Original Article

Liraglutide; A New Hope for Obese Diabetics

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ABSTRACT

OBJECTIVE: To assess the effectiveness of liraglutide in reducing weight and Glycated haemoglobin (HbA1c) in type 2 diabetic patients.

METHODOLOGY: This analytical observational study was conducted at Jinnah medical college hospital Karachi Pakistan. The Convenient sample technique was used for sample collection. Data was collected from January 2018 to April 2019, comprising of 68 patients receiving liraglutide therapy. They were analysed for changes in body weight and HbA1c after 12 and 24 weeks of liraglutide therapy.

RESULT: In patients receiving oral anti-diabetics and liraglutide there was significant reduction in weight at 12 and 24 weeks, while with liraglutide alone weight and HbA1c was reduced at 12 weeks but no further reduction at 24 weeks, same effect was observed in insulin and liraglutide therapy, but in patient receiving insulin, liraglutide and metformin changes were sustained at 24 weeks.

CONCLUSION: Liraglutide is effective therapy for controlling weight and HbA1c especially when given in combination with oral anti-diabetics and insulin.

KEY WORDS: Diabetes mellitus, Obesity, Incretins, Liraglutide, Glucagon like peptides.

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INTRODUCTION

The effective treatment of type 2 diabetes mellitus (T2D) has become a big challenge for physicians, especially in obese/overweight people. After 10 years of diagnosis nearly 75% type 2 diabetics require multiple diabetic medications to manage hyperglycaemia and prevent the risk of developing diabetic complications[1]. Weight gain is the side effect of many oral anti-diabetic drugs (OAD) like sulfonylurea and pioglitazone and insulin, so obese people may face obesity related problems[2]. In recent years, a class of medications has been developed whose actions are based on manipulation of a gut hormones called incretins. The incretin based drugs include Glucagon like peptide 1 Receptor Agonists (GLP 1-RA) increase endogenous insulin, decrease appetite and delay gastric emptying offering good glycaemic control, significant weight loss with minimal risk of hypoglycaemia, moreover Glucagon like peptide 1 RAs has advantage of adding to other oral antidiabetic drugs like metformin and sulfonylureas as well as combination with insulin[3].

American Diabetes Association and the European Association for the Study of Diabetes both recommends that GLP-1 RA can be added, when approximately 3 months of initial treatment with metformin alone has failed to achieve targeted glycosylated haemoglobin (HbA_{1c}) levels, in patients with type 2 diabetes mellitus[4]. Internationally, 6 GLP 1 RAs are available, for treating of Type 2 diabetes: albiglutide (30 or 50 mg once a week), dulaglutide (0.75 or 1.5 mg once a week), exenatide (10 mcg twice daily or 2 mg once a week), liraglutide (1.2 or 1.8 mg once a day),lixisenatide (20 mcg once a day), and semaglutide (0.5 or 1 mg once a week), all can be administered by subcutaneous injections,[5] out of which only liraglutide and dulaglutide is available in Pakistan.

Liraglutide is ainjectable glucagon-like peptide-1 (GLP -1) approved for the treatment of Type 2 diabetes mellitus. It is given subcutaneously once a day. Effectiveness of liraglutide in reducing glycosylated haemoglobin (HbA1c) and body weight in patients with Type 2 Diabetes has been studied in many European countries, largest being Liraglutide Effect and Action in Diabetes (LEAD) study program and data from real-world observational studies have shown significant benefits of liraglutide in reducing body weight and achieving target glycated haemoglobin ($HbA_{1c<7}$)[6-13]. Most of these studies depict data from western population, very few studies shows Asian statistics, so main rationale of our study is observe the effectiveness of liraglutide in Pakistani population, so we designed this study for our hospital. Keeping the primary rationale in mind the aim of the study was to determine the effectiveness of liraglutide in reducing body weight and Glycated haemoglobin (HbA1c) in type 2 diabetic patients, in Jinnah Medical College Hospital Karachi, Pakistan.

METHODOLOGY

It was analytical observational study conducted in

medicine ward and diabetic OPD at Jinnah Medical College Hospital Karachi Pakistan from January 2018 to April 2019. The Convenient sample technique was used for sample collection. Inclusion criteria included diagnosis of type 2 diabetes, aged 30-70 years, receiving liraglutide for at least 15 day, having baseline body weight of >100 kg and HbA1c>7. Exclusion criteria were pregnancy, advanced renal disease (creatinine clearance <50ml/min), having generalized edema, other endocrine disorders (cushings, thyroid dysfunctions), taking systemic steroids or weight reducing drugs and DDP 4 inhibitors (dipepetidyl transferase inhibitors). Diabetes was defined if they fulfilled the ADA (American Diabetes Association) criteria for diagnosis of diabetes mellitus (FBG≥126 mg/dl, RBG ≥200 mg/dl, or HbA1c ≥6.5 %)[14]. HbA1C>7 was considered poorly controlled diabetes. An approval by institutional ethical committee was taken before collecting the data.

The data was collected by trained house physicians under supervision. Before enrolment participants were explained about the details of study and utilization of data and informed consent was taken from all the patients. All the information was recorded on structured questionnaire. The data included age, gender, baseline HbA1C, baseline bodyweight and 5 groups of combination therapies, stated as G 1= monotherapy (only liraglutide), G 2=dual therapy (liraglutide and metformin) and G=3 triple therapy (liraglutide, metformin and pioglitazone/sulfonyl urea). G=4 (insulin plus liraglutide) and G=5(liraglutide plus insulin plus metformin). Follow up HbA1C &weight were recorded at 12- and 24-weeks of therapy. The primary endpoint was change in glycated haemoglobin (HbA1c) and weight. Secondary endpoint was presence of adverse events including hypoglycaemia.

Data was analysed by using SPSS v-23. Age, HbA1c and body weight were quantitative variables presented as mean/SD, while gender and the therapy groups (G1-G5) were qualitative variables presented as frequency/ percentage. Chi–square test was applied. P-Values≤0.05 was considered to be significant.

RESULTS

Out of 68 patients 40(58.8%) were male and 28 (41.1%) were female. Mean age was 56.3±8.8 and mean body weight was 116 kg. Mean HbA1c was 8.2±12.2. 18(26.4 %) were receiving monotherapy (G1=liraglutide), 24 (35.2%) were receiving dual therapy (G2=liraglutide with metformin), 10(14.7%) were on triple therapy (G=3 liraglutide, metformin and sulfonylurea), 8 (11.8%) were on long acting insulin and liraglutide (G=4), 8(11.8%) were on (G=5 liraglutide, metformin and long acting insulin). (Table I) In oral ant diabetic and liraglutide groups i.e; G1, G2, G3, there was significant reduction in weight at 12 and 24 weeks of treatment (Table II), Mean HbA1C was also significantly reduced at 12 and 24 weeks in G2 and G3 group. In G 1 HbA1c was reduced at 12 weeks but no further reduction at 24 weeks. (Table III) In insulin group G 4, there was significant reduction in weight and HbA1c at 12 weeks but no further reduction at 24 weeks (Table IV and V). While in G 5 i.e; people receiving insulin, liraglutide and metformin, weight and HbA1c was significantly reduced both at 12 and 24 weeks (Table IV and V) It is noteworthy to mention that adding metformin to insulin and liraglutide combination had a better response than the combination, which was reflected by low p values (Table V). No major adverse effect noticed especially no hypoglycaemia. Transient mild to moderate gastrointestinal symptoms were experienced by only 3 patients.

TABLE I:
GENERAL CHARACTERISTICS AND VARIABLES

AGE (mean /SD) years	Mean Age (56.3±8.8)
Male n (%) Female n (%)	40(58.8%) 28(41.1%)
Baseline weight (mean/SD)	116± 23
Baseline HbA1c(mean/SD)	8.2±12.2
Type of treatment n (%)	
Monotherapy (Liraglutide alone)	18(26.4%)
Dual therapy (Liraglutide and metformin)	24(35.2%)
Triple therapy (liraglutide, metformin and sulfonyl urea)	10 (14.7%)
Long acting insulin and liraglutide	8(11.7%)
Insulin, liraglutide and metformin	8(11.7%)

TABLE II: CHANGES IN MEAN WEIGHT AT 12 AND 24 WEEKS OF TREATMENT WITH LIRAGLUTIDE AND ORAL ANTI DIABETICS

Type of therapy	Baseline weight(kg)	Weight (12 weeks)	P value	Weight (24 weeks)	P value
G1-Monotherapy	130.6	128.7	0.023	127.4	0.01
G2-Dual therapy	116.2	111.7	< 0.001	105.4	0.003
G3-Triple therapy	107.1	103.2	0.013	98.6	0.013

TABLE III: CHANGES IN MEAN HBA1C AT 12 AND 24 WEEKS OF TREATMENT WITH LIRAGLUTIDE AND ORAL ANTI DIABETICS

Type of therapy	Baseline HbA1c(%)	HbA1C (12 weeks)	P value	HbA1c (24 weeks)	P value
G1- Monotherapy	8.1	7.7	0.002	7.61	0.107
G2- Dual therapy	7.9	7.1	<0.001	6.5	0.001
G3- Triple therapy	8.4	7.7	0.008	7.2	0.002

TABLE IV: CHANGES IN MEAN WEIGHT AT 12 AND 24 WEEKS OF TREATMENT WITH INSULIN AND LIRAGLUTIDE

Type of therapy	Baseline weight(kg)	Weight (12 weeks)	P value	Weight (24 weeks)	P value
G4-Liraglutide+insulin	101	98.4	0.042	97.2	0.061
G5-Liraglutide+insulin+metformin	118	115.1	<0.001	114.1	<0.001

TABLE V: CHANGES IN THE MEAN HBA1C AT 12 AND 24 WEEKS OF TREATMENT WITH LIRAGLUTIDE AND INSULIN

Type of therapy	Baseline HbA1c	HbA1c (12 weeks)	P value	HbA1c (24 weeks)	P value
G4-Liraglutide+insulin	8.5	7.9	0.036	7.7	0.278
G5-Liraglutide+ insulin+metformin	8.4	7.7	<0.0001	7.1	<0.0001

DISCUSSION

Glucagon like peptide receptor agonists acts by increasing insulin secretion from pancreas in response to oral glucose intake and they also suppress glucagon secretion and delays gastric emptying, which reduces appetite. Thus provide good glycaemic control while avoiding hypoglycaemia and weight gain as compared to insulin therapy. As this is a relatively new class of glucose-lowering agents, various questions arise about effectiveness of GLP-RA especially in combination with other available therapies. Least data is available from Asian population, even no studies from Pakistan.

In our study we observed effect of liraglutide on weight and HbA1c. Either alone or with other oral antidiabetics/insulin. When liraglutide was used as monotherapy, it was found to be effective at 12 weeks but no further reduction was observed at 24 weeks follow up. Hemmer A 2019[15] also observed that after one-year HbA1C reduction came to plateau and over period of 4 years this response was maintained in only 1/3 of the patients.

Berkovic MC et al[16] followed the patients with liraglutide monotherapy for 36 months and concluded that sustained reduction in HbA1C was observed in only 50% of the cases.

Fujishima Y et al[17] in a study at Japan also observed that liraglutide produced meaningful long-term weight loss and significantly improved eating behaviours in obese patients with type 2 diabetes.

When compared with oral anti-diabetics we found sustained reduction in weight and HbA1C both at 12 and 24 weeks. In The Scale trial Davies MJ et al[18] also observed that, in addition to clinically relevant weight loss, liraglutide may offer better glycemic control while reducing dose of oral hypoglycemic agents and maintaining a low risk of hypoglycemia. Blonde et al in LEAD-1 trials have demonstrated the efficacy of lirglutide in combination therapy with up to two oral anti-diabetics. Liraglutide provided HbA1c reductions of up to 1.6% across the LEAD 1 to LEAD 5 trials. Moreover improvements in beta cell function was also noted with lower risk of hypoglycemia and in contrast to many other antidiabetic therapies. Reduction in weight and systolicblood pressure was also noted[19]. Ghosal S 2018[20] and Kaur P et al[21] conducted study in India and found similar results.

When liraglutide was added to long acting insulin there was significant change in weight and HbA1C at 12 weeks but no further reduction at 24 weeks. This observation was contradictory to other studies[22-24]. This observation might because of shorter follow up of our patients and use of basal insulin, since other studies used basal-bolus combination hence achieved better and prolong glycemic control but at the cost of more chances of hypoglycemia as compared to our studies[25,26], so Li CJ et al[26] had to decrease the dose

of required insulin, their observation was quite fascinating that adding liraglutide to patients already on insulin therapy especially basal –bolus combination therapy require lesser dose of insulin, thus further decrease the chances of weight gain.

Regarding side effects of liraglutide, there was no event of hypoglycaemia in our study, which might be because of the fact that we only used basal insulin while other studies used basal-bolus combination, had increased risk of hypoglycemia[25,26]. That's why this idea has given rise to fixed dose combination of long acting insulin degludec and liraglutide.

CONCLUSION

Liraglutide is an effective option for controlling body weight and HbA1C in patients with sub-optimal response to insulin therapy and oral hypoglycaemics as compared to monotherapy with liraglutide. In future, studies are required with longer follow-ups to establish long term efficacy and side effects.

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AUTHOR CONTRIBUTIONS

Kumar A: Concept, idea, study design
Kumar D: Concept, study protocol
Razzaque S: Data analysis, manuscript writing
Kumar A: Data collection, data analysis
Kumar R: Data collection
Ghauri MI: Editing, overall supervision
Yaseen M: Help in data collection, analysis, referencing

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