Mediterranean Journal of Pharmacy & Pharmaceutical Sciences
www.medjpps.com

ISSN: 2789-1895 online
ISSN: 2958-3101 print

SHORT COMMUNICATION article

GLP-1RA for glycaemic control and obesity as add-on therapy for type 2 diabetes

Samia A. Elmiladi

National Diabetes Hospital and Department of Medicine, Faculty of Medicine, University of Tripoli, Tripoli, Libya

Received: 15-04-2023, **Revised:** 10-05-2023, **Accepted:** 15-05-2023, **Published:** 30-06-2023

HOW TO CITE THIS

Elmiladi SA (2023) GLP-1RA for glycaemic control and obesity as add-on therapy for type 2 diabetes. Mediterr J Pharm Pharm Sci. 3 (2): 45-50. [Article number: 114]. https://doi.org/10.5281/zenodo.7942952

Keywords: BMI, diabesity, diabetes, GLP-1RAs, Libya, obesity

Abstract: Diabetes mellitus (DM) is a complex and chronic illness requiring continuous medical care. Type 2 diabetes (T2D) is commonly associated with obesity, hypertension, and a tendency to develop thrombosis, and an increased risk of cardiovascular diseases (CVD). Diabesity is a term used to indicate the coexistence of obesity and DM. Diabesity increases as obesity is an emerging epidemic in modern societies, the co-incidence with DM is also rising, so a joint plan of anti-obesity and anti-hyperglycemia for the management approaches. Therefore, this study aimed to identify the impact of glucagon-like peptide-1 receptor agonists (GLP-1RAs) on body weight and glycemic response in obese Libyan patients with T2D at the National Diabetes Centre in Tripoli, between July 2013 and May 2022. This prospective study included obese adults with T2D who were newly prescribed GLP-1RA therapy for six months with dulaglutide once weekly or liraglutide once daily. The study included 170 diabetic patients who were started on GLP1-RA as add-on therapy to their treatment, with a regular follow-up with a dietitian and their physicians to adjust their glucose-lowering medications, then comparing the effect of these agents on body weight and the level of glycated hemoglobin before and after 24 weeks of treatment. Most of the patients (n=99, 58.23%) were in the age period from 54 to 74 years old and 101 of whom were female subjects (59.4%), with a mean duration of DM equal to 8.8±7.3 years. The patients were divided randomly into two groups, the first group included 110 patients who received liraglutide pens and showed a significant reduction in HbA1c from 9.6% (±1.54) to 7.4% (±1.03) by $p<0.001$ and a significant weight loss from 88.3 kg (±10.68) to 80.8 kg (±11.83) by $p<0.001$. The reported adverse events were in 23 cases of minor hypoglycemia due to gastrointestinal upset. The other group included 60 patients for dulaglutide pens and showed significant decrease in HbA1c=9.6% (±1.54) to 7.1% (±1.2) by $p<0.05$ and a significant reduction of bodyweight from 88.3 kg (±10.68) to 83.8 kg (±16.3) by $p<0.05$. The reported adverse events were mild transient gastrointestinal distress for the initial week of a start and then subsided with regular intake. Whereas, 115 patients (67.6%) with HbA1c above 10.0% before starting therapy, no patient with HbA1c above 10.0% after six months of both GLP-RA agents' therapy. Thus, the use of GLP-RA as add-on therapy for obese patients with T2D significantly improved glycemic control with less hypoglycemia, accordingly, reducing insulin requirement for blood glucose control and loss in body weight. It can thus be concluded that GLP-1RA therapy is an effective treatment option when used in obese patients with DM.

ISSN: 2789-1895 online
ISSN: 2958-3101 print

Introduction

Worldwide, obesity is a chronic, complex, relapsing metabolic disease that affects adults and children [1]. It is an emerging epidemic in modern societies [1]. Nowadays, it is the major global chronic health issue according to the WHO, as it is emergent as a more serious world health problem than malnutrition [1]. By the year 2030, 60.0% of the world's population will be overweight or obese [2]. Overweight and obesity are defined as an abnormal or excessive fat accumulation that may harm health, and it is recognized to be the major risk factor for several non-communicable diseases, noteworthy, type 2 diabetes (T2M, accounting for about 45.0% of the cases), cardiovascular diseases (23.0%, CVD) which were the leading cause of death, musculoskeletal disorders as osteoarthritis: a highly disabling degenerative disease of the joints, and some cancers (07.0%-41.0%). In addition, there reasons many psychological problems or physical disabilities [1]. Of these diseases, T2M is most strongly linked with obesity (diabesity) and the frequency of obesity-related DM is projected to double to 300 million by 2025 [3]. Both, they raise the patients' mortality risk 7-fold [4]. Body mass index (BMI) is a simple index of weight for height that is commonly used to classify overweight and obesity in adults. It is defined as a person's weight in kilograms divided by the square of his height in meters. It provides the most useful population-level measure of overweight and obesity as it is the same for both sexes and all the ages of adults. It is used to categorize overweight and obesity as BMI <18.5 = underweight, BMI=18.5 to <25 = healthy, BMI=25 to <30 = overweight. In addition, BMI=30 to <35 = obese (class 1), BMI=35 to <40 = obese (class 2), BMI=40 or higher = obese (class 3, morbid). Obesity rates vary significantly from one country to another as a result of different lifestyles and diets. The highest rate was reported in Nauru (61.0%) of obese adult, in the United States is found to be 36.2%, the highest rate in Arabic countries is found in Kuwait (37.0%), Jordan (35.5%), Saudi Arabia (35.4%), Libya (32.5%), Egypt (32.0%), Tunis (26.9%) and the lowest rate is in Vietnam (2.1%) [5]. Weight reduction can be attained through various plans, involving lifestyle intervention (diet and physical exercise), pharmacotherapy, or bariatric surgery, not all of these strategies are appropriate for the patients, therefore, an individualized therapeutic approach is compulsory [6]. There is a considerable and persistent recovery in the metabolic complications related to obesity associated with 5.0%-10.0% weight reduction [3-5]. However, the Action for Health in Diabetes (Look AHEAD) study showed that 5.0% weight loss did not reduce cardiovascular events, however, 10.0% weight loss was sufficient to achieve a reduction in cardiovascular events [7]. Weight loss of more than 7.0% could help patients achieve remission of T2D and prevent patients with pre-diabetes from progressing further [8]. The Look AHEAD study emphasized the valuable effects of weight reduction in obese patients with diabetes and demonstrated that a loss of 5.0%-10.0% of the body weight could improve the whole physical fitness, improve glycemic control, and reduce CVS risk and diminution the use of anti-hyperglycemic drugs, antihypertensive drugs and lipid-lowering drugs after one year [9]. The diminution of depression symptoms and the severity of obstructive sleep apnea symptoms [10, 11].

The glucagon-like peptide-1 receptor agonists (GLP-1RAs) are effective at reducing the bodyweight, improving the blood pressure, and also having a low risk of hypoglycemia. GLP-1RAs are approved for weight management as an adjunct to diet and exercise in adults with a BMI of obese or adults with a BMI of overweight who have at least one weight-related condition such as hypertension, T2M and dyslipidemia [12]. GLP-1 is an incretin and satiety hormone released from the L-cells of the gastrointestinal tract after food ingestion, liraglutide is a GLP-1 analogue with 97.0% structural homology to human native GLP-1, in contrast with endogenous GLP-1 which has a half-life of 1-2 min. The molecule has two structural modifications allowing it to have a prolonged half-life of 13 hrs. after subcutaneous injection [13], and there is no hepatic or renal dosing adjustments are necessary with liraglutide [14]. In the 2021 ADA guideline, it was announced that GLP-1RAs are the preferred first injectable

ISSN: 2789-1895 online
ISSN: 2958-3101 print

agent for T2D (before insulin therapy) because of their high efficacy and safety [15]. Once-daily subcutaneous administration of liraglutide and once-weekly dulaglutide therapy was approved as anti-diabetic medications [16]. Thus, higher doses of both have been developed for the treatment of obesity and glucose control in people with or without T2D [17, 18]. Liraglutide was the firstly been standard for the treatment of DM, and some studies have then been conducted to evaluate it as therapy for obesity [1], liraglutide dose of 1.8 mg as indicated for T2D and the dose of 3.0 mg indicated for the treatment of obesity [19]. Therefore, this study aimed to recognize the outcomes of the use of GLP-1RAs on the body weight and glycemic response in obese patients with T2D in Libya.

Materials and methods

This prospective cohort study included obese Libyan adults with T2D who have newly been prescribed GLP-1RA therapy with dulaglutide once weekly or liraglutide once daily for six months between July 2013 and May 2022 in Tripoli, at the National Diabetic Center. Primary outcomes have been a change in body weight, and a reduction in HbA1c for the study population. An assessment of each patient with the help of certified dieticians to give them ideal nutrient advice and exercise encouragement to reduce their body weight, regular follow-up with diabetologists to adjust their basic anti-hyperglycaemic drugs, especially insulin and sulphonylurea doses. The participants were divided randomly into two groups, the first group included 110 patients who received liraglutide pens, and the second group involved 60 patients for dulaglutide pens once weekly. This study was done after having ethical approval from the Bioethics Committee at the Biotechnology Research Center, Tripoli (number 100/707) dated November 03rd, 2022.

Statistical analysis: Data of continuous variables were expressed as mean±standard deviation. A Chi-square test was used to calculate the difference with 95.0% confidence intervals (95.0% CI) and a $p<0.05$ was considered as statistically significant. The analysis was performed with the Statistical v10.0 Package (StatSoft, Tulsa, OK, USA).

Results

This study included 170 obese Libyan patients at the National Diabetes Centre with uncontrolled diabetes who started on GLP1-RA as an add-on therapy to their treatment. Their mean age was 54.1±14.6 years, age interval from ≤32 years in 3 (01.76%) and 43 (25.29%) were between 33 and 53 years old, age period from 54 to 74 years was in 99 (58.23%) and 25 (14.7%) above 75 years and 101 of whom were female patients (59.4%), with a mean duration of DM of 08.8±7.3 years. BMI was calculated for each patient shown as obesity class I (BMI>30.0%) in 82 (48.2%), patients with obesity class II (BMI >35.0%) in 88 (51.7%) and 83 (48.2%) with HbA1c within 8.0%-9.0% and 87 (51.8%) with HbA1c >10.0%, there also were 105 (61.7%) of the patients presented with recurrent hypoglycemia. They were randomly distributed into two groups: the first group, 110 patients, received liraglutide once daily injection and were followed for six months (24 weeks) starting dose was 0.6 for one week then increase the dose to 1.2 for the next two weeks thereafter to 1.8 for the next 21 weeks (**Table 1**), there basal anti-hyperglycemic agent reduced according to the self-monitoring blood glucose, liraglutide using group results showed a significant reduction of HbA1c from 9.6% (±1.54) to 7.4% (±1.03), $p<0.001$, and a significant body weight loss from 88.3 kg (±10.68) to 80.8 kg (±11.83), $p<0.001$. The reported adverse events were in 23 cases of minor hypoglycemia due to gastrointestinal upsets (**Table 1**).

In **Table 2**, the other group included 60 patients for dulaglutide pens taken, the results showed a significant reduction of HbA1c from 9.6% (±1.54) to 7.1% (±1.2), $p<0.05$, and a significant body weight loss from 88.3 kg

ISSN: 2789-1895 online
ISSN: 2958-3101 print

(±10.68) to 83.8 kg (±16.3), p<0.05. The reported adverse events were found to be mild transient gastrointestinal distress for the initial week of start which subside with a regular intake. 115 patients with HbA1c above 10.0% before starting therapy (67.6%), and no patients with HbA1c above 10.0% after six months of both GLP-RA agents therapy observed in these patients.

Table 1: Body mass index, HbA1c and hypoglycaemic episodes after liraglutide use in obese diabetic patients

Characters Before and after	Before liraglutide use: Initial No.	After six months: End of study No.
Body mass index		
Normal	00.0	30 (27.2%)
Over-weight	00.0	58 (52.8%)
Obesity class 1	53 (48.0%)	22 (20.0%)
Obesity class 2	57 (52.0%)	00.0
HbA1c		
< 6	00.0	63 (57.0%)
6.5 - 7	00.0	37 (34.0%)
8 - 9	36 (33.0%)	10 (09.0%)
> 10	74 (67.0%)	00.0
Hypoglycaemics episodes	48 (44.0%)	23 (20.0%, minor event)

Table 2: Body mass index and HbA1c levels, hypoglycaemic episodes after the use of dulaglutide in obese diabetic patients

Characters Before and after	Before dulaglutide use	After six months
Body mass index		
Normal	00.0	11 (18.0%)
Over-weight	00.0	45 (75.0%)
Obesity class 1	29 (48.0%)	04 (07.0%)
Obesity class 2	31 (52.0%)	00.0
HbA1c		
< 6	00.0	03 (05.0%)
6.5 - 7	00.0	13 (22.0%)
8 - 9	19 (33.0%)	44 (73.0%)
> 10	41 (67.0%)	00.0
Hypoglycaemics episodes	24 (40.0%)	00.0

Discussion

Recently, the rate of coexisting cardiovascular risk factors such as hypertension and obesity in Libyan patients with DM has been reported by the author [20]. This prospective study aimed to assess the effect of GLP-1RA drugs on body weight and glycemic control, as well as, the incidence of hypoglycemia in obese patients with uncontrolled T2D. In the Satiety and Clinical Adiposity-Liraglutide Evidence in diabetic, individuals (SCALE), obesity and pre-diabetes trials which involved 846 participants with overweight or obesity showed that liraglutide attained superior to placebo, within 56 weeks [17]. In our study, the use of liraglutide for 24 weeks as add-on therapy resulted in a profound significant body weight loss. Liraglutide was superior to placebo in improving glycemic control and reducing cardiovascular events in patients with T2D and high cardiovascular risk in the LEADER trial [21] which is in good agreement with the present study. Thus, there was a highly significant improvement in glycaemic control with a less hypoglycemia response. Similar findings have also been reported [22] in obese patients with T2D followed for one year reported a significant difference in HbA1c from 8.9% (±1.3) to 7.4% (±1.2) and a significant difference in weight reduction from 98.9 kg (±16.0) to 93.8 kg (±15.0) with adverse events in 32 patients mostly as diarrhea (n=11), nausea (n=14) and others (n=7). It was found that after starting liraglutide as add-on therapy, a highly significant improvement in glycaemic control with less hypoglycemia and a highly significant reduction in body weight were observed. A consistent with a systematic literature review by Ostawal and others [23] who reported changes in HbA1c from baseline to study end and found the mean HbA1c change from baseline was -0.6% to -2.26%. The mean change in weight from -1.3 to -8.65 kg and reported data on adverse effects showing rates ranging from 00.0% to 64.3%. The gastrointestinal effects

ISSN: 2789-1895 online
ISSN: 2958-3101 print

were most commonly reported with rates of 0.51% to 42.9%. On the other hand, the use of dulaglutide induced a significant improvement in glycaemic control with a significant reduction in the body weight and in the adverse events mild transient gastrointestinal distress for the initial week of the initiating therapy that subsided with regular intake. A similar finding has previously been reported [24]. In AWARD studies, a large cohort study of T2D patients that dulaglutide provides an effective glucose-lowering together with sustained weight loss and a low incidence of hypoglycemia. However, the current study has some limitations including the small size sample and only one single-center study. Patients were also not followed for a long period to deduce outcome data and link with baseline findings, as the availability of GLP-1RA agents is not continued in the pharmacies.

Conclusion: The use of GLP-1RAs in obese patients with uncontrolled hyperglycemia indicates a profound improvement in glycemic control and reduces insulin requirement for blood glucose control with liraglutide. In addition, weight reduction and less hypoglycemic risk, particularly, with dulaglutide use. The administration of GLP-1RA is the best option in obese patients with diabetes with frequent monitoring to adjust basal glucose-lowering drugs, especially insulin and sulphonylureas doses.

Acknowledgments: The author thanks all the patients who participated in this study and is grateful to all the clinic dieticians & nurses for their support during the conduct of the research.
Conflict of interest: The author declares the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Ethical issues: Including plagiarism, informed consent, data fabrication or falsification and double publication or submission were completely observed by the author.
Data availability statement: The raw data that support the findings of this article are available from the corresponding author upon reasonable request.
Author declarations: The author confirms that all relevant ethical guidelines have been followed and any necessary IRB and/or ethics committee approvals have been obtained.

References

1. Frühbeck G, Toplak H, Woodward E, Yumuk V, Maislos M, Oppert J-M, Executive Committee of the European Association for the Study of Obesity (2013) Obesity: the gateway to ill health - an EASO position statement on a rising public health, clinical and scientific challenge in Europe. Obesity Facts. 6 (2): 117-120. doi: 10.1159/000350627
2. Kelly T, Yang W, Chen CS, Reynolds K, He J (2008) Global burden of obesity in 2005 and projections to 2030. International Journal of Obesity. 32 (9): 1431-1437. doi: 10.1038/ijo.2008.102
3. Dyson PA (2010) The therapeutics of lifestyle management on obesity. Diabetes, Obesity and Metabolism. 12 (11): 941-946. doi: 10.1111/j.1463-1326.2010.01256.x
4. Oldridge NB, Stump TE, Nothwehr FK, Clark DO (2001) Prevalence and outcomes of comorbid metabolic and cardiovascular conditions in middle- and older-age adults. Journal of Clinical Epidemiology. 54 (9): 928-934. doi: 10.1016/s0895-4356(01)00350-x
5. World Health Organization (2021) Obesity and overweight. 7/5/2022, WHO. Int. fact sheet. 9 June 2021.
6. Leitner DR, Frühbeck G, Yumuk V, Schindler K, Micic D, Woodward E, Toplak H (2017) Obesity and type 2 diabetes: two diseases with a need for combined treatment strategies - EASO can lead the way. Obesity Facts. 10 (5): 483-492. doi: 10.1159/000480525
7. The Look AHEAD Research Group (2006) The Look AHEAD study: a description of the lifestyle intervention and the evidence supporting it. Obesity. 14 (5): 737-752. doi: 10.1038/oby.2006.84
8. Ko JH, Kim TN (2022) Type 2 diabetes remission with significant weight loss: definition and evidence-based interventions. Journal of Obesity and Metabolic Syndrome. 31 (2): 123-133. doi: 10.7570/jomes22001

ISSN: 2789-1895 online
ISSN: 2958-3101 print

9. Wing RR, Lang W, Wadden TA, Safford M, Knowler WC, Bertoni AG, Hill JO, Brancati FL, Peters A, Wagenknecht L (2011) Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. Diabetes Care. 34 (7): 1481-1486. doi: 10.2337/dc10-2415
10. Foster GD, Borradaile KE, Sanders MH, Millman R, Zammit G, Newman AB, Waddan TA, Kelley D, Wing RR, Pi-Sunyer FX, Reboussin D, Kuna ST (2009) A randomized study on the effect of weight loss on obstructive sleep apnea among obese patients with type 2 diabetes: the Sleep AHEAD study. Archives of Internal Medicine. 169 (17): 1619-1626. doi: 10.1001/archinternmed.2009.266
11. Rubin RR, Wadden TA, Bahnson JL, Blackburn GL, Brancati FL, Bray GA, Coday M, Crow SJ, Curtis JM, Dutton G, Egan C, Evans M, Ewing L, Faulconbridge L, Foreyt J, Gaussoin SA, Gregg EW, Hazuda HP, Hill JO, Horton ES, Hubbard VS, Jakicic JM, Jeffery RW, Johnson KC, Kahn SE, Knowler WC, Lang W, Lewis CE, Montez MG, Murillo A, Nathan DM, Patricio J, Peters A, Pi-Sunyer X, Pownall H, Rejeski WJ, Rosenthal RH, Ruelas V, Toledo K, Van Dorsten B, Vitolins M, Williamson D, Wing RR, Yanovski SZ, Zhang P (2014) Impact of intensive lifestyle intervention on depression and health-related quality of life in type 2 diabetes: the Look AHEAD Trial. Diabetes Care. 37 (6): 1544-1553. doi: 10.2337/dc13-1928
12. Van Gaal L, Scheen A (2015) Weight management in type 2 diabetes: current and emerging approaches to treatment. Diabetes Care. 38 (6): 1161-1172. doi: 10.2337/dc14-1630
13. Holst JJ, Deacon CF (2005) Glucagon-like peptide-1 mediates the therapeutic actions of DPP-IV inhibitors. Diabetologia. 48 (4): 612-615. doi.org/10.1007/s00125-005-1705-7
14. Agius R, Coelho C, McGowan B (2022) GLP-1 analogues in clinical management of obesity. Current Opinion in Endocrine and Metabolic Research. 25: 100360. doi.org/10.1016/j.coemr.2022.100360
15. American Diabetes Association (2021) 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2021. Diabetes Care. 44 (Suppl 1): S111-S124. doi: 10.2337/dc21-S009
16. Pratley RE, Aroda VR, Lingvay I, Lüdemann J, Andreassen C, Navarria A, Viljoen A (2018) Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. Lancet Diabetes and Endocrinology. 6 (4): 275-286. doi: 10.1016/S2213-8587(18)30024-X
17. Davies MJ, Bergenstal R, Bode B, Kushner RF, Lewin A, Skjøth TV, Andreasen AH, Jensen CB, DeFronze R (2015) Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial. Journal of the American Medical Association. 314 (7): 687-699. doi: 10.1001/jama.2015.9676
18. Buse JB, Nauck M, Forst NT, Sheu WH-H, Shenouda SK, Heilmann CR, Hoogwerf BJ, Gao A, Boardman MK, Fineman M, Porter L, Schernthaner G (2013) Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. Lancet. 381 (9861): 117-124. doi: 10.1016/S0140-6736(12)61267-7
19. Alruwaili H, Dehestani B, le Roux CW (2021) Clinical impact of liraglutide as a treatment of obesity. Clinical Pharmacology: Advances and Applications. 13: 53-60. doi: 10.2147/CPAA.S276085
20. Elmiladi SA (2022) Presentation and character for adult patients with diabetes in Libya. Mediterranean Journal of Pharmacy and Pharmaceutical Sciences. 2 (1): 83-90. doi: 10.5281/zenodo.6399891
21. Zinman B, Nauck MA, Traberg HB, Larsen HF, Ørsted DD, Buse JB (2018) Liraglutide and glycaemic outcomes in the LEADER Trial. Diabetes Therapy: research, treatment and education of diabetes, and related disorders. 9 (6): 2383-2392. doi: 10.1007/s13300-018-0524-z
22. Kaur P, Mahendru S, Mithal A (2016) Long-term efficacy of liraglutide in Indian patients with type 2 diabetes in a real-world setting. Indian Journal of Endocrinology and Metabolism. 20 (5): 595-599. doi: 10.4103/2230-8210.183825
23. Ostawal A, Mocevic E, Kragh N, Xu W (2016) Clinical effectiveness of liraglutide in type 2 diabetes treatment in the real-world setting: A systematic literature review. Diabetes Therapy: research, treatment and education of diabetes and related disorders. 7 (3): 411-438. doi: 10.1007/s13300-016-0180-0
24. Jendle J, Grunberger G, Blevins T, Giorgino F (2016) Efficacy and safety of dulaglutide in the treatment of type 2 diabetes: a comprehensive review of the dulaglutide clinical data focusing on the AWARD phase 3 clinical trial program. Diabetes/Metabolism Research and Reviews. 32 (8): 776-790. doi: 10.1002/dmrr.2810