Patient Preference and Adherence

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ORIGINAL RESEARCH

Medication Adherence to Semaglutide Once-Weekly Injection Among Type-2 Diabetes Patients in Tabuk, Saudi Arabia – A Cross-Sectional Study

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Background: Semaglutide, a once-weekly injection (SOWI), is a glucagon-like peptide-1 receptor agonist for managing type-2 diabetes (T2D). However, it has a high discontinuation rate among users in the first year after treatment initiation. This study investigated the medication adherence level among T2D patients managed with SOWI.

Methods: This cross-sectional study was conducted among T2D patients aged 18 years or above who visited the outpatient pharmacy to refill their prescriptions for SOWI. The patients responded to their sociodemographic characteristics and the Adherence to Refills and Medications Scale (ARMS). The patient's electronic health record obtained details of the proportion of days covered (PDC), glycosylated hemoglobin (HbA1C), and body mass index (BMI). The association of medication adherence and sociodemographic characteristics, as well as the clinical outcomes between patients with different levels of adherence, were analyzed.

Results: A total of 434 patients were included in this study. According to the ARMS score, only 32.48% (141) of the patients adhered to SOWI. Sociodemographic characteristics had lower odds association for medication non-adherence. However, non-adherent patients had a significant association with BMI (overweight and obese) and HbA1C (>7). The adherence level of PDC for SOWI was significantly associated with the ARMS medication adherence level. The mean HbA1C and BMI between adherents and non-adherents were statistically significant ($p<0.001$). The patients who adhered to both ARMS and PDC (n = 126) experienced a significant decline in mean BMI ($p < 0.001$) and HbA1C ($p < 0.001$) compared to patients who adhered to PDC but not ARMS and those who did not adhere to either ARMS or PDC.

Conclusion: Medication adherence to the SOWI is subjective to T2D patients and not influenced by sociodemographic characteristics. T2D patients need more motivation to refill and administer the SOWI according to the schedule since medication adherence directly impacts HbA1C and BMI.

Keywords: adherence to refills and medications scale, body mass index, glycosylated hemoglobin, medication adherence, proportion to days covered, semaglutide, type-2 diabetes

Introduction

Type 2 diabetes (T2D) is a chronic disorder characterized primarily by hyperglycemia due to insulin resistance.[1] The prevalence of T2D was 10.5% in 2019 and is expected to increase to 11.3% and 12.2% in 2030 and 2040, respectively.[2] It requires optimal glycemic control; if not controlled, it can result in several microvascular and macrovascular complications, along with increased healthcare costs and a poor quality of life.[3,4] Glycemic control is influenced by various patient characteristics, particularly medication adherence (MA).[5,6] MA is defined as the "active, voluntary, and collaborative

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involvement of the patient in a mutually acceptable course of behavior to produce a therapeutic result".[7] A lack of MA is already linked to suboptimal glycemic control, as previous researchers have established.[8,9] Once-weekly dosing of Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) was found to have better MA among T2D patients.[10,11] MA with GLP-1 RAs was closely positively correlated with the clinical outcomes of T2D.[12] In contrast, another study found that only half of the patients were adherent to the GLP-1 RAs, and one in five patients discontinued treatment within the first 12 months.[13]

Semaglutide once-weekly injection (SOWI) was approved by the Food and Drug Administration (FDA) in 2017[11] and established for its superior MA compared to other GLP-1 receptor agonists (GLP-1 RAs).[10,14] The reduction in HbA1c and body weight was greater among users of SOWI compared to those using daily GLP-1 RAs. These would protect the patients from micro- and macrovascular complications of T2D.[10] The real-world adherence and persistence data also favor SOWI over other GLP-1 RAs, and the patients were highly satisfied.[15–17] There is no gold standard method for accurately measuring a patient's medication adherence (MA), as each method has numerous disadvantages.[18] Numerous researchers have measured the medication MA of GLP-1 receptor agonists (GLP-1 RAs) using the proportion of days covered (PDC) for refilling medications.[10–14] Generally, the PDC is calculated by the denominator, the number of days between the first prescription fill date and a defined end date. At the same time, the numerator is the number of days covered by the prescription fills during the denominator period.[19] The PDC indirectly observes MA, which has several disadvantages, including the lack of a standardized method to calculate the PDC in more complex medication-related issues, such as medication pre-supply, early refills, and changes within the same pharmacological class.[20] Complex medication-related issues regarding SOWI have risen to the patient's preference for SOWI over other GLP-1 RAs since its approval for weight loss in June 2021, followed by a shortage.[21,22]

Such supply and refilling issues can be assessed using a self-reported questionnaire; the Adherence to Refills and Medications Scale (ARMS) consists of 12 items divided into two domains: refilling prescriptions and medication adherence, and performs well across various literacy levels. Self-reported questionnaires are widely used, and researchers need speed, efficiency, and cost-effective methods. A validated self-reported questionnaire must be used to assess MA and can test its efficacy by comparing it with clinical outcomes. The ARMS is widely used and is free of charge to assess MA. The ARMS has already been validated in the Arabic language among patients with chronic conditions, including diabetes and hypertension, and can be administered free of any cost.[23–25]

The ARMS is distinguished from other self-reported MA questionnaires since it focuses on the refilling behavior of patients. Hence the dual approaches of ARMS and PDC could highlight their association and additional benefits in assessing medication adherence in T2D patients administering SOWI. This study primarily aimed to assess the MA of SOWI among T2D patients using the ARMS. The secondary objectives were to assess the influence of patient demographics in MA and the impact of MA on clinical outcomes of T2D. Following this, the association between ARMS response and PDC for SOWI on clinical outcomes was evaluated.

Methods

Study Design and Site

A cross-sectional survey was conducted at the Governmental Hospital in Tabuk, Saudi Arabia, between 1st January and 31st December 2024. The study site was a multi-specialty tertiary care hospital equipped with adequate facilities for managing Type 2 diabetes (T2D) in its medical, pharmacy, and laboratory departments, as well as qualified healthcare professionals. The study conductance and manuscript were drafted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cross-sectional studies (Supplementary file 1).[26]

Ethical Approval and Informed Consent from the Patients

The study was approved by the Research Ethics Committee of the King Salman Armed Forces Hospital (protocol code KSAFH-REC-2023-541; approved on 31 December 2023). Informed consent was obtained from all study participants prior to their enrollment in the study.

Sample Size Calculation

The sample size calculation was done using the following method:[27]

Sample size (n) = $(Z_1\text{-}\alpha/2)^2$ (p) (q)/d^2

n = sample size.

$Z_1\text{-}\alpha/2$ = Critical value and a standard corresponding confidence interval (CI).

(a 95% CI or 5% level of significance (type-I error), it is 1.96).

d = Margin of error or precision considered 5% (0.05)

P = prevalence or based on previous research; q = 1-p.

According to recent statistics, the prevalence of T2D in Saudi Arabia was 28% (0.28).[28]

Sample size (n) = $(1.96)^2$ (0.28) (0.72)/$(0.05)^2$

n = 0.7744/0.0025 = 309.78 ≈ 310

The expected participant refusal rate is 30% = 310/100*30 = 93

Total sample size = 310 + 93 = 403 T2D patients

Patients' Recruitment

The patients were initially screened for inclusion and exclusion criteria. The study included all patients with T2D aged 18 years or above who visited the outpatient pharmacy to refill their prescriptions for SOWI. T2D patients with non-metabolic comorbidities (eg, cancer, autoimmune disease) were excluded. Patients who were prescribed SOWI for under six months were excluded from the study. The study was explained to the patients in detail, and their consent was requested to participate. Patients were included in the survey after they consented to participate. In addition, the reasons for refusal were recorded for those who were unwilling to participate in the study.

Data Collection

Instrument

The ARMS was adopted for the SOWI, and the patients were informed that they would respond. The questionnaire has two parts: 1. Patient demographics, and 2. ARMS. Patient demographics include age, gender, marital status, level of education, employment status, monthly income in Saudi Arabian Riyals (SAR), duration of T2D, and any metabolic comorbidities. The ARMS is a 4-point Likert scale with 12 items. The responses were recorded as "none", "some", "most", or "all" of the time, which were given values from 1 to 4. A total ARMS score of less than 16 is considered adherence, and 16 or more is considered non-adherence.[23,24] It has two subscales: 1. To assess the patient's ability to administer the medication according to the prescribed schedule (Items 1, 2, 5, 6, 7, 8, 9, and 10), and 2. To assess the patient's ability to refill the medications (3, 4, 11, and 12).[23] Both the validated English and Arabic versions of the instrument were adopted, which minimizes potential recall and social desirability biases. The Arabic version of the ARMS was adopted for patients who could speak and understand Arabic, and the English version was used for those who could not.[23,24]

Clinical Outcomes and Medications

The studied clinical outcomes included body mass index (BMI), glycosylated hemoglobin (HbA1C), number of medications, details of medications, and SOWI dose obtained from the patient's electronic health records in the hospital. The BMI is categorized as underweight (15–19.9), normal weight (20–24.9), overweight (25–29.9), and obese (more than 30).[29] Glycemic control was assessed using HbA1c levels: values <7% were considered within target, 7–9% were considered above target, and >9% indicated uncontrolled T2D.[30] A patient who was taking five or more medications, including SOWI, is considered polypharmacy.[31]

PDC Calculation

The PDC calculation is illustrated as follows.

Example

PDC = (Number of days covered by the pharmacy-supplied SOWI ÷ Number of days an SOWI is required during the period of interest) x 100

PDC = 28 (days)/30 (days) x 100 = 93.33%

PDC of SOWI ≥ 80% considered adherence, and < 80% was nonadherence.[19]

Statistical Methods

The distribution of patient characteristics among the adherents and non-adherent patients was assessed using chi-square statistics. Simple logistic regression was used to assess the association between patient characteristics using an unadjusted odds ratio. Multinomial logistic regression analysis was used to assess the effects of confounding variables (patient characteristics) on medication adherence. The mean±SD (standard deviation) of the clinical outcome variables (BMI and HbA1C) and PDC of SOWI were compared between adherent and non-adherent patients using a Mann–Whitney *U*-test. One-way Analysis of Variance (ANOVA) was used to compare the mean±SD between different patient groups (ie, Adherence according to both ARMS and PDC, adherence to PDC and non-adherence to ARMS, non-adherence according to both ARMS and PDC, adherence to ARMS and non-adherence to PDC). Normality and homogeneity of variance were not tested. Tukey's post-hoc analysis was conducted to assess the inter-group variability. Differences were considered statistically significant with $p < 0.05$ at a 95% confidence interval, was considered statistically significant. Statistical Package for Social Sciences version 25.0 was used in statistical analysis.

Results

Patient Recruitment

Figure 1 represents the patient recruitment process. A total of eleven hundred and forty-five T2D patients were screened initially, followed by 676 eligible to participate in the study. SOWI treatment of less than six months (n=274) was a primary reason for exclusion, followed by diagnosis with other comorbidities (n=195). Two hundred forty-two patients were refused participation in the study. One hundred and twenty-six patients were not interested in participating, followed

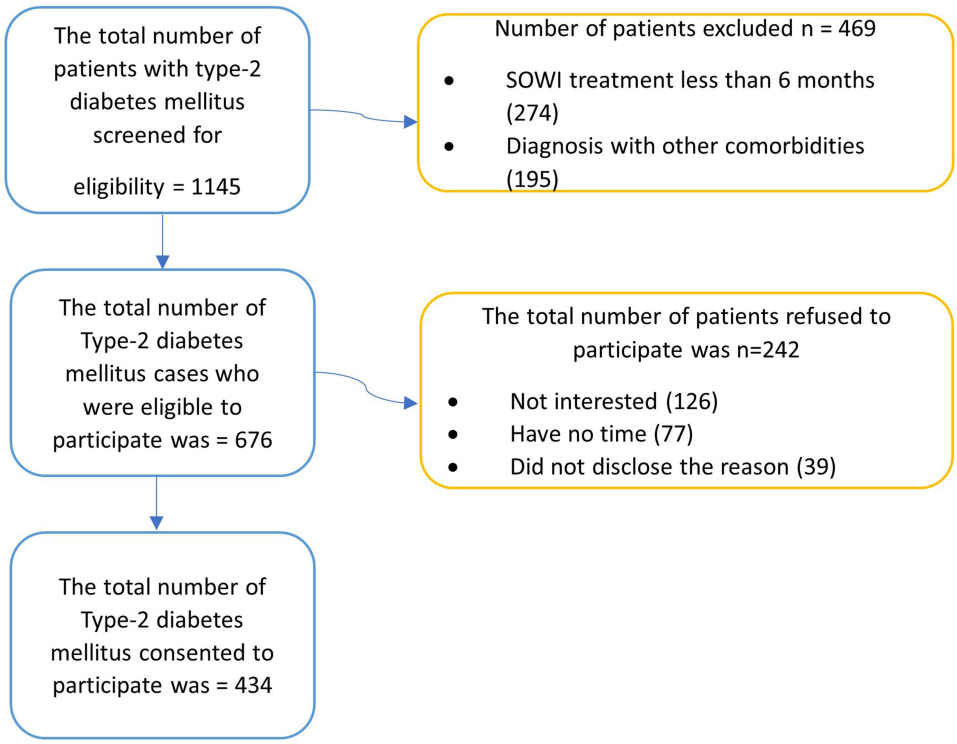

Figure 1 Schematic diagram of the study participants' recruitment.

by 77 who had no time, and 39 did not disclose the reason for refusal. Finally, 434 patients were recruited for this cross-sectional survey.

Prevalence of Medication Adherence Among T2D Patients Prescribed with SOWI

Among the 434 patients, 141 (32.48%) who scored an ARMS score of less than 16 were considered adherents to the medications, while 293 (67.51%) were nonadherent, as they scored an ARMS score of 16 or higher (Table 1).

Table 1 Distribution of Sociodemographic and Clinical Characteristics Between Adherents and Non-Adherents

Patient Characteristics	Total (434)		Adherent (141)		Non-Adherent (293)		χ^2	df	p
	N	%	N	%	N	%			
Age									
30 to 40 years	54	12.44	14	9.93	40	13.65	3.734	4	0.443
41 to 50 years	69	15.90	27	19.15	42	14.33			
51 to 60 years	237	54.61	74	52.48	163	55.63			
61 to 70 years	49	11.29	19	13.48	30	10.24			
Above 70 years	25	5.76	7	4.96	18	6.14			
Gender									
Female	224	51.61	67	47.52	157	53.58	1.402	1	0.236
Male	210	48.39	74	52.48	136	46.42			
Nationality									
Non-Saudi	15	3.46	6	4.26	9	3.07	0.400	1	0.527
Saudi	419	96.54	135	95.74	284	96.93			
Marital status									
Divorcee	39	8.99	8	5.67	31	10.58	5.08	3	0.166
Married	310	71.43	108	76.60	202	68.94			
Widow	39	8.99	14	9.93	25	8.53			
Single	46	10.60	11	7.80	35	11.95			
Level of education									
Diploma	104	23.96	27	19.15	77	26.28	4.649	3	0.199
Graduates	172	39.63	65	46.10	107	36.52			
Secondary/High school	53	12.21	15	10.64	38	12.97			
Illiterate/Primary school	105	24.19	34	24.11	71	24.23			
Occupation									
Business	142	32.72	33	23.40	109	37.20	9.323	2	**0.009**
Employed	170	39.17	67	47.52	103	35.15			
House wife/Retired/Unemployed	122	28.11	41	29.08	81	27.65			

(*Continued*)

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Table 1 (Continued).

Patient Characteristics	Total (434)		Adherent (141)		Non-Adherent (293)		χ^2	df	p
	N	%	N	%	N	%			
Monthly income in Saudi Riyal									
≥ 10,000	150	34.56	47	33.33	103	35.15	0.719	2	0.698
5000 to < 10000 SAR	109	25.12	39	27.66	70	23.89			
< 5000 SAR	175	40.32	55	39.01	120	40.96			
T2D duration									
Less than 1 year	57	13.13	21	14.89	36	12.29	4.666	3	0.198
1 to 5 years	112	25.81	41	29.08	71	24.23			
6 to 10 years	79	18.20	29	20.57	50	17.06			
More than 10 years	186	42.86	50	35.46	136	46.42			
Comorbidities									
No	153	35.25	47	33.33	106	36.18	15.368	9	0.081
Dyslipidemia	6	1.38	3	2.13	3	1.02			
Dyslipidemia and Obesity	13	3.00	3	2.13	10	3.41			
Hypertension	17	3.92	7	4.96	10	3.41			
Hypertension and CVD	110	25.35	26	18.44	84	28.67			
Hypertension and Dyslipidemia	32	7.37	9	6.38	23	7.85			
Hypertension and Obesity	7	1.61	3	2.13	4	1.37			
Obesity	68	15.67	29	20.57	39	13.31			
Obesity, Dyslipidemia, Hypertension and CVD	17	3.92	10	7.09	7	2.39			
Obesity, Hypertension and CVD	11	2.53	4	2.84	7	2.39			
T2D management									
Semaglutide + Insulin	46	10.60	12	8.51	34	11.60	1.300	3	0.729
Semaglutide + Insulin +OHA	17	3.92	6	4.26	11	3.75			
Semaglutide only	140	32.26	44	31.21	96	32.76			
Semaglutide with OHA	231	53.23	79	56.03	152	51.88			
Semaglutide dose									
0.25 mg	18	4.15	6	4.26	12	4.10	0.069	2	0.966
0.5 mg	53	12.21	18	12.77	35	11.95			
1 mg	363	83.64	117	82.98	246	83.96			

(*Continued*)

Table 1 (Continued).

Patient Characteristics	Total (434)		Adherent (141)		Non-Adherent (293)		χ^2	df	p
	N	%	N	%	N	%			
Number of medications									
0-2 medications	163	37.56	50	35.46	113	38.57	4.370	2	0.112
3-4 Medications	100	23.04	41	29.08	59	20.14			
5 or more medications	171	39.40	50	35.46	121	41.30			
Body Mass Index in kg/m^2									
Ideal	72	16.59	56	39.72	16	5.46	84.128	2	**<0.001**
Obese	118	27.19	20	14.18	98	33.45			
Overweight	244	56.22	65	46.10	179	61.09			
HbA1C in %									
Less than 7%	252	58.06	109	77.30	143	48.81	31.824	2	**<0.001**
7 to 9%	146	33.64	25	17.73	121	41.30			
Above 9%	36	8.29	7	4.96	29	9.90			
The proportion of days covered for semaglutide									
≥ 80% (Adherent)	307	70.74	126	89.36	181	61.77	34.998	1	**<0.001**
< 80% (non-adherent)	127	29.26	15	10.64	112	38.23			

Notes: p- is a value of chi-square statistics between the patient characteristics and medication adherence; p<0.05 is considered statistically significant and mentioned in bold letters.

Abbreviations: BMI, Body mass index; CVD, cardiovascular disease; HbA1C, Glycosylated hemoglobin; PDC, Proportion to days covered; T2DM, Type-2 Diabetes Mellitus; χ^2, Chi-square.

Association of Characteristics Between Adherents and Non-Adherents

The distribution of patient characteristics between adherent and non-adherent patients is illustrated in Table 1. Most of the patients (54.61%) were between 51 and 60 years old; however, they were distributed almost equally among adherents (52.48%) and non-adherents (55.63%). However, this difference was not statistically significant. 51.61% were female, most were married (71.43%), and Saudi (96.54%). There was no statistically significant difference in the distribution of gender, marital status, and nationality between adherents and non-adherents. Most adherents (46.10%) and non-adherents (36.52%) had graduated with no significant statistical difference. Graduation (39.63%) and diploma-level education (23.96%) were the predominant qualifications of patients in this study. Most adherents (46.10%) and non-adherents (36.52%) had graduated, with no statistically significant difference. Predominant adherents were employed (47.52%), and 35.15% of non-adherents were doing business. This association showed a statistically significant difference between the two groups (p = 0.016). Most patients earned less than 5000 Saudi Riyals per month (40.32%) and have a duration of T2D of more than ten years (42.86%). These characteristics were not statistically different between the adherent and nonadherent groups. Many patients had no metabolic comorbidities (35.25%), followed by hypertension with cardiovascular disease (25.35%) and obesity (15.67%); however, the distribution of comorbidities between adherent and non-adherent patients was not significantly different. The number of medications, management of T2D, and SOWI dose were not statistically different between adherents and non-adherent patients. Patients with overweight were significantly more likely to be non-adherents (61.09%) than adherents (46.10%), and this difference was statistically significant (p = 0.005). The HbA1c level was on target (<7%) in adherents (77.30%) compared to non-adherents (48.81%), with statistically

significant differences ($p < 0.001$). According to the PDC score (≥80%), adherence was predominant (89.36%), and only 61.77% were non-adherents, with statistical significance ($p < 0.001$).

Logistic regression analysis was employed to investigate the relationship between the patient characteristics and medication adherence (Table 2). Age, gender, marital status, education, occupation, monthly income, duration of T2D,

Table 2 Regression Analysis of Characteristics Between Adherents and Non-Adherents According to the ARMS Score

	Simple Logistic Regression				Multiple Logistic Regression			
	p	OR	95% CI		p	AOR	95% CI	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Age								
41-50 years	0.125	1.836	0.844	3.996	**0.007**	6.501	1.667	25.357
51- 60 years	0.445	1.297	0.665	2.529	**0.012**	5.510	1.453	20.893
61 - 70 years	0.164	1.809	0.783	4.179	0.264	2.649	0.479	14.640
Above 70 years	0.846	1.111	0.383	3.220	0.665	1.595	0.192	13.249
30 to 40 years	Reference range				Reference range			
Gender								
Female	0.260	0.784	0.524	1.173	0.071	0.521	0.257	1.057
Male	Reference range				Reference range			
Nationality								
Non-Saudi	0.578	1.402	0.489	4.020	0.952	1.053	0.196	5.652
Saudi	Reference range				Reference range			
Marital status								
Married	0.146	0.587	0.287	1.203	0.142	0.376	0.102	1.387
Divorcee	0.707	1.217	0.434	3.415	0.978	0.976	0.172	5.535
Widow	0.229	1.781	0.694	4.569	0.180	3.024	0.600	15.239
Single	Reference range				Reference range			
Education								
Graduate	0.362	0.788	0.472	1.315	0.137	0.233	0.034	1.593
Diploma	0.308	0.732	0.402	1.333	0.517	0.646	0.172	2.420
Secondary/High school	0.601	1.213	0.588	2.502	0.929	1.054	0.329	3.384
Illiterate/Primary school	Reference range				Reference range			
Occupation								
Business	0.311	1.285	0.790	2.088	0.313	2.082	0.501	8.654
Employed	0.062	1.671	0.973	2.872	**0.025**	9.976	1.334	74.623
Housewife/Retired/Unemployed	Reference range				Reference range			

(*Continued*)

Table 2 (Continued).

	Simple Logistic Regression				Multiple Logistic Regression			
	p	OR	95% CI		p	AOR	95% CI	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Monthly income in Saudi Riyal								
More than 10000	0.985	1.004	0.627	1.607	0.930	0.966	0.449	2.081
5000 to 10000	0.448	0.822	0.496	5.000	0.282	1.585	0.684	3.671
Less than 5000	Reference range				Reference range			
T2D duration								
One to five years	0.976	1.010	0.521	1.957	0.087	3.233	0.843	12.402
Six to ten years	0.987	1.005	0.496	2.038	0.120	2.639	0.777	8.959
More than ten years	0.149	1.586	0.846	2.974	0.239	2.059	0.620	6.843
Less than a year	Reference range				Reference range			
Metabolic comorbidities								
Hypertension	0.382	0.633	0.227	1.765	**0.001**	0.011	0.001	0.151
Dyslipidemia	0.330	0.443	0.086	2.278	**0.001**	0.009	0.001	0.135
Obesity	0.086	0.596	0.330	1.076	0.118	0.089	0.004	1.848
Dyslipidemia and obesity	0.566	1.478	0.388	5.617	0.814	0.789	0.110	5.687
Hypertension and dyslipidemia	0.771	1.133	0.487	2.634	**0.045**	0.105	0.012	0.946
Hypertension and obesity	0.502	0.591	0.127	2.746	**0.000**	0.002	0.000	0.023
Obesity, hypertension, and CVD	0.696	0.775	0.216	2.778	0.141	0.157	0.013	1.853
Hypertension and CVD	0.206	1.432	0.819	2.503	0.188	0.188	0.016	2.267
Obesity, Dyslipidemia, Hypertension, and CVD	**0.025**	0.310	0.111	0.865	**0.000**	0.013	0.002	0.093
No comorbidities	Reference range				Reference range			
T2D management								
Semaglutide and OHA	0.582	1.134	0.724	1.775	0.468	0.521	0.089	3.036
Semaglutide and Insulin	0.493	0.770	0.364	1.628	0.144	0.224	0.030	1.668
Semaglutide, Insulin and OHA	0.746	1.190	0.413	3.424	0.687	1.600	0.163	15.737
Semaglutide only	Reference range				Reference range			
Semaglutide dose								
0.5 mg	0.961	1.028	0.331	3.193	0.872	1.164	0.184	7.357
1 mg	0.922	0.951	0.348	2.597	0.340	0.465	0.097	2.240
0.25 mg	Reference range				Reference range			

(*Continued*)

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Table 2 (Continued).

	Simple Logistic Regression				Multiple Logistic Regression			
	p	OR	95% CI		p	AOR	95% CI	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Number of other medications								
3-4 medications	0.088	0.636	0.378	1.070	**0.025**	3.381	1.169	9.775
5 or more medications	0.774	1.070	0.670	1.710	0.145	2.905	0.692	12.195
0-2 medications	Reference range				Reference range			
BMI								
Overweight	**0.000**	0.103	0.055	0.193	**0.000**	0.012	0.004	0.038
Obese	**0.000**	0.058	0.028	0.121	**0.000**	0.000	0.000	0.002
Ideal	Reference range				Reference range			
HbA1C								
7 to 9	**0.000**	0.271	0.164	0.445	**0.000**	0.134	0.060	0.301
Above 9	**0.008**	0.316	0.133	0.750	**0.008**	0.168	0.045	0.632
Less than 7	Reference range				Reference range			
Adherence according to PDC								
PDC more than 80%	**0.000**	11.614	6.330	21.310	**0.000**	12.751	5.187	31.345
PDC less than 80%	Reference range				Reference range			

Note: p <0.05 considered statistically significant, mentioned in bold letters.
Abbreviations: AOR, Adjusted odd ratio; CI, Confidence interval; HbA1C, Glycosylated hemoglobin; PDC, Proportion to days covered; T2DM, Type-2 Diabetes Mellitus; UOR, Unadjusted odd ratio.

management of T2D, SOWI dose, and number of medications showed no significant association with medication adherence before and after adjusting for confounding variables. The patients who were employed had a higher odds association with medication adherence after adjusting for confounding variables (OR=9.976; p=0.025).

- Non-adherent patients were significantly associated with obesity and overweight before (Overweight: OR=0.103; p=0.000; Obese: OR=0.058; p=0.000) and after (Overweight: OR=0.012; p=0.000; Obese: OR=0.000; p=0.000) adjusting for confounding variables.
- Also, non-adherent patients most likely to have HbA1C 7 to 9 and more than 9 before (HbA1C 7 to 9: OR=0.271; p=0.000; HbA1C more than 9: OR=0.316; p=0.008) and after (HbA1C 7 to 9: OR=0.134; p=0.000; HbA1C more than 9: OR=0.168; p=0.008) adjusting for confounding variables.
- The adherence to PDC for SOWI was predominantly associated with adherence to the ARMS score before (unadjusted odds ratio, 11.614; p = 0.000) and after adjusting for confounding patient characteristics (adjusted odds ratio, 21.310; p = 0.000).

Patient Responses to ARMS

The mean difference was statistically significant (p<0.001) between adherents and non-adherents regardless of items in ARMS according to the Mann–Whitney *U*-test (Table 3). Items 3, 4, 11, and 12 are related to refilling medications. The

Table 3 Responses of Adherents and Non-Adherents to ARMS

No.	Items	Adherents (141)		Non-Adherents (293)		Mean Difference	Z	p
		Mean	SD	Mean	SD			
1	How often do you forget to take your medicine?	1.04	0.20	1.34	0.67	−0.302	−5.276	**0.000**
2	How often do you decide not to take your medicine?	1.13	0.38	1.68	0.85	−0.548	−7.080	**0.000**
3	How often do you forget to get prescriptions filled?	1.34	0.63	2.13	0.97	−0.796	−8.405	**0.000**
4	How often do you run out of medicine?	1.07	0.26	1.76	0.82	−0.686	−9.316	**0.000**
5	How often do you skip a dose of your medicine before you go to the doctor?	1.07	0.34	1.62	0.73	−0.543	−8.589	**0.000**
6	How often do you miss taking your medicine when you feel better?	1.12	0.41	1.89	0.92	−0.767	−9.146	**0.000**
7	How often do you miss taking your medicine when you feel sick?	1.03	0.18	1.33	0.58	−0.299	−6.024	**0.000**
8	How often do you miss taking your medicine when you are careless?	1.07	0.31	1.28	0.52	−0.202	−4.274	**0.000**
9	How often do you change the dose of your medicines to suit your needs (like when you take more or less pill than you are supposed to)?	1.06	0.24	1.71	0.76	−0.646	−9.546	**0.000**
10	How often do you forget to take your medicine when you are supposed to take it more than once a day?	1.25	0.52	1.84	0.87	−0.584	−7.209	**0.000**
11	How often do you put off refilling your medicines because they cost too much money?	1.05	0.23	1.27	0.54	−0.216	−4.421	**0.000**
12	How often do you plan ahead and refill your medicines before they run out?	1.17	0.48	1.97	1.05	−0.795	−8.372	**0.000**

Notes: p: mean ± SD difference between adherents and non-adherents; $p < 0.05$ considered statistically significant and mentioned in bold letters.
Abbreviations: ARMS, Adherence to Refills and Medications Scale; Z, "Z" score of Mann–Whitney *U*-test.

lowest mean ± SD value of item 11 reflects the poor influence of the cost of medication among both adherents (1.057 ± 0.23) and non-adherents (1.27 ± 0.54). Meanwhile, the higher mean difference between adherent and non-adherent patients in item 3 (−0.796), item 4 (−0.686), and item 12 (−0.795) contributed significantly to non-adherence. The remaining items in ARMS (1, 2, 5, 6, 7, 8, 9, and 10) concern the patient's ability to administer the medication according to the prescribed schedule. In this regard, the major cause of poor adherence since higher mean difference noticed on non-adherents from adherents was due to: 1. They miss taking their medicine when they feel better (item 6; mean difference: −0.767), 2. Change the dose of their medicines to suit their needs (item 9; mean difference: −0.646), 3. Forget to take their medicine when they are supposed to take it more than once a day (item 10; mean difference: −0.584), 4. They decide not to take their medicine (item 2; mean difference: −0.548), and 5. They skip a dose of their medicine before going to the doctor (item 5; mean difference: −0.543). The following items has least influence for non-adherence since the mean difference between adherents and non-adherents was low among the items 1 (How often do you forget to take your medicine?; mean difference: −0.302), 7 (How often do you miss taking your medicine when you feel sick?; mean difference: −0.299), and 8 (How often do you miss taking your medicine when you are careless?; mean difference: −0.202).

Differences in Medication Adherence Score and Clinical Outcomes

The differences between medication adherence and clinical outcomes using the Mann–Whitney *U*-test have been revealed in Table 4. The mean (SD) BMI of adherents was significantly lower than the non-adherents according to the ARMS score ($p<0.001$) and PDC score ($p<0.043$). Meanwhile, according to the ARMS score, the mean HbA1C level is significantly lower in adherents ($p<0.001$) but not in PDC ($p=0.357$). The mean (SD) PDC score between the adherents and non-adherents according to the ARMS was statistically significant ($p<0.001$); in vice-versa, the mean (SD) ARMS score between the adherents and non-adherents according to the PDC for SOWI was also statistically significant ($p<0.001$).

Table 4 Differences in HbA1C and BMI, ARMS, and PDC Scores Between the Adherents and Non-Adherents

Variable	Adherence According to the ARMS Score				p	Adherence According to the PDC Score				p
	Adherent (141)		Non-Adherent (293)			Adherent (307)		Non-Adherent (127)		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
ARMS score	–	–	–	–	**–**	17.24	4.24	19.08	4.07	**<0.001**
PDC score	90.78	10.78	82.43	17.12	**<0.001**	–	–	–	–	**–**
HbA1C	6.21	1.27	7.10	1.66	**<0.001**	6.86	1.62	6.70	1.53	0.357
BMI	25.99	3.29	28.74	3.36	**<0.001**	27.62	3.69	28.39	3.24	**0.043**

Notes: p- is a value of the Mann–Whitney *U*-test of mean (SD) between adherents and non-adherents; p<0.05 is considered statistically significant and mentioned in bold letters.
Abbreviations: ARMS, Adherence to Refills and Medications Scale; BMI, Body mass index; HbA1C, Glycosylated hemoglobin; PDC, Proportion to days covered; SD, Standard deviation.

In Table 5, the patients were divided into four groups: 1. Adherence according to both ARMS and PDC (126), adherence to PDC and non-adherence to ARMS (181), non-adherence according to both ARMS and PDC (112), and Adherence to ARMS and Non-adherence to PDC (15). The means (SD) of HbA1C and BMI between the groups mentioned above were statistically significant (p<0.001). Further, a post-hoc analysis was performed to understand the inter-group differences in the mean (SD) of HbA1C and BMI (Table 6). Adherence, according to both the ARMS and PDC groups of patients, has a significantly lower HbA1C and BMI than the groups' adherence to PDC and non-adherence to ARMS (p=0.000), and non-adherence according to both ARMS and PDC (p=0.027). Notably, there was no significant difference between adherence to ARMS and non-adherence to the PDC group of patients in HbA1C (p=0.834) and BMI (p=0.999). The patient group with adherence to ARMS and non-adherence to PDC had significantly lower HbA1C (p=0.005) and BMI (0.012) than the group with adherence to PDC and non-adherence to ARMS. Meanwhile, the patient group with adherence to ARMS and non-adherence to PDC had significantly lesser BMI (p=0.018) than those with non-adherence according to the ARMS and PDC group. However, these groups have significant differences in HbA1C (p=0.136).

Table 5 Comparison of Clinical Outcome Variables Between Patients' Adherence with ARMS and PDC Score

Variable	Adherence According to Both ARMS and PDC (126)	Adherence to PDC and Non-Adherence to ARMS (181)	Non-Adherence According to Both ARMS and PDC (112)	Adherence to ARMS and Non-Adherence to PDC (15)	p
HbA1C					
Mean	6.25	7.28	6.81	5.90	**<0.001**
SD	1.31	1.69	1.57	0.91	
BMI					
Mean	25.98	28.76	28.71	26.00	**<0.001**
SD	3.38	3.46	3.19	2.62	

Notes: p- is a value of the one-way ANOVA of mean (SD) between different adherence groups; p<0.05 is considered statistically significant and mentioned in bold letters.
Abbreviations: ARMS, Adherence to Refills and Medications Scale; BMI, Body mass index; HbA1C, Glycosylated hemoglobin; PDC, Proportion to days covered; SD, Standard deviation.

Table 6 Tukey's Posthoc Analysis on the Comparison of Clinical Outcome Variables Between Patients' Adherence with ARMS and PDC Score

Patient Group		HbA1C					BMI				
		Mean Difference	SD	p	95% Confidence Interval		Mean Difference	SD	p	95% Confidence Interval	Mean Difference
					Lower Bound	Upper Bound				Lower Bound	Upper Bound
Adherence according to both ARMS and PDC	Adherence to PDC and Non-adherence to ARMS	−1.028	0.178	**0.000**	−1.488	−0.569	−2.778	0.388	**0.000**	−3.779	−1.778
	Non-adherence according to both ARMS and PDC	−0.558	0.199	**0.027**	−1.073	−0.044	−2.721	0.434	**0.000**	−3.841	−1.601
	Adherence to ARMS and Non-adherence to PDC	0.353	0.419	0.834	−0.728	1.435	−0.015	0.913	1.000	−2.371	2.340
Adherence to PDC and Non-adherence to ARMS	Non-adherence according to both ARMS and PDC	0.469	0.185	0.055	−0.006	0.946	0.0570	0.402	0.999	−0.980	1.094
	Adherence to ARMS and Non-adherence to PDC	1.381	0.412	**0.005**	0.318	2.446	2.762	0.898	**0.012**	0.445	5.080
Non-adherence according to both ARMS and PDC	Adherence to ARMS and Non-adherence to PDC	0.912	0.422	0.136	−0.177	2.001	2.705	0.919	**0.018**	0.334	5.077

Notes: p- is a value of Tukey's post hoc analysis one-way ANOVA of mean (SD) between different adherence groups; p<0.05 is considered statistically significant and mentioned in bold letters.
Abbreviations: ARMS, Adherence to Refills and Medications Scale; BMI, Body mass index; HbA1C, Glycosylated hemoglobin; PDC, Proportion to days covered; SD, Standard deviation.

Discussion

This is the first cross-sectional study to assess medication adherence using ARMS among patients with T2D who were administered SOWI. Although previous studies have already documented good medication adherence to once-weekly SOWI, this study showed medication non-adherence (ARMS score ≥16) in 67.51% (n=293) of T2D patients.[10,16,17] This higher non-adherence rate could be due to the adverse effects and patients' perceived inconvenience with injectables.[32–34]

This study includes patients who had more than six months of SOWI treatment since absolute discontinuation of SOWI was at least 6 months, as reported by the recent nationwide registry study in Denmark and another researcher from the United States addressed that only 50% of patients are consistent with SOWI in their first year of treatment due to adverse drug reactions.[13,34] Previous studies have highlighted that SOWI has higher patient satisfaction and improved clinical benefits compared to other GLP-1 RAs.[16,17,35] Also, a recent study has suggested that adherence to SOWI could improve glycemic control.[32] Hence, this study highlights that SOWI benefits T2D patients who adhere to treatment more than non-adherents in terms of clinical outcomes, including BMI and HbA1C.

This study is consistent with a recently published Danish cohort study regarding the SOWI, which is predominantly used among females at a median age of 50 with T2D and metabolic comorbidities.[34] We did not find the patients between the age groups of 18–29 years in the study site during the study period. The patient's sociodemographic and clinical characteristics (that includes age, gender, nationality, marital status, level of education, occupation, monthly income, T2D duration, metabolic comorbidities, T2D management, SOWI dose, and number of medications) in this study were not associated with medication adherence, either before or after adjusting for confounding variables using logistic regression analysis. According to the previous studies, regardless of age, gender, comorbidities, semaglutide dose, and co-prescribed medications for T2D, SOWI substantially decreased body weight and HbA1C, which was verified in the present study, particularly for those who adhered. As reported in previous studies,[35] SOWI in T2D management remains complex in clinical practice and varies according to the individual patient. Meanwhile, the present study found no significant association between medication adherence and the patient's treated SOWI monotherapy or SOWI administered in combination with other medications.[32]

Monthly income was not associated with medication adherence (Table 2), as medications were provided free of charge at the study site, which is under the governance of the Ministry of Defense, Saudi Arabia. Additionally, among all the items in ARMS, the very low mean difference between adherents and non-adherents regarding item 11 (How often do you put off refilling your medicines because they cost too much money?) suggests that the cost has minimal influence on medication adherence (Table 3). SOWI was reported to be cost-effective for the healthcare system, particularly in managing T2D with existing metabolic comorbidities.[36] Other items related to refill in the ARMS (3, 4, and 12) had a higher mean difference between adherents and non-adherents, ascertaining that the refilling of SOWI potentially influences patient medication adherence. The present study did not investigate the barriers to SOWI refilling, and future studies are warranted to investigate and rule out them for enhancing the adherence followed by better clinical outcomes.[13,21,22,34]

Eight items (1, 2, 5, 6, 7, 8, 9, and 10) in ARMS were relevant to the patient's ability to administer the medication according to the prescribed schedule. The higher mean difference was noticed among the items that include 1. They miss taking their medicine when they feel better (item 6), 2. Change the dose of their medicines to suit their needs (item 9), 3. Forget to take their medicine when they are supposed to take it more than once a day (item 10), 4. They decide not to take their medicine (item 2), and 5. They skip a dose of their medicine before going to the doctor (item 5). This study contradicts earlier literature, despite previous studies reporting that patients were more satisfied with SOWI regarding its use.[16,17,36,37] Therefore, ARMS can help practitioners assess what causes non-adherence to SOWI among T2D patients. Also, many studies in the future still need to highlight the barriers involved in medication adherence to SOWI, which help the practitioners rule out them and achieve the desired clinical outcomes.

According to ARMS and PDC scores (p=0.043), adherents have a significantly lower mean (SD) body mass index than non-adherents (Table 4). Moreover, according to ARMS, adherents have lower HbA1c Levels ($p < 0.001$) than non-adherents, whereas there was no significant difference between them according to the PDC score. Meanwhile, patients who adhered to both ARMS and PDC experienced a significant decline in BMI and HbA1C compared to those who

adhered to PDC but not ARMS, as well as those who adhered to neither ARMS nor PDC. In this regard, according to the ARMS and PDC scores, the adherence level clearly demonstrates the impact on clinical outcomes and is consistent with previous findings (Table 5).[10,13,17,35,37] Therefore, the combined monitoring with ARMS and PDC in T2D patients initiated with the SOWI could help enhance their clinical outcomes.

The adherence level of patients in this study, as measured by ARMS and PDC, was inconsistent, with ARMS detecting 67.05% (291) of non-adherence, whereas PDC detected only 29.2% (127) of non-adherence. In this regard, the threshold level of PDC ≥80% for adherence remains questionable, as only 18% of studies in a scoping review and 1% of studies in another systematic review recommended this threshold to improve health outcomes.[20,38] The PDC calculation could be more appropriate with the prescribed daily dose, which is difficult to calculate with a once-weekly SOWI.[39] Hence, the pitfalls in implementing the PDC method for SOWI must be ruled out in future studies to assess adherence accurately.

Strengths and Limitations

The study assessed medication adherence among the T2D patients who were prescribed SOWI using ARMS for the first time. The patient's responses are explored under two domains of the ARMS. Patient adherence was evaluated in a real-world setting based on a combination of self-report and prescription refill data, which is likely more reflective of the medication adherence patterns encountered by clinicians when treating patients in clinical practice. The patients were grouped into four according to their adherence to ARMS and PDC. This study highlights monitoring medication adherence and its impact on clinical outcomes by combining the ARMS and PDC. To improve the integrity of the findings, the authors of this study had face-to-face meetings with the patients for data collection. The ARMS was already validated in both English and Arabic, and it helps minimize the bias among the diverse, multilingual population in this study. However, the study has several limitations: 1. The single-center study findings cannot be generalized; 2. The power analysis has not been performed in the sample size calculation to detect differences between subgroups. 3. The patients were prescribed drugs other than SOWI, which might have influenced their response, even though they were informed of the responses for only SOWI; 4. Baseline BMI and HbA1C were unknown, which limits our ability to attribute changes solely to adherence.

Conclusion

This study found that sociodemographic characteristics were not significant predictors of adherence. SOWI can be effective in improving glycemic control and BMI among adherent patients. The ARMS could help healthcare practitioners measure adherence to SOWI and be more accurate when combined with the PDC method. This should be adopted routinely in each clinical visit of the patient until the dosage optimization of SOWI. Those who are not adhering need to be investigated further to address the barrier to non-adherence and need to be counseled accordingly. In this regard, future studies need to explore the barriers to non-adherence in two domains of ARMS: the patient's refilling ability and the patient's ability to administer the medication according to the prescribed schedule.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical Approval and Patient Consent

The Research Ethics Committee of the King Salman Armed Forces Hospital approved the study (KSAFH-REC-2023-541), which complies with the Declaration of Helsinki. Written consent was obtained from all participants before enrolment.

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Disclosure

The authors declare no conflicts of interest in this work.

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