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A single-center study on the biochemical effect and clinical effectiveness of liraglutide in Turkish patients

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Abstract. – OBJECTIVE: The approval of liraglutide as a treatment option for obesity is a significant development in addressing the major health concerns of diabetes and obesity in recent years. Considering the duration of liraglutide use, pancreatic and hepatic enzymes, weight loss, homeostatic model assessment of insulin resistance (HOMA-IR), discontinuation rationales, and adverse events were studied.

PATIENTS AND METHODS: From September 2019 to October 2022, 201 participants (125 females and 76 males) aged 18 to 75 were recruited from a single medical facility. The inclusion criteria were a body mass index (BMI) of ≥ 27 with comorbidities or a BMI of ≥ 30. A retrospective analysis evaluated demographic profiles and clinical/biological data collected at 3, 6, 9, and 12 months of continuous liraglutide usage.

RESULTS: The study participants experienced weight loss of > 5% at 3, 6, 9, and 12 months compared to baseline. The baseline HOMA-IR values were significantly higher than those at months 3, 6, 9, and 12 (p = 0.0001). Participants who adhered to the drug regimen for 6 months showed a statistically significant increase in lipase levels compared to baseline, followed by a decline at 9 and 12 months. Amylase levels steadily increased until month 9 and then declined. Liver enzymes, particularly alanine aminotransferase (ALT), consistently decreased in patients on liraglutide treatment over the 12-month period. 41.29% had no adverse events, while 58.71% experienced adverse events, with nausea being the most prevalent (20%).

CONCLUSIONS: Liraglutide showed significant weight loss and improved liver enzyme levels. It did not cause a clinically significant increase in pancreatic enzyme levels. However, monitoring pancreatic enzyme levels during liraglutide treatment could be helpful to minimize the risk of pancreatitis.

Key Words:
Liraglutide, Pancreas and liver enzymes, HOMA-IR, Weight loss.

Introduction

Diabetes and obesity represent prominent health challenges in the modern era, thereby emphasizing the escalating significance of "glucagon-like peptide-1 receptor (GLP-1) agonist" medications in the management of these conditions. Liraglutide, an exemplar of GLP-1 receptor agonists, has exhibited efficacious outcomes in the treatment of type 2 diabetes (T2DM) in recent years. Furthermore, the utilization of liraglutide has been associated with the additional benefit of weight loss. Consequently, liraglutide has been incorporated into obesity treatment protocols, necessitating the adoption of a higher dosage formulation for this specific indication[1]. The United States Food and Drug Administration (FDA) granted approval to liraglutide in December 2014 for the treatment of obesity, specifically as a once-daily dose of 3 mg[2].

Incretins, namely GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), are gastrointestinal hormones that play a crucial role in regulating the postprandial production of glucagon and insulin. GLP-1 is primarily secreted from endocrine L cells in the distal intestinal mucosa in response to the presence of nutrients within the intestinal lumen. It is also secreted in small amounts from pancreatic alpha cells and neurons in the brain as preproglucagon[3]. GLP-1 suppresses glucagon secretion, controls blood glucose levels, slows gastric emptying, and protects β-cells from apoptosis[4]. These effects are thought to result from the GLP-1-mediated stimulation of neurons related to appetite and satiety via vagal and brainstem pathways[5,6]. Additionally, these effects have been shown to contribute to the reduction of body weight. Individuals with prediabetes and diabetes often exhibit impaired secretion of GLP-1 in response to food intake. Furthermore, pancreatic beta cells in these individuals tend to develop resistance to the effects of GLP-1 even at endogenous physiological levels.

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However, high levels of GLP-1 overcome this resistance and stimulate insulin secretion. It has been reported[7] that hyperglycemia in experimental animals reduces beta cell GLP-1 receptor production and ultimately causes GLP-1 resistance. GLP-1 secretion remains normal in the majority of patients with type 2 diabetes mellitus (T2DM). However, resistance to GLP-1 is observed in relation to impaired insulin secretion.

Liraglutide, a GLP-1 receptor agonist, has 97% structural homology to native GLP-1. While native GLP-1 has a short duration of action, liraglutide is classified as a long-acting GLP-1 receptor agonist[8]. Natural GLP-1 molecules have a brief half-life of 1-2 minutes due to rapid degradation by an enzyme called dipeptidyl peptidase-4 (DPP-4). In contrast, the half-life of liraglutide is considerably longer, ranging from 10 to 14 hours[9]. The extended half-life of liraglutide is attributed to two key modifications: the substitution of an amino acid within the peptide and the addition of a fatty acid[10]. These alterations enable liraglutide to bind to circulating plasma proteins, resulting in reduced absorption and increased resistance to degradation[10]. Moreover, liraglutide exerts its effects on insulin and glucagon secretion in a glucose-dependent manner, minimizing the risk of hypoglycemia[11].

Liraglutide, through its action on the arcuate nucleus in the hypothalamus, effectively suppresses appetite, leading to a reduction in energy intake and subsequent weight loss[12]. It is indicated as an adjunct to diet and exercise for weight management in patients who have a BMI equal to or greater than 27 when accompanied by additional comorbidities, or a BMI equal to or greater than 30[2]. Liraglutide is administered as a once-daily dose, regardless of meals, at the same time each day. It is generally well tolerated, although the most commonly reported adverse event is nausea. The weight loss impact of liraglutide is dependent on the dosage, with higher doses leading to greater weight loss. Studies[13,14] evaluating liraglutide at doses of 1.2 mg, 1.8 mg, 2.4 mg, and 3.0 mg demonstrated a dose-dependent increase in weight loss. The highest weight loss of 7.3 kg was observed with the 3.0 mg dose (statistical comparison was made only with placebo and Orlistat)[13].

Both GLP-1 analogs and incretins share a common mechanism of action, as they regulate the production of glucagon and insulin by the pancreas in response to postprandial stimuli. However, there have been concerns regarding the potential risk of pancreatitis associated with these drugs due to their effects on the pancreas. Reports[15] have documented cases of pancreatitis with GLP-1 analogs and acute complications of gallstone disease during the use of liraglutide. Considering the higher prevalence of pancreatitis in patients with diabetes, GLP-1 group drugs require additional monitoring for potential pancreatitis, although the exact association is not fully established. In this study, the objective was to monitor the levels of pancreatic enzymes in patients using liraglutide throughout the treatment period, aiming to assess the changes in pancreatic enzyme levels and investigate the potential occurrence of pancreatitis. In addition to evaluating the impact of liraglutide on liver enzyme levels over time, this study aimed to investigate various other factors, including weight loss, hemoglobin A1c (HbA1C), homeostatic model assessment of insulin resistance (HOMA-IR) levels, reasons for discontinuation, and drug-related adverse events.

Patients And Methods

The study was carried out at a private internal medicine clinic located in Istanbul, Turkey. Patients who provided informed consent for the use of their medical data were included in the study. Relevant information such as diagnosis, prescribed medications, demographic characteristics, laboratory results, and abdominal ultrasound findings were retrieved from the electronic records of patients who gave permission for research purposes. The data collection period spanned from September 2019 to October 2022.

Participants

The study included a total of 201 individuals between the ages of 18 and 75 who met the criteria of having a body mass index (BMI) greater than or equal to 27 and comorbidities (such as hypertension, T2DM, or hyperlipidemia), or a BMI greater than or equal to 30. Clinical and biological data were collected, specifically focusing on individuals who continued taking the drug for a minimum of 3 months. Participants who had previously used GLP-1 analogues, undergone bariatric surgery, or had conditions that could contribute to weight loss, such as malignancy or chronic infection, were excluded from the study.

Age, body weight (kg), height (cm), BMI (kg/m^2), waist circumference (WC) (cm) at baseline and fasting blood glucose (FBG), HbA1c, HOMA-IR, pancreatic enzyme levels (amylase, lipase), hepatic measurements including aspartate

aminotransferase (AST), ALT, γ-glutamyltransferase (GGT) at 3, 6, 9 and 12 months of continued medication were obtained from standard biological assays performed in accredited laboratories. Prediabetes was defined as HbA1c (< 6%). A liver ultrasound (Toshiba, Aplio 500) was performed on each patient.

All 201 patients included in the study had been using the drug for a minimum of 3 months. Out of these, 106 patients had been on the drug for 6 months, 49 for 9 months, 28 for 12 months, and 4 for longer than 12 months. Throughout the treatment period, data regarding weight loss, pancreatic enzyme levels, liver function tests, and insulin resistance were recorded at 3, 6, 9, and 12 months. The weight loss achieved during this period was measured consistently using the Tanita F1BC-601PRO weighing device at each clinic visit.

The patients underwent a titration phase with liraglutide lasting 6-8 weeks, followed by a 3.0 mg treatment dose. During the initial 12 weeks of diet, the patients followed a low-calorie diet consisting of 1,200-1,400 calories per day.

Statistical Analysis

Statistical analyses were conducted using the Number Cruncher Statistical System (NCSS) 2007 Statistical Software package program (Utah, USA). The data were assessed using descriptive statistical methods, including measures such as mean, standard deviation, frequency, and percentage distributions. The Shapiro-Wilk normality test was used to examine the distribution of variables. For non-normally distributed variables, the Friedman test was utilized for comparisons between different time points, subgroup comparisons were conducted using Dunn's multiple comparison test, and paired time points were compared using the Wilcoxon test. The significance level was considered as $p < 0.05$.

Results

Patient Characteristics

The study included a total of 201 patients, consisting of 125 women and 76 men. Table I provides information regarding the age, weight (kg), BMI (kg/m^2), WC (cm), FBG (mg/dl), GGT (IU/ml), insulin (IU/ml), HbA1C (%) total weight loss, and duration of medication usage.

Furthermore, abdominal ultrasounds were performed on all patients at the study onset to investigate the presence of hepatosteatosis. The ultrasound findings were used to grade the severity of hepatosteatosis as Grade 1, Grade 2, or Grade 3. Hepatosteatosis was not detected in 63 (31.34%) patients. Grade 1 hepatosteatosis was detected in 59 (29.35%) patients. Grade 2 hepatosteatosis was detected in 58 (28.86%) patients. Grade 3 hepatosteatosis was detected in 21 (10.45%) patients.

The Weight Loss Data of the Patients Resulting from the Use of Liraglutide

Table II includes weight loss at the baseline, months 3, 6, 9, and 12 and >12 months.

During the first 3 months of liraglutide use, 72.14% (n = 145) of the patients experienced a weight loss of more than 5%; 27.86% (n = 56) of the patients experienced a weight loss of less than 5%. Among the 106 individuals who continued taking the drug for 6 months, 96.57% (n = 96) of them achieved a weight loss of more than 5% compared to their baseline weight; 3.43% (n = 10) of them achieved a weight loss of less than 5% compared to their baseline weight. Among the 49 individuals who continued taking the drug for 9 months, 100% (n = 49) of them achieved a weight loss of more than 5% compared to their baseline weight. Among the 28 individuals who continued taking the drug for 12 months, 100% (n = 28) of them achieved a weight loss of more than 5% compared to their baseline weight. Lastly, among the 4 individuals who continued taking the drug for longer than 12 months, 100% (n = 4) of them achieved a weight loss of more than 5% compared to their baseline weight.

The Adverse Events due to Liraglutide Usage

In this cohort, while no side effects were observed in 83 (41.29%) patients, 34 (16.92%) patients had heartburn, 8 (3.98%) patients had diarrhea, 36 (17.91%) patients had constipation, 39 (19.40%) patients had nausea and 1 (0.50%) patient had flatulence.

Factors Contributing to Liraglutide Discontinuation by Patients

When evaluating the reasons for patients discontinuing liraglutide, it was found that 98 individuals (48.75%) achieved their target weight and decided to discontinue the medication. The remaining participants discontinued liraglutide due to various reasons: 6 (2.99%) patients had diarrhea, 36 (17.91%) patients could not achieve sufficient weight loss, 29 (14.43%) patients had financial constraints, 24 (11.94%) patients had lack of appetite, 5 (2.49%)

Table I. Patient characteristics.

		N	Mean±SD	Minimum	Maximum
Age	Male	76	43.13 ± 10.69	21	70
	Female	125	42.42 ± 11.08	18	74
	All Participants	201	42.69 ± 10.91	18	74
Height (cm)	Male	76	176.2 ± 6.68	152	190
	Female	125	162.24 ± 6.31	150	177
	All Participants	201	167.52 ± 9.35	150	190
Weight (kg)	Male	76	109. 46 ± 17.95	79	173
	Female	125	87.33 ± 15.82	64	140
	All Participants	201	95.7 ± 19.8	64	173
WC (cm)	Male	76	113.21 ± 17.54	80	146
	Female	125	94.09 ± 16.88	68	135
	All Participants	201	101.32 ± 19.45	68	146
BMI (kg/m^2)	Male	76	35.41 ± 5.1	27	55
	Female	125	33.38 ± 6.19	27	60
	All Participants	201	34.15 ± 5.87	27	60
GGT (IU/ml)	Male	76	52.77 ± 50.11	6	391
	Female	125	26.16 ± 17.65	4	105
	All Participants	201	36.22 ± 36.08	4	391
FBG (mg/dl)	Male	76	108.73 ± 24.51	70	203
	Female	125	97.38 ± 16.52	74	173
	All Participants	201	101.67 ± 20.61	70	203
Insulin (IU/ml)	Male	76	22.46 ± 10.58	5.1	61
	Female	125	17.31 ± 12.23	4.1	87
	All Participants	201	19.27 ± 11.87	4.1	87
Baseline HbA1C (%)	Male	76	5.82 ± 0.8	4.82	9.5
	Female	125	5.48 ± 0.75	1.76	8.1
	All Participants	201	5.61 ± 0.78	1.76	9.5
Total Weight Loss (kg)	Male	76	10.75 ± 8.21	0	36
	Female	125	9.62 ± 5.97	0	33
	All Participants	201	10.05 ± 6.9	0	36
Duration of Drug Use/Month	Male	76	5.32 ± 3.02	3	18
	Female	125	6.28 ± 3.93	3	24
	All Participants	201	5.92 ± 3.64	3	24

WC (Waist circumference-cm), BMI (body mass index), FBG (fasting blood glucose), HbA1c (hemoglobin A1c), GGT (γ-glutamyltransferase).

patients had elevated pancreatic enzymes, and 1 (0.5%) patient had pancreatitis, 2 (1%) patients had gastroesophageal reflux disease (GERD).

The Effects of Liraglutide on Pancreatic and Liver Enzyme Levels and HOMA-IR

Calculations were based on time of drug onset and durations of drug use for 3, 6, 9, and 12 months.

Changes During the 3 Months of Liraglutide Usage

AST, ALT, HOMA-IR, amylase, and lipase levels were compared at the baseline and 3 months in 201 patients who were on liraglutide for at least 3 months (Table III) (Figure 1).

At 3 months, the mean AST and ALT levels statistically significantly decreased compared to baseline (p = 0.0001).

At 3 months, the mean HOMA-IR levels were statistically significantly lower than the baseline mean HOMA-IR levels (p = 0.0001).

At 3 months, the mean amylase levels were statistically significantly higher than the baseline mean amylase levels (p = 0.026).

At 3 months, the mean lipase levels were statistically significantly higher than the baseline mean lipase levels (p = 0.0001). However, it was noted that the increases in amylase and lipase levels were less than 2 times the baseline values.

Changes During the 0-6 Months of Liraglutide Usage

AST, ALT, HOMA-IR, amylase, and lipase levels were compared at baseline, months 3 and 6 in 106 patients who remained on liraglutide treatment (Tables IV and V (Figure 2).

Table II. The weight loss achieved with the use of liraglutide for 3, 6, 9, 12 months, and > 12 months.

		Weight Loss			Weight Loss Change %		
	n (%)	Mean ± SD	Min.	Max.	Mean ± SD	Min.	Max.
Weight loss at 0-3 months	201 (100%)	7.1 ± 4.01	0	23	7.39 ± 3.58	0	18.31
Weight loss at 0-6 months	106 (52.74%)	11.38 ± 6.35	1	30	11.35 ± 5.22	0	23.89
Weight loss at 0-9 months	49 (24.38%)	15.4 ± 7.61	5	30	15.08 ± 5.82	5.56	27.71
Weight loss at 0-12 months	28 (13.93%)	17.79 ± 8.93	5	36	17.91 ± 6.72	5.56	32.68
Weight loss at > 12 months	4 (1.99%)	22.5 ± 10.41	13	32	23.11 ± 6.51	17.15	30.27

Table III. AST, ALT, HOMA-IR, amylase and lipase levels at the baseline and month 3 in 201 patients.

n: 201 (100%)	Baseline	3-month	*p*
AST (U/L)	22.2 ± 11.72	19.84 ± 9.29	0.0001
ALT (U/L)	32.11 ± 26.79	27.46 ± 23.95	0.0001
HOMA-IR	4.84 ± 3.11	3.38 ± 2.09	0.0001
Amylase (U/L)	62.6 ± 38.94	68.46 ± 25.61	0.026
Lipase (U/L)	38.13 ± 17.5	46.85 ± 23.85	0.0001

Wilcoxon test. AST (aspartate aminotransferase), ALT (alanine aminotransferase), HOMA-IR (Homeostatic Model Assessment of Insulin Resistance).

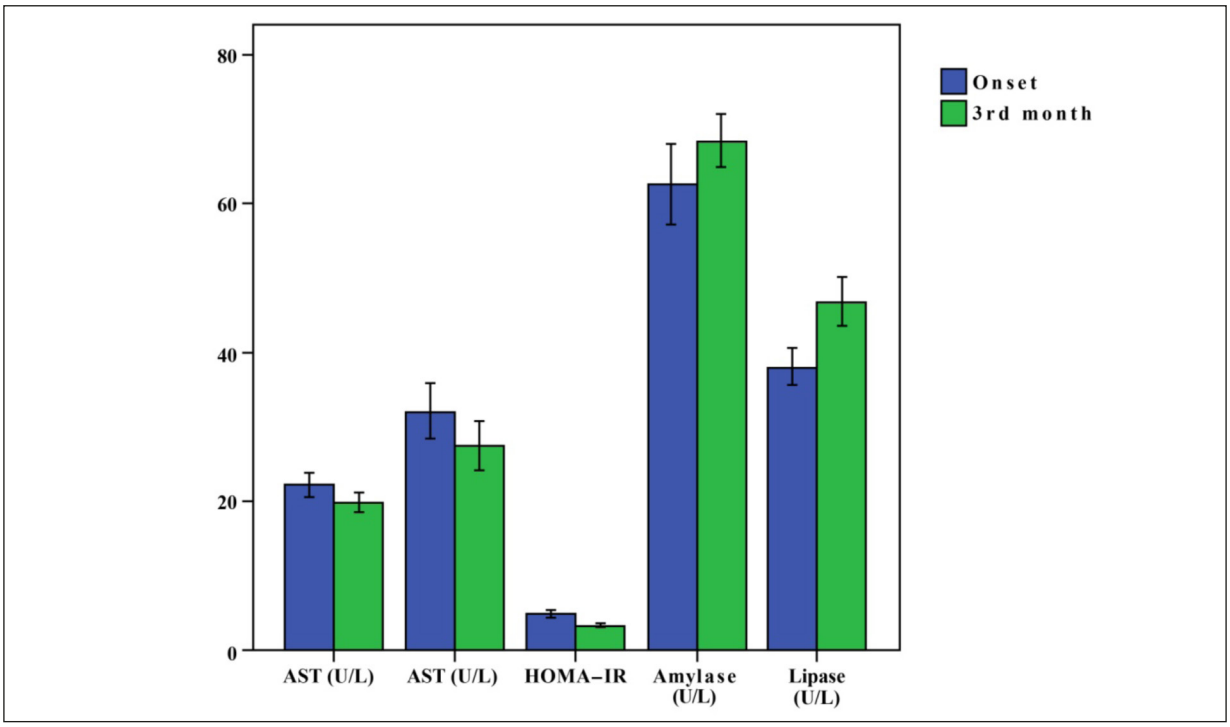

Figure 1. AST, ALT, HOMA-IR, amylase and lipase levels at the baseline and month 3 in 201 patients. AST (aspartate aminotransferase U/L), ALT (alanine aminotransferase U/L), HbA1C (Homeostatic Model Assessment of Insulin Resistance), Amylase (U/L), Lipase (U/L).

Significant differences were observed in mean AST levels between baseline, month 3, and month 6 (p = 0.0001). The mean AST levels were significantly lower at 6 months compared to both baseline and month 3 (p = 0.0001). Similar findings were observed for

Table IV. AST, ALT, HOMA-IR, amylase and lipase levels at the baseline and months 3 and 6 in 106 patients.

n: 106 (52.74%)	Baseline	3-month	6-month	*p*
AST (U/L)	22.37 ± 11.91	20.13 ± 10.28	17.67 ± 7.84	0.0001
ALT (U/L)	32.2 ± 25.29	28.47 ± 25.74	22.21 ± 14.89	0.0001
HOMA-IR	5.16 ± 3.26	3.47 ± 2.13	2.86 ± 1.67	0.0001
Amylase (U/L)	65.08 ± 48.21	68.29 ± 26.82	71.6 ± 29.48	0.0001
Lipase (U/L)	40.15 ± 19.24	50.33 ± 27.14	52.71 ± 29.85	0.0001

Friedman Test. AST (aspartate aminotransferase), ALT (alanine aminotransferase), HOMA-IR (Homeostatic Model Assessment of Insulin Resistance).

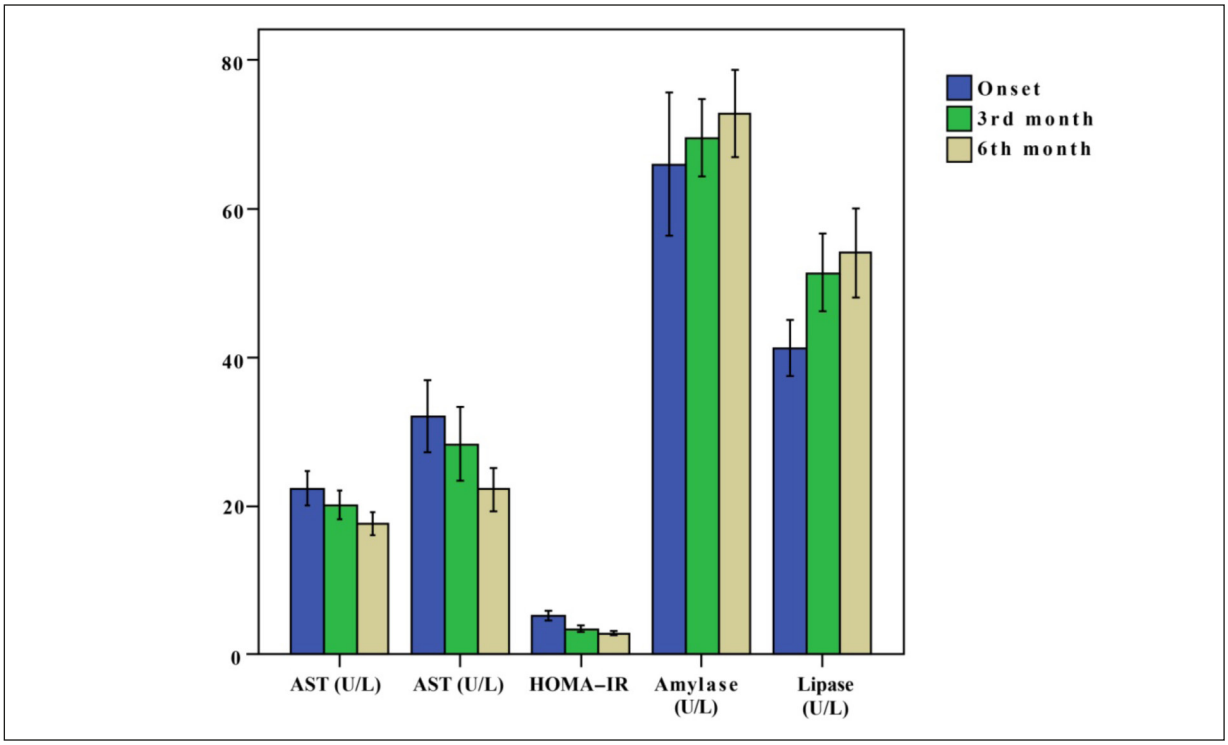

Figure 2. AST, ALT, HOMA-IR, amylase, and lipase levels at the baseline and months 3 and 6 in 106 patients who remained on liraglutide. AST (aspartate aminotransferase U/L), ALT (alanine aminotransferase U/L), HbA1C (Homeostatic Model Assessment of Insulin Resistance) , Amylase (U/L), Lipase (U/L).

mean ALT levels, with the 6-month values significantly lower than baseline and 3-month values ($p = 0.0001$).

A statistically significant difference was observed between the baseline, month 3, and month 6 mean HOMA-IR levels ($p = 0.0001$). The month 6 mean HOMA-IR levels were statistically significantly lower than the baseline and month 3 mean HOMA-IR levels ($p = 0.0001$). A statistically significant difference was observed in amylase levels between baseline, month 3, and month 6 ($p = 0.0001$). The 6-month mean amylase levels were found to be statistically significantly higher than the baseline mean amylase levels ($p = 0.0001$). No statistically significant difference was observed between the month 3 and month 6 mean amylase levels ($p = 0.055$).

A statistically significant difference was observed between the mean of baseline, months 3 and 6 lipase levels ($p = 0.0001$). The 6-month mean lipase levels were found to be statistically significantly higher than the baseline mean lipase levels ($p = 0.0001$). No statistically significant difference was observed between the months 3 and 6 mean amylase levels ($p = 0.303$). However, the increases in amylase and lipase levels were less than 2 times the baseline values.

Changes During the 0-9 Months of Liraglutide Usage

49 of 201 patients continued the drug for 9 months. The AST, ALT, HOMA-IR, amylase, and lipase levels were compared at baseline and months 3, 6, and 9 (Tables VI-VII) (Figure 3).

A statistically significant difference was observed between the mean AST at baseline, 3, 6, and 9 months ($p = 0.0001$). The 9-month mean AST levels were found to be statistically significantly lower than baseline, months 3 and 6 mean AST levels ($p = 0.041$, $p = 0.007$, $p = 0.0001$), and there was no statistical difference between months 3 and 6 mean AST levels ($p = 0.062$).

A statistically significant difference was observed between the mean ALT at baseline, months 3, 6, and 9 ($p = 0.0001$). The 9-month mean ALT levels were found to be statistically significantly lower than baseline and months 3 and 6 mean ALT levels ($p = 0.007$, $p = 0.0001$, respectively).

The baseline mean HOMA-IR values were found to be significantly higher than the mean HOMA-IR values at 3, 6, and 9 months ($p = 0.0001$). The mean HOMA-IR values at 3 months were also significantly higher compared to the months 6 and 9 values ($p = 0.003$). However, there was no statistically significant difference observed in mean HOMA-IR values between the months 3 and 6 ($p = 0.452$).

There was a statistically significant difference in the mean amylase levels between baseline, months 3, 6, and 9 ($p = 0.0001$). The baseline mean amylase levels were significantly lower than the mean amylase levels at 3, 6, and 9 months ($p = 0.003$, $p = 0.0001$). However, there was no statistically significant difference between the mean amylase levels at the 3-6 months and 6-9 months ($p = 0.147$, $p = 0.186$).

There was a statistically significant difference in the mean lipase levels between baseline, months 3, 6, and 9 ($p = 0.0001$). The baseline mean lipase levels

Table V. Multiple comparison of AST, ALT, HOMA-IR, amylase and lipase levels at the baseline and months 3 and 6 in 106 patients.

Dunn's Multiple Comparison Test	AST(U/L)	ALT(U/L)	HOMA IR	Amylase (U/L)	Lipase (U/L)
Baseline / 3-month	0.0001	0.0001	0.0001	0.0001	0.0001
Baseline / 6-month	0.0001	0.0001	0.0001	0.0001	0.0001
3-month / 6-month	0.0001	0.0001	0.0001	0.055	0.303

AST (aspartate aminotransferase), ALT (alanine aminotransferase), HOMA-IR (Homeostatic Model Assessment of Insulin Resistance).

Table VI. AST, ALT, HOMA-IR, amylase and lipase levels at the baseline and months 3, 6, and 9 in 49 patients.

n: 49 (24.38%)	Baseline	3-month	6-month	9-month	p
AST(U/L)	23.65 ± 14.2	20.75 ± 11.84	18.62 ± 9.92	17.3 ± 7.00	0.0001
ALT(U/L)	34.73 ± 29.39	30.73 ± 32.52	22.81 ± 17.12	19.72 ± 13.02	0.0001
HOMA IR	5.22 ± 3.18	3.31 ± 1.71	2.76 ± 1.31	2.62 ± 1.1	0.0001
Amylase (U/L)	59.1 ± 22.98	68.87 ± 31.17	71.7 ± 34.63	75.71 ± 40.36	0.0001
Lipase (U/L)	41.62 ± 19.75	50.4 ± 30.03	54.74 ± 33.22	53.61 ± 37.3	0.0001

Friedman Test. AST (aspartate aminotransferase), ALT (alanine aminotransferase), HOMA-IR (Homeostatic Model Assessment of Insulin Resistance).

Table VII. Multiple comparison of AST, ALT, HOMA-IR, amylase and lipase levels at the baseline and months 3, 6, and 9 in 49 patients.

Dunn's Multiple Comparison Test	AST (U/L)	ALT (U/L)	HOMA-IR	Amylase (U/L)	Lipase (U/L)
Baseline / 3-month	0.003	0.019	0.0001	0.003	0.017
Baseline / 6-month	0.0001	0.0001	0.0001	0.0001	0.001
Baseline / 9-month	0.0001	0.0001	0.0001	0.0001	0.001
3-month / 6-month	0.062	0.0001	0.003	0.147	0.247
3-month / 9-month	0.007	0.0001	0.003	0.011	0.271
6-month / 9-month	0.041	0.007	0.452	0.186	0.813

AST (aspartate aminotransferase), ALT (alanine aminotransferase), HOMA-IR (Homeostatic Model Assessment of Insulin Resistance).

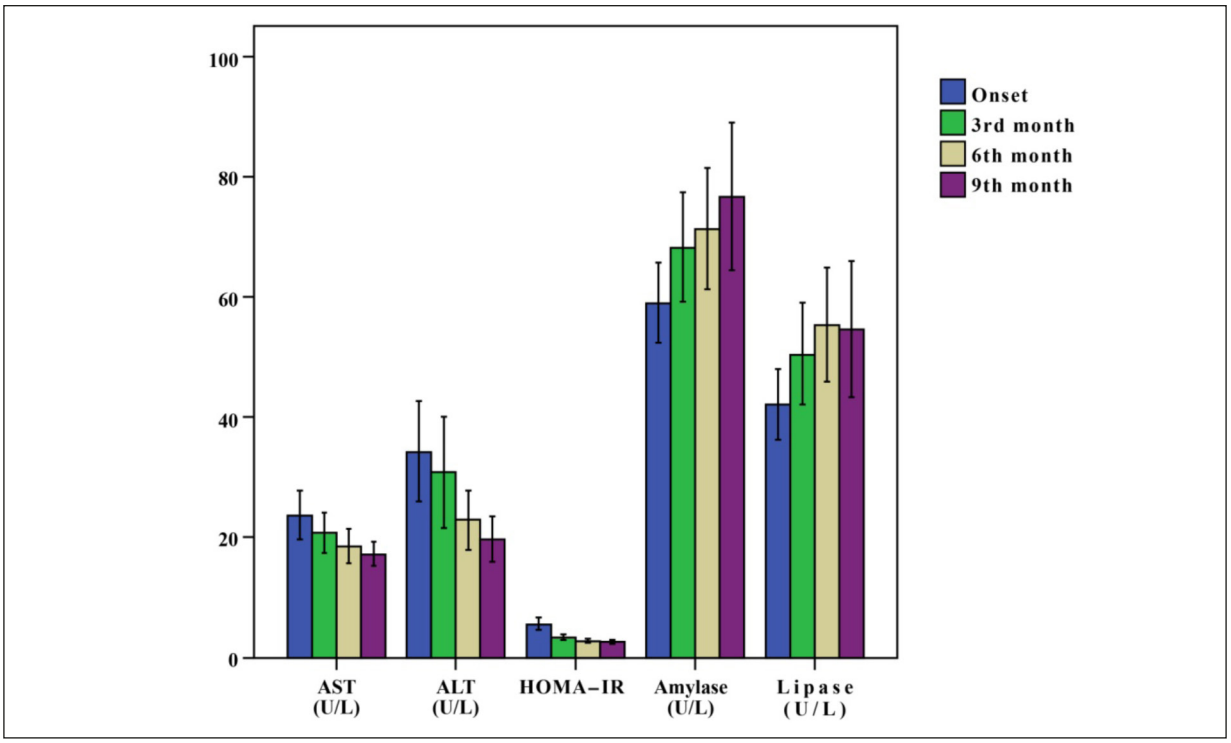

Figure 3. AST, ALT, HOMA-IR, amylase, and lipase levels at the baseline and months 3, 6, and 9 in 49 patients who remained on liraglutide. AST (aspartate aminotransferase U/L), ALT (alanine aminotransferase U/L), HbA1C (Homeostatic Model Assessment of Insulin Resistance), Amylase (U/L), Lipase (U/L).

were significantly lower than the mean lipase levels at months 3, 6, and 9 ($p = 0.017$, $p = 0.001$). No statistically significant difference was observed in the lipase levels between other time points ($p > 0.05$).

Changes During the 0-12 Months of Liraglutide Usage

Of 201 patients, 28 continued the drug for 12 months. The AST, ALT, HOMA-IR, amylase, and lipase levels were compared at baseline, months 3, 6, 9, and 12 (Table VIII-IX) (Figure 4).

There was a statistically significant difference in the mean AST levels between baseline, months 3, 6, 9, and 12 ($p = 0.0001$). The mean baseline AST levels were significantly higher than the mean AST levels at months 3, 6, 9, and 12 ($p = 0.01$, $p = 0.0073$, $p = 0.001$). No statistically significant difference was observed in the AST levels between other time points.

There was a statistically significant difference in the mean ALT levels between baseline, months 3, 6, 9, and 12 ($p = 0.0001$). The mean ALT levels at 12 months were statistically significantly lower than the baseline, 3-month, and 6-month values ($p = 0.049$, $p = 0.0001$, $p = 0.0001$). However, no statistically significant difference was observed in the mean ALT levels between baseline and 3-month values and between 9-month and 12-month values ($p = 0.254$, $p = 0.918$).

The mean HOMA-IR levels at 12 months were statistically significantly lower than the months 6 and 9 mean HOMA-IR levels ($p = 0.003$, $p = 0.0001$). However, no statistically significant difference was observed in HOMA-IR levels between 6-month and 9-month values ($p = 0.829$).

A statistically significant difference was found in the mean amylase levels between baseline, months 3, 6, 9, and 12 ($p = 0.003$). A decrease was observed in the 12-month mean amylase values. The 12-month mean levels of amylase were significantly lower than the 9-month levels ($p = 0.004$), while no statistically significant difference was observed between the mean amylase measurements at other time points ($p > 0.05$). A statistically significant difference was found in the mean lipase levels between baseline, months 3, 6, 9, and 12 ($p = 0.048$). The baseline mean levels of lipase were significantly lower than those at months 6 and 9 ($p = 0.017$, $p = 0.001$), while no statistically significant difference was observed between the mean lipase measurements at other time points ($p > 0.05$).

Table VIII. AST, ALT, HOMA-IR, amylase and lipase levels at the baseline and months 3, 6, and 9 in 49 patients.

n: 28 (13.93%)	Baseline	3-month	6-month	9-month	12-month	p
AST (U/L)	21.29 ± 10.4	19.03 ± 9.48	17.17 ± 6.87	16.04 ± 5.23	19.85 ± 18.99	0.0001
ALT (U/L)	30.18 ± 25.56	26.83 ± 27.56	21.38 ± 19.37	17.59 ± 12.96	17.58 ± 10.79	0.0001
HOMA IR	5.14 ± 2.88	3.4 ± 1.82	2.65 ± 1.05	2.6 ± 1.07	2.18 ± 0.92	0.0001
Amylase (U/L)	61.72 ± 24.96	69.71 ± 35.64	73.82 ± 40.53	79.35 ± 48.89	70.54 ± 37.63	0.003
Lipase (U/L)	43.01 ± 20.45	48.06 ± 22.69	56.16 ± 32.25	51.59 ± 25.31	47.34 ± 28.58	0.048

Friedman Test. AST (aspartate aminotransferase), ALT (alanine aminotransferase), HOMA-IR (Homeostatic Model Assessment of Insulin Resistance).

Table IX. Multiple comparison of AST, ALT, HOMA-IR, amylase and lipase levels at the baseline and months 3, 6, 9 and 12 in 28 patients.

Dunn's Multiple Comparison Test	AST (U/L)	ALT (U/L)	HOMA IR	Amylase (U/L)	Lipase (U/L)
Baseline / 3-month	0.085	0.254	0.0001	0.07	0.269
Baseline / 6-month	0.001	0.0001	0.0001	0.007	0.014
Baseline / 9-month	0.003	0.0001	0.0001	0.0001	0.044
Baseline / 12-month	0.01	0.0001	0.0001	0.119	0.943
3-month / 6-month	0.104	0.02	0.007	0.255	0.258
3-month / 9-month	0.056	0.001	0.011	0.028	0.342
3-month / 6-month	0.290	0.001	0.0001	0.727	0.516
6-month / 9-month	0.303	0.008	0.829	0.179	0.952
9-month / 12-month	0.707	0.049	0.003	0.296	0.083
9-month / 12-month	0.405	0.918	0.0001	0.004	0.094

AST (aspartate aminotransferase), ALT (alanine aminotransferase), HOMA-IR (Homeostatic Model Assessment of Insulin Resistance).

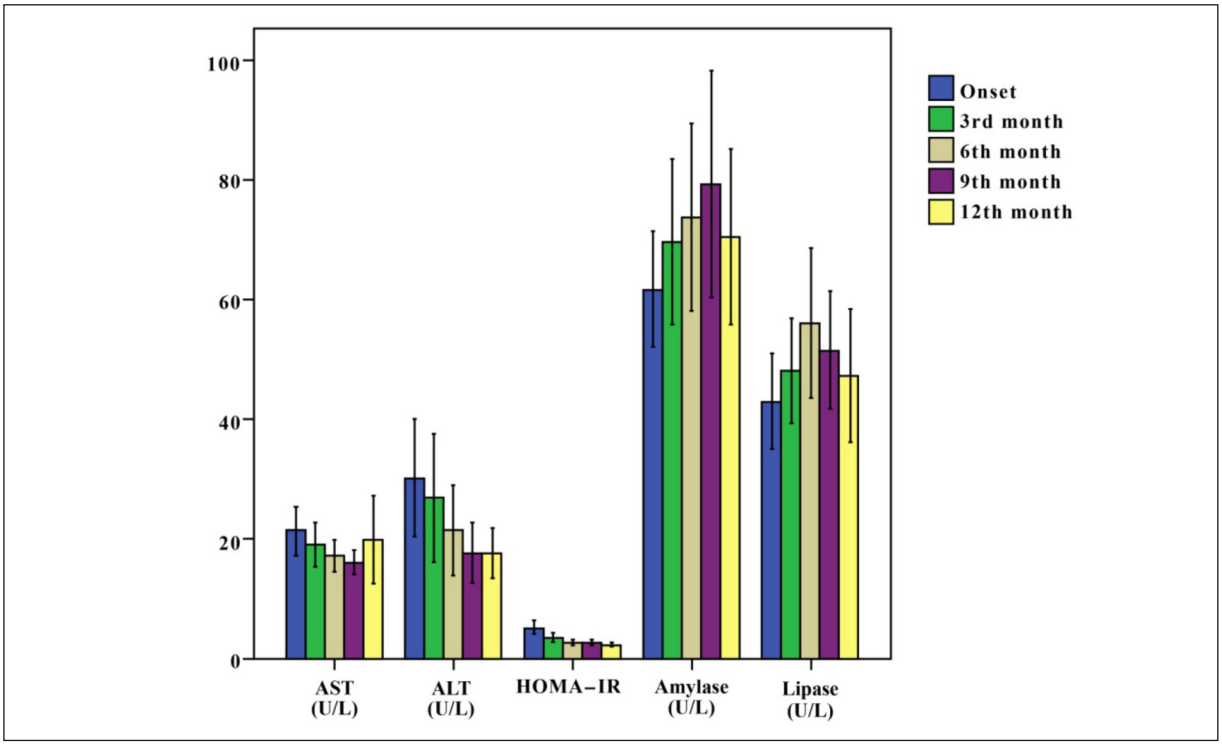

Figure 4. AST, ALT, HOMA-IR, amylase, and lipase levels at the baseline and months 3, 6, 9, and 12 in 28 patients who remained on liraglutide. AST (aspartate aminotransferase U/L), ALT (alanine aminotransferase U/L), HbA1C (Homeostatic Model Assessment of Insulin Resistance), Amylase (U/L), Lipase (U/L).

Discussion

In Turkey, this study marks the first investigation of the patients receiving liraglutide for a period exceeding 6 months. Notably, it is the sole investigation conducted in Asia to comprehensively assess pancreatic secretions and liver enzymes at 3-months intervals over a span of 12 months while administering liraglutide. In line with the study objectives, liraglutide administration elicited favorable effects on metabolic parameters and liver enzymes. Importantly, no clinically significant adverse events were noted during this follow-up period, in a recent study conducted by Altunal et al[16] in Turkey, the impact of botulinum toxin, either alone or in combination with liraglutide on weight loss were investigated. Thus, our study stands as the sole research in Turkey that specifically examines the effects of liraglutide alone, including its impact on liver-pancreatic enzymes and its adverse event profile.

In our study, we assessed the levels of pancreatic and liver enzymes in patients before the drug onset and at 3-months intervals for up to 12 months, considering the duration of drug utilization. Out of the 201 individuals studied, a single case exhibited pancreatitis along with the presence of gallstones. In the remaining cases, pancreatic enzyme levels increased by less than two times compared to baseline, depending on the duration of drug usage, without causing pancreatitis. Additionally, there was a notable improvement in liver enzyme levels. Specifically, in patients using the drug for 12 months, ALT levels demonstrated a continuous tendency to decrease.

In clinical trials[15] of incretin-based therapies, such as GLP-1 receptor agonists and dipeptidyl peptidase 4 inhibitors, amylase and lipase are commonly measured as biomarkers for pancreatic inflammation. It has been noted that elevations in these biomarkers, particularly serum lipase levels, reaching or exceeding 2 times the normal upper limit, can occur following treatment with these medications[15]. In our study, we found that liraglutide increased pancreatic enzyme levels within normal ranges, and the degree of increase was dependent on the duration of use. Specifically, during the first 3 months of treatment, there was a more pronounced elevation in both amylase and lipase levels. However, only a small number of patients experienced a doubling of these enzyme levels, with the upper limits set at 100 U/L for amylase and 60 U/L for lipase. In patients who remained on the drug for more than 3 months, we observed a decline in lipase values at 9 months and amylase values at 12 months. In the SCALE Weight-management study[2], which monitored individuals receiving liraglutide (3 mg) for 56 weeks, it was reported that serum amylase and lipase levels started to increase from week 4 and consistently remained elevated compared to baseline throughout the treatment period. In the same study, it was observed that liraglutide 3.0 mg treatment resulted in a 7% increase in amylase levels and a 31% increase in lipase levels compared to the placebo group. However, the occurrence of a three-fold increase above normal levels for amylase and lipase was not significantly observed, with only a small percentage of patients experiencing such elevations (0.1% for amylase and 2.9% for lipase)[2]. In the same study, it was observed that the mean amylase and lipase activity returned to baseline levels after the discontinuation of liraglutide treatment during the 12-week follow-up period without treatment. Similarly, in our study, due to a three-fold increase in pancreatic enzyme levels observed in only 5 out of 201 patients (2%), the drug was discontinued, and enzyme levels returned to normal during the follow-up period after discontinuation of the drug. Given that the pancreatic enzyme levels in the remaining patients were within the normal range, the drug administration continued without encountering any issues. Pancreatitis was identified in one individual; however, since that patient also had cholelithiasis, it was presumed that the pancreatitis was not induced by the drug. In conclusion, minimal fluctuations in pancreatic enzyme levels were observed in the study participants as long as they continued using the drug, and it can be inferred that regular monitoring of the enzyme levels helped prevent the occurrence of pancreatitis. Similarly, in the LEADER study[17], which examined the use of liraglutide in nearly 10.000 patients over a period of more than 3 years, there were numerically fewer cases of pancreatitis in the liraglutide-treated group, although the difference did not reach statistical significance.

In the previously published declarations by the FDA and European Medicines Agency (EMA) in 2014, it was stated that no definitive causal relationship was established between the use of GLP-1 receptor agonists and the occurrence of acute pancreatitis[18]. Upon reviewing literature conducted on incretin-based drugs authorized for use in the European Union, the EMA found no evidence of drug-induced pancreatic tumors in rats and mice exposed to these drugs for up to a 2-years duration. Furthermore, the exposure levels in mice

were significantly higher than those experienced by humans. In the four phase-3 randomized controlled trials evaluating the efficacy and safety of liraglutide, which included a total of over 5,000 patients, no cases of pancreatitis were reported in three of these studies[1,19,20] (Scale Diabates, Scale Maintanence, Scale Sleep Apnea). In the SCALE Obesity and Prediabetes study[15], in which patients were randomized 2:1 to liraglutide and placebo groups, a total of 8 cases of acute pancreatitis were observed. Out of the reported cases of pancreatitis, seven occurred in the liraglutide group, while one case was observed in the placebo group. It is important to note that the liraglutide group had twice the number of patients compared to the placebo group due to a 2:1 randomization ratio. Furthermore, out of the cases of pancreatitis in the liraglutide group, three were caused by gallstones, which was also the case for one instance in the placebo group. Weight loss, which was notably higher in the liraglutide group, is a known factor in gallstone formation. Recent studies[21] have indicated a potential increased risk of biliary tract disease associated with the use of GLP-1 analogues. There is a possibility that GLP-1 receptor agonists could contribute to the development of gallstones and potentially exacerbate existing gallstone disease through mechanisms such as weight loss, changes in biliary motility, or other unknown factors[22]. Conducting analyses of large-scale studies can provide further insights and help shed light on these questions.

In our study, we conducted an assessment of liver enzymes as well. It was hypothesized that the use of liraglutide treatments, along with associated weight loss and potential improvement in hepatosteatosis levels, could have contributed to the observed changes in AST and ALT levels. Particularly, a notable decrease in ALT levels was observed. Previous trials[23-26] have reported inconsistent findings regarding the effectiveness of liraglutide in improving liver enzyme levels such as ALT, AST, GGT, and alkaline phosphatase (ALP) Some studies[26,27] have demonstrated no significant improvement in these liver enzyme levels with liraglutide treatment. However, Armstrong et al[26] reported an improvement in GGT and ALT levels in their study. A recent study by Malik et al[27] reported that liraglutide effectively improved the lipid profile, specifically HDL and LDL, in patients with non-alcoholic steatohepatitis (NASH). However, the study did not observe a remarkable effect of liraglutide on reducing liver enzymes. Although data on the efficacy of liraglutide for NASH treatment is limited, ongoing research may establish its potential as a therapeutic option for preventing NASH progression or even reversing the disease. In our study, the observed decrease in ALT levels, specifically, can be regarded as an indicator of fatty liver regression. To gain a clearer understanding, it would be informative to conduct liver ultrasounds at regular intervals and to monitor changes in patients' liver health throughout the treatment period. This approach would provide valuable guidance in assessing the impact of liraglutide on NASH and its associated liver-related parameters.

Our study also found a significant reduction in insulin resistance. Diets high in saturated fatty acids (SFAs) are known to impair peripheral insulin action and contribute to insulin resistance. However, GLP-1 receptor agonists like liraglutide can counteract SFA-induced insulin resistance by suppressing postprandial lipids and improving endothelial dysfunction. Another study[28] demonstrated that liraglutide effectively reduces postprandial lipid levels, which may contribute to its protective effect against insulin resistance. These findings suggest that liraglutide's ability to regulate postprandial lipids plays a role in its beneficial effects on insulin resistance. In our study, we observed a rapid decrease in insulin resistance, particularly within the first 3 months of treatment. This reduction continued at a rapid pace in patients who continued taking the drug for 6 months. However, the rate of decline in insulin resistance slowed down at months 9 and 12. This can be attributed to the improvement in metabolic functions as patients lose weight. These positive outcomes collectively contribute to an improvement in metabolic risk factors associated with cardiovascular disease.

Currently, it is widely recognized that a weight loss exceeding 5% can significantly improve morbidity, mortality, and overall quality of life[29]. Studies[14] have shown that liraglutide leads to weight loss of more than 5%, and the extent of weight loss increases with the dose. Among the study groups, the highest degree of weight loss was observed in the group receiving liraglutide at a dose of 3.0 mg. The effectiveness of liraglutide in combination with diet and exercise has been demonstrated in real-world data from Canada. In this study, over 60% of the patients achieved a weight loss of more than 5%[14]. Similar findings of significant weight loss have also been reported in studies conducted in Spain and South Korea[30,31]. In our study, we specifically included patients

who could tolerate liraglutide 3 mg. The results revealed that more than 70% of the patients who used the drug for the initial 3 months achieved a weight loss of more than 5%. Furthermore, among those who continued the treatment for 12 months or longer (with the exception of one patient), the weight loss exceeded 10%, with an average of 17.79 ± 8.93 kg lost over the course of 12 months. The results of our study demonstrated a higher weight loss in Turkey compared to the study conducted by Pi-Sunyer et al[2] with 3,731 participants, where the average weight loss was reported as 8.4 ± 7.3 kg over 56 weeks. This disparity in weight loss outcomes may be attributed to the differences in dietary habits between the two populations. In Turkey, where carbohydrate consumption is relatively high, the transition to a low-calorie diet combined with the appetite-suppressing effects of liraglutide may have resulted in greater weight loss. Additionally, longer treatment duration with liraglutide led to even more substantial weight loss.

In our evaluation of the adverse events of liraglutide, it was found that 41.29% (83 patients) of the patients did not experience any adverse events, while 58.71% (113 patients) reported adverse events. Among the observed adverse events, nausea was the most commonly reported, affecting approximately 20% of all patients. Other reported adverse events included constipation, heartburn, mild diarrhea, and severe flatulence. Gastrointestinal side effects, such as nausea, vomiting, and diarrhea, have been commonly reported in the literature. However, these effects are generally mild to moderate in severity and temporary. Approximately 10% of patients may experience these gastrointestinal disturbances. Dose titration is often utilized to minimize significant adverse gastrointestinal effects[32].

Upon examining the reasons for discontinuation, it was found that 48.75% (98) of the patients in our study achieved their target weight and ceased the medication. Among the remaining patients, 17.91% did not achieve sufficient weight loss, while 14.43% discontinued due to financial constraints. The inclusion of drugs like liraglutide in the coverage of social health insurance is indeed a crucial necessity. The substantial proportion of patients who discontinued the medication due to financial reasons emphasizes the significance of making these treatments accessible and affordable. Considering the potential complications of obesity in the future and the associated costs to the healthcare system, it becomes imperative for GLP-1 analogues to be covered by state health insurance as soon as possible. Other factors contributing to the discontinuation include lack of loss of appetite, gastrointestinal symptoms such as diarrhea and gastroesophageal reflux, as well as elevated pancreatic enzymes. Diarrhea, in particular, was more commonly observed in male patients. In cases where the drug was temporarily interrupted and then given, discontinuation occurred due to the recurrence of diarrhea attacks.

Limitations

Despite obtaining valuable data in our study, it is important to acknowledge the limitations and areas for improvement. One notable limitation is the retrospective nature of the study design. The study would benefit from a prospective design with increased patient numbers and longer-term follow-up data, including metabolic and ultrasonographic assessments at the end of the first year and beyond, to enhance its significance and power.

Conclusions

The study demonstrated that liraglutide 3.0 mg facilitated significant weight loss, improved liver enzyme levels, and did not lead to a clinically significant rise in pancreatic enzyme levels in Turkish patients. Close monitoring of pancreatic enzyme levels while using liraglutide could help prevent the potential development of pancreatitis. Providing access to these drugs through state health insurance could make valuable contributions to public health by aiding in the prevention of obesity.

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Conflict of Interest

The author declared no conflicts of interest.

Availability of Data and Materials

The data that support the findings of this study are available on request from the corresponding author.

Ethics Approval

The study was performed in accordance with the Declaration of Helsinki and was approved by the Bakırkoy Dr Sadi Konuk Hospital Clinical Research Ethics Committee (Date: 31.05.2023, Decision No.: 2023/249).

Informed Consent

The need for informed consent was waived under the approval of the Local Ethics Committee due to the retrospective design.

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