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Effects of Liraglutide on Glycemic Control and Lipid Profile in Obese Type 2 Diabetes Mellitus Iraqi Patients

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ABSTRACT

Introduction: Diabetes mellitus is the most common endocrine illness, affecting over 100 million individuals globally (6% of the population). **Methods:** A prospective open-label study was conducted from November 2021 to June 2022 at Baquba Teaching Hospital/ Diyala., In current study, 50 patients (23 males and 27 females) had type 2 Diabetic from 2 to 4 years and they were obese, hypertensive and dyslipidemic. They received liraglutide for 12 weeks as 0.6 mg/day. Patients underwent measurements for fasting glucose level, lipid profile, glycosylated hemoglobin and their liver function before and after 12 weeks of treatment. **Results:** The results of current study revealed that treatment with liraglutide for 12 weeks showed significant beneficial effects on fasting glucose level, lipid profile and glycosylated hemoglobin ($P<0.05$) but without adversely affecting liver function ($P>0.05$). **Conclusion:** In obese type 2 diabetic patients, liraglutide can exert beneficial effects on glycemic control and lipid profile but without producing adverse effects on liver functions.

Keywords: Blood sugar, Glycosylated hemoglobin, Lipid profile, Liraglutide, Liver function.

INTRODUCTION

Diabetes mellitus (DM) is the most common endocrine illness, affecting over 100 million individuals globally (6% of the population). It is caused by a lack, or inadequate synthesis, of insulin by the pancreas, which causes an increase in blood glucose concentrations. It has been discovered to harm a variety of biological systems, including blood vessels, eyes, kidneys, heart, and nerves[(1)]. In only 34 years, the number of diabetic patients has quadrupled (from 108 million in 1980 to 422 million in 2014) [(2)]. Diabetes is expected to be the 7th leading cause of death by 2030, according to the WHO [(3)]. Obesity, diet and physical inactivity, advancing age, insulin resistance, a family history of diabetes, genetic variables, and race and ethnicity are all risk factors for type II diabetes [(4)].

Moreover, the complications of diabetes may be in the form of short-term (Hypoglycemia, hyperglycemia, diabetic ketoacidosis, and hyperosmolar hyperglycemia) or long-term (neuropathy, nephropathy, retinopathy, and cardiovascular disease) diabetic problems [(5)].

Regarding treatment of type 2 diabetes mellitus (T2DM), lifestyle changes alone can help people having reduced glucose tolerance to avoid developing diabetes. Also, it might sometimes be the only treatment option in the early stages of the disease [(6)].

Liraglutide stimulates insulin secretion in a glucose-dependent manner, lowers plasma glucagon levels, delays stomach emptying, suppresses appetite via neural mechanisms, and lowers hepatic glucose synthesis [(7-9)].

As a consequence, weight reduction in diabetic obese patients may pave the way for successful and long-term control of their diabetes. Therefore, current study aimed to evaluate the effectiveness of liraglutide on glycemic control, lipid profile and liver function in obese type 2 diabetic Iraqi patients.

METHODS

A prospective open-label study was conducted from November 2021 to June 2022 at Baquba Teaching Hospital/ Diyala. In current study, 50 patients (23 males and 27 females) had type 2 diabetic from 2 to 4 years and they were obese (Body mass index ≥ 30), hypertensive and dyslipidemic. Moreover, recruited patients were on treatment with statins, angiotensin receptor blockers and metformin, in a dose of 1 g/day, before starting the study and liraglutide (0.6 mg/day by subcutaneous route) was added on for 12 weeks. Patients who met the above criteria underwent measurements for fasting glucose level, lipid profile, glycosylated hemoglobin and their liver function.

Ethical Approval:

Ethical approval was obtained from the Scientific Research Ethics Committee and Department of Pharmacology, College of Medicine, University of Baghdad and that at Baquba Teaching Hospital/ Diyala. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis of data

Was performed using SAS (Statistical Analysis System - version 9.1). Data were expressed as number and p ercentage for qualitative data and mean $\pm$ standard deviation (SD) for quantitative data. Paired t-test was used to compare quantitative data. $P<0.05$ was considered significant.

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RESULTS

Demographic data of participants

There was no significant difference between males and females regarding demographic data (Table 1).

Table 1: Demographic data of participants

Gender	Number (%)	P-value	Age/ years (Mean±SD)	P-value
Male	23(46%)	0.57	39.04±1.66	0.47
Female	27(54%)		40.70±1.60	

SD: standard deviation.

Effect of liraglutide on fasting glucose level

Liraglutide significantly decreased the fasting glucose level for male and female patients as well as for all patients when compared before and after 12 weeks of using liraglutide (Table 2).

Table (2): The effects of liraglutide before and after 12 weeks of treatment

Gender	Fasting Blood Sugar (mg/dL)		P value
	Before	**After 12 weeks**	
Male (N=23)	262.69±10.98	127.95±3.99	**<0.001**
Female (N=27)	261.40±9.93	137.03±5.53	
Overall (N=50)	262.00±7.29	132.86±3.53	**<0.0001**

Each value is represented as mean ± standard deviation (SD)

Effect of liraglutide on lipid profile

Liraglutide significantly decreased the cholesterol and LDL while significantly increased HDL for male and female, and total patients as compared before and after 12 weeks of using liraglutide (Table 3).

Table (3): The effect of liraglutide on lipid profile before and after 12 weeks of treatment with liraglutide

Gender	Cholesterol		Low Density Lipoprotein		High Density Lipoprotein		P value
	Before	After	Before	After	Before	After	
Male (N=23)	255.26±12.9	170.30±4.8	153.26±7.08	88.86±4.15	35.65±1.25	41.60±0.94	**<0.001**
Female (N=27)	234.37±7.49	170.25±3.5	135.81±5.44	84.77±2.42	39.33±1.02	42.03±0.90	
Overall (N=50)	243.98±7.26	170.28±2.9	143.84±4.51	86.66±2.30	37.64±0.83	41.84±0.64	**<0.0001**

Each value is represented as mean ± standard deviation (SD)

Effect of liraglutide on glycosylated hemoglobin (HbA1c)

Liraglutide significantly decreased mean HbA1c level for males and females as well as for all patients, when compared before and after 12 weeks of using liraglutide (Table 4).

Table (4): The effect of liraglutide on glycosylated hemoglobin (HbA1c) before and after 12 weeks of treatment with liraglutide

Gender	HbA1c %		P value
	Before	**After**	
Male (N=23)	12.17±0.42	7.53±0.12	P<0.001
Female (N=27)	12.16±0.31	7.54±0.11	
Overall (N=50)	12.16±0.25	7.53±0.08	P<0.0001

Each value is represented as mean ± standard deviation (SD)

Effect of liraglutide on liver function

Liraglutide did not significantly change the liver function for male and female patients, as well as for all patients when compared before and after 12 weeks of using liraglutide (Table 5).

Table (5): The effect of liraglutide on liver function tests before and after 12 weeks of treatment with liraglutide

Gender	Alanine transaminase		Alkaline phosphatase		Aspartate transaminase		P value
	Before	After	Before	After	Before	After	
Male (N=23)	21.42±1.48	21.02±1.58	62.42±3.56	63.26±3.35	20.11±1.41	20.37±1.37	
Female (N=27)	20.89±1.31	20.72±1.32	65.94±4.20	64.21±3.68	17.47±1.15	17.87±1.09	P>0.05
Overall (N=50)	21.13±0.97	20.86±1.01	64.32±2.78	63.78±2.49	18.69±0.91	19.02±0.87	P>0.05

Each value is represented as mean ± standard deviation (SD).

DISCUSSION

Demographic data of participants

Results from current study showed that the study recruited 50 patients; 23 (46%) males and 27 (54%) females. The mean age for male patients was 39.04 years and that for females was 40.7 years without significant differences regarding gender distribution of age of patients.

The mean age of the patients enrolled in current study was younger than that (59.8 years) of patients enrolled in a previous study **(10)**. However, gender distribution of patients in the latter study (51.16% males and 48.84% females) was comparable to that in current study.

Effect of liraglutide on fasting glucose level

Current study showed that liraglutide significantly decreased fasting glucose level as compared for male and female patients as well as for all patients before and after 12 weeks of treatment with liraglutide.

Similar effects for liraglutide on fasting glucose level were reported in a previous study [11-18] that showed a significant decrease in mean of fasting glucose level from (173.7±6.3) mg/dl before to (115.5±25.1) after 3 months of treatment with liraglutide; initial dose of liraglutide was 0.6 mg/day, which was up-titrated to 1.2 mg/day after 1 week; further up-titration to 1.8 mg/day was done according to the tolerance and adverse effect [19, 20].

Another study in which liraglutide was administered to 41 obese individuals with T2DM or prediabetes for 6 months at doses of 3 mg/day or 1.8 mg/day according to the recommended dosing schedule for treating T2DM, showed significant decrease in mean fasting glucose level in T2D from (156.24 ± 2.31) before to (121.86 ± 1.36) after 3 months of treatment [21].

However, the reduction in fasting glucose level reported in current study was greater than that was reported in the previous studies mentioned above. This finding may be explained by the fact that in, current study, liraglutide was added to metformin in a dose of 1 g/day while in those two studies, all participants were treated with liraglutide as monotherapy. The effectiveness of liraglutide in reducing fasting glucose level might be attributed to the fact that it is a type of incretin therapy, works by increasing insulin secretion, reducing glucagon secretion and hepatic glucose output, delaying gastric emptying, and increasing satiety [12].

Effect of liraglutide on lipid profile

Current study showed a significant decrease in lipid profile variables as compared for male and female patients as well as for all patients before and after 12 weeks of treatment with liraglutide.

Similar effects for liraglutide on lipid profile were reported by another study where the drug was administered at a dose of 1.2 mg/day for 12 months. Another study reported similar significant effects for liraglutide (at a dose of 1.2 mg/day for 12 months) on lipid profile of diabetic patients **(13)**.

Liraglutide treatment showed positive effects in improving the ability of β-cells to secrete hormones and in reducing the synthesis of free fatty acids. Less is known, however, about the particular methods by which glucagon-like peptide-1 affects lipid metabolism. It has been proposed that postprandial lipoprotein production and secretion depend on enterocyte GLP-1 receptor signaling, inhibits the postprandial rises in triacylglycerol, cholesterol, and apo-B48 levels and decreases intestinal lipid synthesis and absorption [14]. Additionally, GLP-1 is connected to the direct regulation of fatty acids binding protein 2 (FABP2), which is necessary for the synthesis of chylomicrons containing apo-B48 [15]. Additionally, despite increased insulin production, GLP-1 caused sustained drops in NEFA concentrations after meals and slowed postprandial increases in ApoCIII [16,17]. A small glycoprotein called ApoCIII, which is mostly found on the surface of ApoB-containing lipoproteins and HDL, is produced in the liver and gut. Since ApoCIII reduces lipoprotein lipase activity and prevents receptor-mediated absorption of TG-rich lipoproteins, TG-rich lipoproteins take longer to be cleared from the body[18].

Effect of liraglutide on glycosylated hemoglobin

Current study showed a significant decrease in HbA1c as compared for male and female patients as well as for all patients before and after 12 weeks of treatment with liraglutide.

A previous study comprised 196 obese T2D patients, 30 patients were treated with liraglutide for 12 weeks as 0.6 mg/day increased up to 1.8 mg/day according to tolerance and requirement and metformin. That study showed significant decrease in the mean of HbA1c

between the baseline and after 12 weeks of treatment with liraglutide as (9.15±2.59) vs (7.08±1.04) respectively [19].

Moreover, another study that comprised 195 (108 males and 87 females) type 2 diabetic patients who received liraglutide for 24 weeks as 0.6 mg a day during the first week, which was gradually increased to 1.2 mg and up to 1.8 mg a day according to tolerance and requirement. The study showed significant decrease in the mean of HbA1c between the baseline and after 12 weeks of treatment with liraglutide [22].

The incretin hormone glucagon-like peptide-1 (GLP-1) has a strong blood-glucose-lowering effect only when there is hyperglycemia by increasing insulin secretion and decreasing secretion of glucagon in a glucose-dependent way [17]. Beyond its ability to reduce blood sugar, GLP-1 also slows stomach emptying and promotes satiety, both of which help people lose weight. The combined actions of GLP-1 on the gastrointestinal system help to partially explain the process [11].

Effect of liraglutide on liver function

Current study showed that liraglutide did not significantly affect the liver function of participants as compared for male and female patients as well as for all patients before and after 12 weeks of treatment with liraglutide.

A previous study which included 28 obese women with PCOs where 14 women were treated with 1.2 mg/day of liraglutide for 12 weeks, which showed non-significant change in liver function tests [23]. The findings of current study might indicate the safety of liraglutide as it does not affect liver function.

CONCLUSION

In obese type 2 diabetic patients, liraglutide exerts beneficial glycemic control as well as can correct dyslipidemia, but without adversely affecting hepatic function.

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