original article

Efficacy and safety of semaglutide: real-world tertiary care experience from Saudi Arabia

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BACKGROUND: Semaglutide, a glucagon-like peptide-1, is an effective antidiabetic drug promoting weight loss and providing cardiovascular protection. The original trials did not include participants from Saudi Arabia; hence, the study's findings are expected to be useful.

OBJECTIVES: Explore the efficacy, safety, and favorable effects of once-weekly subcutaneous semaglutide (1 mg) in patients with type 2 diabetes and those who received it as an off-license prescription without having diabetes.

DESIGN: Retrospective review of medical records.

SETTING: Department of medicine at our institution.

PATIENTS AND METHODS: This retrospective observational study evaluated patients receiving the glucagon-like peptide-1 analog semaglutide, with the trade name Ozempic. The weight, height, body mass index, blood pressure, and laboratory data, including serum creatinine and hemoglobin A1c (HbA1c) levels and urine albumin/creatinine ratio, were recorded. Moreover, any history of medical comorbidities, such as cardiovascular diseases, cerebrovascular diseases, and heart failure, was documented before and after drug administration.

MAIN OUTCOME MEASURES: Glycemic and weight loss efficacy

SAMPLE SIZE: 1007 patients

RESULTS: The median age of the patients was 57.0 years, comprising 60.28% females. Among them, 955 and 442 patients received the medication for at least 3 and 6 months, respectively. Our results show a 4.4% weight loss and 0.4% improvement in HBA1c in patients with diabetes. Similar results were observed in the patients without diabetes in terms of weight along with a significant decrease in diastolic blood pressure. Our results also show stability in the serum creatinine and urine albumin creatinine ratio. The drug was equally effective in males and females.

CONCLUSION: Treatment with once-weekly subcutaneous semaglutide (1 mg) led to clinically significant weight loss and improved HbA1c level and cardiometabolic risk factors such as blood pressure.

LIMITATIONS: Retrospective design.

CONFLICT OF INTEREST: None.

Type 2 diabetes mellitus (DM), a metabolic disorder characterized by hyperglycemia, is caused by impaired pancreatic beta cell function coupled with insulin resistance. The global burden of type 2 DM is 10.5% and is projected to increase to 12.2% by 2045, with a similar prevalence between women and men.[1] In Saudi Arabia, type 2 DM affects approximately 28% of the Saudi population aged >18 years, with a more significant increase in prevalence observed among those aged ≥40 years; moreover, an association was observed between overweight and obesity and type 2 DM.[2] Type 2 DM is a multifactorial disease induced by several factors, such as genetic predisposition, patient sedentary lifestyle, and high consumption of sugary beverages. These factors contribute to weight gain and increase the risk of morbidity and mortality due to cardiovascular diseases, hypertension, and DM.[3,4]

Semaglutide, a gastric hormone produced by intestinal L cells and a member of the glucagon-like peptide-1 (GLP-1) family, stimulates insulin synthesis and suppresses glucagon in a glucose-dependent manner, thereby promoting glucose uptake by peripheral tissues.[5] It decreases circulating leptin levels, which further aids in weight loss, and reduces energy intake by slowing stomach emptying, resulting in decreased hunger and body weight.[6] The Food and Drug Administration (FDA) approved Ozempic by the Danish company Novo Nordisk in 2017 for the treatment of type 2 DM.[7]

In the SUSTAIN 6 global, randomized, double-blind trial, which aimed to assess cardiovascular outcomes among high-risk patients with type 2 DM, treatment with semaglutide significantly reduced the primary outcomes of myocardial infarction, stroke, and cardiovascular death compared with the placebo group.[8] Another trial revealed that individuals without DM showed significant weight loss by 11.85% compared with the placebo group.[9] However, these trials did not include any respondents from Saudi Arabia, heightening the importance and uniqueness of information from this region.

Although semaglutide is considered an off-label indication in many countries, including Saudi Arabia, for the management of obesity, the 2015 Ministry of Health guidelines for managing obesity recommended that adults with obesity can use it as a conditional recommendation in addition to dieting and physical activity.[10] The FDA has approved additional medications known as weight management medication; however, some of these medications, such as lorcaserin, were found to elevate the risk of cancer.[11]

Therefore, the current study aimed to explore the efficacy, safety, and favorable effects of once-weekly subcutaneous semaglutide (1 mg; Ozempic) in patients with type 2 DM. Moreover, this study assessed the effects of semaglutide when prescribed as an off-label indication for weight loss in patients without DM and compared its efficacy between populations with and without DM in terms of BMI, weight, and laboratory data.

PATIENTS AND METHODS

This retrospective observational study was conducted in a tertiary healthcare center in Saudi Arabia, targeting patients receiving the glucagon-like peptide-1 (GLP-1) analog semaglutide. Data were retrospectively collected from medical records from January to December 2021. Patients aged 18 years or more who received and continued semaglutide for at least six months were enrolled regardless of their weight and the presence of type 2 DM. We included patients who received semaglutide without the presence of type 2 diabetes as an off-licence indication to facilitate weight loss.

Patients already receiving semaglutide or another GLP1 analog from an outside facility were excluded. We excluded patients who had bariatric surgery procedures, those receiving treatment for active cancer or taking steroids. Follow-up data were obtained after 3 and 6 months. The patient's weight was measured during the hospital visit using a calibrated scale and recorded in the electronic patient records. We emphasized adherence to a healthy, balanced diet during each clinic interaction with the patient. However, our clinics did not have a specialist dietician service. Our dose titration protocol included:

- Initiation to 4 weeks 0.25 mg/week.
- 5-8 weeks on 0.5 mg per week.
- 9 weeks onwards on 1 mg per week.

A standardized electronic data collection form was used to collect patient data from medical records, which comprised age, weight, height, body mass index (BMI), blood pressure measurements, and laboratory data, including serum creatinine and hemoglobin A1c (HbA1c) levels and the urine albumin/creatinine ratio (ACR). Any history of medical comorbidities or hospitalization and duration of DM were also recorded.

Data were stored using the password-protected Redcap software hosted at the institution. The hospital research and ethics committee provided ethical approval under the confirmation number RAC (2221267). Complete data confidentiality was ensured throughout the study. Our study conformed to the guidelines set in the Declaration of Helsinki.

Data were analyzed using IBM SPSS program for Windows (standard version 20). Data normality was initially tested using the one-sample Kolmogorov–

Smirnov test. Qualitative data were presented as numbers and percentages. The association between categorical variables was tested using the chi-squared test. For nonparametric data, continuous variables are presented as median and either minimum-maximum or the interquartile range. The two groups were compared using the Mann–Whitney U test for nonparametric data. The Friedman test was employed to compare baseline, first follow-up, and second follow-up readings between patients with and without DM. A *P* value of ≤.05 was considered to indicate statistical significance. A *P* value of ≤.001 was considered to indicate a highly significant difference.

RESULTS

At baseline, 1007 patients who met the eligibility criteria were enrolled in this study. The median (25th-75th percentile) age of our study population was 57.0 (46.0-64.0) years, and 60.28% of the participants were females. Two-thirds of the population had type 2 DM, with a median duration of 14 (range, 5–20) years. Overall, 12.02% and 2.98% of the studied participants had established cardiovascular and cerebrovascular diseases (**Table 1**). From a baseline patient population of 1007, a continuous decline was observed in the number of patients to 955 and 442 at the first and second follow-up visits, respectively (**Figure 1**).

Table 1. Baseline characteristics of this study population (n=1007).

	Median	Min-Max
Age (years)	57.0	46.0–64.0
Weight (kg)	90.0	80.0–103.0
Height (cm)	163.0	156.0–170.0
Body mass index (kg/m^2)	33.9	30.5–38.9
Systolic blood pressure (mmHg)	127.0	117.0–137.0
Diastolic blood pressure (mmHg)	78.0	73.0–87.0
Hemoglobin A1c%	6.9	5.7–8.3
Serum creatinine (μmol/L)	68.0	57.0–84.0
Urine albumin/creatinine ratio (mg/mol)	1.4	0.5–3.0
	Number of patients	**Percentage**
Sex		
Male	400	39.72
Female	607	60.28
History of diseases		
Type 2 diabetes mellitus	675	67.03
Established coronary artery disease	121	12.02
Pre-existing heart failure	30	2.98
Established cerebrovascular disease	30	2.98
History of hospitalization (within 12 months before treatment)		
For heart failure	11	1.09
For pancreatitis	2	0.19
Duration of diabetes (years) (n=675)[a]		
Known (n=105, 15.56%)	14 (median)	5.0-20.0 (range)
Unknown (n=570)	--------	--------

Comment on course duration: short; [a]675 were all of short duration; the unknown refers to patients who were uncertain as to precisely when their diabetes began.

Among patients with DM, compared with baseline measurements, a statistically significant decrease in weight, BMI, and HbA1c levels was observed after treatment with semaglutide during the first and second follow-up visits (*P*<.001, .001, and .001, respectively). In the diabetic group, the median weight loss was 4 kg (4.4%), and the HbA1c level improved by 0.4% (**Table 2**).

In patients without DM, compared with baseline measurements, a statistically significant decrease in weight, BMI, diastolic blood pressure (mmHg), and HbA1c level was observed after treatment with semaglutide during the first and second follow-up visits (*P*= .001, .001, .03, and .007, respectively). In the nondiabetic group, the median weight loss was 3 kg (3.4%) (**Table 3**).

A statistically significant difference was observed in the baseline, first follow-up, and second follow-up measurements of HbA1c level, systolic blood pressure, and serum creatinine level between patients with and without DM (**Tables 2 and 3**). Renal parameters, including serum creatinine level and urine albumin/creatinine ratio, remained stable throughout the follow-up period in all patient profiles (**Tables 2 and 3**).

Among patients with DM, a statistically significant difference in weight and BMI was observed between males and females at baseline, first follow-up, and second follow-up (*P*=.001) (**Table 4**). In patients without DM, a statistically significant difference in weight was observed between males and females at baseline, first follow-up, and second follow-up (*P*=.001). Fourteen patients with pre-existing ischemic heart disease experienced a new episode, requiring hospitalization. Three patients had another episode of cerebrovascular disease. Five patients were admitted with a clinical diagnosis of heart failure.

The most common side effects were gastrointestinal problems (9.7%) followed by hypoglycemia requiring hospitalization (0.5%), and pancreatitis (0.3%). There were no reported hypoglycemic episodes during the month of Ramadan.

DISCUSSION

Semaglutide has been approved for treating type 2 DM, and many trials have also reported its efficacy in inducing weight loss in patients with DM, making it suitable for weight management. In April 2021, the FDA approved a once-weekly subcutaneous injection of 2.4 mg of semaglutide (Wegovy, Novo Nordisk, Denmark)) for weight management in patients with overweight and obesity, irrespective of the presence of DM.[12] The guidelines recommended that 5%–10% weight loss can enhance metabolic functions and improve health impacts, as 5% weight loss is associated with improved multiorgan insulin sensitivity and 0.6%–1% decrease in HbA1c level.[13] A cohort study revealed that 15% weight loss is associated with a 37.4% decrease in the risk of developing type 2 DM.[14]

This study included 1007 patients with and without DM and revealed the efficacy,

Table 2. Changes in clinical parameters in patients with diabetes mellitus after treatment with semaglutide.

Variables	Baseline	Follow-up		*P* value
		First (3 months)	Second (6 months)	
Weight (kg)	91.0 (80.0–104.0)	88.0 (77.8–101.0)	87.0 (76.0–100.0)	**<.001**
Body mass index (kg/m^2)	33.65 (30.38–37.83)	32.45 (29.2–37.33)	32.35 (28.87–36.6)	**<.001**
Systolic blood pressure (mmHg)	130.0 (120.0–140.0)	127.0 (118.0–138.0)	127.0 (119.0–137.0)	.072
Diastolic blood pressure (mmHg)	78.00 (72.0–83.50)	77.0 (71.0–82.0)	78.0 (72.0–83.0)	.292
Hemoglobin A1c (%)	7.6 (6.9–8.9)	7.2 (6.4–8.1)	7.2 (6.4–8.2)	**<.001**
Serum creatinine (μmol/L)	70.5 (59.0–92.0)	71.5 (57.0–89.25)	73.0 (58.0–93.0)	.153
Urine albumin/creatinine ratio (mg/mol)	1.5 (0.6–6)	1.6 (0.7–6.7)	1.7 (0.6–4.95)	.072

Data are median and interquartile range.

Table 3. Changes in clinical parameters in patients without diabetes mellitus after treatment with semaglutide.

Variables	Baseline	Follow-up		*P* value
		First (3 months)	Second (6 months)	
Weight (kg)	88.0 (79.0–102.25)	86.0 (75.0–100.0)	85.0 (72.0–100.25)	**<.001**
Body mass index (kg/m^2)	33.8 (30.25–37.9)	32.4 (28.85–36.75)	32.0 (28.0–36.3)	**<.001**
Systolic blood pressure (mmHg)	124.0 (112.25–134.0)	121.00 (112.0–128.75)	121.50 (113.0–129.0)	.403
Diastolic blood pressure (mmHg)	79.00 (74.0–83.75)	79.00 (71.25–83.75)	78.00 (72.25–83.0)	**.03**
Hemoglobin A1c (%)	5.6 (5.3–5.9)	5.5 (5.2–5.7)	5.5 (5.2–5.8)	**.007**
Serum creatinine (μmol/L)	67.0 (58.75–79.75)	64.0 (54.75–78.0)	66.0 (54.0–76.25)	.086
Urine albumin/creatinine ratio (mg/mol)	1.1 (0.58–2.6)	1.0 (0.5–2.5)	0.7 (0.5–2.5)	.4723

Data are median and interquartile range.

fects of subcutaneous semaglutide in terms of weight, BMI, glycemic control, HbA1c, blood pressure control, and other laboratory measurements. The number of participants decreased during the follow-up period. This decrease can be explained by factors such as the lack of treatment compliance, missing follow-up appointments, failure to perform periodic laboratory tests, and transfer of care to another healthcare facility.

In this study, compared with baseline measurements, a statistically signifcant decrease in weight and BMI was observed between patients with obesity in diabetic and nondiabetic groups during the frst and second follow-up visits (**Table 2**). A meta-analysis of 8 studies involving 4567 patients revealed signifcant weight loss and marked BMI decrease among patients with obesity receiving 2.4 mg of semaglutide (*P*<.0001). This study also showed a positive effect on blood pressure, which is consistent with our fnding,[15] despite the difference in the semaglutide dose. The SUSTAIN 6 trial indicated that 0.5 mg of semaglutide signifcantly reduces systolic blood pressure.[16]

In a previous study, semaglutide led to 5%, 10%, and 15% weight loss in 86.4%, 69.1%, and 50.5% of the participants, respectively; moreover, the difference in weight loss between the treatment and placebo groups was 12.7 kg.[17] Another study reported 5.9% and 10.9% weight loss between patients with and without DM at 3 and 6 months, respectively.[18] The 1-year follow-up results of semaglutide in randomized studies in the USA revealed 4.03% weight loss in patients with DM.[19] Similarly, statistically signifcant weight losses of 5.8 and 4.2 kg were reported in UK and German studies, re-

Table 4. Differences in the weight, body mass index, and hemoglobin A1c level in male and female patients with and without diabetes mellitus

Variables	Diabetic		*P* value[a]	Nondiabetic		*P* value[a]
	Male	Female		Male	Female	
Weight (kg)						
Baseline	94.0 (83.2–106.5)	88.0 (78.0–100.0)	**<.01**	101.5 (93.0–115.8)	84.0 (77.3–95.9)	**<.001**
First follow-up	91.0 (81.0–103.0)	86.0 (76.0–97.0)	**<.01**	97.0 (87.5–114.5)	81.0 (72.8–94.0)	**<.001**
Second follow-up	90.0 (79.0–102.0)	84.2 (73.2–96.8)	**<.01**	98.0 (86.9–115.0)	81.0 (69.0–92.0)	**<.001**
Body mass index (kg/m^2)						
Baseline	32.7 (29.4–36.5)	35.6 (31.9–40.4)	**<.01**	34.7 (30.9–38.9)	33.4 (29.9–37.9)	.257
First follow-up	31.8 (28.7–35.3)	34.9 (30.8–39.3)	**<.01**	33.1 (29.1–37.6)	32.0 (28.3–36.9)	.449
Second follow-up	31.2 (28.7–34.0)	33.7 (29.2–37.9)	**<.01**	33.1 (29.1–37.9)	30.9 (27.7–34.9)	.237
Hemoglobin A1c (%)						
Baseline	7.5 (6.8–8.9)	7.7 (6.8–9.0)	.557	5.6 (5.2–5.9)	5.4 (5.1–5.8)	.151
First follow-up	7.3 (6.5–8.1)	7.2 (6.4–8.2)	.677	5.5 (5.2–5.7)	5.4 (5.2–5.6)	.367
Second follow-up	7.0 (6.4–8.1)	7.2 (6.3–8.2)	.774	5.5 (5.2–5.7)	5.4 (5.2–5.7)	.263

Data are median and interquartile range. [a]Mann–Whitney U test.

spectively.[20,21] In addition to the inhibition of glucagon secretion, the effect of semaglutide on weight loss is related to delayed gastric emptying, which is considered a more crucial factor in controlling postprandial hyperglycemia than insulin secretion.[22]

Our real-world study results revealed that the administration of semaglutide was associated with a statistically significant beneficial effect in decreasing weight, BMI, and HbA1c levels, consistent with the findings of the SUSTAIN 1 trial.[7] In addition, patients with DM reported a significant improvement in cardiometabolic and renal parameters with the administration of semaglutide. Consistent with these findings, other trials in patients with DM who were treated with semaglutide showed improved cardiometabolic parameters, such as systolic and diastolic blood pressure, total cholesterol level, and HbA1c level.[23] These findings suggest that treatment with semaglutide has a positive effect on the overall health of patients.

In Pakistan, a real-world cohort study reported a statistically significant reduction in HbA1c level by 1.4% with a weight loss of 3.7 kg.[24] Similarly, a Canadian retrospective analysis of the medical records of patients with DM reported an improvement in HbA1c levels by −1.03 (1.24%) with no evidence of hypoglycemic events.[25] A Swedish real-world study reported a 1.2% reduction in HbA1c levels.[26] Another meta-analysis showed a 1.36% reduction in HbA1c levels with the injection of 1 mg of semaglutide weekly compared with placebo.[27]

A statistically significant difference in HbA1c levels was observed between patients with and without DM at baseline and follow-up. This is a standard and expected statistical result that is influenced by the presence or absence of DM (**Tables 2 and 3**).

In contrast to our study, a local real-world study revealed the compelling beneficial effect of semaglutide on body weight and HBA1c.[28] This difference in results was attributed to the diverse study populations in both studies. While their study included all patients with established type 2 diabetes, a third of our patients did not have diabetes, and the drug was used off-label for its weight loss efficacy. Moreover, our patients had much lower baseline HBA1c (6.9% median) and body weight (90 kg median) than their study population, with baseline mean HBA1c of 10.02% and mean body weight of 114.2 kg. This diversity in our patient population is crucial in understanding the lesser magnitude of change in these parameters with treatment.

Both groups had well-controlled blood pressure, and patients without DM had significantly lower systolic blood pressure at baseline and follow-up. A higher systolic blood pressure in patients with DM than in those without DM can be attributed to the presence of chronic kidney disease, hyperglycemia, and hyperinsu-

linemia, which promote sodium retention and expand the vascular volume.[29,30]

A higher BMI was observed in females (**Table 4**). Our finding is consistent with the published data showing an increased background prevalence of obesity in females[31] and females with DM.[32] Our results also demonstrated that semaglutide, when administered in patients with DM, was equally effective in decreasing weight, BMI, and HbA1c levels in both sexes. The off-license use of semaglutide to achieve weight loss in patients without DM did not alter their HbA1c levels as expected due to the glucose-dependent action of GLP1 analogs. However, both males and females showed improved weight and BMI.

Most studies have reported an increasing frequency of GI adverse effects such as nausea, vomiting, constipation, and diarrhea.[7,17] Our results from the real-world study showed that 9.6% of patients reported GI side effects as the most typical adverse effects, consistent with the findings of large-scale trials.[7,17] However, the frequency of these side effects is lower than that in large-scale trials. The reduced frequency is likely due to recall bias. The incidences of pancreatitis and hypoglycemia were 0.5% and 0.3%, respectively. The severity of most GI adverse events was mild to moderate.

The main limitations of this study were the recruitment from a single centre, retrospective design without a control group. The participants were often recruited via convenience sampling. Thus, they were not representative of the general population and were prone to selection, recall, and misclassification biases. Without a control group, factors such as concomitant use of insulin and SGLT2 inhibitor drugs, compliance with the prescribed medicine, and maintenance of a healthy lifestyle could have influenced the results. To address these biases and enhance the validity of the results, a larger study is needed. Semaglutide is effective in patients with fatty liver. However, due to the retrospective nature of our study, much information on liver enzymes was unavailable. A new study can focus on the hepatic benefits of semaglutide. Our study's strength lies in the availability of data from the local population, which was not observed in original randomized controlled trials.[7,17]

This real-life study demonstrated that semaglutide is safe and effective in patients with DM for weight, BMI, and HbA1c management after 3–6 months, without any evidence of serious complications. This benefit is observed even in patients with good baseline glycemic control. Moreover, in patients without DM, semaglutide significantly promoted weight loss and improved BMI without any significant change in glycemic control, mitigating any risk of hypoglycemia.

1. Sun H, Saeedi P, Karuranga S, Moritz Pinkepank, Katherine Ogurtsova, Bruce B Duncan, et al. IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract 2022;183:109119.

2. Alwadeai KS, Alhammad SA. Prevalence of type 2 diabetes mellitus and related factors among the general adult population in Saudi Arabia between 2016–2022: A systematic review and meta-analysis of the cross-sectional studies. Medicine 2023;102:e34021.

3. Aljulifi MZ. Prevalence and reasons of increased type 2 diabetes in Gulf Cooperation Council Countries. Saudi Med J 2021;42:481-490.

4. Singh SK, Singh R, Singh SK, Iquebal MA, Jaiswal S, Rai PK. Prevalence of obesity in newly onset diabetes mellitus and its relationship with uric acid: an e CoĎ aÔ a< Monset diW C (-- S nse;