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Research Article

Exploring Side Effects and Discontinuation Reasons of Glucagon-Like-Peptide-1 Agonist (Liraglutide, Semaglutide) for Weight Loss Among Patients at King Abdulaziz University, Jeddah in 2021 to 2023

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Abstract

Background: Obesity is a metabolic syndrome that poses adverse health effects and established outcomes. Glucagon-Like-Peptide-1 Receptor Agonists (GLP1-RAs), are a class of injectable anti-diabetic medications that are approved for obesity and chronic weight management. There's not enough data on how possible Side Effects (SE) affect reasons for discontinuing GLP1-RAs. Our aim in this study is to examine the common side effects and reasons for discontinuation of GLP1-RAs (liraglutide, semaglutide) in a tertiary care hospital.

Methods: A cross-sectional phone-interview analysis, included users of GLP1-RAs in a large tertiary care hospital in Saudi Arabia between 2021 and 2023. A pre-made data collection sheet based on previous literature was used to acquire data from the record system and patients were contacted via phone interview method. Descriptive statistics were used to summarize demographic characteristics and outcomes. Fisher's exact test was employed to assess the statistical differences in the outcomes of interest.

Results: The study analyzed a total of 354 patients, with the majority being females (79.1%), aged between 45 and 60 years (33.3%), and presenting a median weight of 85.0 kg (IQR: 74.0-97.0) along with a median BMI of 32.4 kg/m² (IQR: 28.8-36.6). Side effects were reported in 80.2% of participants, with nausea and vomiting being the most frequently documented. No significant differences were observed in the development of side effects across various age groups (p=0.356). However, depression was significantly more prevalent among patients aged 45 to 60 years (20.4%, p=0.005), while nausea was notably more common in patients under 30 years and those aged 30 to less than 45 years (100% and 85.7%, respectively, p=0.011). Prolonged use of GLP-1 receptor agonists (more than six months) significantly reduced the incidence of common side effects (28%, p<0.001) and was associated with substantial weight loss of 20 kg or more (24.3%, p<0.001). Despite these benefits, over half of the participants (73.4%) discontinued the medication due to various reasons, including unclear personal decisions (45.8%), cost-related issues (21.9%), and scheduling challenges (20%).

Conclusion: GLP1-RAs users for weight loss particularly, long-acting GLP1-RAs, suffer from a high likelihood of SE development, predominantly nausea and vomiting, that could interplay and cause discontinuation and medication ineffectiveness.

Keywords: GLP1-Ras; Liraglutide; Semaglutide; Side Effects; Discontinuation; Weight Loss

Introduction

The proglucagon cleavage product, Glucagon-Like Peptide-1 (GLP-1), is synthesized by L cells in the intestinal mucosa and is

believed to function as a hormone, relaying signals from the intestine to the endocrine pancreas via the circulatory system, as plasma GLP-1 levels rise following food intake [1]. GLP-1 stimulates pancreatic beta cells to reduce glucagon secretion and increase insulin release [2]. Additionally, some of this hormone can cross the blood-brain barrier to activate brain regions that promote satiety [3]. In patients with Type 2 Diabetes (T2D), GLP-1 receptor agonists-an injectable class of anti-diabetic medications—enhance glycemic control and improve several atherosclerosis-related markers [2]. These agents are also effective in managing obesity by slowing gastric emptying, which lowers postprandial blood glucose, reduces calorie intake, and sometimes necessitates gradual dose adjustments to mitigate potential side effects [5]. For weight management, a higher dose (3.0 mg) is recommended, while a 1.8 mg dose is commonly used for T2D treatment [4]. Among commonly prescribed GLP-1 receptor agonists, Saxenda accounts for 39.4% of usage, followed by Ozempic (37.5%) and Trulicity (14.4%), with an additional 8.8% of patients using a combination of these medications. A cross-sectional study in Abha revealed that obesity was the primary reason for GLP-1 usage (48.1%), followed by T2D (30.6%), type 1 diabetes mellitus (13.8%), and gestational diabetes mellitus (7.5%). Commonly reported side effects included nausea and vomiting (51.3%), mood changes (40.6%), indigestion (33.8%), dizziness and hypoglycemia (33.8%), and either diarrhea or constipation (25%). Approximately 38.6% of participants lost 4-7 kg, while 31% lost 1-3 kg, though 6.3% did not achieve any weight loss. Additionally, 56.3% of participants achieved an HbA1c level below 7.5% [6]. With the increasing use of GLP-1 receptor agonists, gastrointestinal side effects such as nausea, vomiting, abdominal discomfort, diarrhea, and constipation are frequently observed [8]. These adverse effects may be linked to the activation of both central and peripheral GLP-1 receptors and could arise from direct or indirect interactions with the central nervous system, activation of afferent parasympathetic pathways or effects on brain regions unprotected by the blood-brain barrier [8-19]. Other mechanisms may involve altered secretion of gastrointestinal peptides, delayed gastric emptying, or changes in intestinal motility [11,12]. GLP-1 receptor agonists can be categorized as short-acting (exenatide, lixisenatide) or long-acting (liraglutide, dulaglutide, extended-release exenatide, and semaglutide) based on their plasma half-life. Short-acting agents tend to lower Postprandial Glucose (PPG) more effectively and delay gastric emptying to a greater extent than long-acting agents, thereby decreasing the rate of post-meal glucose spikes [9,20]. However, prolonged exposure to long-acting GLP-1 receptor agonists may induce tachyphylaxis, resulting in diminished effects on gastric emptying over time [12,21]. Notably, delayed gastric emptying associated with GLP-1 receptor agonists has been linked to nausea, with prolonged-acting agents exhibiting a potentially reduced impact on gastric motility, thereby decreasing nausea [3,21,23]. By mimicking endogenous incretin hormones, GLP-1 receptor agonists improve glycemic control while reducing the risk of hypoglycemia and weight gain commonly associated with insulin therapy [24-27]. In 2017, a real-world survey explored reasons for non-adherence to GLP-1 receptor agonists among T2D patients and their physicians. The survey revealed a preference for oral over injectable therapies as a primary cause of non-compliance, reported by 56% of patients and 33% of physicians. Commonly cited reasons for discontinuation included gastrointestinal side effects, with 64% experiencing nausea and 45% reporting vomiting, as well as cost and limited perceived efficacy [24]. Notably, exenatide has been associated with acute kidney injury in several cases, primarily due to hemodynamic disturbances from nausea, vomiting, and diarrhea [3,28-34]. Other side effects include nasopharyngitis, headaches, minor increases in heart rate, and injection site reactions, though these rarely lead to discontinuation [3]. Currently, there is limited research on the side effects and reasons for discontinuation of GLP-1 receptor agonists, particularly liraglutide and semaglutide, among patients using these agents for weight management in Jeddah, specifically at King Abdulaziz University. This study aims to investigate the side effects and discontinuation reasons for GLP-1 receptor agonists (liraglutide, semaglutide) in this population between 2023 and 2024.

Method and Materials

This cross-sectional study was approved by the Institutional Review Board of King Abdulaziz University Hospital (KAUH) (Ref: 623-23). A non-probability convenience sampling technique was utilized to select patients from the Medicine and Family Medicine departments at KAUH in Jeddah, Saudi Arabia. The study covered the period between January 2021 and January 2023. Given the observational nature of the study, informed consent was waived. A total of 354 adult patients, aged 18 years and older, who had been prescribed GLP-1 receptor agonists (Liraglutide, Semaglutide) specifically for weight management, were included. Patients under the age of 18 or those receiving GLP-1 receptor agonists for other medical indications were excluded from the study.

Clinical Data

Patient data were carefully gathered from hospital medical records and supplemented with information obtained through phone interviews. Data collection tools included a pre-designed Google Form and Microsoft Excel, ensuring organized and consistent

data entry. The dataset encompassed a wide range of patient information, such as demographics, comorbidities, reasons for discontinuing GLP-1 receptor agonists, and any reported side effects. A standardized data collection sheet, developed based on previous studies, was employed to ensure comprehensive and accurate data gathering from both the medical record system and phone interviews.

Statistical Analysis

The statistical analysis was conducted using RStudio software (R version 4.3.1). Descriptive statistics, including frequencies, percentages, and medians with Interquartile Ranges (IQR), were used to summarize demographic characteristics and outcomes. Fisher's exact test was employed to assess the statistical differences in the development of side effects between different age groups and durations of using GLP-1 receptor agonists. A p-value of less than 0.05 was considered statistically significant.

Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore, was exempt.

Results

Demographic Characteristics of Patients

The study included a total of 354 patients. One-third of patients were between the ages of 45 and 60 years (33.3%), followed closely by those aged 60 years or more (32.8%). The majority of participants were female (79.1%) and Saudi nationals (79.7%). The median weight of the patients was 85.0 kg (IQR 74.0 - 97.0), the median height was 162.0 cm (IQR 156.0 - 168.0), and the median BMI was 32.4 kg/m^2 (IQR 28.8 - 36.6). Most patients were classified as obese (64.2%), 26.7% were overweight and 9.1% had a healthy BMI (Table 1).

Characteristics and Outcomes of Using GLP-1 Receptor Agonists

Regarding the duration of use, 41.2% of the patients used GLP-1 receptor agonists for more than 6 months, while 30.5% used them for 3 to 6 months and 24.9% for less than 3 months (Fig. 1 and Table 2). The median weight loss was 6.0 kg (IQR 3.0 - 11.0); the frequency distribution of weight loss is depicted in Fig. 2. The majority experienced a weight loss of 1 to less than 10 kg (46.6%), followed by 10 to less than 20 kg (22.4%), and 20 kg or more (13.8%, Table 2).

A significant proportion of patients (73.4%) stopped using GLP-1 receptor agonists, among whom the most common reason for stopping was personal choice, reported by 45.8% of the patients. Cost was the second most common reason, cited by 21.9% of the patients, followed by issues with the medication schedule (20.0%, Fig. 3).

Interestingly, 63.6% of patients under study did not reach their weight loss goals (Table 2). Side effects were reported by 80.2% of the patients. Nausea was the most commonly reported side effect, affecting 77.5% of those who reported side effects. Loss of appetite and vomiting were both reported by 36.6% of the patients each. Abdominal pain was experienced by 33.8%, while headache was reported by 19.0% (Fig. 4).

Statistical Differences in the Development of Side Effects Between Different Age Groups

There were no significant differences in the development of side effects among different age groups (p=0.356). Among patients who experienced side effects (n=284), depression was significantly more common in patients aged 45 to 60 years (20.4%) compared to other age groups, with a p-value of 0.005. Nausea was significantly more common in patients under 30 years (100%) and 30 to less than 45 years (85.7%) compared to older age groups, with a p-value of 0.011 (Table 3).

Statistical Differences in the Development of Side Effects Between Different Groups of Duration of Using GLP-1 Agonists

The duration of using GLP-1 receptor agonists significantly affected the development of side effects and weight loss categories. Patients using GLP-1 agonists for more than 6 months were associated with experiencing weight loss of 20 kg or more (24.3%) compared to those using it for 3 to 6 months (7.4%) or less than 3 months (6.8%) ($p < 0.001$). Side effects were significantly less common in patients using GLP-1 agonists for more than 6 months (28.8%) compared to those using it for less than 3 months (90.9%) and 3 to 6 months (92.6%) ($p < 0.001$, Table 4).

Abdominal pain was reported significantly more frequently among patients who used GLP-1 receptor agonists for less than 3 months (42.5%) compared to those who used it for 3 to 6 months (38.0%) and for more than 6 months (24.0%, p = 0.019). Depression was significantly more common in patients who used GLP-1 receptor agonists for 3 to 6 months (22.0%) compared to those who used it for more than 6 months (8.0%, p = 0.036). Headaches occurred significantly more often in patients who used GLP-1 receptor agonists for 3 to 6 months (28.0%) compared to those who used it for less than 3 months (17.5%) and for more than 6 months (12.0%, p = 0.029). The incidence in patients using the medication. Vomiting was significantly more frequent among patients who used GLP-1 receptor agonists for less than 3 months (45.0%) and for 3 to 6 months (42.0%) compared to those who used it for more than 6 months (22.0%, p < 0.001, Table 4).

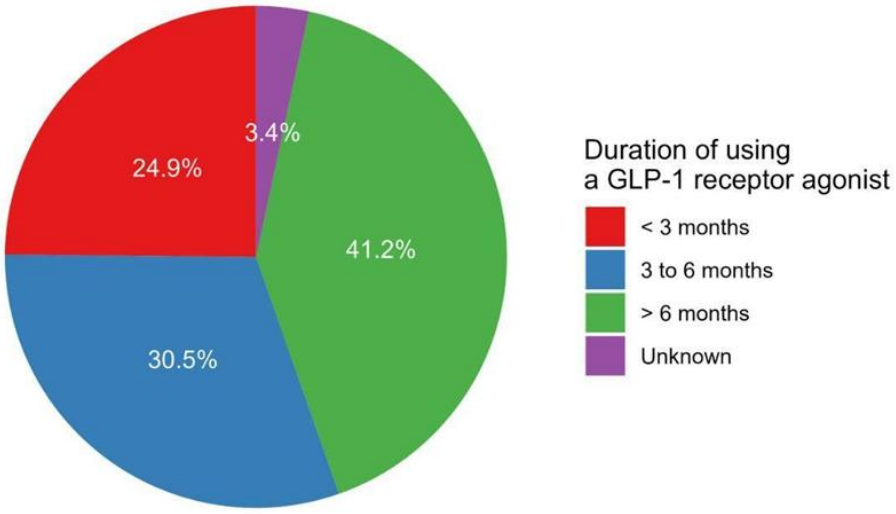

Figure 1: The proportions of duration categories for using a GLP-1 receptor agonist.

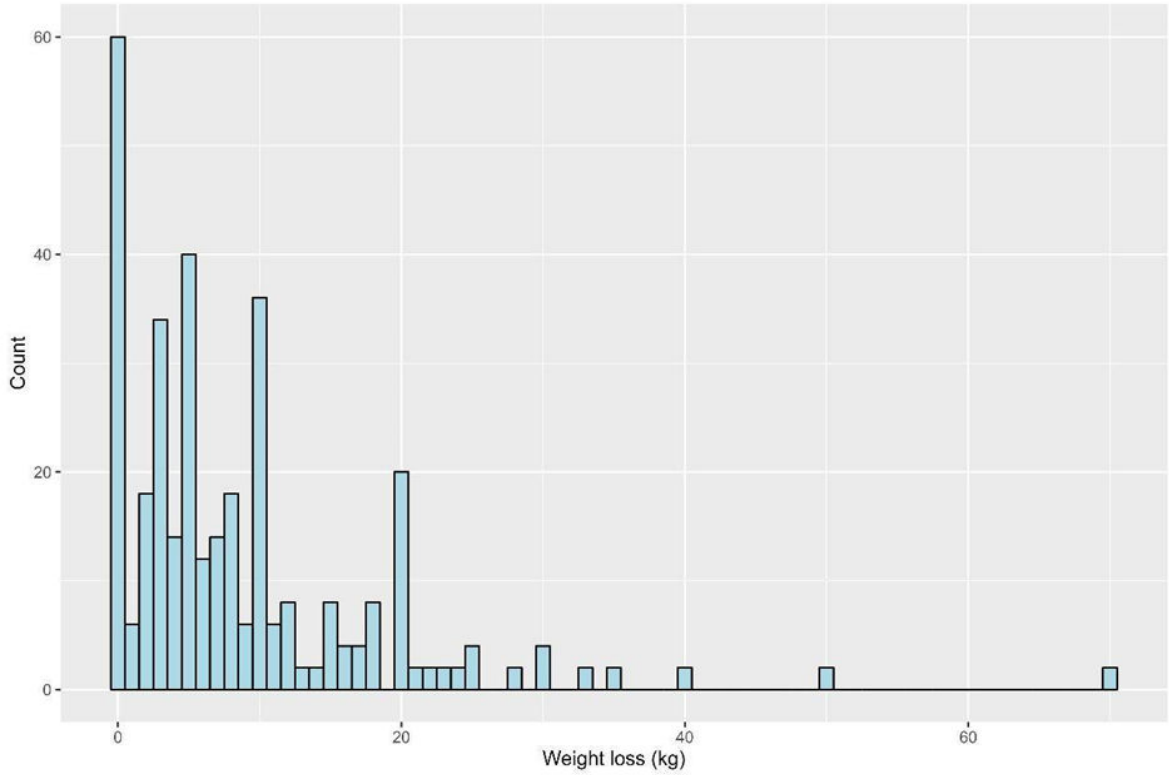

Figure 2: The frequency distribution of weight loss in kg.

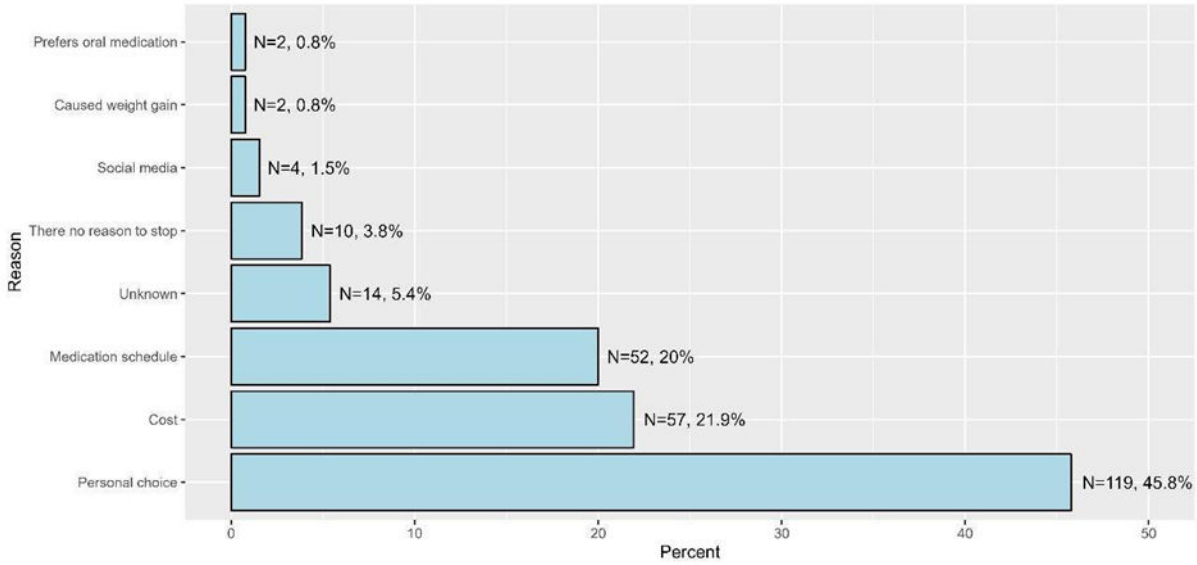

Figure 3: Primary reasons for stoppage of GLP among patients who stopped the medications (n=260).

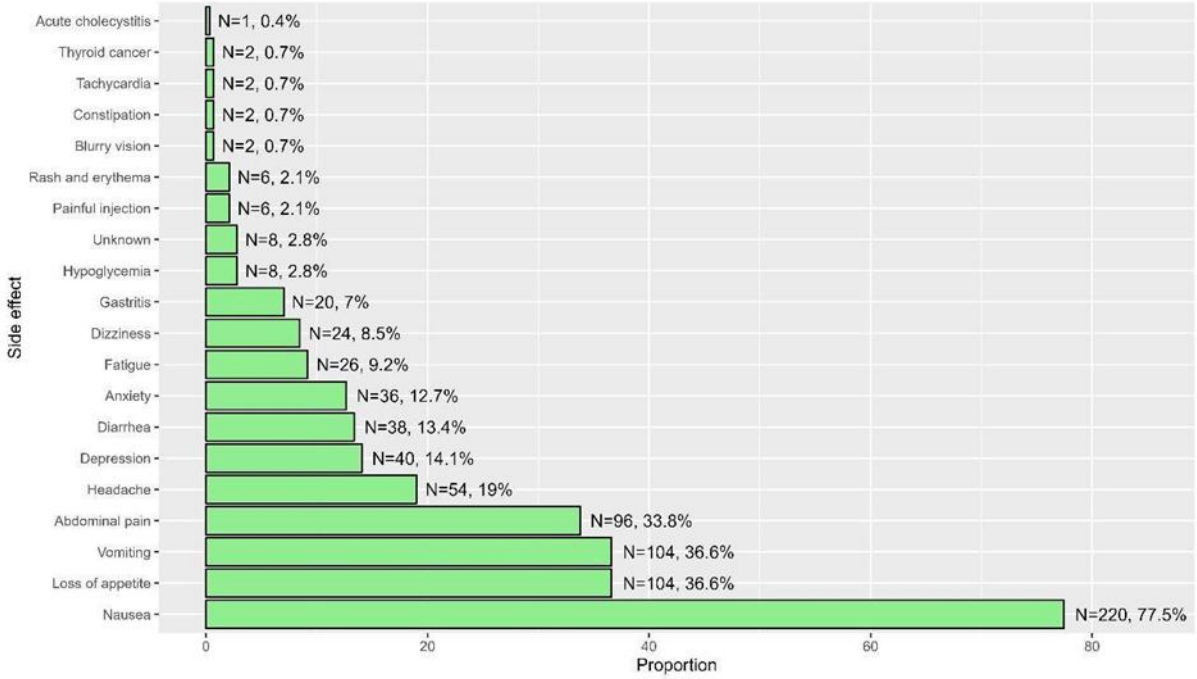

Figure 4: The proportions of side effects among patients who reported adverse events (n=284).

Characteristic	Missing	Description
Age	0 (0%)	
< 30		18 (5.1%)
30 to < 45		102 (28.8%)
45 to < 60		118 (33.3%)
60 or more		116 (32.8%)
Gender	0 (0%)	
Male		74 (20.9%)
Female		280 (79.1%)
Nationality	0 (0%)	
Saudi		282 (79.7%)

Non_Saudi		72 (20.3%)
Weight (kg)	0 (0%)	85.0 (74.0 - 97.0)
Height (cm)	2 (0.6%)	162.0 (156.0 - 168.0)
BMI (kg/m^2)	2 (0.6%)	32.4 (28.8 - 36.6)
BMI	2 (0.6%)	
Healthy		32 (9.1%)
Overweight		94 (26.7%)
Obese		226 (64.2%)
n (%); Median (IQR)		

Table 1: Demographic characteristics of patients.

Characteristic	Missing	Description
Duration of use	0 (0%)	
< 3 months		88 (24.9%)
3 to 6 months		108 (30.5%)
> 6 months		146 (41.2%)
Unknown		12 (3.4%)
Weight loss (kg)	6 (1.7%)	6.0 (3.0 - 11.0)
Weight loss categories	6 (1.7%)	
None		60 (17.2%)
1 to <10 kg		162 (46.6%)
10 to <20 kg		78 (22.4%)
20 or more kg		48 (13.8%)
Stop using a GLP-1 receptor agonist	0 (0%)	
No		86 (24.3%)
Yes		260 (73.4%)
Unknown		8 (2.3%)
Reached the goal	2 (0.6%)	
No		224 (63.6%)
Yes		102 (29.0%)
Unknown		26 (7.4%)
Side effect	0 (0%)	
No		58 (16.4%)
Yes		284 (80.2%)
Unknown		12 (3.4%)
n (%); Median (IQR)		

Table 2: Characteristics and outcomes of using GLP-1 Receptor Agonists.

Characteristic	Age (years)				p-value
	< 30 N=18	30 to < 45 N=102	45 to < 60 N=118	60 or more N=116	
Side effect					0.356
No	6 (33.3%)	14 (13.7%)	18 (15.3%)	20 (17.2%)	
Yes	12 (66.7%)	84 (82.4%)	98 (83.1%)	90 (77.6%)	
Unknown	0 (0.0%)	4 (3.9%)	2 (1.7%)	6 (5.2%)	
Side effects*					
Abdominal pain	6 (50.0%)	32 (38.1%)	26 (26.5%)	32 (35.6%)	0.193
Depression	2 (16.7%)	14 (16.7%)	20 (20.4%)	4 (4.4%)	0.005

Anxiety	2 (16.7%)	14 (16.7%)	12 (12.2%)	8 (8.9%)	0.387
Gastritis	0 (0.0%)	10 (11.9%)	6 (6.1%)	4 (4.4%)	0.232
Loss of appetite	8 (66.7%)	32 (38.1%)	32 (32.7%)	32 (35.6%)	0.153
Blurry vision	0 (0.0%)	0 (0.0%)	2 (2.0%)	0 (0.0%)	0.388
Diarrhea	2 (16.7%)	14 (16.7%)	14 (14.3%)	8 (8.9%)	0.398
Fatigue	0 (0.0%)	10 (11.9%)	10 (10.2%)	6 (6.7%)	0.510
Headache	0 (0.0%)	16 (19.0%)	24 (24.5%)	14 (15.6%)	0.148
Hypoglycemia	0 (0.0%)	0 (0.0%)	4 (4.1%)	4 (4.4%)	0.205
Dizziness	0 (0.0%)	8 (9.5%)	8 (8.2%)	8 (8.9%)	0.907
Nausea	12 (100.0%)	72 (85.7%)	74 (75.5%)	62 (68.9%)	0.011
Painful injection	0 (0.0%)	2 (2.4%)	2 (2.0%)	2 (2.2%)	>0.999
Acute cholecystitis	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0.338
Thyroid cancer	0 (0.0%)	0 (0.0%)	2 (2.0%)	0 (0.0%)	0.388
Rash and erythema	0 (0.0%)	0 (0.0%)	2 (2.0%)	4 (4.4%)	0.244
Vomiting	6 (50.0%)	34 (40.5%)	36 (36.7%)	28 (31.1%)	0.441
Constipation	0 (0.0%)	1 (1.2%)	1 (1.0%)	0 (0.0%)	0.781
Tachycardia	0 (0.0%)	0 (0.0%)	2 (2.0%)	0 (0.0%)	0.388
Unknown	0 (0.0%)	0 (0.0%)	4 (4.1%)	4 (4.4%)	0.205
n (%)					
Fisher's exact test *Data are based on 284 patients who experienced side effects					

Table 3: Statistical differences in the development of side of effects between different age groups.

Characteristic	Duration of using GLP-1 receptor agonists				p-value
	< 3 months N=88	3 to 6 months N=108	> 6 months N=146	Unknown N=12	
Weight loss categories					<0.001
None	30 (34.1%)	12 (11.1%)	12 (8.6%)	6 (50.0%)	
1 to <10 kg	52 (59.1%)	54 (50.0%)	52 (37.1%)	4 (33.3%)	
10 to <20 kg	0 (0.0%)	34 (31.5%)	42 (30.0%)	2 (16.7%)	
20 or more kg	6 (6.8%)	8 (7.4%)	34 (24.3%)	0 (0.0%)	
Side effect					<0.001
No	8 (9.1%)	8 (7.4%)	42 (28.8%)	0 (0.0%)	
Yes	80 (90.9%)	100 (92.6%)	100 (68.5%)	4 (33.3%)	
Unknown	0 (0.0%)	0 (0.0%)	4 (2.7%)	8 (66.7%)	
Side effects*					
Abdominal pain	34 (42.5%)	38 (38.0%)	24 (24.0%)	0 (0.0%)	0.019
Depression	10 (12.5%)	22 (22.0%)	8 (8.0%)	0 (0.0%)	0.036
Anxiety	14 (17.5%)	16 (16.0%)	6 (6.0%)	0 (0.0%)	0.052
Gastritis	6 (7.5%)	10 (10.0%)	4 (4.0%)	0 (0.0%)	0.380
Loss of appetite	32 (40.0%)	40 (40.0%)	30 (30.0%)	2 (50.0%)	0.350
Blurry vision	0 (0.0%)	0 (0.0%)	2 (2.0%)	0 (0.0%)	0.353
Diarrhea	8 (10.0%)	20 (20.0%)	10 (10.0%)	0 (0.0%)	0.141
Fatigue	10 (12.5%)	8 (8.0%)	8 (8.0%)	0 (0.0%)	0.661
Headache	14 (17.5%)	28 (28.0%)	12 (12.0%)	0 (0.0%)	0.029
Hypoglycemia	0 (0.0%)	2 (2.0%)	6 (6.0%)	0 (0.0%)	0.099
Dizziness	8 (10.0%)	10 (10.0%)	6 (6.0%)	0 (0.0%)	0.657
Nausea	64 (80.0%)	78 (78.0%)	74 (74.0%)	4 (100.0%)	0.669

Painful injection	0 (0.0%)	0 (0.0%)	6 (6.0%)	0 (0.0%)	0.009
Acute cholecystitis	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	>0.999
Thyroid cancer	0 (0.0%)	2 (2.0%)	0 (0.0%)	0 (0.0%)	0.353
Rash and erythema	2 (2.5%)	0 (0.0%)	4 (4.0%)	0 (0.0%)	0.191
Vomiting	36 (45.0%)	42 (42.0%)	22 (22.0%)	4 (100.0%)	<0.001
Constipation	1 (1.3%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0.751
Tachycardia	0 (0.0%)	2 (2.0%)	0 (0.0%)	0 (0.0%)	0.353
Unknown	6 (7.5%)	0 (0.0%)	2 (2.0%)	0 (0.0%)	0.022
n (%)					
Fisher's Exact test *Data are based on 284 patients who experienced side effects					

Table 4: Statistical differences in the development of side of effects between different groups of duration of using GLP-1 agonists.

Discussion

In this retrospective study, we aimed to investigate the side effects and causes of GLP1 (liraglutide, semaglutide) discontinuation in patients who were using it to lose weight. We discovered that a significant portion of patients (80.2%) reported experiencing adverse symptoms, with nausea accounting for the majority (77.5%). The high rate of discontinuations may be explained by the high frequency of adverse effects. Despite this, the two main reasons why 73.4% of patients stopped taking the drug were cost (21.9%) and personal preference (45.8%). The fact that 63.6% of patients failed to meet their weight loss objectives is noteworthy and raises concerns regarding the efficacy and expectations around GLP-1 receptor therapy.

The overall development of adverse effects did not differ significantly between age groups, according to our study (p=0.356). But patients between the ages of 45 and 60 had significantly higher rates of depression (20.4%, p = 0.005), and younger patients (under 45) had higher rates of nausea (85.7%) than older patients (p = 0.011). These results point to variations in certain adverse effects with age, which may help with individualized patient care.

Our findings revealed that the duration of GLP-1 receptor agonist use significantly impacted both adverse effects and weight loss. Patients who used the medication for over six months experienced greater weight loss (20 kg or more in 24.3% of cases, p<0.001) and reported fewer side effects (28.8%, p<0.001) compared to those with shorter usage periods. This pattern suggests the possibility of an adaptation phase, where prolonged use leads to improved tolerability and effectiveness.

In our study, the majority of individuals (80.2%) developed adverse effects from using GLP-1RAs. The most common symptom reported was nausea (77.5%), which was followed by vomiting and loss of appetite (36.6%) Each of loss of appetite and vomiting was reported by 36.6% of the patients. Abdominal discomfort (33.8%), and headache (19.0%). Given that semaglutide and liraglutide were the drugs evaluated in this research, a large percentage of individuals reporting adverse responses may be explained by the fact that Semaglutide and Liraglutide exhibited the highest rate of adverse events among different GLP-1RAs in a previous real-world analysis [8]. In keeping with previous studies, the majority of GLP-1RA side effects that occur in clinical practice are Gastrointestinal (GI) in nature. These effects include nausea, vomiting, diarrhea and constipation. Side effects seem to be dose-dependent, usually brief, mild to moderate in severity, and primarily occur during the start of treatment and upon uptitration [35]. In a clinical trial, which comprised older patients with overlapping illnesses, the prevalence of GI problems was greater than their counterparts controls [36].

One third of participants in the current study were middle-aged, within the age of 45 to 60 years old, and 79.1% of them were female. According to earlier studies, women experienced more adverse effects than men did (65.89% vs. 30.96%), and the median age of those patients was 56 years [37]. Age and duration of GLP1-RAs use were associated with a higher likelihood of adverse effects. Significantly, adverse effects decrease with extended usage, which may indicate improved tolerance or, conversely, drug tachyphylaxis. The duration of GLP-1 receptor agonist usage was found to have a significant impact on the development of side effects, with patients taking GLP-1 agonists for more than 6 months reporting a lower incidence of side effects (28.8%), compared to those using them for less than 3 months (90.9%) and those using them for 3 to 6 months (92.6%) (p < 0.001). indicating that

adverse effects are an uncommon phenomena after six months of usage and are more common during the initial stages of therapy, which occur within the first three to six months of using the medication as these side effects mostly develop at the beginning and at times of dose increase, this finding is consistent with previous results from several clinical trials that suggested there may be a dose and class effect dependency [35, 38-40].

It was observed that individuals using GLP-1RAs for less than three months experienced a significant increase in both vomiting and abdominal pain; those using the drug for three to six months experienced a delayed onset of headache, and those using it for more than six months experienced a late finding of depression ($p = 0.019$, $p < 0.001$, $p = 0.029$,$p = 0.036$, respectively). Nausea was also substantially more prevalent in patients under 30 years old (100%) and in individuals 30 to less than 45 years old (85.7%) compared to older age groups ($p = 0.011$). Depression was significantly more common in patients 45 to 60 years old (20.4%) ($p = 0.005$). It is implied that age is a factor that may influence the occurrence of depression and nausea in various patient populations. This might be explained by hormonal and metabolic variables that have not yet been identified but may interact with GLP-1RA usage in those specific age groups. This result, however, is at odds with other research that suggested GLP-1RAs had antidepressant effects [41-43]. The study's self-reported nature may provide an explanation for this finding, since patients may have mistakenly classified feelings of worry, dread, or despair for depression.

Inflammation, mood and appetite hormones, such as cortisol and thyroid hormones, are also said to be regulated by GLP-1 RAs [43-45]. GLP-1 RAs causing anxiety have been reported [46], despite its potential antidepressant effects [41-43]. In fact, complex symptoms including anxiety, sleep difficulties, and depression alleviation may be explained by the GLP-1 RA-related potential change of GABAergic neurotransmission [47,48]. Yet, a recent systematic review analysis of individuals with Type-2 diabetes mellitus identified a dearth of evidence that raised the possibility that GLP-1RA users may experience ambiguous side effects or perhaps see an increase in depression incidence [49].

More than half (73.4%) of GLP-RA users in this study stopped using the drug. Personal issues accounted for 45.8% of the causes, followed by costs (21.9%) and medication schedule (20.0%). In a cross-sectional study that evaluated the reasons for discontinuation of GLP-1 Receptor Agonists (GLP-1RAs) among patients with type 2 diabetes mellitus, while excluding cost as a factor, it was found that gastrointestinal symptoms, specifically vomiting and nausea were the predominant reasons for discontinuation reported by both patients and physicians [24]. A recent retrospective cohort study found that the percentage of people who stopped taking GLP-1 agonists was 26.2%, 30.8%, and 36.5% at 3, 6, and 12 months, respectively [50]. Compared to individuals with diabetes mellitus or both conditions combined, obese patients were more likely to discontinue treatment after a year [50].

Regarding GLP-RA effectiveness, 63.6% of research participants did not reach their set weight loss goals. The average weight reduction was 6 kg, 46.6% of individuals lost less than 10 kg, 22.4% lost between 10 and less than 20 kg, and only 13.8% of the participants lost 20 kg or more. As might be expected, those who used the drug for more than six months were substantially more likely to lose twenty kg or more (24.3%, $p < 0.001$). In a follow-up analysis including 175 patients, those who took GLP-1RAs for three months lost 6.7 kg of weight; those who continued using them for a full year lost 12.3 kg [51]. Additionally, a benefit-harm balance analysis showed that the significant factors influencing the net benefit of weight loss were patient preferences, risk aversion and willingness to accept risks. Even a 5% weight loss may be net beneficial for those who are more eager in decreasing weight and less concerned about the potential risks [52].

The significant prevalence of nausea as a side effect is likely contributing to the high rate of discontinuation, with 73.4% of patients stopping the medication. The distress associated with nausea can lead to negative perceptions of the treatment, prompting individuals to reassess the benefits versus the discomfort they experience. Additionally, the study showed that a substantial number of patients (63.6%) did not reach their weight loss goals, which may have further exacerbated feelings of frustration and disappointment, leading them to stop the medication. Given that nausea can be a challenging side effect to manage, it is crucial for healthcare providers to address this issue directly with patients.

Limitations

Self-Reported Data: The reliance on self-reported side effects and reasons for discontinuation may lead to inaccuracies, as patients might underreport or overreport their experiences.

Sample Size and Demographics: Although 354 patients were included in the study, most of them were Saudi nationals and female, which may limit the applicability of the results to other populations or genders.
Short Follow-Up Period: Participants used GLP-1 receptor agonists for varying lengths of time, thus it's possible that long-term effects or side effects from prolonged use were not fully captured in the study.

Conclusion

This study highlights the significant side effects and reasons for discontinuation of GLP-1 receptor agonists (liraglutide and semaglutide) among patients seeking weight loss. With 80.2% of participants reporting adverse symptoms, particularly nausea, the high discontinuation rate of 73.4% raises concerns about the efficacy and patient experience with these medications. According to the results, in order to improve patient adherence, healthcare professionals should anticipate possible side effects and establish reasonable goals for weight loss. Further research is necessary to explore long-term effects and to assess the impact of these medications on weight loss.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Consent to Participate

Informed consent was obtained from each participant prior to specimen collection.

Financial Disclosure

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Data Availability

Data is available for the journal. Informed consents were not necessary for this paper.

Author's Contribution

The authors contributed equally.

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