Original Article

SEMAGLUTIDE: Weight loss, glycaemic control and safety profile in obese patients with and without type-II diabetes-An experience from Karachi, Pakistan

Muhammad Y. Memon, Tasnim Ahsan, Rukhshanda Jabeen, Saba Latif, Saeeda F. Qasim, Paras Imran

Department of Endocrinology, Jinnah Postgraduate Medical Centre (JPMC)/Medicell Institute of Diabetes, Endocrinology and Metabolism (MIDEM), Karachi, Pakistan

Abstract

Objective: To assess the efficacy and safety of Semaglutide (a GLP-1 receptor agonist) in obese patients with and without Type-II Diabetes Mellitus. **Methods:** This observational analytic cohort study was conducted in a private medical institute in Karachi Pakistan; from August 2022 to January 2023. A total of 65 obese individuals >18 years of age, with or without T2D were included. Semaglutide was started with an initial dose of 0.25 mg with an increase in dose to 0.5 mg, 1 mg and 2 mg with gap of 4 weeks between each dose escalation. Patients were kept on the maximally tolerated dose, not exceeding 2 mg/week. Patients were evaluated on the first and second follow-up at 3 and 6 months respectively, for the same parameters as noted at the initial visit, along with documentation of any adverse effect. **Results:** Out of 65 patients, 49.2% were female and 50.8% were male. Mean age was 49.16 ± 14.20 years. 47.7% of the patients had hypertension, 46.2% had diabetes mellitus, 35.4% had dyslipidemia and 13.8% had ischemic heart disease. All patients were using 0.5 mg of semaglutide after three months, however by six months 33.8% were using 1 mg, and 24.6% were on 2 mg, whereas 40% decided to adhere to 0.5 mg and only 1.5% decided to reduce the dose to 0.25 mg due to adverse effects. Patients reported start of the first adverse effect by 3.44 ± 2.27 weeks of starting the drug. By the end of three months, 55.4% of patients in our study reported adverse effect, which declined to 34.5% by the end of six months, and the majority being mild to moderate and the most frequent side effects were gastrointestinal in origin. There was no significant difference in side effect profile in between those with and without diabetes mellitus. The average weight loss was 5.81 ± 2.64 kg and 9.86 ± 3.54 kg after three and six months respectively and the amount of weight loss was almost equal in those with and without T2D. A significant decline was observed in the average HbA1c levels, body mass index (p = <0.001), systolic blood pressure (p = <0.001), diastolic blood pressure (p = <0.001), total cholesterol (p = <0.001), high-density lipoprotein (p = <0.001), low-density lipoprotein (p = <0.001), triglycerides (p = <0.001) and alanine transaminase levels (p = <0.001). **Conclusion:** Semaglutide showed substantial weight, HbA1c and cholesterol reductions in those with or without type-II diabetes.

Keywords: Alanine aminotransferase, blood pressure, diabetes mellitus, dyslipidemia, glycemic control, HbA1c, obesity, semaglutide

Introduction

Obesity is a chronic and complex public health problem that has become an epidemic worldwide, and with all its complications like type-II diabetes (T2D), insulin resistance, hypertension, dyslipidaemia, cardiovascular diseases, metabolic dysfunction-

Address for correspondence: Dr. Muhammad Y. Memon, Flat 401, Happy Heights, MCHS Block-2, Shaheed-e-Millat Road, Karachi - 75400, Pakistan.
E-mail: dr.muhammadyahya@yahoo.com

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associated steatotic liver disease (MASLD) and many more[1-3]; it has become a global challenge to have control on its rampant spread.[4,5] According to a report issued in 2016 by World Health Organization (WHO), around 13% of the world's adult population were obese (BMI ≥30 kg/m^2),[6] and using the same BMI cut off values 4.8% of Pakistani population was reported as obese.[7] But differences exist in body composition between Indo-Asian and non-Asian populations, and that is why the definition of obesity also varies among them. Using the Indo-Asian specific BMI cut off values for obesity (BMI ≥25 kg/m^2),[8] a study conducted in 2006 in Pakistan reported the prevalence of Obesity in 15.7% of the Pakistani population.[9]

Globally, diabetes mellitus is a long-term crucial public health problem and it is associated with a wide array of complications. According to International Diabetes Federation Diabetes Atlas the global diabetes prevalence is estimated at 10.5% (537 million people) rising to 11.3% (643 million) by 2030 and 12.2% (783 million) by 2045[10] The prevalence of diabetes in Pakistan is also increasing and reported as 26.4% in a national survey.[11] There is a continuing unmet need for novel glucose-lowering therapies that provide durable glycaemic control while avoiding hypoglycaemia, weight gain and fluid retention, which are recognized problems with several existing glucose-lowering drugs.[12-14]

A better understanding of the basic pathophysiology involved in the diabetes opened the new horizons in the management of diabetes particularly glucagon like peptide -1 (GLP-1) receptor agonist. These agents represent a unique approach to the treatment of diabetes, with benefits extending outside glucose control, including positive effects on weight, blood pressure, cholesterol levels, beta-cell function and cardiovascular mortality.[15] They mimic the effects of the incretin hormone GLP-1, which is released from the intestine in response to food intake. Their effects include increasing insulin secretion and satiety, where as it decreases glucagon release, and slows the gastric emptying. GLP-1 receptor agonists are an innovative and effective option to improve blood glucose control, with other potential benefits of preserving beta-cell function, weight loss, increasing insulin sensitivity.

There were previously five approved GLP-1 receptor agonists in the United States: exenatide, liraglutide, albiglutide, dulaglutide and lixisenatide, Newer, once-weekly semaglutide, is the only GLP-1 RA approved for the treatment of chronic weight management in adults with BMI >27 kg/m^2 or greater who have at least one weight-related comorbidity such as T2D or hypertension, or in adults with a BMI of 30 kg/m^2.

The most common adverse effects seen with GLP-1 therapy include nausea, vomiting, and injection-site reactions. Other warnings and precautions include pancreatitis and medullary thyroid carcinoma. Once-weekly formulations may also improve patient adherence. Overall, these are effective agents for patients with T2D, who are either uncontrolled on metformin or intolerant to metformin; and for those with obesity.

GLP-1 receptor agonists have shown promising outcomes in the management of Diabetes as well as in reducing obesity. As Semaglutide was launched recently in Pakistan that's why there is not much local published data on its effects and outcomes. Hence this study aims to assess the efficacy of Semaglutide in weight reduction and control of diabetes mellitus along with observing its effects on other associated comorbidities, and its side effects.

Objective

To assess efficacy and safety of Semaglutide (a GLP-1 receptor agonist) in obese patients with and without T2D

Methodology

A sample size of 65 was calculated by using PASS 2020 Power Analysis and Sample Size Software (2020), which produced a two-sided 95% confidence interval with a width equal to 0.190, when prevalence of obesity in the adult Pakistani population considered was 15.7%.[9] The time period of the study was six months.

After the informed consent, all patients fulfilling the eligibility criteria were stratified in two different groups (Obese with T2D and Obese without Diabetes Mellitus). Patients' baseline BMI, duration of diabetes (if present), HbA1c, blood pressure and lipid profile were noted before starting Semaglutide. All the data was recorded in the predefined proforma. Semaglutide was started only after discussing in detail with the patients about the indication, risks and possible adverse effects; at the dose of 0.25 mg subcutaneous injection once weekly, self-administered by the patients. The dose was escalated to 0.5 mg after 4 weeks and thereafter increased further to 1 mg and 2 mg with the minimum interval of 4 weeks between each escalation of dose. Patients were kept on the maximally tolerated dose, not exceeding 2 mg/week.

Patients were evaluated on the first and second follow up at 3 and 6 months respectively, for the same parameters as noted at the initial visit, along with documentation of any adverse effect. The severity of side effects was decided by patients' self-assessment as mild, moderate or severe. The 2nd follow-up was the endpoint of the study.

This study included obese patients with or without Diabetes. Among patients with diabetes, Semaglutide was started as an add-on to other anti-diabetic drugs, in those patients who needed escalation of treatment for failing to achieve HbA1c target on usual anti-diabetic drugs (Metformin, Sulphonylurea, Thiazolidinediones, SGLT2 inhibitors or Insulin) or when the change of anti- diabetic medication was required for cardiovascular and renal protective benefits of this drug. DPP4 inhibitors were stopped.

This is a prospective cohort study, and Semaglutide has been studied in several experimental and real-world trials throughout the world. This is an FDA approved drug for diabetes mellitus as well as obesity. Because Semaglutide was launched in Pakistan in November 2021, hence there is not much published research

on its effects and outcomes in Pakistani population with diabetes and obesity.

Inclusion criteria

1. Obese (BMI >25 Kg/m^2) patients with T2D, who need escalation of treatment for failing to achieve HbA1c target on standard anti diabetic medication (HbA1c ≥7) or those who have difficulty losing weight.
2. Drug naïve patients (CV disease or renal disease and obesity with BMI >25 Kg/m^2).

Exclusion criteria

1. Patients aged below 18 years
2. Patients with type-I diabetes
3. Personal or family history of medullary thyroid cancer / MEN-2.
4. Patients with history of Pancreatitis.
5. Pregnancy

Study design

An Observational Analytic Cohort Study.

Ethical approval

Institutional Review Board (IRB) Committee approved the research synopsis with letter NO. F.2,81/2022-GENL/214/JPMC, Jinnah Postgraduate Medical Centre (JPMC) Karachi.

Statistical analysis

Data analysis was done by using IBM SPSS Statistics v27. Mean and standard deviation were calculated for quantitative variables while frequency and percentage were reported for qualitative variables. Mean comparison was done by dependent *t*-test, independent *t*-test and repeated measures of ANOVA. *P* value < 0.05 were considered as significant.

Primary outcome variables

1. Weight Loss
2. HbA1c reduction.

Secondary outcome variables

- Effect on lipid profile
- Effect on blood pressure
- Effect on Alanine aminotransferase levels
- Side-effect profile of the drug.

Results

Out of 65 patients, 49.2% were female and 50.8% were male. Mean age was 49.16 ± 14.20 years. The majority of patients were from the province of Sindh (90.8%), most of them being from Karachi, while the most prevalent occupations were those of home-makers (26.2%), doctors (18.5%), and businessmen (13.8%). 47.7% of the patients had hypertension, 46.2% had diabetes mellitus, 35.4% had dyslipidemia and 13.8% had ischemic heart disease. All patients were using 0.5 mg of Semaglutide after three months, however by six months the majority of patients were successful in escalating the dose as 33.8% were using 1 mg, and 24.6% were on 2 mg, whereas 40% decided to adhere to 0.5 mg and only 1.5% decided to reduce the dose to 0.25 mg due to adverse effects.

Patients reported the start of the first adverse effect by 3.44 ± 2.27 weeks of starting the drug. By the end of three months, 55.4% of patients in our study reported adverse effects and the most frequent side effects were bloating (24.6%), nausea (18.5%), constipation (10.8%), rash (6.2%), and itching (6.2%). Almost all of the patients reported the side effects to be mild to moderate in severity. Improved tolerance with lesser side effects (35.4%) along with a reduction in their severity was reported by the end of six months. Majority of patients reported the side effects to be of mild nature. There was no significant difference in the side effect profile in those with and without diabetes mellitus. Table 1 provides thorough descriptive statistics and Figure 1 presents a detailed frequency distribution of the side effects by the end of three and six months.

Table 1: Descriptive statistics of study population (*n*=65)

	***n* (%)**
Gender	
Male	33 (50.8)
Female	32 (49.2)
Age (years); mean±std. dev	49.16±14.20
Marital Status	
Single	8 (12.3)
Married	57 (87.7)
Comorbid	
Hypertension	31 (47.7)
Ischemic Heart Disease	9 (13.8)
Dyslipidemia	23 (35.4)
Depression	1 (1.5)
Hypothyroidism	1 (1.5)
Metabolic dysfunction-associated steatotic liver disease (MASLD)	2 (3.1)
Polycythemia	1 (1.5)
Impaired glucose tolerance	8 (12.3)
Diabetes Mellitus	30 (46.2)
Adverse effect after 3rd month	
Yes	36 (55.4)
No	29 (44.6)
Severity of Adverse effect after 3rd month (*n*=36)	
Mild	25 (69.4)
Moderate	10 (27.8)
Severe	1 (2.8)
Adverse effect after 6th month	
Yes	23 (35.4)
No	42 (64.6)
Severity of Adverse effect after 6th month (*n*=23)	
Mild	22 (95.7)
Moderate	1 (4.3)
Severe	0 (0)

The average weight loss was 5.81 ± 2.64 kg and 9.86 ± 3.54 kg after three and six months respectively and the amount of weight loss was almost equal in those with and without T2D [Figure 2 and Table 2]. A significant decline was observed in the average glycated haemoglobin (HbA1c) levels with the mean value of 7.17 ± 2.19%, 6.32 ± 1.72%, and 5.85 ± 1.30% at baseline, three, and six months, respectively, specially in those with T2D [Table 2 and Figure 3]. We discovered a significant mean difference for body mass index (p = <0.001), systolic blood pressure (p = <0.001), diastolic blood pressure (p = <0.001), total cholesterol (p = <0.001), high-density lipoprotein (p = <0.001), low-density lipoprotein (p = <0.001), triglycerides (p = <0.001) and alanine transaminase levels (p = <0.001) [Tables 2 and 3].

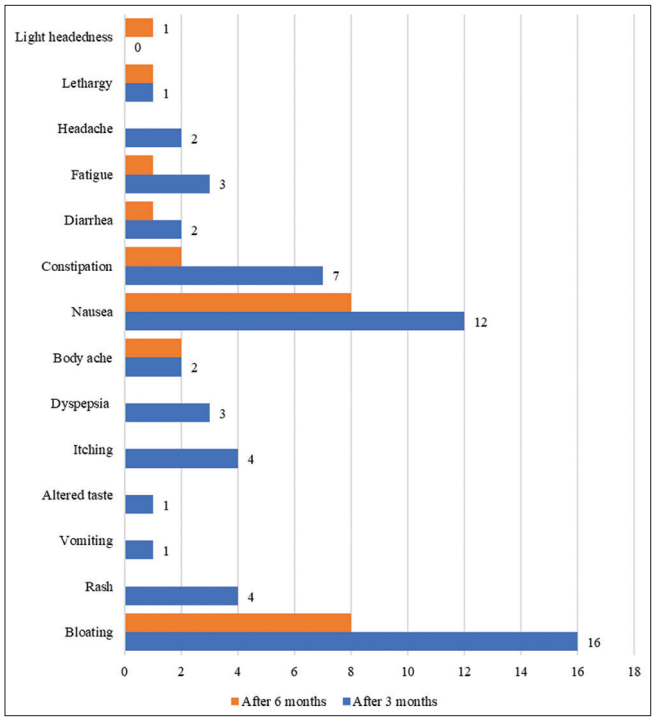

Figure 1: Adverse effects by the end of 3 and 6 months

Discussion

This observational cohort study demonstrated the positive outcomes of semaglutide in an obese population irrespective of their diabetes status. The outcomes were significant with respect to reduction in glycated haemoglobin (HbA1c), Body mass index, systolic and diastolic blood pressure, total cholesterol levels along with the differential components, alanine aminotransferase and weight of the individuals regardless of the patient characteristics and co-morbidities.

Though there have been several studies across the globe that report the modest effects of GLP-1 receptor agonist like semaglutide in persons with diabetes in terms of weight reduction, a recent systematic review and meta-analysis of RCTs conducted in 2022 at Wuhan, China revealed a weight loss in the range of 5-20%, along with improvement in the lipid profile and blood pressure of the individuals without diabetes, the finding well consistent with the results of our study.[16]

One RCT conducted in Japan reported that the effect of semaglutide on weight loss was dose dependant,[17] in our study we witnessed that not only weight loss but other parameters having significant contribution in overall cardio-metabolic health like blood pressure, cholesterol and alanine aminotransferase levels reduced as the dose was increased.

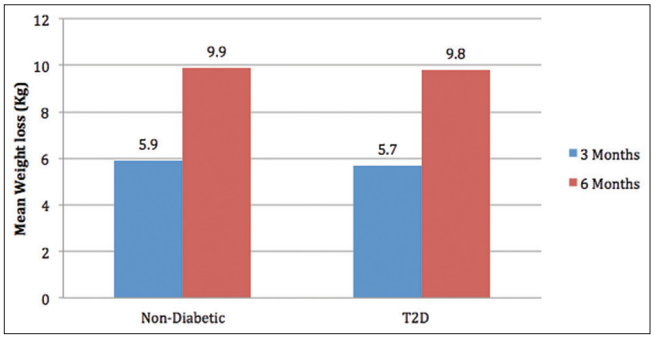

Figure 2: Mean comparison of weight loss at different time frames

Table 2: Mean comparison at baseline, after 3 months and after 6 months

	Mean±std. dev			*P*
	At Baseline	At 3rd Month	At 6th Month	
Weight (Kg)	95.98±11.17	90.16±9.82	86.07±9.63	<0.001
Body mass index (kg/m^2)	34.60±3.83	32.54±3.55	31.06±3.50	<0.001
Systolic blood pressure (mmHg)	128.53±15.82	122.20±9.97	116.00±7.71	<0.001
Diastolic blood pressure (mmHg)	97.12±127.97	78.52±7.17	86.92±99.42	<0.001
Lipid profile				
Glycated hemoglobin (%)	7.17±2.19	6.32±1.72	5.85±1.30	<0.001
Total cholesterol (mg/dL)	178.75±37.16	162.33±31.58	144.46±25.76	<0.001
High-density lipoprotein (mg/dL)	38.83±7.35	41.32±5.44	44.27±4.58	<0.001
Low-density lipoprotein (mg/dL)	124.04±35.33	111.52±31.84	93.89±26.27	<0.001
Triglycerides (mg/dL)	211.16±86.11	183.26±58.00	160.84±43.10	<0.001
Alanine transaminase (U/L)	38.76±10.07	33.72±6.43	30.84±5.49	<0.001
Weight loss (Kg)	-	5.81±2.64	9.86±3.54	<0.001

Repeated measures of ANOVA were applied. Dependent *t*-test was applied. P<0.05 considered as significant

Table 3: Mean comparison of lab parameters at 3rd and 6th month among persons with and without diabetes

	After 3 months Mean±Std. Deviation			After 6 months Mean±Std. Deviation		
	Diabetic	Non-Diabetic	*P*	Diabetic	Non-Diabetic	*P*
Body mass index (kg/m^2)	31.63±3.79	33.32±3.18	0.055	30.10±3.57	31.89±3.27	0.040*
Systolic blood pressure (mmHg)	126.16±9.43	118.80±9.25	0.002*	117.16±7.27	115.00±8.044	0.262
Diastolic blood pressure (mmHg)	81.00±6.99	76.40±6.71	0.009*	74.66±5.24	73.95±5.52	0.362
Glycated hemoglobin (%)	7.90±1.25	4.96±0.43	0.000*	7.04±0.94	4.83±0.35	0.000*
Total cholesterol (mg/dL)	169.53±36.08	156.17±26.12	0.089	150.10±29.40	139.62±21.43	0.103
High-density lipoprotein (mg/dL)	40.36±6.57	42.14±4.18	0.192	43.63±4.60	44.82±4.55	0.298
Low-density lipoprotein (mg/dL)	116.86±34.96	106.94±28.62	0.213	99.93±30.01	88.71±21.70	0.086
Triglycerides (mg/dL)	193.70±68.28	174.31±46.66	0.181	167.26±45.10	155.34±41.16	0.270
Alanine transaminase (U/L)	33.80±7.09	33.65±5.92	0.930	30.80±6.02	30.88±5.08	0.951
Weight loss (Kg)	5.70±2.38	5.91±2.88	0.748	9.76±3.00	9.94±3.99	0.844

Independent *t*-test was applied. *P*<0.05 considered as significant. *Significant at 0.05 level

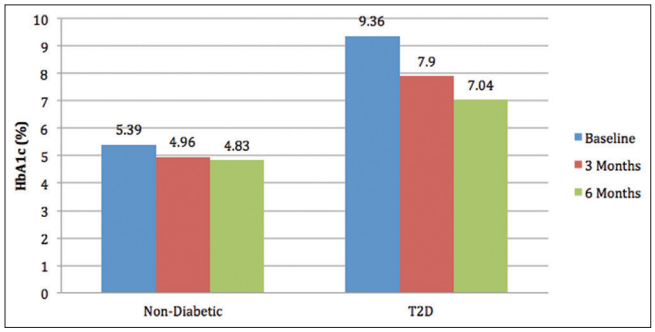

Figure 3: Mean comparison of Glycated Hemoglobin (HbA1c) at different time frames

The side effects linked to semaglutide were seen to start within few weeks of start of therapy and comprised mostly of gastrointestinal side effects like bloating, nausea, constipation and dyspepsia, which varied in severity from mild to moderate in the majority of cases, observations which are consistent with the finding of other studies.[18-20] Other side effects included rash and itch. Despite the initial various side effects, the subjects reported tolerability towards the side effects with time and by the end of 6 months the majority of people reported decline in frequency and severity of side effects. As a result of this tolerability, individuals continued and rather increased the dose of semaglutide to achieve its potential effects with the exception of a few.

This study has some limitations. First, it was a short-term study, which observed the effects only for a period of 6 months, hence long term implications of semaglutide on these parameters could not be observed. Second, the study population was restricted because of multiple factors including the cost of semaglutide, resulting in limited affordability and a transient problem of unavailability for few months in Pakistan, which resulted in interruption and discontinuation of drug by many participants, hence they were not included in the final results.

Conclusion

Semaglutide belongs to the class of drugs that along with controlling the blood glucose levels also has weight reduction potential. The key results of semaglutide are mirrored irrespective of the demographic characteristics and co-morbidities and are accepted worldwide. Various studies including this study assert the positive effects brought on by the drug with limited side effects. Our study confirms its discussed effects in the Pakistani population.

Despite the fact that semaglutide promises to be a very useful drug for the treatment of T2D as well as obesity, its prohibitive cost makes it unlikely to be used in the wider population of Pakistan.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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