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Effect of Semaglutide on Weight, HbA1c Reduction, and Side Effect Profile in Type 2 Diabetes Patients

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ABSTRACT

Background: Type 2 Diabetes Mellitus (T2DM) is a major public health challenge, with a rising prevalence in Pakistan and globally. Poor glycemic control and obesity are common among patients with T2DM, increasing the risk of complications. Semaglutide, a once-weekly GLP-1 receptor agonist, has shown promise in reducing both HbA1c levels and body weight. This study aimed to evaluate the impact of Semaglutide on glycemic control and weight loss, and to assess the frequency of its side effects in patients with T2DM.

Methods: A quasi-experimental study was conducted over six months at the Department of Medicine, Rehman Medical Institute, Peshawar over six months i-e from 1th March 2025 to 31st August 2025. A total of 101 patients with T2DM, aged 25–60 years, with a BMI ≥27 kg/m² and HbA1c >7.5%, were included using non-probability consecutive sampling. Semaglutide was administered weekly for 12 weeks. Baseline and post-treatment weight and HbA1c were recorded. Side effects were also documented. Data were analyzed using SPSS v20; paired t-tests were applied with $p \leq 0.05$ as statistically significant.

Results: Mean HbA1c decreased from $9.1 \pm 1.2\%$ to $7.5 \pm 1.1\%$ ($p < 0.001$) and mean weight reduced from 88.5 ± 9.3 kg to 82.9 ± 8.7 kg ($p < 0.001$). Common side effects included nausea (27.7%), diarrhea (11.9%), and vomiting (8.9%); 40.6% reported no side effects.

Conclusion: Semaglutide significantly improved glycemic control and promoted weight loss with an acceptable safety profile. It is an effective therapeutic option for managing T2DM in real-world clinical settings.

Keywords: Diabetes Mellitus; Hypoglycemic Agents; Glucagon-Like Peptide 1; Weight Loss; Semaglutide; HbA1c; Adverse Effects.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a global metabolic disorder that is defined by insulin resistance and progressively dysfunctional β-cells, leading to chronic hyperglycemia[1]. The incidence of type 2 diabetes and its comorbidities, risk factors, and side effects (primarily cardiovascular disease, neuropathy, nephropathy, and retinopathy) makes it a significant risk factor for public health[2]. In 2021 alone, the International Diabetes Federation (IDF) Diabetes Atlas reported that an estimated 537 million adults (20–79 years) worldwide have diabetes[3]. By 2030, that number is expected to reach 643 million, and by 2045, it may be as high as 783 million[4]. It is estimated that 33 million adults in Pakistan have diabetes, ranking the country in the top 10 countries in the prevalence of diabetes[5]. In addition to diminishing longevity and quality of life for affected individuals, type 2 diabetes adds stress on healthcare systems.

Keeping blood sugar levels near normal, achieving a healthy weight, and preventing further complications from diabetes are the goals of type 2 diabetes management. Historically, this has involved the use of antidiabetic agents such as metformin and sulfonylureas, insulin injectables, as well as DPP-4 (dipeptidyl peptidase-4) and SGLT2 (sodium–glucose cotransporter-2) inhibitors taken either as monotherapy or in some combination with a diet and exercise program[6]. Obesity is a significant comorbidity that adds to the risk of diabetes, insulin resistance, and heart disease; unfortunately, many patients do not meet glycemic goals despite multiple agents available to treat their diabetes[7, 8].

In the past few years, a class of drugs called glucagon-like peptide-1 receptor agonists (GLP-1 RAs) has emerged as a potential therapeutic option for type 2 diabetes[9]. An example of a GLP-1 RA, semaglutide, has generated a plethora of attention for its ability to elicit both substantial weight loss while also reducing glycemia[10]. Semaglutide has similar actions to the incretin hormone GLP-1, enhancing glucose-dependent insulin secretion, inhibiting glucagon release, delaying gastric emptying, and promoting satiety[11]. The reduction in HbA1c is the main marker of glucose control improvement, and weight loss is especially important for those with diabetes and either overweight or obesity[12] Semaglutide has demonstrated efficacy in several randomized controlled trials (RCTs), which include the SUSTAIN and STEP series of trials; HbA1c decreases of 1.0% to 1.5%, and weight loss in the range of 5-15%, were achieved depending on treatment dose and duration[13-15].

Despite the advantages, semaglutide has downsides. The most reported side effects are GI symptoms such as nausea, vomiting, and diarrhea, which are so common that they could ultimately lead to

discontinuation of treatment. Reports of serious, yet infrequent, adverse events such as pancreatitis and medullary thyroid carcinoma need to be monitored as well. In summary, the benefits of semaglutide should be considered with the safety and tolerability profile when making decisions.

Type 2 Diabetes Mellitus is a growing epidemic in Pakistan, with many patients struggling to achieve optimal glycemic control and manage obesity, both key factors in preventing complications. Traditional antidiabetic medications often fall short in promoting weight loss and may cause adverse effects with long-term use. Semaglutide, a once-weekly GLP-1 receptor agonist, has shown promising results internationally in lowering HbA1c and supporting weight reduction. However, limited local data exist on its real-world effectiveness and safety in the Pakistani population, which differs in genetics, diet, and healthcare access. This study bridges that gap by evaluating the impact and side effect profile of Semaglutide in local type 2 diabetic patients, thereby guiding clinicians toward more effective and tailored diabetes management strategies. The current study aimed to determine the frequency of weight and HbA1C% reduction in semaglutide users and its side effects in type 2 diabetic patients.

METHODS

This quasi-experimental study was conducted in the Department of Medicine at Rehman Medical Institute, Peshawar, over six months, i-e, from 1st March 2025 to 31st August 2025, following approval from the Institutional Ethical Committee. Ethical approval was provided by the Research Ethics Committee of Rehman Medical Institute, KPK (Approval No. RMI-REC/Ethical approvals/76, dated 13th February 2025).

The sample size was calculated using the WHO sample size calculator, assuming a 95% confidence level, 5% absolute precision, and an expected frequency of vomiting in Semaglutide users of 7.1% as reported in prior literature[16]. Based on these parameters, the required sample size was 101 patients.

A non-probability consecutive sampling technique was used to enroll participants for the study. Patients aged 25 to 60 years of either gender with a confirmed diagnosis of type 2 diabetes mellitus for more than one year were included. Additional inclusion criteria were a body mass index (BMI) of 27 kg/m² or greater and a baseline HbA1c level of more than 7.5%. Patients were excluded if they had been diagnosed with diabetes for one year or less, had type 1 diabetes mellitus, a history of renal disease, malignancy, pancreatitis, hypersensitivity to Semaglutide, or previous use of GLP-1 receptor analogues.

After obtaining informed written consent, patients attending the outpatient medical department who met the selection criteria were enrolled. Baseline data were collected, including age, gender, weight, duration of diabetes, education level, area of residence (rural or urban), baseline HbA1c, and current diabetes medications. Participants were then prescribed injection Semaglutide 0.5 mg subcutaneously once weekly for four weeks, followed by 1.0 mg once weekly for the remainder of the three months. Patients were monitored throughout the treatment for any side effects, particularly gastrointestinal symptoms. If a patient developed a severe adverse effect, such as pancreatitis, that warranted discontinuation of the drug, the patient was withdrawn from the study and replaced by a new eligible participant. All information was documented on a pre-designed, structured proforma. The confidentiality and anonymity of all participants were strictly maintained, and no personal identifiers were recorded.

Data analysis was carried out using SPSS version 20. Numerical variables such as age, weight, HbA1c, and duration of diabetes were presented as mean ± standard deviation (SD) or median (IQR), based on the normality of distribution assessed using the Shapiro-Wilk test. Categorical variables such as gender, education level, area of residence, and side effects were reported as frequencies and percentages. The frequencies of HbA1c and weight reduction, as well as the occurrence of side effects, were stratified by age, gender, and duration of diabetes to identify potential effect modifiers. The Chi-square test or Fisher's exact test was applied post-stratification, and a p-value ≤ 0.05 was considered statistically significant.

RESULTS

Table 1: Baseline Characteristics of Participants (n = 101)

Variable	Mean ± SD / n (%)
Age (years)	48.2 ± 7.1
Gender	
Male	53 (52.5%)
Female	48 (47.5%)
Duration of Diabetes (years)	7.8 ± 3.2
BMI (kg/m²)	31.6 ± 2.8
Area of Residence	
Urban	65 (64.4%)

Rural	36 (35.6%)
Education Level	
No formal education	28 (27.7%)
Primary/Secondary	49 (48.5%)
Graduate or higher	24 (23.8%)
Baseline HbA1c (%)	9.1 ± 1.2
Baseline Weight (kg)	88.5 ± 9.3

The baseline characteristics of the 101 study participants showed a mean age of 48.2 ± 7.1 years, with males comprising 52.5% and females 47.5% of the sample. The mean duration of type 2 diabetes was 7.8 ± 3.2 years, and the average BMI was 31.6 ± 2.8 kg/m², indicating that most participants were obese. A majority of the participants (64.4%) resided in urban areas, while 35.6% were from rural settings. In terms of educational status, 27.7% of individuals had no formal education, 48.5% had attained primary or secondary level education, and 23.8% were graduates or held higher qualifications. The mean baseline HbA1c was 9.1 ± 1.2%, and the average baseline weight was 88.5 ± 9.3 kg, reflecting poor glycemic control and significant overweight status at the start of the study **(Table 1)**.

During the 12-week treatment period with Semaglutide, a variety of side effects were reported among the 101 participants. The most commonly observed side effect was nausea, affecting 28 patients (27.7%), followed by diarrhea in 12 patients (11.9%) and vomiting in 9 patients (8.9%). Constipation was reported by 7 participants (6.9%), while injection site reactions were the least frequent, occurring in 4 patients (4.0%). Notably, 41 participants (40.6%) did not report any side effects throughout the treatment course, indicating that Semaglutide was generally well tolerated in a significant proportion of the study population **(Figure 1)**.

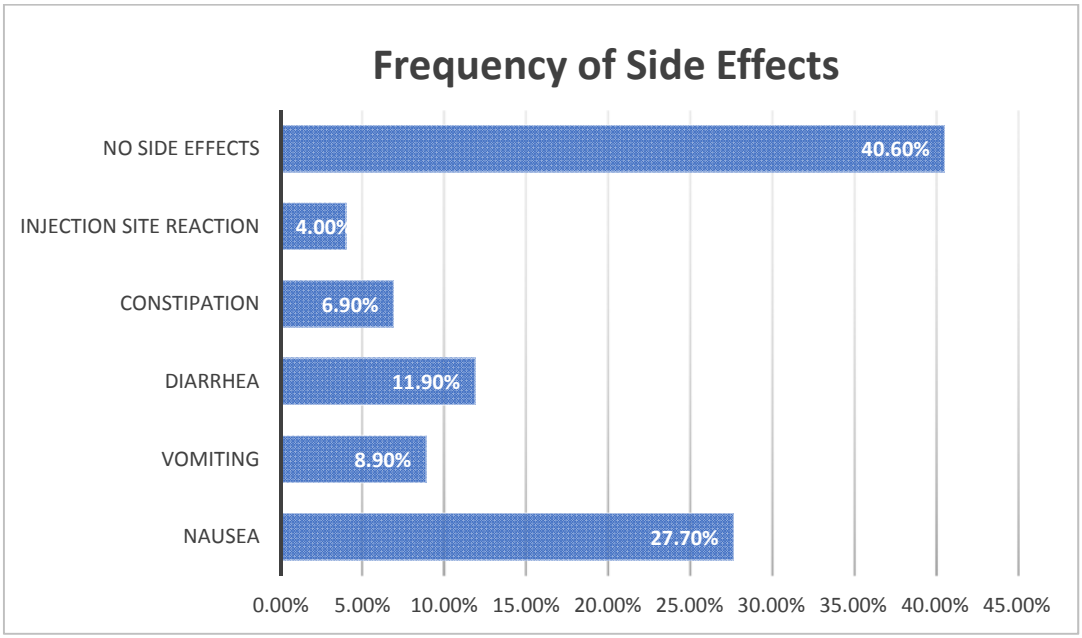

Figure 1: The Frequency of Side Effects of the Study Participants

Table 2: Pre- and Post-Treatment Comparison of HbA1c and Weight (n = 101)

Variable	Baseline Mean ± SD	After 12 Weeks Mean ± SD	Mean Difference	p-value
HbA1c (%)	9.1 ± 1.2	7.5 ± 1.1	-1.6 ± 0.6	0.001*
Weight (kg)	88.5 ± 9.3	82.9 ± 8.7	-5.6 ± 2.1	0.001*

**Paired t-test applied*
**Statistically significant at $p \leq 0.05$*

A comparison of pre- and post-treatment values revealed a statistically significant improvement in both glycemic control and weight among the 101 participants after 12 weeks of Semaglutide therapy. The mean baseline HbA1c was 9.1 ± 1.2%, which reduced to 7.5 ± 1.1% following treatment, showing a mean difference of -1.6 ± 0.6% ($p = 0.001$). Similarly, the mean body weight decreased from 88.5 ± 9.3 kg at baseline to 82.9 ± 8.7 kg post-treatment, reflecting a mean reduction of -5.6 ± 2.1 kg ($p = 0.001$). These findings demonstrate that Semaglutide was highly effective in lowering both HbA1c levels and body weight in patients with type 2 diabetes.

Table 3: HbA1c Reduction Stratified by Gender, Duration of Diabetes, and Age Group (n = 101)

Variable	Mean HbA1c Before (%)	Mean HbA1c After (%)	Mean Reduction (%)	p-value
Gender				
Male	9.0 ± 1.3	7.4 ± 1.2	1.6 ± 0.5	0.002*

Female	9.2 ± 1.1	7.6 ± 1.0	1.6 ± 0.6	0.001*
Duration of DM				
≤ 5 years	8.9 ± 1.2	7.3 ± 1.1	1.6 ± 0.6	0.001*
> 5 years	9.3 ± 1.1	7.6 ± 1.1	1.7 ± 0.5	0.001*
Age Group				
25–40 years	9.0 ± 1.2	7.3 ± 1.0	1.7 ± 0.6	0.001*
> 40 years	9.2 ± 1.1	7.6 ± 1.2	1.6 ± 0.5	0.003*

*Paired t-test applied; p ⩽ 0.05 considered statistically significant

Subgroup analysis revealed a consistent and statistically significant reduction in HbA1c across gender, duration of diabetes, and age groups following 12 weeks of Semaglutide therapy. The p-values were 0.002 for males and 0.001 for females. Among patients with a diabetes duration of ≤ 5 years, the p-value was 0.001, while for those with > 5 years of diabetes, it was also 0.001. In the age group of 25–40 years, the p-value was 0.001, and for those aged > 40 years, the p-value was 0.003, confirming statistically significant glycemic improvement across all subgroups.

Table 4: Weight Reduction Stratified by Gender, Duration of Diabetes, and Age Group (n = 101)

Variable	Mean Weight Before (kg)	Mean Weight After (kg)	Mean Reduction (kg)	p-value
Gender				
Male	89.3 ± 9.6	83.6 ± 8.9	5.7 ± 2.0	0.003*
Female	87.6 ± 8.9	82.1 ± 8.4	5.5 ± 2.2	0.004*
Duration of DM				
≤ 5 years	86.9 ± 8.7	81.2 ± 8.3	5.7 ± 2.0	0.002*
> 5 years	90.1 ± 9.8	84.6 ± 9.1	5.5 ± 2.2	0.003*
Age Group				
25–40 years	87.2 ± 9.1	81.5 ± 8.6	5.7 ± 2.1	0.002*
> 40 years	89.4 ± 9.4	84.0 ± 8.9	5.4 ± 2.2	0.004*

*Paired t-test applied; p ⩽ 0.05 considered statistically significant

Stratified analysis showed that weight reduction after Semaglutide treatment was statistically significant across all subgroups. The p-values for weight reduction were 0.003 for males and 0.004 for females. For patients with a diabetes duration of ≤ 5 years, the p-value was 0.002, while for those with > 5 years, it was 0.003. In the age group 25–40 years, the p-value was 0.002, and for participants older than 40 years, it was 0.004, indicating significant weight reduction in all categories.

DISCUSSION

In our study, Semaglutide led to a statistically and clinically significant reduction in HbA1c (mean decrease 1.6%) and body weight (mean decrease 5.6 kg) after 12 weeks. These results align closely with findings from real-world practice that reported average HbA1c and weight reductions[17], and mirror randomized controlled trial meta-analyses showing mean HbA1c and BMI reductions[18].

Our weight loss surpassed the ~4–6 kg reductions achieved in RCTs of obese non-diabetic patients over 68 weeks and parallels the ~10–12 kg loss observed in the STEP trials[19, 20]. Differences in treatment duration likely account for the magnitude variation, whereas our 12-week results are consistent with shorter-duration arms in large trials. The subgroup analysis confirmed similar efficacy across gender, diabetes duration, and age categories, consistent with pooled patient-level data indicating HbA1c decreases of 1.4–1.8% and weight loss of 3.8–5.8 kg irrespective of diabetes duration. This supports that Semaglutide's benefits are uniform across diverse clinical subgroups.

Regarding safety, 59.4% of our participants experienced side effects, primarily nausea (27.7%), diarrhea (11.9%), and vomiting (8.9%), with 40.6% reporting none. This aligns with international real-world data in Pakistan reporting side effects in Semaglutide users[16]. Clinical trial data also support that most GI side effects are mild to moderate, tend to peak early, and decline with continued use[21]. Importantly, less than 5% discontinued because of side effects in the present study.

In summary, our findings corroborate global evidence that once-weekly Semaglutide significantly improves glycemic control (mean HbA1c reduction ~1.6%) and promotes meaningful weight loss (~6%), with a tolerable side-effect profile characterized mainly by transient gastrointestinal symptoms[22, 23]. These results support Semaglutide's adoption in real-world settings, including South Asian populations[24, 25]. However, longer-term studies would be useful to verify the sustainability of these benefits and further evaluate rare adverse events such as pancreatitis or thyroid-related risks.

This study highlights the effectiveness of Semaglutide in significantly improving glycemic control and promoting weight loss in patients with type 2 diabetes mellitus. The consistent reductions in HbA1c and weight across all subgroups, regardless of gender, age, or duration of diabetes, support its broad clinical utility. Its once-weekly dosing enhances convenience and may improve patient

compliance, while its tolerable side-effect profile, mainly limited to mild gastrointestinal symptoms, makes it a practical choice in real-world settings. However, the study's limitations include a short 12-week duration, single-center non-randomized design, and reliance on self-reported side effects. Additionally, unmeasured confounders such as diet and physical activity may have influenced outcomes. Despite these limitations, the findings support Semaglutide as a promising therapeutic option, with longer and larger studies recommended to confirm its long-term benefits.

CONCLUSION

This study demonstrated that once-weekly Semaglutide is highly effective in reducing both HbA1c and body weight in patients with type 2 diabetes mellitus over 12 weeks. Significant improvements were observed across all subgroups, regardless of gender, age, or duration of diabetes. The medication was generally well tolerated, with gastrointestinal symptoms being the most commonly reported side effects. These findings support the use of Semaglutide as a valuable therapeutic option in real-world clinical settings for improving metabolic outcomes in patients with poorly controlled type 2 diabetes. Further long-term studies are recommended to evaluate its sustained efficacy and safety.

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CONFLICT OF INTEREST

None

ETHICAL APPROVAL

Ethical approval was provided by the Research Ethics Committee of Rehman Medical Institute, KPK (Approval No. RMI-REC/Ethical approvals/76, dated 13th February 2025

AUTHORS' CONTRIBUTION

All authors contributed equally as per ICMJE

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