ORIGINAL ARTICLE

EFFECTIVENESS OF LIRAGLUTIDE IN REDUCING BODY WEIGHT AND IMPROVING GLYCEMIC CONTROL IN PATIENTS WITH T2DM

Sifat Ullah[1], Arshad Hussain[1], Shaista Kanwal[2], Arif Jamal[3], Muhammad Saleh Faisal[4]

[1]Department of Endocrinology, Northwest General Hospital & Research Centre, Peshawar - Pakistan

[2]Department of Endocrinology, Hayatabad Medical Complex, Peshawar - Pakistan

[3]Health Department, Khyber Pakhtunkhwa - Pakistan

[4]Department of Pharmacology, Khyber Medical College, Peshawar - Pakistan

ABSTRACT

Objective: This study aimed to determine the effects of Liraglutide on glycosylated hemoglobin (HbA1c) and body weight in patients with type 2 diabetes.

Material and Methods: A prospective observational study was conducted in a private tertiary healthcare setting. A total of 58 adult patients with T2DM using oral anti-diabetic agents with or without insulin were enrolled in the study from November 2020 to April 2022. Liraglutide was administered at a dose of 0.6 mg/day which was raised to 1.2 mg/day after 1 week and later to 1.8 mg/day depending upon patient preferences and tolerability. Patients were assessed for changes in their body weight, fasting blood glucose (FBG) level, random blood glucose (RBG) level, and HbA1c at the 1st and 2nd follow-up visits i.e. 8th and 16th week, respectively.

Results: At the 16th week, the mean weight was 100.78±17.56 vs 102.74±17.26 and 104.11±17.95 at the 8th week and baseline visit, revealing a significant difference across three-time points [F(1.4, 36.45)=8.57, p=0.003]. A post hoc pairwise analysis showed that weight significantly decreased from baseline and 16th-week follow-up visits (p=0.011). Similarly, a significant decrease was observed in mean HbA1c across three-time points [F (2, 39.40) =8.81, p=0.001]. Mean HbA1c at 16th week was 6.61±1.13% vs 8.09±1.43% at baseline (P = 0.001). No significant reduction in FBG, RBG, blood pressure, and serum lipid profile were observed. Moreover, no major side effects occurred in any patient.

Conclusion: Liraglutide is an effective and well-tolerable drug in improving glycemic control, causing significant weight loss in the study population when used as a monotherapy or in combination therapy.

KEYWORDS: Liraglutide, Glucagon-like peptide-1 agonist, Type 2 diabetes mellitus, Glycemic control, Weight loss

This article may be cited as: Ullah S, Hussain A, Kanwal S, Jamal A, Faisal MS. Effectiveness Of Liraglutide In Reducing Body Weight And Improving Glycemic Control In Patients With T2dm. J Med Sci 2022 October;30(4):306-310

INTRODUCTION

Diabetes mellitus (T2DM) is a chronic disorder defined by insulin resistance and beta cell dysfunction, associated with several complications.[1] Despite the availability of a range of anti-diabetic agents, attainment, and maintenance of glycemic control are quite challenging with the progression of the condition.[2] There are multiple pharmacological options available for the management of T2DM, with varying effects on blood pressure and body weight, making it difficult for the physician in selecting the appropriate regimen.[3] Thus a patient-centered approach should be used in deciding upon the optimal regimen taking into account the comorbid conditions, disease progression, and complications with the primary aim of attaining individualized glycemic goals with minimum adverse effects.[4]

After many years of cardiovascular outcome trials, two classes of anti-diabetic agents, i.e. Sodium-glucose co-transporter (SGLT-2) inhibitors and Glucagon-like peptide 1 receptor agonists (GLP-1RA) demonstrated cardiovascular advantages independent of glycemic control. This led to new treatment avenues in the management of T2DM.[5] Liraglutide is a long-acting GLP-1RA that improves glycemic control by promoting insulin secretion, suppressing the production of glucagon, and inducing weight loss.[6] It reduces systolic blood pressure and has a direct cardioprotective effect as well.[7]

LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial was commenced in 2010 to evaluate the long-term effects of Liraglutide on cardiovascular outcomes and other important clinical parameters. This study demonstrated a 23%

Correspondence
Dr. Muhammad Saleh Faisal
Assistant Professor
Department of Pharmacology, Khyber Medical College
Peshawar - Pakistan
Email: drsalehfaisal@gmail.com
Cell: +92-333-9806131
Date Received: 18-10-2022
Date Revised: 03-12-2022
Date Accepted: 24-12-2022

decrease in the primary endpoint.[8] Furthermore, a systemic review demonstrated that all GLP-1 RA improves HbA1c and decreases body weight, however; the long-acting agents including Liraglutide were found to be more effective in reducing fasting blood glucose and glycated hemoglobin (HbA1c).[9]

Studies conducted on the Indian population with T2DM showed that Liraglutide is effective in controlling glycemic levels, inducing weight loss, and is associated with a lower risk of hypoglycemia.[10, 11] Few such studies are also performed on Pakistani T2DM patients demonstrated significant improvement in Hb1Ac and reduction in their body weights.[3, 12] But keeping in view the fact that Liraglutide effectiveness varies greatly by region and scarcity of currently available data in the literature on Pakistani population, this study was designed to look into the effects of Liraglutide on HbA1c and body weight in T2DM patients in the local population of Khyber Pakhtunkhwa.

MATERIAL AND METHODS

A prospective study was conducted in the Department of Endocrinology, North-west General Hospital & Research Center, Peshawar from November 2020 to April 2022 after getting ethical approval from the institutional committee. Adult patients of either gender with T2DM were enrolled in the study. Patients of age less than 18 years, having Type 1 DM, or those receiving Liraglutide already were excluded. After informed consent, data regarding the demographics of the patient, duration of T2DM, and presence of co-morbidities like hypertension, thyroid disorders, ischemic heart disease, chronic kidney disease, and dyslipidemia was recorded on a predesigned proforma. Baseline information like type and number of anti-diabetic agents, BMI, Blood pressure, HbA1c, fasting blood glucose (FBG), random blood glucose (RBG), Urine Albumin to creatinine ratio (ACR) and lipid profile was recorded. A total of 67 patients with T2DM, obesity (BMI ≥ 23 kg/m^2), and poor glycemic control (HbA1c > 7%) were prescribed Liraglutide. But 9 patients were lost during follow-up or discontinued the treatment. All patients were on oral anti-diabetic agents with or without insulin. Liraglutide was initiated at the dose of 0.6 mg/day. After 1 week, the dose was increased to 1.2 mg/day and later to 1.8 mg/day depending upon patient preferences and tolerability. Patients were assessed for change in their body weight, FBG, RBG, and HbA1c at 1st and 2nd follow-up visits of 8 and 16 weeks, respectively.

In addition, BP and common GI adverse effects like nausea, vomiting, and diarrhea were also enquired about at each follow-up visit.

Data were analyzed by SPSS version 22 and frequencies and proportions were calculated for categorical variables. Mean, SD and IQR were calculated for variables with continuous nature. Repeated measure ANOVA was used for within-group comparison of the patient's anthropometric, biochemical parameters, and blood pressure across baseline, week 8, and week 16. Post hoc analysis was conducted using paired t-tests with Bonferroni adjustment. A p-value <0.05 was taken as a level of significance.

RESULTS

A total of 58 patients were included in the final analysis having a mean age of 49.29±9.15 years and a female predominance of 45 (77.59%). The mean duration of DM since diagnosis was 5.48±4.78 years. The most common co-existing illness was dyslipidemia 15 (37.5%) followed by hypertension 14 (24.14%), thyroid disorder 6 (10.34%), and ischemic heart disease 4(6.90%). Medication history revealed that most of the patients were using oral antidiabetic drugs (OADs), with biguanide being the most common group i.e. 14 (30.44%) followed by biguanide + DDP4 and biguanide + SGLT2. On the other hand, 6 patients were on both OADs and Insulin. Anthropometric characteristics and biochemical parameters at different intervals are given in Table I.

Liraglutide's starting dose was 0.6 mg/day at the baseline. After the first week, 72.0% of patients were switched to 1.2 mg/day, and later on, 17% were started on 1.8 mg/day. Moreover, 25 (43.10%) patients were given Liraglutide monotherapy whereas the remaining subjects were prescribed Liraglutide combination therapy (Table II).

None of the participants discontinued Liraglutide as no major side effects occurred. Nearly half of the participants reported nausea followed by diarrhea 4(6.89%).

A repeated-measures ANOVA with a Greenhouse-Geisser correction ascertained a significant reduction in mean weight across three-time points [F (1.4, 36.45) = 8.57, p = 0.003]. A post hoc pairwise analysis with a Bonferroni's correction showed that there was a considerable difference in weight between baseline vs. 16th week and 8th week vs. 16th week with p values <0.05 as shown in Figure 1.

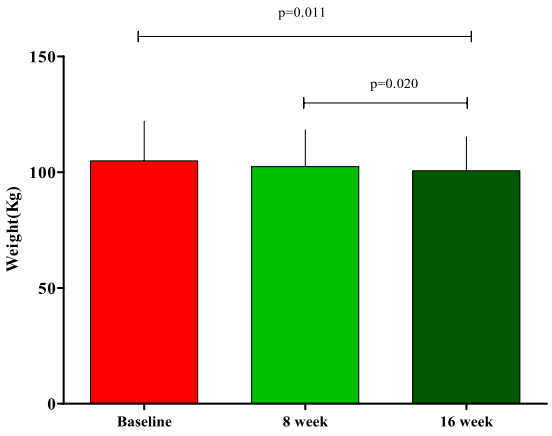

Fig 1: Bonferroni post hoc analysis of weight over three-time points

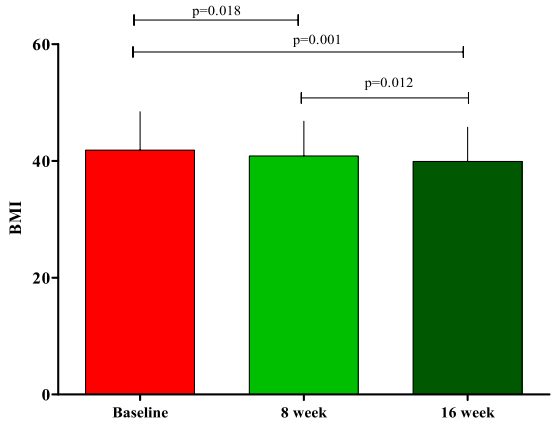

Fig 2: Bonferroni post hoc analysis of BMI over three-time points

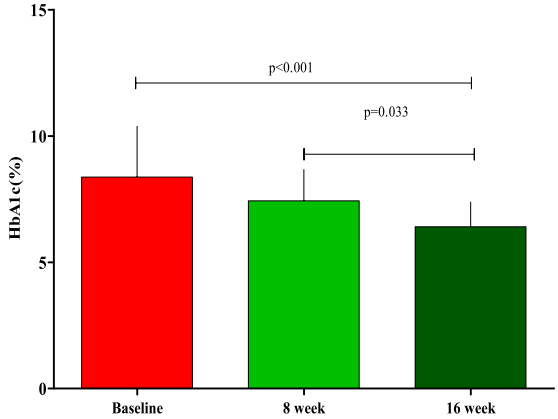

Fig 3: Bonferroni post hoc analysis of HbA1c over three-time points

Table 1: Descriptive statistics and Repeated-measures ANOVA within subjects

Parameters	Baseline Mean± SD	8th week Mean± SD	16th week Mean± SD	p-value
Weight (kg)	104.11±17.95	102.74±17.26	100.78±17.56	0.003
Body Mass Index	41.73±7.03	40.80±6.41	39.92±6.60	0.000
HbA1c (%)	8.09±1.43	7.45±1.96	6.61±1.13	0.001
FBG (mg/dl)	147.40±19.23	132.40±41.62	125.60±14.71	0.403
RBG (mg/dl)	214.83±104.14	189.67±70.66	166.17±27.50	0.262
Systolic Blood Pressure	135.33±14.54	137.57±20.15	130.61±21.20	0.178
Diastolic Blood Pressure	90.61±11.59	93.33±13.26	88.52±16.69	0.392

Table 2: Liraglutide as Monotherapy and Polytherapy

Therapy		N (%)
Liraglutide Only		25 (43.1)
Liraglutide+ Insulin	Liraglutide + Basal bolus insulin	1 (1.72)
	Liraglutide + Premix insulin	2 (3.45)
Liraglutide + OADs + Insulin	Liraglutide + Premix insulin + Metformin + DDP4	1 (1.72)
	Liraglutide + Premix insulin + Metformin + SGLT2	3 (5.17)
	Liraglutide+ Basal bolus insulin + Metformin	1 (1.72)
Liraglutide + OADs	Liraglutide + Metformin	11 (18.97)
	Liraglutide + Metformin + SGLT2	11 (18.97)
	Liraglutide + Sulphonylurea	1 (1.72)
	Liraglutide + Sulphonylurea + Metfromin + DDP4	1 (1.72)
	Liraglutide+ Sulphonylurea + Metformin+ SGLT2	1 (1.72)

Similarly, BMI on repeated measures ANOVA with Greenhouse-Geisser correction revealed a significant reduction in mean values across three-time points [F (1.5, 38.45) = 13.86, p <0.001]. Bonferroni's correction for pairwise comparisons found that there was a considerable difference in BMI between baseline vs. 8th week, baseline vs. 16th week, and 8th week vs. 16th week with p values <0.05 as shown in Figure 2.

Repeated measures ANOVA with conformance of assumption of Mauchly's test of sphericity, $\chi 2$ (2) = 2.49, p = 0.288, showed that change in HbA1c level over time was significant in the study participants as a whole. Bonferroni's correction for pairwise comparisons found that there was a considerable difference in HbA1c between baseline vs. 16th week and 8th week vs. 16th week with p values <0.05 as shown in Figure 3.

DISCUSSION

Liraglutide has been observed to be an effective treatment option in lowering the blood glucose level and

also the risk of non-fatal cardiovascular (CV) events and CV mortality in adults with T2DM and CV disease.[6, 9] Since 2016, Liraglutide is approved for use in Pakistan for the management of T2DM. Because GLP-1 agonists are relatively new class of glucose-lowering drugs; there are several concerns about their efficacy. The effectiveness has largely varied by region as identified in published literature[13] so we conducted this study to investigate the effects of Liraglutide on HbA1c and weight in T2DM. Liraglutide in obese type 2 diabetics with poor glycemic control on OADs (±insulin) was assessed. A significant reduction of 0.64% in the 8th week and 1.48% in the 16th week in HbA1c was observed from the baseline resembling the results of LEAD (Liraglutide Effect and Action in Diabetes) trials, where HbA1c reduction of up to 0.8-1.6% at recommended doses (1.2 and 1.8mg) over a period of 6 months of treatment has been demonstrated.[16-20] Though the maximum reduction was higher than the findings of our study. Likewise, in Italy, a group of 400 patients who received Liraglutide demonstrated a substantial decrease in HbA1c following a year follow-up.[14] Another study with 5 years of Liraglutide therapy revealed a drop in HbA1c from 7.9± 0.9% at baseline to 7.0±0.7%.[15] Therefore, it appears that the results on HbA1C (a total reduction of roughly 1.5 %) in our patients are the best that could be obtained in our real-world setting in Pakistan. A local study conducted by Rashid, Muhammad Owais et al. reported HbA1c reduction of 0.95% and 1.05% at 3 and 6 months respectively from baseline.[3]

In contrast to many other treatment options, which often result in weight gain, incretin-based medications can help patients lose weight. Liraglutide was also found to be effective in reducing weight and BMI when administered alone or in combination with other anti-diabetic drugs in our study. The respective mean weight and BMI reduction from baseline were 3.33kg and 1.81 kg/m^2. The mean weight loss in our study was although the same as expected after 16 weeks of therapy, it was greater than the weight loss in the LEAD trial, which was less than 3 kg, and equivalent to LEAD-6, which revealed 3.24 kg of weight loss.[21] The reason for this could be that weight reduction with Liraglutide is dose-dependent, and the majority of the study patients have received titrated doses up to a daily maximum dose of 1.8 mg. Parjeet et al reported the weight loss as early as one month, further describing the continued trend and maximum weight loss of around 4 kg was seen in 3rd month. [10] Along with adequate glycemic control, losing weight was one of the most crucial elements in keeping the patients motivated to continue taking Liraglutide.

Literature showed that Liraglutide therapy reduces blood pressure.[3,10,12] This study also demonstrated a reduction in mean SBP and DBP of 4.72 mm Hg and 2.09 mm Hg, respectively from the baseline at follow-up visits. These findings were higher than the reported figures of LEAD trials i.e. a drop of SBP ranged from 2.7 to 2.9 mmHg. [16-21] On the other hand, a review of real-world data from India revealed a reduction in SBP of 9.7 mmHg, which is rather higher than our findings.[11]

Liraglutide is generally well tolerated, some clinical studies documented GI adverse effects such as nausea, vomiting, and diarrhea.[3, 10, 12] Though, no major side effects occurred in our study, nearly half of the participants reported nausea followed by diarrhea. In the LEAD trials, nausea was the most reported adverse event. Other side effects were vomiting, constipation, dyspepsia, and diarrhea.[16-21] These GI events were frequently dose-dependent, minor, and observed to diminish within a few days or weeks of continued treatment.

This study has a few worth mentioning limitations like its observational study design and small sample size. Secondly, the time interval between HbA1c assessments was not consistent. Some patients did not report dose adjustment of insulin after initiation of therapy. While good BMI and HbA1c% were reported at follow-up, various variables like diet and physical activity could not be tracked.

CONCLUSION

Liraglutide is found to be an effective and well-tolerable drug in improving glycemic control, causing considerable weight loss in the obese study population with T2DM, when used as a monotherapy or in combination with other anti-diabetic drugs. Longer follow-up studies with large sample sizes are needed to establish its long-term efficacy and safety profile.

REFERENCES

1. Liang Y, Meng H, Li R, Yang J, Jia J, Hou Y. A randomized controlled trial protocol of the cardiovascular safety and efficacy of liraglutide in the treatment of type 2 diabetes. Medicine. 2021;100(3).
2. Wysham CH. New perspectives in type 2 diabetes, cardiovascular risk, and treatment goals. Postgrad Med. 2010;122(3):52-60.
3. Rashid MO, Jabeen S, Khoja A, Islam N. Efficacy of Liraglutide in clinical practice: Single centre experience. Pak J Med Sci. 2020;36(3):432-437.
4. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes, 2015: A patient-centred approach. Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia. 2015;58(3):429-442.
5. Advani A, Bugyei-Twum A, Connelly KA. Cardiovascular effects of incretins in diabetes. Can J Diabetes 2013;37(5):309-314.
6. Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): A multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet. 2016;387(10019):679-690.

7. Bizino MB, Jazet IM, Westenberg JJM, van Eyk HJ, Paiman EHM, Smit JWA, et al. Effect of liraglutide on cardiac function in patients with type 2 diabetes mellitus: randomized placebo-controlled trial. Cardiovasc Diabetol. 2019;18(1):55.

8. Thompson PL, Davis TME. Cardiovascular effects of glucose-lowering therapies for type 2 diabetes: New drugs in perspective. Clin Ther. 2017;39(5):1012-1025.

9. Htike ZZ, Zaccardi F, Papamargaritis D, Webb DR, Khunti K, Davies MJ. Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: A systematic review and mixed-treatment comparison analysis. Diabetes Obes Metab. 2017;19(4):524-536.

10. Kaur P, Mishra SK, Mithal A, Saxena M, Makkar A, Sharma P. Clinical experience with Liraglutide in 196 patients with type 2 diabetes from a tertiary care center in India. Indian J Endocrinol Metab. 2014;18(1):77-82.

11. Kesavadev J, Shankar A, Gopalakrishnan G, Jothydev S. Efficacy and safety of liraglutide therapy in 195 Indian patients with type 2 diabetes in real world setting. Diabetes Metab Syndr 2015; 9(1):30-33.

12. Zameer R, Kamin M, Raja U, Wahab MU, Ishtiaq O, Raashid K, et al. Effectiveness, safety, and patient satisfaction of liraglutide in type 2 diabetic patients. Cureus 2020; 12(8):e9937.

13. Yousef CC, Thomas A, Matar MA, Ghandoura L, Aldossary I, Almuhanna SM, et al. Liraglutide effects on glycemic control and weight in patients with type 2 diabetes Mellitus: A real-world, observational study and brief narrative review. Diabetes Res Clin Pract. 2021; 177:108871.

14. Lapolla A, Frison V, Bettio M, Dal Pos M, Rocchini P, Panebianco G, et al. Correlation between baseline characteristics and clinical outcomes in a large population of diabetes patients treated with liraglutide in a real-world setting in Italy. Clin Ther. 2015; 37(3):574-584

15. Mirabelli M, Chiefari E, Caroleo P, Arcidiacono B, Corigliano DM, Giuliano S, et al. Long-term effectiveness of liraglutide for weight management and glycemic control in type 2 diabetes. Int J Environ Res Public Health. 2019; 17(1):207.

16. Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. Diabetes Care. 2009; 32(1):84-90.

17. Zinman B, Gerich J, Buse JB, Lewin A, Schwartz S, Raskin P, et al. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). Diabetes Care. 2009; 32(7):1224-1230.

18. 1Russell-Jones D, Vaag A, Schmitz O, Sethi BK, Lalic N, Antic S, et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): A randomised controlled trial. Diabetologia. 2009; 52(10):2046-2055.

19. Marre M, Shaw J, Brändle M, Bebakar WM, Kamaruddin NA, Strand J, et al. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). Diabet Med. 2009; 26(3):268-278.

20. Garber A, Henry R, Ratner R, Garcia-Hernandez PA, Rodriguez-Pattzi H, Olvera-Alvarez I, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): A randomised, 52-week, phase III, double-blind, parallel-treatment trial. Lancet. 2009;373(9662):473-481.

21. Buse JB, Rosenstock J, Sesti G, Schmidt WE, Montanya E, Brett JH, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomized, parallel-group, multinational, open-label trial (LEAD-6). Lancet. 2009; 374(9683):39-47.

CONFLICT OF INTEREST: Authors declare no conflict of interest

GRANT SUPPORT AND FINANCIAL DISCLOSURE: NIL

AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under

Ullah S: Concept, Design, Data collection

Hussain A: Execution of study , Data collection

Kanwal S: Data analysis and interpretation

Jamal A: Critical review and Bibliography

Faisal MS: Manuscript writting and statical analysis

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.