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# Cost consequence analysis of adding semaglutide to treatment regimen for patients with Type II diabetes in Saudi Arabia

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ABSTRACT

*Introduction:* Semaglutide, a Glucagon-like Peptide-1 Receptor Agonist (GLP-1 RA), is often prescribed for managing type 2 diabetes, particularly in cases unresponsive to other hypoglycemic agents. Despite its popularity, the real-world efficacy and cost-effectiveness of Semaglutide relative to other treatments remain understudied.

*Objective:* This study aimed to examine the direct medical cost and consequences of adding Semaglutide to the treatment regimen for patients with type 2 diabetes in Saudi Arabia.

*Methods:* We conducted a single-center, retrospective review of Electronic Medical Records (EMRs) for adults with type 2 diabetes. Patients who had been on Semaglutide for at least three months were matched with those receiving alternative hypoglycemic therapies. Exclusions were made for patients with cancer, incomplete EMRs, or lacking prescription data. Investigated outcomes included changes in HbA1C levels and weight, and the direct costs comprised medications, clinic visits, and emergency care. Baseline adjustments were made through inverse probability treatment weighting, and uncertainty was assessed via bootstrapping with 10,000 replications.

*Results:* Out of 350 patients meeting the criteria, 116 were on Semaglutide. Predominantly females (62%), the cohort had an average age of 60 and a disease duration of 22 years. The difference in HbA1C (%) reductions between Semaglutide and non-Semaglutide users over 3,6, and 12 months were 0.154 (95% CI: –0.452-0.483), –0.031(95% CI: –0.754-0.239), –0.16(95% CI: –1.425-0.840), respectively. Semaglutide users did experience modest weight reductions ranging from 0.42 kg to 1.16 kg. The annual additional direct medical cost for Semaglutide was USD 4,086.82 (95% CI: $3,710.85 - $4,294.99).

*Conclusion:* Although Semaglutide induced modest weight reductions, it did not offer significant advantages in lowering HbA1C levels compared to other hypoglycemic treatments. These findings suggest the need for further research involving larger and more diverse cohorts to corroborate these findings.

## 1. Introduction

Diabetes Mellitus (DM) is a metabolic syndrome characterized by inappropriate hyperglycemia due to impaired insulin secretion, insulin resistance, or a combination of both (World Health Organization: WHO, 2019). There are various types of DM, including Type 1, Type 2, and gestational diabetes. In Saudi Arabia, Type 2 diabetes mellitus (T2DM) is the most commonly diagnosed form of diabetes mellitus (DM) (SHC, 2021). If poorly managed, DM can lead to severe macrovascular and microvascular complications (Cole and Florez, 2020). The prevalence of T2DM in Saudi Arabia is alarmingly high, ranking the country among the top five in the Middle East and North Africa. According to the

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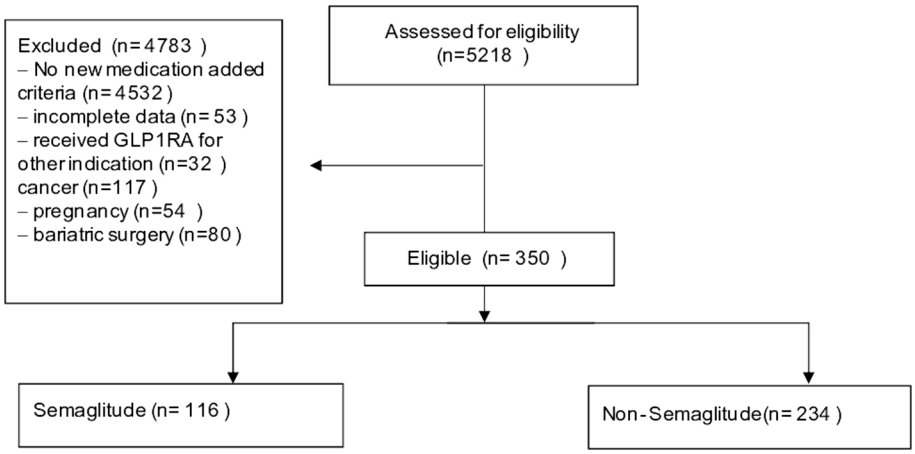


**Fig. 1.** Study Flow Diagram

International Diabetes Federation, 18.3% of adults were diagnosed with T2DM in 2019, indicating that nearly one in five adults in the country is affected by DM (The International Diabetes Federation, 2019; Robert et al., 2021). In 2015, the annual total (direct and indirect) costs of diabetes was estimated to range from USD 2.51 billion in low-income countries to USD 804.36 billion in high-income countries; and the annual global diabetes-related health expenditures is projected to increase from USD 760 billion in 2019 to USD 845 billion by 2045 (The International Diabetes Federation, 2019).

Various treatment approaches exist for T2DM, which generally

**Table 1**
Patients baseline characteristics.

| Characteristic | Treatment (n=350) Semaglutide-based regimen (n=116) | Non-Semaglutide based antidiabetic treatment regimens (n=234) | *p*-value | Total |
|---|---|---|---|---|
| Age (yrs.), mean±SD | 58.25±9.31 | 61.50±8.82 | 0.0046 | 60.42 ±10.84 |
| Male, n (%) | 46(39.66) | 85(36.32) | 0.5445 | 148(38.44) |
| Weight at baseline (kg), mean±SD | 88.59±15.83 | 78.93±16.98 | <.0001 | 82.12 ±17.19 |
| Duration of diabetes (yrs.), mean±SD | 22.33±7.84 | 22.14±8.82 | 0.8436 | 22.20±8.49 |
| Charlson's' Comorbidity Index <2, n(%) | 107(92.24) | 184(78.63) | 0.0003 | 291(83.14) |
| HbA1C at baseline (%), mean±SD | 8.23±1.34 | 8.89±1.69 | <0.0001 | 8.68±1.61 |
| Baseline HbA1C (%), n (%) | | | | |
| <7.0% | 18(15.93) | 24(10.43) | 0.04 | 42(12.24) |
| 7.0-7.9% | 37(32.74) | 51(22.17) | | 88(25.66) |
| 8.0-8.9% | 29(25.66) | 76(33.04) | | 105(30.49) |
| ≥9.0% | 29(25.66) | 79(34.35) | | 108(31.49) |
| Urinary Albumin to creatinine ratio >30 mg/g, n(%) | 14(19.18) | 55(40.15) | 0.002 | 69(32.86) |
| EGFR (mL/min/1.73m2), mean±SD | 92.72±19.76 | 82.79±25.53 | 0.0007 | 86.0±24.24 |
| Diabetes complications, n (%) | | | | |
| Retinopathy | 34(66.67) | 35(13.21) | <0.0001 | 78(22.29) |
| Nephropathy | 8(15.69) | 21(7.92) | 0.079 | 29(9.18) |
| Neuropathy | 16(31.37) | 16(6.04) | <0.001 | 32(10.13) |
| Diabetic foot ulcer | 1(1.96) | 0(0) | | 1(0.32) |
| Amputation | 1(1.96) | 0(0) | | 1(0.32) |
| Myocardial Infarction | 4(7.84) | 20(7.55) | 0.94 | 24(7.59) |
| Peripheral Vascular Disease | 4(7.84) | 2(0.75) | 0.001 | 6(1.9) |
| Duration of the previous treatment regimen (months), mean±SD | 14.85±4.59 | 14.15±5.57 | 0.2150 | 14.38±5.27 |
| Metformin, n(%) | 107(92.24) | 203(86.75) | 0.1287 | 310(88.57) |
| SGLT2 inhibitors (e.g. empagliflozin, dapagliflozin), n (%) | 9(7.76) | 71(30.34) | <0.0001 | 80(22.86) |
| DPP-4 inhibitors (e.g., sitagliptin, linagliptin) | 13(11.21) | 195(83.33) | <0.0001 | 208(59.43) |
| Meglitinides (e.g., repaglinide), n(%) | 0(0.00) | 7(2.99) | 0.1005 | 7(2.00) |
| Thiazolidinediones (e.g., pioglitazone), n(%) | 5(4.31) | 25(10.68) | 0.0450 | 30(8.57) |
| Sulfonylurea (e.g., glimepiride, glibenclamide), n(%) | 3(2.59) | 34(14.53) | 0.0006 | 37(10.57) |
| Insulin, n(%) | 77(66.38) | 101(43.16) | <0.0001 | 178(50.86) |
| Concomitant medications | | | | |
| Antiplatelets (e.g., clopidogrel), n(%) | 47(40.52) | 131(55.98) | 0.0064 | 178(50.86) |
| Statins (e.g., atorvastatin, rosuvastatin), n(%) | 111(95.69) | 191(81.62) | 0.0003 | 302(86.29) |
| β-blockers (e.g., metoprolol, bisoprolol), n(%) | 40(34.48) | 70(29.91) | 0.3862 | 110(31.43) |
| Calcium channel blockers (e.g., amlodipine), n(%) | 25(21.55) | 86(36.75) | 0.0040 | 111(31.71) |
| Diuretics (e.g., Hydrochlorothiazide), n(%) | 27(23.28) | 61(26.07) | 0.5708 | 88(25.14) |
| ACEIs/ARBs (e.g., lisinopril, valsartan), n(%) | 36(31.03) | 42(17.95) | 0.0056 | 78(22.29) |

**Table 2**
Longitudinal Comparison of Mean Weight Reduction (kg), Mean HbA1C Reduction and Treatment Costs in Patients on Semaglutide (N=109) Versus Non-Semaglutide-Based Antidiabetic Treatments (N=221) at 3, 6, and 12 Months Follow-Up.

| | Follow Up | Semaglutide-based regimen | Non-Semaglutide based antidiabetic treatment regimens | Mean difference (95% confidence interval) |
|---|---|---|---|---|
| Cost of treatment (USD), mean ± SD | 3 months | 1335.96 ±104.34 | 328.31±149.86 | 1,015.06 (984.764-1059.36) |
| Difference in weight reduction (%) | | –2.17±5.82 | –1.75±7.83 | –0.42(–0.543 - –0.434) |
| Difference in HbA1C reduction (%) | | –0.447±1.086 | –0.601±1.62 | 0.154 (–0.452-0.483) |
| Cost of treatment (USD), mean ± SD | 6 months | 2731.90 ±220.77 | 709.75±319.49 | 2,022.15 (2,008.09-2,232.76) |
| Difference in weight reduction (%) | | –2.621±3.94 | –1.536±4.42 | –1.085(–1.59-–0.780) |
| Difference in HbA1C reduction (%) | | –0.757±1.313 | –0.7265±1.628 | –0.031 (–0.754-0.239) |
| Cost of treatment (USD), mean ± SD | 12 months | 5,833.43 ± 506.55 | 1502.62 ± 663.94 | 4,330.81 (3,989.61-4,818.97) |
| Difference in weight reduction (%) | | –2.82±4.43 | –1.66 ±4.88 | –1.16(–2.262 - –1.619) |
| Difference in HbA1C reduction (%) | | –0.833±1.45 | –0.673±1.76 | –0.16(–1.425-0.840) |

involve medications alongside lifestyle modifications and dietary changes. Medications are typically classified into oral antihyperglycemic agents and injectable antihyperglycemic agents, each comprising multiple classes with differing efficacies and safety profiles (Davies et al., 2022). According to the consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), type II diabetic patients with established cardiovascular disease (e.g., myocardial infarction, stroke, any revascularization procedure) as well as those with indicators of high risk of cardiovascular disease (e.g., ≥55 years of age with two or more additional risk factors, such as obesity, hypertension, smoking, and dyslipidemia) should be treated with GLP1-RA or SGLT2 inhibitors (Davies et al., 2022).

Semaglutide is a GLP1RA that regulates insulin secretion, glucagon levels, and gastric emptying, and also influences appetite and caloric intake (Shi et al., 2018) . It is remarkably effective in reducing HbA1C levels and has a favorable safety profile (Vilsbøll et al., 2018). Recent evidence suggests that GLP1RAs like Semaglutide are increasingly becoming the preferred initial injectable agents due to their multiple benefits including lower hypoglycemia risk and more convenient weekly administration (Davies et al., 2022).

Furthermore, comprehensive DM management extends beyond glycemic control, considering other risk factors like body weight, lipid profiles, and blood pressure to reduce the overall risk of complications (Gaede et al., 2008; Griffin et al., 2011; Kearney et al., 2008; UKPDS, 1998). In terms of cardiovascular outcomes, GLP1RAs have been shown to significantly reduce the risk in major adverse cardiovascular events (Marsico et al., 2020).

Despite their efficacy, GLP1RAs like Semaglutide face challenges such as higher costs, supply chain shortage and tolerability issues, which can deter their widespread use (Aroda et al., 2017; Alexopoulos and Buse, 2019). However, multiple studies have demonstrated the cost-effectiveness of Semaglutide compared to other antidiabetic medications among white Caucasian population, highlighting its potential to improve clinical outcomes while reducing overall costs (Viljoen et al., 2019; Malkin et al., 2019; Igarashi et al., 2020; Johansen et al., 2019; Johansen et al., 2020). However, Semaglutide cost-effectiveness was not evaluated among Arab population. Therefore, this study aims to evaluate the real-world cost and clinical outcomes of once-weekly Semaglutide in comparison to other antidiabetic treatment regimens, using data sourced from Saudi Arabia.

## 2. Methods

### 2.1. Study design

This investigation utilized a retrospective, single-center electronic medical records (EMRs) data. The reviewed data was between January 1, 2016, and January 1, 2021 at the ambulatory clinics and Diabetic Center located at King Saud University Medical City (KSUMC) in Riyadh, Saudi Arabia. The KSUMC is a tertiary academic center. The decisions for initiating new hypoglycemic treatment was based on comprehensive evaluations made by endocrine or diabetes specialists, while also accounting for patient preferences and drug availability. Special attention was given to prioritize the administration of Semaglutide for patients with a history of cardiovascular disease or those presenting with overweight and obesity. As per standard practice, the Semaglutide treatment protocol followed a dose escalation regimen: an initial subcutaneous injection of 0.25 mg was administered once weekly for the first month, increased to 0.5 mg once weekly for the subsequent month, and then, based on patient tolerance, the final increase to 1 mg once weekly.

### 2.2. Study participants

The study population comprised patients who were more than 18 years old, diagnosed with T2DM, and were started on a new antidiabetic regimen for at least 3 months that included either Semaglutide or other antidiabetic agents. Patients were excluded if they were pregnant, had cancer, underwent bariatric surgery, have incomplete medical record, received Semaglutide for prediabetes or obesity, did not have follow up laboratory data within 6 months of starting the new regimen, or were diagnosed with cancer. The follow-up periods ranged from 3 months to 12 months based on the date of treatment initiation. Those who were treated with Semaglutide or non-Semaglutide treatment regimens for type II diabetes for less than 3 months were excluded as well.

### 2.3. Measures

Data on sociodemographic characteristics, such as age, gender, educational attainment, and marital status, were retrieved from EMRs. Moreover, patient medical characteristics, such as chronic health conditions, Charlson's' Comorbidity Index, DM duration, detailed list of prescribed medications, medication side effects, weight, HbA1C , urinary albumin to creatinine ratio, and EGFR were collected. In order to estimate the direct medical cost, the micro-costing method was used, and all utilized healthcare services were documented and assigned a monetary value per unit using the healthcare cost data from the Council of Cooperative Health Insurance (CHI) database. Therefore, the frequency of hospitalization, admitting department (e.g., general ward, intensive care unit, etc.……), length of stay, frequencies of outpatient clinic visits and emergency department encounters, laboratory tests and

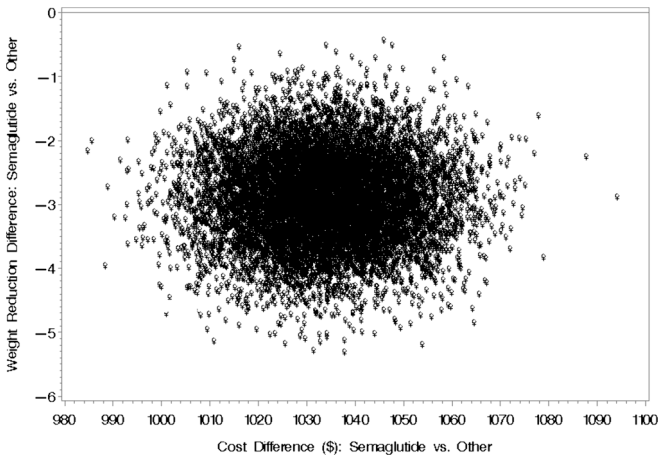


**Fig. 2.** Bootstrap Distribution of Cost and Weight Reduction Differences Between Semaglutide and Non-Semaglutide-Based Antidiabetic Treatments at 3-Month Follow-Up

imaging studies, as well as their frequencies, prescription medications administered in inpatient settings or filled in outpatient settings, and medication side effects management, if any, were collected to estimate healthcare costs.

### *2.4. Costs and consequences*

The outcomes of this study were weight and HbA1C reductions from baseline (i.e., prior to the initiation of semaglutide or other antidiabetic treatment regiments) in order to estimate the consequence of therapy. In order to estimate the costs, direct medical costs from the perspective of public healthcare payer were captured (i.e., overall treatment costs, hospitalization rate, and medication side effects).

### *2.5. Ethical considerations*

Ensuring the ethical integrity of this study is of paramount importance. To safeguard patient confidentiality, all data were anonymized by removing any information that could be used to identify individual participants. The comprehensive dataset was securely stored on a computer protected by robust password encryption, and access is limited strictly to those who have received explicit authorization from the principal investigator. There was no anticipated risk of harm to participants, nor were there any identified conflicts of interest. The study was conducted by the relevant guidelines and regulations and the Institutional Review Board of College of Medicine, King Saud University, Saudi Arabia reviewed and approved the protocol (E-21-6190).The study operated in full compliance with the ethical guidelines set forth by the Declaration of Helsinki and adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) standards.

### *2.6. Data collection / Data source*

Data were collected from the electronic health records of patients and entered in a REDCap database.

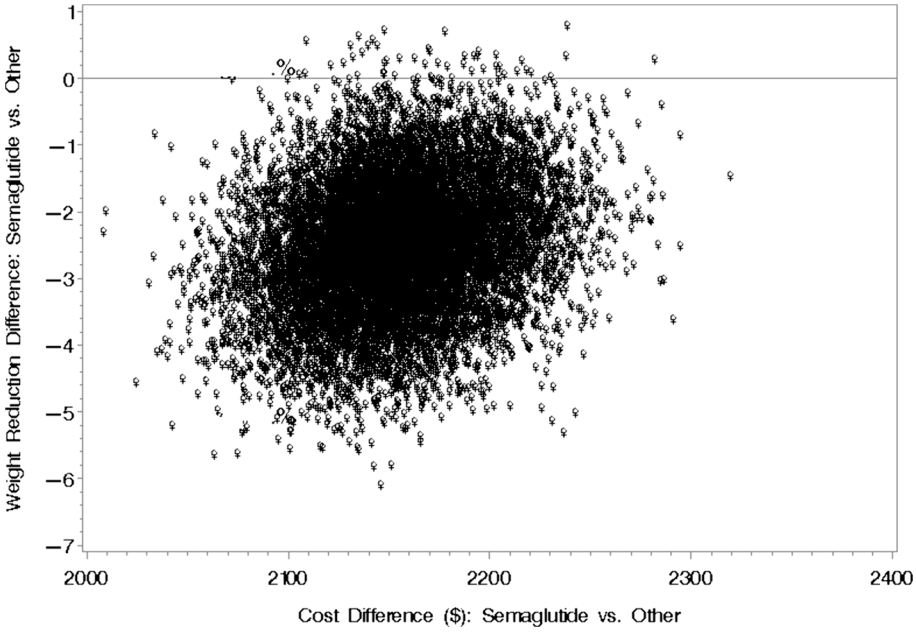


**Fig. 3.** Bootstrap Distribution of Cost and Weight Reduction Differences Between Semaglutide and Non-Semaglutide-Based Antidiabetic Treatments at 6-Month Follow-Up

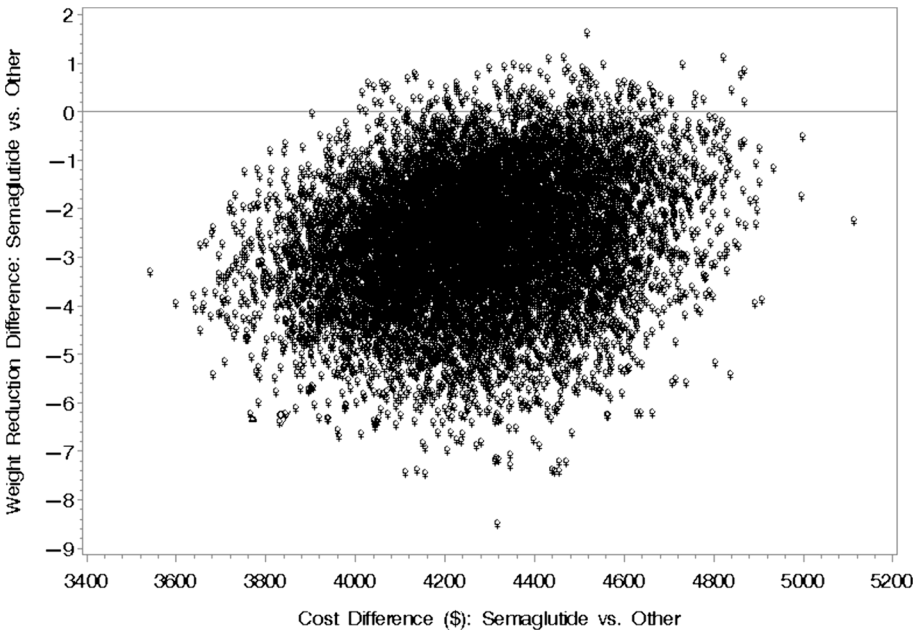


**Fig. 4.** Bootstrap Distribution of Cost and Weight Reduction Differences Between Semaglutide and Non-Semaglutide-Based Antidiabetic Treatments at 12-Month Follow-Up

**Table 3**
Subgroup analysis for weight and HbA1C changes from baseline.

| | | 6 months change from baseline | | | | 6 months change from baseline | | | | 12 months change from baseline | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total cohort size | n | mean weight change 3 months±SD | n | HbA1C change 3 months ±SD | n | mean weight change 6 months±SD | n | HbA1C change 6 months±SD | n | mean weight change 12 months±SD | n | HbA1C change 12months ±SD |
| Semaglitude | 114 (32.66) | 97 | -2.19± 3.82 | 105 | -0.47±1.05 | 38 | -2.87±3.65 | 46 | -0.78±1.32 | 17 | -2.82±4.43 | 27 | -1.09±1.29 |
| DPP-4 inhibitors | 93 (26.65) | 69 | -1.83±7.28 | 74 | -0.94±1.65 | 54 | -1.81±7.28 | 59 | -0.97±1.93 | 41 | -0.95±4.9 | 35 | -1.03±2.19 |
| SGLT2 inhibitors | 55 (15.76) | 44 | -1.70±2.71 | 44 | -0.46±1.60 | 40 | -3.27±5.84 | 34 | -0.32±1.16 | 17 | -3.41±4.11 | 15 | -0.66±1.83 |
| Sulfonylurea | 35 (10.03) | 28 | -0.35±3.59 | 26 | -0.36±1.32 | 24 | -0.43±4.66 | 25 | -0.49±1.22 | 16 | -1.38±3.29 | 13 | -0.63±1.54 |
| Meglitinides | 3(0.86) | 2 | 1.35±5.02 | 3 | -0.33±1.80 | 1 | -2.90±0 | 2 | -0.75±0.78 | 2 | 0.95±7.14 | 1 | -3.30±0 |
| Thiazolidinediones | 5(1.43) | 5 | -0.70±1.86 | 5 | -0.06±1.23 | 2 | -0.90±1.56 | 2 | -0.15±.092 | 1 | -6.00±0 | 1 | -1.90±0 |
| Metformin | 19(5.44) | 17 | -0.41±2.64 | 13 | -0.24±1.03 | 10 | -1.83±5.42 | 8 | -0.43±0.78 | 10 | -0.18±4.54 | 8 | -0.51±0.99 |
| Combination of 2 or more OHA | 23(6.59) | 16 | -0.95±4.20 | 17 | -0.90±1.67 | 15 | -1.08±4.65 | 15 | -0.97±1.50 | 9 | -2.48±7.53 | 10 | -1.09±1.58 |
| alpha-glucosidase inhibitors | 1(0.29) | 1 | -1±0 | 1 | -0.90±0 | 1 | -1±0 | 1 | 1.40±0 | 1 | -4±0 | 1 | 1.50±0 |
| Insulin | 1(0.29) | 1 | -12.5±0 | 1 | 1.30±0 | | | | | | | | |

All comparisons are not statistically significant

### *2.7. Statistical analysis*

The required minimum sample size for this study was calculated to be 37 patients for each group (Semaglutide and non-Semaglutide based treatment regimens) bringing the total to 74 patients, utilizing parameters such as an alpha level of 0.05, a beta of 0.8, 80% statistical power, and a mean difference of 1% in HbA1C between the two treatment groups favoring Semaglutide. Baseline patient characteristics were summarized using descriptive statistics, including means, standard deviations for normally distributed data, and frequencies or percentages for categorical data. To enable a balanced comparison, inverse probability treatment weighting was implemented to adjust for the differences among Semaglutide users and non-users, factoring in variables such as sociodemographic characteristics, disease duration, number of comorbidities, and other prescription drugs. A bootstrapping technique involving 10,000 replications was used to establish 95% confidence intervals for both outcomes and associated costs. The analysis focused solely on direct medical costs and was conducted from the standpoint of the healthcare payer in public hospitals. Pricing data for health services and medications were sourced from the published Council of Cooperative Health Insurance (CHI) database. All statistical procedures were carried out using SAS® version 9.4 software.

## 3. Results

### *3.1. Baseline Characteristics*

A total of 5218 records were reviewed, only 350 patients met the inclusion criteria and included in the analysis (116 in Semaglutide group and 234 in non-Semaglutide group) Figure 1 shows the study flow chart.

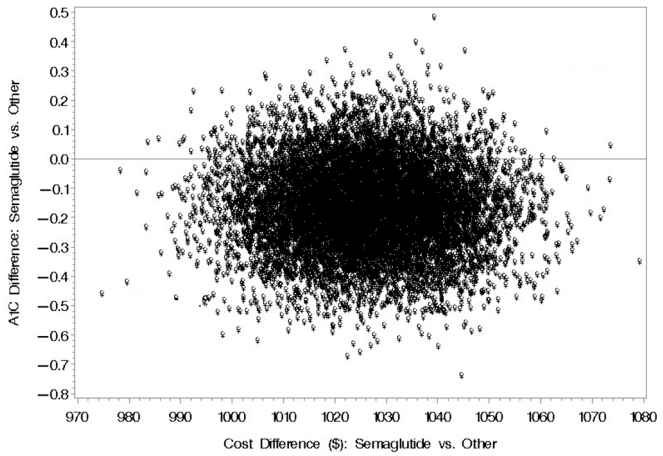


**Fig. 5.** Bootstrap Distribution of Cost and A1C Reduction Differences Between Semaglutide and Non-Semaglutide-Based Antidiabetic Treatments at 3-Month Follow-Up

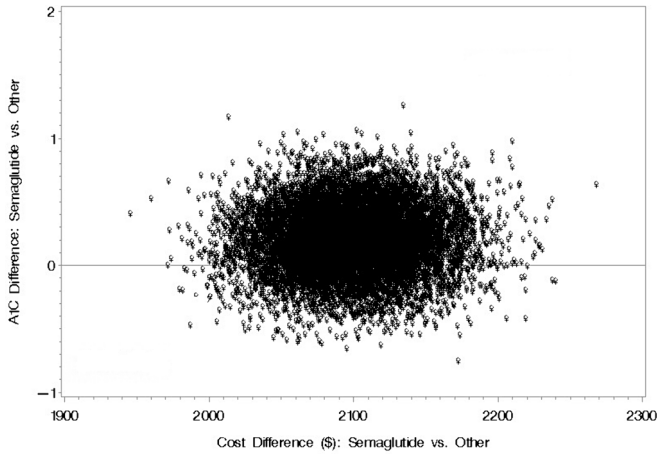


**Fig. 6.** Bootstrap Distribution of Cost and A1C Reduction Differences Between Semaglutide and Non-Semaglutide-Based Antidiabetic Treatments at 6-Month Follow-Up

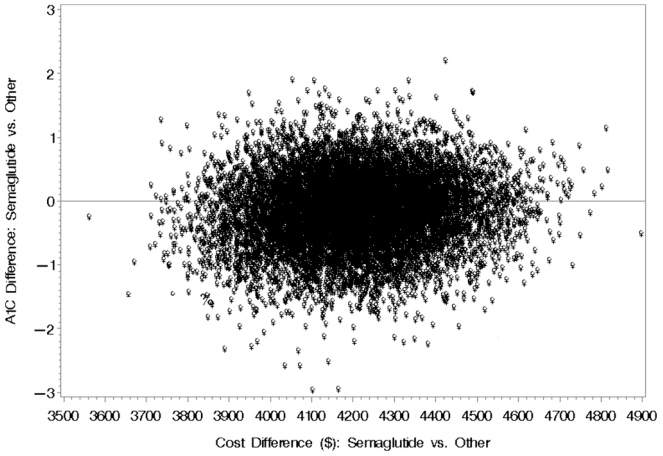


**Fig. 7.** Bootstrap Distribution of Cost and A1C Reduction Differences Between Semaglutide and Non-Semaglutide-Based Antidiabetic Treatments at 12-Month Follow-Up

Both groups at baseline were similar in terms of gender distribution; with 39.66% males in the Semaglutide group and 36.32% in the non-Semaglutide group (p=0.5445). The mean age was significantly higher in the non-Semaglutide group (61.50±8.82 years) compared to the Semaglutide group (58.25±9.31 years, p=0.0046). However, the duration of diabetes and treatment with the current antidiabetic regimen, excluding Semaglutide, were comparable between the groups.

The baseline weight was higher in the Semaglutide group 88.59 ±15.83 kg vs. 78.93±16.98 kg for others, p<0.0001) (Table 1). In the Semaglutide group 92.24% had a Charlson's Comorbidity Index (CCI) of <2 compared to 78.63% in the non-Semaglutide group (p=0.0003). However, Semaglutide group had notably higher diabetes complications namely retinopathy, and neuropathy.

### 3.2. Prescription Medication Utilization

Significant differences were observed in the utilization of prescription medications between the two groups. Notably, more patients in the Semaglutide group were on insulin (66.38% vs. 43.16%, p<0.0001) and fewer were on DPP-4 inhibitors (11.21% vs. 83.33%, p<0.0001).

### 3.3. Weight Reduction

After 3, 6, and 12 months of follow-up, patients on Semaglutide experienced greater weight reduction compared to those on non-Semaglutide regimens (Table 2). At 3 months, the mean weight reduction was –2.17±5.82% for the Semaglutide group compared to –1.75 ±7.83% for others (mean difference: –0.42%, 95% CI: –0.543 to –0.434) with more than 95% confidence level as shown in bootstrap distributions in Figures 2-4. Subgroup analysis for differences in weight reduction across all antidiabetic agents did not show significant differences (Table 3).

### 3.4. HbA1C Reduction

The Semaglutide group experienced a variable HbA1C reduction over 3, 6, and 12 months compared to the non-Semaglutide group, with no consistent difference. For example, at 3 months, the mean HbA1C reduction was –0.447±1.086% for the Semaglutide group and –0.601 ±1.62% for the non-Semaglutide group (mean difference: 0.154%, 95% CI: –0.452-0.483) (Table 3). However, the confidence levels that Semaglutide will result in greater HbA1C reductions over 3,6, and 12 months versus other alternative hypoglycemic regimens were under 95% confidence levels as shown in the bootstrap distributions in Figures 5–7. Subgroup analysis for differences in HbA1C reduction across all antidiabetic agents did not show significant differences (Table 3).

### 3.5. Treatment Cost

The cost of treatment was significantly higher in the Semaglutide group at all follow-up periods. For instance, after 12 months, the mean cost of treatment in the Semaglutide group was $5,833.43±506.55 (i.e., lab/imaging [15.96%], clinic [1.51%], medications [82.53%]), compared to $1,502.62±663.94 (i.e., lab/imaging [56.73%], clinic [3.46%], medications [39.84%]) in the non-Semaglutide group (mean difference: $4,330.81, 95% CI: 3,989.61- 4,818.97) (Figure 8).

### 3.6. Additional outcomes

Both groups showed a similar rate of all-cause hospitalization, with 17.24% in the Semaglutide group and 17.09% in the non-Semaglutide group (p=0.9485), suggesting no significant difference in this clinical outcome between the two treatment regimens (Table 4).

In summary, while Semaglutide treatment was associated with greater weight reduction, it came at a significantly higher cost compared to non-Semaglutide antidiabetic regimens. Moreover, the HbA1C

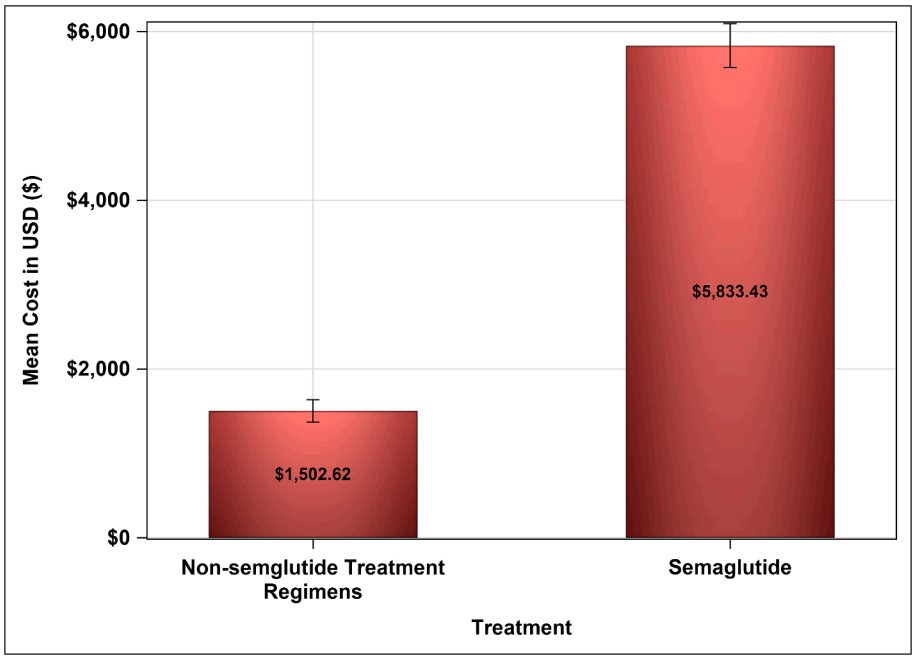


**Fig. 8.** The mean treatment costs of Semaglutide and other treatment groups for the management of type II DM from the public health sector's perspective in Saudi Arabia.

**Table 4**
Additional outcomes.

| Characteristic | Treatment (n=350) | | *p*-value | Total |
|---|---|---|---|---|
| | Semaglutide-based regimen (n=116) | Non-Semaglutide based antidiabetic treatment regimens (n=234) | | |
| Rates of all-cause hospitalization, n(%) | 20(17.24) | 40(17.09) | 0.9485 | 60 (17.14) |
| Side effects | | | | |
| Headache | 0(0) | 2(0.85) | 0.32 | 2(0.57) |
| Dizziness | 2(1.74) | 0(0) | 0.17 | 2(0.57) |
| Nausea | 2(1.74) | 2(0.85) | 0.46 | 4(1.14) |
| Vomiting | 2(1.74) | 0(0) | 0.17 | 2(0.57) |
| Stomach upset | 7(6.09) | 4(1.70) | 0.045 | 11 (3.14) |
| Indigestion | 3(2.61) | 0(0) | 0.17 | 3(0.86) |
| Diarrhea | 0(0) | 1(0.43) | 0.46 | 1(0.29) |
| Constipation | 1(0.87) | 3(1.28) | 0.74 | 4(1.14) |
| Local skin reaction at injection site | 0(0) | 0(0) | - | 0(0) |
| Severe hypoglycemia | 0(0) | 0(0) | - | 0(0) |
| Genitourinary infection | 0(0) | 1(0.43) | 0.48 | 1(0.29) |

reduction was not consistently better, and there was no difference in the rate of all-cause hospitalization between the two groups.

## 4. Discussion

Semaglutide has gained considerable favor in Saudi Arabia due to its superior efficacy in both lowering HbA1C levels and promoting weight loss when compared to other GLP-1 analogues (Witkowski et al., 2018). Several local studies and a systematic review have endorsed its effectiveness among its class (Alabdulkarim et al., 2019; Alkhatib et al., 2022; Ruan et al., 2021). However, this study stands out as the first study, to the best of our knowledge, that assessed the cost-effectiveness of Semaglutide versus other antidiabetic treatments using local real-world evidence. Our findings are in line with real-world evidence showing a range of HbA1C reductions from 0.3% to 3.4% and weight loss from 0.6 kg to 8.4 kg following Semaglutide initiation at 3, 6, and 12 months compared to other antidiabetic treatments (Ruan et al., 2021). However, our study diverged from randomized controlled trials (RCTs), which reported more pronounced differences in HbA1C (mean reduction of -1.03%) and weight loss (mean reduction of -3.61 kg) when comparing Semaglutide to other antidiabetic treatments among patients with T2DM (Pagada et al., 2018). Several factors could contribute to this discrepancy. First, the retrospective nature of our study may have introduced uncontrolled variables that could have skewed the outcomes. Second, patients in the Semaglutide group had lower baseline HbA1C, which might have tempered the drug's impact on HbA1C reduction (Thewjitcharoen et al., 2023). Additionally, about 11% of patients in the Semaglutide group had been on DPP4 inhibitors, which are often discontinued when Semaglutide is started. Moreover, the high rate of insulin utilization in the Semaglutide group compared to non-Semaglutide group as well as the previous exposure to GLP-1RA, such as Liraglutide, could also have mitigated its weight loss and HbA1C reduction effects (Yamada et al., 2022). Notably, around 30% of patients in the non-Semaglutide group were on SGLT2 inhibitors, compared to just 8% in the Semaglutide group, which could account for these differences (Laursen et al., 2023). Moreover, no differences were observed in the rates of all-cause hospitalization during the follow-up periods among users and non-users of Semaglutide.

On the financial front, the annual total cost of Semaglutide therapy was approximately five times higher than other antidiabetic regimens, translating to a significant extra expense of around $4200 USD per patient per year (Laursen et al., 2023). The existing literature presents conflicting views on the cost-effectiveness of GLP-1 analogues compared to other hypoglycemic agents, largely due to variations in study methodology, choice of decision-analytical models, and potential sponsorship bias (Laursen et al., 2023). Recent reviews and studies from other countries suggest that new hypoglycemic agents are cost-effective when added to metformin for managing uncontrolled T2DM, although SGLT2 inhibitors often emerge as the most economical option (Zhu et al., 2023; Chien et al., 2020; Thomsen et al., 2022; Wysham et al., 2018; Poonawalla et al., 2021). Rose et al. also noted a significant increase in the monthly cost of hypoglycemic agents after initiating GLP-1 analogues

(Rose et al., 2020). Our study found that Semaglutide had higher cost and comparable outcomes with regard to HbA1C reductions compared to other diabetes treatments, a finding that contrasts with some studies while aligning with others (Ramos et al., 2020; Ehlers et al., 2022; Guzauskas et al., 2021; Gorgojo-Martínez et al., 2020; Bain et al., 2020; Hunt et al., 2019; Capehorn et al., 2021).

Finally, the dosage-dependent efficacy of Semaglutide is undeniable, as shown in studies that noted considerable benefits in HbA1C levels, weight loss, and blood pressure management across various dosages (Sorli et al., 2017; Wilding et al., 2021; Kaku et al., 2018; Wadden, T.A. et al., 2021). Though these investigations focused on different outcomes, they uniformly attest to the multifaceted efficacy of Semaglutide.

### *4.1. Study strengths and limitations*

Our study stands out as the first local real-world, retrospective analysis examining both the clinical and financial implications of Semaglutide therapy among Saudi patients with uncontrolled T2DM. By comparing Semaglutide with other antidiabetic medications over a 12-month period, we were able to shed light on its actual performance beyond clinical trials. The study benefits from robust design aspects, including the focus on a range of metrics beyond just glycemic control, such as weight reduction, all-cause hospitalization rates, and treatment costs, as well as the control for a myriad of variables in the analysis. One of the most significant findings is that patients treated with Semaglutide experienced greater weight reduction, an important secondary goal in diabetes management. Our nuanced approach even considers various pre-existing conditions and comorbidities, providing a more comprehensive picture of the drug's effectiveness and cost implications. Therefore, the results of this study serve not only as a valuable academic contribution but also as a practical guide for healthcare providers in Saudi Arabia.

While this study breaks new ground by investigating the real-world cost-consequence of Semaglutide in Saudi Arabia, its limitations warrant a cautious interpretation of the findings. Specifically, the study's retrospective design, focus on a small patient cohort from just one tertiary diabetes center, and the short duration of follow-up all limit the generalizability of the results. Furthermore, the limitations of the study include several potential confounding factors, such as medication adherence, physical activity, lifestyle changes, and healthcare resource utilization from other hospitals, were not accounted for. Additionally, there were incomplete follow up data for key indicators like HbA1C and weight at 6 and 12 months that is typically seen in retrospective cohort studies, which may lead to the observation of lower effectiveness and higher costs. In addition, the choice of antidiabetic agent to start the patient on are impacted by medication availability at our centre and patient preference. Lastly, the study mainly correlates the medication's cost with its effectiveness in terms of glycemic control and weight loss, missing other important outcomes like cardiovascular disease prevention, chronic kidney disease progression, and mortality rates reduction. Future research is needed to address these limitations through a larger, multi-center, prospective design that includes a broader array of clinical endpoints and health-related quality of life.

## 5. Conclusion

Our study found that Semaglutide was effective in achieving greater weight reduction compared to other antidiabetic agents for patient who were GLP1RA non-naïve. However, this benefit came at a significantly higher treatment cost, and it did not consistently outperform alternative treatments in reducing HbA1C levels. Furthermore, there was no significant difference in the rate of all-cause hospitalization between the Semaglutide and non-Semaglutide groups. Future research should aim to address the aforementioned limitations of this study to provide a more comprehensive understanding of Semaglutide role in T2DM management.

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## CRediT authorship contribution statement

**Yazed AlRuthia:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Software, Writing – original draft, Writing – review & editing. **Khaled Hani Aburisheh:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing – review & editing. **Sondus Ata:** Conceptualization, Data curation, Resources, Supervision, Writing – review & editing. **Raghad Bin Salleeh:** Data curation, Methodology, Resources, Writing – review & editing. **Shahad B. Alqudhibi:** Data curation, Project administration, Resources, Writing – review & editing. **Raghad B. Alqudhibi:** Data curation, Methodology, Resources, Writing – review & editing. **Ziad Alkraidis:** Data curation, Project administration, Resources, Writing – review & editing. **Hala Humood Alkhalaf:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Abdulrahman Abdullah Almogirah:** Conceptualization, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. **Muhammad Mujammami:** Supervision, Writing – review & editing. **Reem Al Khalifah:** Conceptualization, Data curation, Formal analysis, Supervision, Writing – original draft, Writing – review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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