both $n = 11$) were frequently initiated/escalated during follow-up [Table 3]; however, this addition was not significant.

Changes in weight metrics and BCA

When compared to baseline, both weight and BMI reduced significantly at each follow-up. Weight reduction per follow-up was as follows: 1st 1.8 kg (0.2–3), 2nd 3 kg (1–5.5), 3rd 3.9 kg (1.5–6.9) and 4th 3.7 kg (2–6.8) [Table 4]. Up until the 3rd follow-up, the loss in weight and BMI was significantly better than the previous/2nd follow-up. The percentage of patients with weight loss ≥5% was 10%, 33.3%, 42.4% and 43.4% in successive follow-ups. WHR improved significantly at 1st and 3rd follow-ups [Table 4].

Data for BCA was only available till 3rd follow-up. The weight lost was both fat (significant reductions in TBF, FM and VF) and muscle mass (significant reductions in SMM and ALM) [Supplementary Table 2]. The reductions in TBF and FM were more pronounced than SMM and ALM. By 3rd follow-up, significant gain (from baseline) was observed in SMM and ALM. Intra-follow-up reductions were significant for FM, FFM, SMM and ALM at the 2nd follow-up.

Changes in other laboratory parameters

Data was available till 2nd follow-up visit for other parameters. There was significant lowering of ALT, LDL-C and TG at 1st follow-up but not at the 2nd follow-up.

Table 3: Changes in medications on follow-up

Drug (name/*n*)	Baseline	Reduction	*P*	Discontinued	*P*	Added	*P*
Secretagogues	169	32	<0.001	28	<0.001	9	0.323
Metformin	285	18	0.031	16	0.050	10	0.218
SGLT2i	203	4	0.641	8	0.023	11	0.766
Pioglitazone	12	2	0.092	2	0.184	0	–
Insulin	95	26	0.846	5	0.997	11	0.911

Legend: sodium–glucose co-transporter type 2 inhibitors (SGLT2i)

Table 4: Changes in weight metrics

Follow-up	Value	*P* (baseline)	*P* (previous)
Weight (kg)			
Baseline (*n*=351)	91 (79–103)		
1st (*n*=341)	89 (78–100)	<0.001	
2nd (*n*=200)	88 (77–101)	<0.001	<0.001
3rd (*n*=106)	87 (76–99)	<0.001	<0.001
4th (*n*=53)	86 (75–101)	<0.001	0.139
Weight loss (kg/%)			
1st (*n*=341)	1.8 (0.2–3)/2 (0.2–3.5)		
2nd (*n*=200)	3 (1–5.5)/3.3 (1–5.6)		
3rd (*n*=106)	3.9 (1.5–6.9)/4.1 (1.8–6.8)		
4th (*n*=53)	3.7 (2–6.8)/4.3 (2.7–7.7)		
Body Mass Index (kg/m^2)			
Baseline (*n*=351)	32.7 (29.3–36.6)		
1st (*n*=342)	31.9 (29.1–36)	<0.001	
2nd (*n*=200)	31.5 (28.9–35.4)	<0.001	<0.001
3rd (*n*=106)	31.3 (28.7–34.1)	<0.001	<0.001
4th (*n*=53)	31.2 (28.5–34.7)	<0.001	0.412
Waist-Hip Ratio			
Baseline (*n*=257)	1.03 (0.97–1.08)		
1st (*n*=187)	1.02 (0.97–1.07)	<0.001	
2nd (*n*=121)	1.01 (0.98–1.08)	0.186	0.963
3rd (*n*=70)	1.02 (0.97–1.08)	0.037	0.127
4th (*n*=26)	1.02 (0.95–1.06)	0.094	0.343

Weight metrics per follow-up

	Weight loss (*n*/%)	Weight stable (*n*/%)	Weight gain (*n*/%)
1st (*n*=341)	261 (76.5%)	32 (9.4%)	48 (14.1%)
2nd (*n*=200)	158 (79%)	14 (7%)	28 (14%)
3rd (*n*=106)	90 (84.9%)	3 (2.8%)	13 (12.3%)
4th (*n*=53)	44 (83%)	4 (7.5%)	5 (9.5%)

Serum creatinine, HDL-C and AST were not significantly improved [Supplementary Table 3].

Safety and tolerability

Sema-o was generally fairly tolerated. A total number of side-effects were 299 in 184 patients (52.4%), while 167 (47.6%) patients did not report any events. Side-effects were mainly gastro-intestinal (GI), and their frequency was as follows: nausea (99/28.2%), vomiting (26/7.4%), bloating (40/11.4%), pain abdomen (27/7.7%), constipation (30/8.5%), diarrhoea (38/10.8%) and dyspepsia (32/9.1%). These side-effects were common at initiation and dose escalation and resulted in both infrequent dose escalation (patient resistance) and de-escalation (20/18.5% at 3rd follow-up; eight patients 7 to 3 mg, 12 patients 14 to 7 mg) during follow-up. Other side-effects were as follows: lethargy (18/5.1%) and hypoglycaemia (21/6%) due to existing hypoglycaemic medications, glycaemic control and/or nausea. Sema-o was discontinued by 34/9.7% patients. Reasons for discontinuation included as follows: multiple (≥3) side-effects, persistent nausea and expense.

Discussion

In this retrospective real-world study, Sema-o was found to be an effective and relatively safe medication when added to the existing therapy in patients with T2D in India. It lowered HbA1c by >1% and weight by nearly 5% when used for a period of five or more months. Other cardiometabolic benefits were derived in terms of lowering of lipids, visceral and TBF (while preserving lean mass) and reduction in the use of insulin secretagogues (associated with hypoglycaemia). GI side-effects were frequent which resulted in dose de-escalation, discontinuation and loss to follow-up.

Previously, PIONEER trials have established the benefits of adding Sema-o to insulin, SGLT2i, metformin or multiple drug combinations.[1–7] These trials have spurred real-world studies at various centres.[14–20] Their results [Supplementary Table 4] are remarkably similar with reductions in HbA1c, weight, BMI and cardiovascular risk biomarkers such as blood pressure and lipids. The extra-glycemic benefits and ease of administration of Sema-o encouraged us to plan this study.

The glycaemic improvements seen in this study were immediate [Table 2], with 0.5% HbA1c reduction and normalisation of FPG at the 1st follow-up (38 days). There was near-normalisation of HbA1c and PPPG by the 2nd follow-up (89 days). Further reduction was gradual leading to a HbA1c of 6.8% (1.1% reduction) by 3rd follow-up (160 days). Intra-visit HbA1c and PPPG were significantly better till the 3rd follow-up. At the 4th follow-up (270 days), the glycemic improvements were maintained but not significantly better than the previous values. The proportion of patients with HbA1c <7% increased from 28.6% at baseline to 67.5% at the last follow-up [Figure 1]. There was reduction in the dose of insulin secretagogues and metformin and significant discontinuations of SGLT2i and the former two medications [Table 3]. The improved glycemic control in our study could have been attributed to intensification of existing therapy; however, the additions/escalations in insulin, and other ADAs were not significant.

Weight and BMI reductions in this study were modest and significant (from baseline and intra-visit), with % weight reduction nearly reaching the clinically significant value of 5% by the 3rd follow-up. These reductions were independent of addition/escalation of SGLT2i for glycemic control. More than 80% of the patients either maintained or lost their weight during follow-up [Table 4]. Percentage of patients with ≥5% weight loss at the 3rd follow-up was 42.4% (45/106). Weight reduction could be attributed to frequent nausea, decreased food intake, besides loss of fat mass. Our study participants had a baseline BMI of 32.7 kg/m^2, which goes against the Asian–Indian phenotype, however, in a study from Japan,[19] participants with a baseline BMI of 27.3 kg/m^2 achieved both reduction in weight and cardiometabolic parameters (ALT, cholesterol, TG).

There were early and significant reductions in both fat parameters (TBF%, FM, VF) as well as muscle parameters (SMM, ALM and FFM) of body composition. TBF, FM and VF lowered significantly till the 2nd follow-up and thereafter remained static. On the contrary, muscle parameters initially lowered followed by a rise to baseline (or greater in case of FFM and SMM) which was clinically significant [Supplementary Table 2]. Similar findings have been reported by another study.[18] Selective fat loss and conserved muscle/FFM likely are the driver of multitude of benefits of Sema-o including weight loss, decreased IR (better glycemic control), decreased lipids, inflammation and lipotoxicity. Likewise, in this study, there were mild (significant) reductions in ALT, LDL-C and TG at 1st follow-up [Supplementary Table 3]. These findings are of particular importance for the Asian–Indian phenotype with T2D. Preservation of lean muscle mass and reduction in VF is likely to benefit IR and antecedent cardiovascular morbidity in the Indian population with T2D.[21] It is known that GLP1RAs promote glucose delivery into skeletal muscle (via AMP-activated protein kinase), leading to less breakdown and more muscle synthesis.[22]

While other real-world studies have reported good tolerance of Sema-o,[18,19] we write it as relatively safe as only 47.6% patients did not have any side-effects. Although the GI side-effects and discontinuations (9.7%) were similar to PIONEER trials and other real-world studies, our tentativeness derives from the fact that escalation was often delayed (7 mg/14 mg: 5/12 weeks), and de-escalation was common (n = 20/18.5%, 3rd follow-up). In the Indian real-world setting, GI side-effects still remain common obstacles to initiate or escalate GLP1RAs and can result in loss to follow-up.[23] Despite these problems, acceptance of Sema-o is better than the injectable GLP1RAs available in India due to convenience of the oral formulation and the guideline to start earlier in management of T2D.[11,24]

The major limitation of this study was the high loss to follow-up. Attrition has resulted in pushing the numbers up at 3rd and 4th follow-ups; hence, the results cannot be generalised. Nevertheless, the numbers at 3rd follow-up are similar to or

better than other real-world studies on Sema-o [Supplementary Table 3]. Other limitations included inconsistent numbers of laboratory and BCA parameters, retrospective nature of the study, lack of control arm and lack of data on urine protein excretion and blood pressure improvement during follow-up. Strengths included a single-centre and endocrinologist-based patient care, and robust glycaemic control in follow-up (2/3rd patients with HbA1c <7%) and data derived from patients with long-standing diabetes with CAD risk factors or disease. This is the first study from India to evaluate and prove the efficacy of Sema-o in the management of T2D.

Conclusions

In this retrospective real-world study, intensification of existing treatment in patients with moderately uncontrolled diabetes with Sema-o proved to be an effective and relatively safe strategy. Normalisation of HbA1c (1.1% reduction) and modest reduction in weight (4.3%), lipids and body fat/VF with Sema-o was observed. This may confer a much needed cardiometabolic benefit in obese patients with diabetes. GI side-effects were common and may represent an obstacle to more widespread utilisation of this medication.

Authors' contribution

AD (design, literature search, data analysis, statistical analysis, manuscript preparation), SM (design, data acquisition, data analysis), RJ (design, data acquisition, data analysis), AM (concept, design, data acquisition, manuscript review).

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Conflicts of interest

There are no conflicts of interest.

Data availability

Data available on request from the corresponding author.

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Supplementary Table 1 describes the baseline medications for diabetes in study group. This table is for comparison with change in medication upon follow-up [Table 3] which was a significant finding in this study

Supplementary Table 1: Baseline medications for diabetes

Medication	Dose {median (range)}
Insulin secretagogues	
Glimepiride (*n*=110)	4 mg (0.5–8)
Gliclazide (*n*=53)	90 mg (15–240)
Repaglinide (*n*=6)	0.5 mg (0.5–1)
DPP4i	
Linagliptin (*n*=50)	5 mg
Teneligliptin (*n*=7)	20 mg
Sitagliptin (*n*=86)	50 mg (50–100)
Vildagliptin (*n*=56)	100 mg
SGLT2i	
Dapagliflozin (*n*=108)	10 mg (5–10)
Empagliflozin (*n*=73)	10 mg (10–25)
Canagliflozin-100 (*n*=12)	100 mg
Canagliflozin-300 (*n*=10)	300 mg
Metformin (*n*=285)	1500 mg (1000–2000)
Thiazolidinedione (Pioglitazone) (*n*=12)	15 mg (15–30)
AGI (Voglibose) (*n*=22)	0.2 mg (0.2–0.3)
GLP1RAs	
Liraglutide (*n*=12)	1.2 mg (1.2–3)
Dulaglutide (*n*=4)	1.5 mg (0.75–1.5)
Insulin	
Basal (*n*=41)	0.41 U/kg (0.1–1.75)
Premixed (*n*=32)	
Basal-bolus (*n*=22)	

Legend: dipeptidyl peptidase-4 inhibitors (DPP4i), sodium–glucose co-transporter type 2 inhibitors (SGLT2i), alpha-glucosidase inhibitors (AGI), glucagon like peptide-1 receptor analogue (GLP-1RA)

Supplementary Table 2 depicts the gradual changes in body composition analysis when compared with baseline. The improvements were significant as discussed in the results

Supplementary Table 2: Changes in body composition analysis

Follow-up	Value	*P* (baseline)	*P* (previous)
Total body fat %			
Baseline (*n*=212)	45 (38.1–50.4)		
1st (*n*=196)	44.2 (36.9–50.5)	<0.001	
2nd (*n*=123)	42.6 (37.1–48.2)	<0.001	0.278
3rd (*n*=51)	42.8 (35–48.3)	<0.001	0.353
Fat mass (kg)			
Baseline (*n*=212)	39.4 (32.1–49)		
1st (*n*=196)	38.2 (30.7–47.9)	<0.001	
2nd (*n*=123)	35.8 (30.2–43.1)	<0.001	0.003
3rd (*n*=51)	35.7 (30.8–45.4)	<0.001	0.099
Fat-free mass (kg)			
Baseline (*n*=212)	51.4 (42.7–59.8)		
1st (*n*=196)	51.1 (42.3–59.3)	0.022	
2nd (*n*=123)	50 (43.2–59)	0.007	0.007
3rd (*n*=51)	53.5 (43.4–60.3)	0.018	0.442
Skeletal muscle mass (kg)			
Baseline (*n*=212)	28.1 (23.3–33.5)		
1st (*n*=196)	28.1 (22.7–33)	0.022	
2nd (*n*=123)	27.3 (23.2–32.9)	0.004	0.002
3rd (*n*=51)	29.1 (23.3–33.4)	0.006	0.335
Appendicular lean mass (kg)			
Baseline (*n*=212)	21.5 (17.2–25.6)		
1st (*n*=196)	21.2 (16.9–25.3)	0.009	
2nd (*n*=123)	20.6 (17.2–25)	<0.001	0.001
3rd (*n*=51)	21.8 (17.2–25.8)	0.115	0.952
Visceral fat (%)			
Baseline (*n*=212)	20 (16–20)		
1st (*n*=196)	19 (15–20)	<0.001	
2nd (*n*=123)	19 (14–20)	<0.001	0.543
3rd (*n*=51)	18 (15–20)	<0.001	0.455

Supplementary Table 3 depicts the gradual changes in creatinine, transaminases and lipid parameters on follow-up

Supplementary Table 3: Changes in other laboratory parameters

Follow-up	Value	*P* (baseline)
Creatinine (mg/dL)		
Baseline (*n*=312)	0.8 (0.6–0.9)	
1st (*n*=175)	0.8 (0.7–0.9)	0.874
2nd (*n*=72)	0.8 (0.7–1)	0.329
AST (IU/mL)		
Baseline (*n*=286)	25 (20–36)	
1st (*n*=166)	26 (20–38)	0.115
2nd (*n*=66)	25 (20–36)	0.101
ALT (IU/mL)		
Baseline (*n*=289)	31 (20–46)	
1st (*n*=166)	29 (21–44)	0.018
2nd (*n*=66)	26 (19–40)	0.01
LDL-C (mg/dL)		
Baseline (*n*=299)	87 (64–114)	
1st (*n*=177)	72 (53–97)	<0.001
2nd (*n*=78)	68 (50–91)	0.002
HDL-C (mg/dL)		
Baseline (*n*=273)	42 (36–50)	
1st (*n*=164)	42 (36–51)	0.841
2nd (*n*=75)	40 (35–47)	0.808
TG (mg/dL)		
Baseline (*n*=294)	151 (110–211)	
1st (*n*=169)	142 (113–185)	0.003
2nd (*n*=79)	137 (112–168)	0.159

Legend: Aspartate aminotransferase (AST), alanine aminotransferase (ALT), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG)

Supplementary Table 4 describes the comparison of real-world studies of oral semaglutide

Supplementary Table 4: Comparison of real-world studies on oral semaglutide

Study parameter	Aroda VR *et al.*[14]	Candido R *et al.*[15]	Klobucar S *et al.*[16]	Moreno-Perez O *et al.*[17]	Volpe S *et al.*[18]	Yamada H *et al.*[19]	Amamoo J *et al.*[20]
Number of patients	782	129	53	170	130	88	398
Follow-up duration (months)	6	6	6	6	6	6	12
Age (years)	57.8	72	59	63	66.3	62	59.9
Duration of diabetes (years)	6.9	11	NA	8	8.7	10.5	NA
Baseline HbA1c (%)	8.2 (*n*=145)	7.2	8.8	7.8	6.4	8.53	8.8
Final HbA1c (%)	7.2 (*n*=66)	6.9	7.4	6.9	6	7.29	7.8
Final HbA1c <7%	NA	Present/% NA	NA	Present/% NA	NA	48	32.4
Baseline weight (kg)	104.9	NA	97.3	95	75.3	73.6	102.4
Final weight (kg)	NA	NA (2 kg loss)	91.4	90	71.6	72.2	98.9
≥5% weight loss (%)	NA	27.6	56.7	Present/% NA	Present/% NA	NA	33.4
Baseline BMI (kg/m^2)	36.2	28.8	32.87	36.03	28.2	27.3	35.2
Final BMI (kg/m^2)	NA	28.4	NA	NA	26.8	26.1	34.1
Side-effects: GI	NA	6.2	NA	8.7	16	11.4	NA
Discontinuation	NA	10	NA	23.8	0	0	NA

Legend: glycated haemoglobin (HbA1c), body mass index (BMI), gastro-intestinal (GI), not available (NA)