ORIGINAL ARTICLE

Efficacy of Liraglutide: GLP 1 Receptor Agonist on Glycemic Control and Weight Loss among Patients with Type 2 Diabetes

Fatima Jehangir, Noor Rahman, Fatema Ropani, Tariq Adnan
Department of Family Medicine, Ziauddin University, Karachi, Pakistan.

ABSTRACT

Background: American Diabetes Association (ADA) made conspicuous changes in its 2019 Standards of Care Diabetes guidelines by choosing Glucagon like Peptide 1 (GLP1) receptor agonists and Sodium Glucose co-transporter 2 (SGLT2) inhibitors as the second line treatment options after metformin because both classes of drugs are cardiovascular friendly as proved in the Cardiovascular Outcome Trials (CVOT). GLP analogs show massive weight loss benefits apart from offering good glycemic control. We aimed to determine the impact of liraglutide on correction of hyperglycemia and body weight in Asian population.

Methods: A cross sectional pre-post observational study enrolling 49 Type 2 diabetic patients with uncontrolled blood glucose, 15 years and above who agreed to use liraglutide apart from standard care, for glycemic control were recruited in the study. Study site was general practice clinic in Clifton and family medicine health care center Ziauddin University. Pre and post treatment HbA1C and BMI were observed after adding on Liraglutide 1.8 mg to metformin 1 gm bid, over a period of 12 weeks. Differences in the changes in BMI and HbA1C were examined using McNemar's test.

Results: Mean age of the participants was 44.4 years. Duration of Diabetes was 65.1 months i.e. 5.4 years. At week 12, liraglutide 1.8 mg significantly reduced HbA1C levels by 0.94% (8.53+1.07 vs. 7.56+1.04 p-value <0.05) and BMI by 6.2kg (37.23+ 5.3 vs. 31.27.6+5.5 p-value <0.05) statistically significant.

Conclusion: Liraglutide 1.8 mg over a period of 12 weeks, significantly reduced body weight (6.2kg p-value 0.05) and improved glycemic control (0.94% p-value<0.05) without causing hypoglycemia.

Keywords: Glycemic Control; Liraglutide; GLP1; SGLT2, CVOT; Type 2 Diabetes; Asian.

Corresponding Author:
Dr. Fatima Jehangir
Department of Family Medicine,
Ziauddin University, Karachi, Pakistan.
Email: fatima.jehangir@zu.edu.pk
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INTRODUCTION

In the past twenty years, the incidence of obesity has soared up in the developing countries due to adopting the western lifestyle of consuming high caloric food and sedentary lifestyle. So much so that the youth is also being affected in these countries, the burden of overweight and obesity among them ranges from 10 to 25% and 2 to 10% respectively. The Southeast Asia Middle East, China and Pacific Islands, face the maximum threat[1].

The economical and human burden of obesity is also escalating. The total health care costs attributed to obesity in the developed world is 2 to 7%. In the United States, in the year 2001, the total direct and indirect health care cost of obesity was amounting to be $123 billion. In the Pacific Islands, the economic repercussions of non-communicable diseases, majorly obesity and diabetes is costing $1.95 million in 2004 — almost 60% of the health care budget of Tonga[2]. The world is going to endure a pandemic of Diabetes by 2030 as it is coming up as a global issue in health care that threatens to increase morbidity and mortality by causing complications, diabetic population globally is expected to augment from 171 million in 2000 to 366 million by 2030[3].

Again the under developed countries are going to face the massive increase, where the diabetic population is projected to climb from 84 million to 228 million[4]. International Diabetes Federation in its Atlas 9thEdition ranks Pakistan as the fourth topmost country afflicted with diabetes after China, United States and India. Prevalence of Diabetes in Pakistan is 17.1% and pre-diabetes contributes to 10.9%. Type 2 diabetes mellitus (T2DM) is part of metabolic syndrome demonstrated by insulin resistance and later on insulin depletion resulting inhyperglycemia[5]. It leads to micro and macro-vascular changes, which include retinopathy, nephropathy, neuropathy, cardiovascular disease and cerebrovascular disease. Combined with obesity and hypertension, diabetes is the major cause of death around the world. It is now believed that diabetes and obesity have taken over world hunger as leading health crisis[6]. We aimed to determine the effect of liraglutide on controlling hyperglycemia and evaluate its weight reduction benefits in Asian population.

METHODS

This was a cross sectional study done in a general practice clinic in Clifton and family medicine health care center in Ziauddin University, Karachi. All patients with uncontrolled Type 2 Diabetes, having no prior usage of insulin or liraglutide, aged 15 years and older who were on mono therapy with metformin 2gm b.i.d. and lifestyle modification and who agreed to use liraglutide as add on therapy were recruited in the study. Patients with malignancy and pregnant and lactating women were excluded from the study. Ethics review committee of Ziauddin University Pakistan approved this study.

Sample size was 49 subjects. At the start of the study, HbA1C was done and BMI calculated after taking informed consent. Duration of diabetes, level of physical activity ,dietary habits were determined before and after 12 weeks BMI was evaluated and HbA1c reassessed. Episodes of hypoglycemia and gastrointestinal side effects were evaluated as well. Liraglutide was started on initial dose of 0.6mcg for 1 week, and then dosage was increased to 1.8mg.

Gastrointestinal side effects were evaluated and if bloating, early satiety, diarrhea, nausea or vomiting occurred then they were categorized into mild, moderate and severe. Exercise was assessed by at least 30 minutes of physical activity such as brisk walk, gymming, cycling etc.

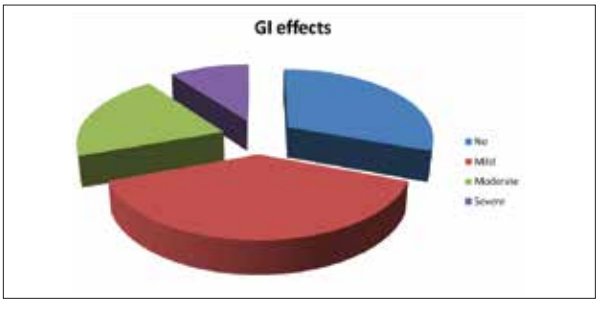
Hypoglycemia was categorized, as either no, single, 3-4 or 5 episodes of fasting blood sugar of less than 60mg/dl. Data was analyzed using SPSS software version 20. Numerical variables were analyzed by frequency and standard deviation. Differences between the variables were analyzed using McNemar's test and p-value <0.05 was considered significant.

RESULTS

Mean age of the participants was 44.4 years. Duration of Diabetes was 65.1months i.e. 5.4 years. Majority participants were females 30(61.2%), rest 19 (38.8%) were males. 28 (57.1%) participants reported to have a regular exercise routine while 21(42.9%) subjects had a sedentary lifestyle. Most patients denied any gastro-intestinal effects. 19(38.8%) reported to have mild GI effects. 15(30.6%) had no GI adverse effects. 10(20.4%) and 5 (10.2%) reported to have moderate and severe GI effects respectively. Majority study population denied any hypoglycemic events 42(85.7%) while 7(14.3%) had 1-2 hypoglycemic episodes (Table 1, Graph 1).

Table 1: Demographic Profile of Study Population.

Characteristics X, (SD)	n (%)
Age in years	44.4 (7.78)
Duration of Diabetes in months	65.1(35.1)
Gender	
Male	19(38.8)
Female	30(61.2)
Exercise	
Yes	28(57.1)
None	21(42.9)
GI effects	
None	15(30.6)
Mild	19(38.8)
Moderate	10(20.4)
Severe	5(10.2)
Hypoglycemic episodes	
0	42(85.7)
1-2	7(14.3)



Graph 1: Pie chart demonstrating the GI effects of Liraglutide on the study population.

Liraglutide with a dose of 1.8mg showed dip in the glycated hemoglobin by 0.94% after the 12 weeks period from 8.5+1.2% to 7.56+1.2% with a p-value of <0.00 being statistically significant. Body mass index

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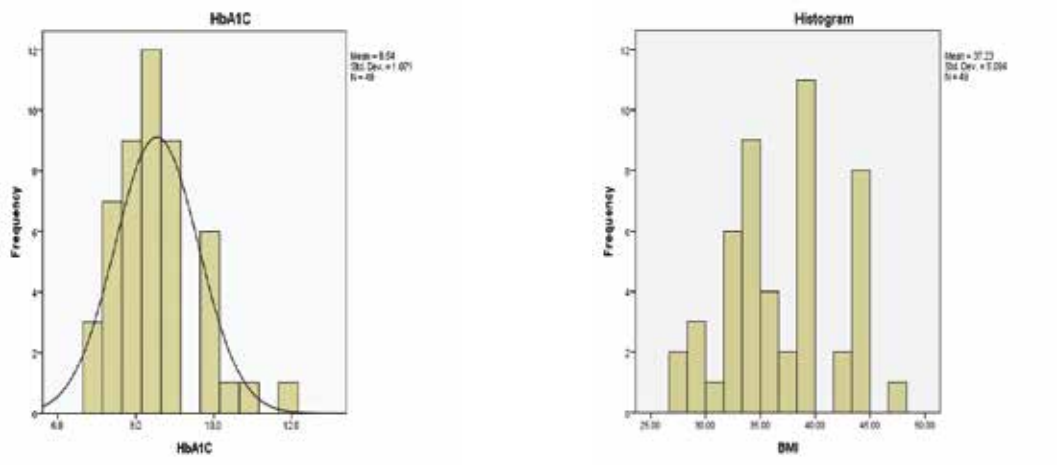
was also reported to decline from 37.23+5.1kg/m2- to 31.27+5.5kg/m2 making a change of 6.2kg/m2 with a p-value of <0.00 i.e. statistically significant (Table 2). Graph 2 showed the comparison in the Histograms in HbA1 C levels pre (0 weeks) and post (12 weeks) Liraglutide.

Table 2: Biochemical parameters at baseline and at the end of week 12 of Liraglutide 1.8 mg.

Variables	X+SD		Change	p-value
	0 weeks	12 weeks		
HbA1C in %	8.5±1.2	7.56±1.2	0.94	<0.00
BMI kg/m²	37.23±5.1	31.27±5.5	6.2	<0.00

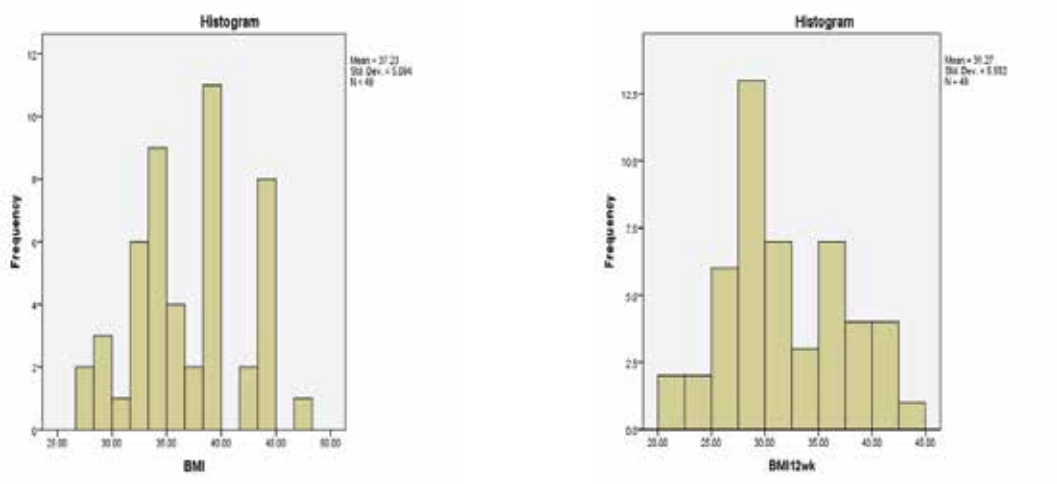
Pre Liraglutide HbA1C **Post Liraglutide HBA1CA**



Graph 2: Histograms showing glycemic control pre (0 wks) and post (12 wks) of Liraglutide.

Graph 3 demonstrated the comparison in Body Mass Index pre (0 weeks) and post (12 weeks) Liraglutide.

Pre Liraglutide BMI **Post Liraglutide BMI**



Graph 3: Histograms showing Body Mass Index pre (0 wks) and post (12 wks) of Liraglutide.

DISCUSSION

In the present study, we concluded that after 12 weeks of Liraglutide (1.8mg), a reduction of 6.2 kg was seen, whereas glycemic control was achieved by 0.64%. Likewise, in a separate randomized control trial, patients with diabetes were given 3 mg liraglutide for 56 weeks. The mean weight loss was noted as 8.7 kg in the test group and 2.6 kg in the placebo group[7].

In similar studies, five randomized, placebo controlled trials of liraglutide for weight management were identified. Liraglutide consistently caused a 4 to 6 kg weight loss, apart from recommended diet and physical activity with a greater proportion of patients achieving at least 5.0 and 10% weight loss compared with placebo[8].

In patients who used liraglutide alongside diet and exercise, over a long-term period of 2 years, the weight loss was noted to be 5.8 kg more than the weight loss in patients who only took a low calorie diet and exercised[9]. Almarshad et al. revealed in his case study that dosage up to 3 mg of Liraglutide, with mild exercise and diet control, showed positive changes in BMI with 13.55% weight loss[10]. This is in consistence with other studies, which demonstrated an average of 8.9- to 13.3-lb (4–6 kg) weight loss followed by yearlong lifestyle modification with the adjunctive usage of Liraglutide[10-12].

The SCALE study found that three groups of people were identified. Group A had baseline weight 105.7 kg and were treated with liraglutide (3.0-mg dose). Group B had baseline weight 105.8 kg and were given liraglutide (1.8-mg dose), whereas group C weighed 106.5 kg and were given placebo. Weight loss was 6.0% (6.4 kg) with liraglutide (3.0-mg dose), 4.7% (5.0 kg) with liraglutide (1.8-mg dose), and 2.0% (2.2 kg) with placebo[13].

A series of recent studies have indicated the weight reducing property of Liraglutide[14-16]. Suzuki et al. analyzed a Japanese patient population with type 2 diabetes mellitus, who did not receive any prior treatment for insulin resistance. They concluded that there was momentous reduction in subcutaneous fat but not visceral fat, with decreased adiponectin levels. This weight-losing property was further postulated to be enhanced by the adjunctive use of insulin and oral anti-diabetics[15]. In 2019, Ahmadi et al. affirmed the above predictions in his study by showing a decrease in both subcutaneous and visceral fat in people with type 2 diabetes mellitus, pretreated with insulin. In addition, there were no significant changes observed in adiponectin levels[16].

In 2002, a study was conducted to see the effect of weight loss by gastric band surgery on the development and prevalence of diabetes. Patients lost up to 27kg, and 1 year after surgery, the prevalence of Type 2 DM was down from 10% to 5.6%, whereas 64% of patients went into remission[17]. For patients who do not require such drastic weight loss, and/or cannot afford surgery, drugs such as the Glucagon like Polypeptide (GLP) 1 receptor agonist, liraglutide have proven beneficial.

Higher adequacy of a drug can be achieved with a greater patient compliance by ensuring patient's contentment. The numerous positive effects pertaining to the use of Liraglutide has increased the quality of life in DM2 patients by reducing the number of hypoglycemic/hyperglycemic events experienced by the patient. Moreover, improvements in fasting blood sugar, HbA1c and body weight have been reported. Such attainments are proposed to boost patient's confidence and commitment towards treatment[18]. Similarly, in our study, a large proportion of the study participants (85.7%) did not report of any hypoglycemic events and reduction in glycated hemoglobin levels were seen by 0.94% at the end of the 12th week of using Lira.

In a Meta Analysis including 3395 participants, it was established that there was marked reduction in body weight for patients using GLP-1 agonists than those in the control group (on placebo, oral anti-diabetics or insulin) which was –2.9 kg, 95% confidence interval –3.6 to –2.2. Moreover, greater number of patients who took GLP-1 agonists had their levels of glycosylated hemoglobin under normal limits (HbA1c <7%) than the control[19]. When added to baseline insulin, without making changes to the pre trial dose of insulin, liraglutide brought down HbA1C by 1.3% vs. 0.1% with placebo. Weight loss and reduction in systolic blood pressure were also noted at 3.0 kg and almost 5 mm Hg in the liraglutide group[20].

In accordance with our findings, Liraglutide has proven to be a novel drug with its high yielding therapeutic effect against obesity with minimum side effects[21]. The effect of liraglutide on glycemic control and body weight has been noted with regard to patients with renal impairment. It indicated no changes in baseline GFR, and only nausea as a significant side effect[22]. In another study, renal effects GLP-1 receptor agonist, Liraglutide, were assessed in obese patients with Type 2 Diabetes Mellitus without chronic kidney disease because of renal hemodynamics, tubular function and markers of renal injury. It was concluded that our drug in question did not influence the glomerular filtration rate; neither did it affect plasma renin concentration and renal hemodynamics[23]. As seen in our study, mild gastrointestinal side effects are common with Liraglutide due to deferred gastric emptying[24]. Consistent with our study, Rai et al. concluded similar findings whereby prohibiting additional doses of Liraglutide in a type 2 diabetic patient with gastroparesis, relieved the symptoms[25].

Recent literature provides substantial evidence that GLP-1 receptor agonists like Liraglutide alleviates the risk of asymptomatic diabetic cardiomyopathy, which is predominant in around 50% diabetics[26]. In a study by Andersen et al., decline in the possibility of cardiovascular diseases have also been demonstrated with the use of Liraglutide[27]. However, severe cardiovascular effects resulting in mortality have been reported with Liraglutide treatment as compared to Glimepiride[28].

We could only recruit 49 subjects. Larger studies with big sample are required to demonstrate the weight loss in Asian population. The high cost of the drug and being an injectable agent are the two major factors that hampers the clinician to use it as effectively as given in the guidelines of American Diabetes Association 2019.

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CONCLUSION

In conclusion, Liraglutide had been found very effective in lowering glycated hemoglobin and BMI. It can therefore, be safely prescribed in obese diabetics. Many studies are underway to combine Liraglutide with long acting insulins because of the potential benefits in correcting hyperglycemia along with neutralizing the weight gain effect of insulin.

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CONFLICT OF INTEREST

There was no conflict of interest among the authors.

ETHICS APPROVAL

Ethics review committee of Ziauddin University Pakistan approved this study.

PATIENTS CONSENT

Verbal and written consent was taken from all patients in this study.

AUTHORS' CONTRIBUTIONS

FJ was involved in the conception, data acquisition, analysis and interpretation as well as manuscript writing and proof reading. NR was involved in manuscript writing and proof reading. FR and TA participated in manuscript writing.

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