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Influence of Liraglutide Alone and in Combination With Glimepiride on Body Weight in Obese-Diabetic Rabbits

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The objective of the study was to identify the influence of Liraglutide alone and in combination with Glimepiride on body weight in obese diabetic rabbits. Obesity was produced in rabbits with HFD (High fat diet) given for 10 weeks and diabetes was induced with dithizone (5 mg/kg i.p.). Liraglutide decreased the body weight in obese-diabetic rabbits significantly ($p<0.05$). However, decrease in body weight with the combination of liraglutide and glimepiride was not significant ($p>0.05$). It is concluded that Liraglutide alone and not in combination with glimepiride is effective in reducing the body weight of obese diabetic rabbits.

Keyword: Liraglutide, Glimepiride, Body Weight, Obese Diabetic Rabbits

1. Introduction

The incidence of obesity rises rapidly in association with type 2 diabetes mellitus which may be linked to a switch towards a more affluent life style [1]. Thus the increasing prevalence of type 2 diabetes mellitus along with obesity represents one of the major health-economic challenges of the 21st century[2]. Obesity is a multifactorial disease that arises as a result of interaction among numerous behavioural, environmental, genetic factors and associated with dysregulation of energy homeostasis. The close link between overweight, obesity and the development of diabetes mellitus is well documented. Moreover it has been observed that majority of individuals with type 2 diabetes are overweight or obese at the time of diagnosis [3]. The conventional treatment to reduce body weight in obese-diabetics is unsatisfactory. GLP-1 has potential to be harnessed as a type 2 diabetes treatment that lowers blood glucose, decreases gastric emptying rate and appetite. These properties of GLP-1 are most desirable to be given in type 2 diabetes with obesity and in obesity associated with insulin resistance[4]. Liraglutide, a GLP-1 analogue in combination with oral hypoglycemic drugs is effective in controlling hyperglycemia in type 2 diabetes and is also helpful in reducing body weight in obesity without diabetes [5]. Liraglutide has shown reduction of blood glucose with a low risk of hypoglycaemia and a concomitant decrease in body weight [8]. It decreases gastric emptying rate and appetite that are therapeutically desirable to be given in patients of obese diabetes with insulin resistance [7, 8]. Most conventional medications for type 2 diabetes are associated with weight gain and/or hypoglycaemia, which pose significant barriers to treatment intensification [9]. Liraglutide has the potential to overcome these limitations and acquire an important role not only in the treatment of type 2 diabetes but also in

preservation of β-cell function, weight loss and prevention of chronic diabetic complications [10]. Glimepiride, a second generation sulfonylurea has been available for over a decade in the treatment of type 2 diabetes. Its convenient dosing schedule has led to its widespread use and appears to be a useful treatment option for diabetic patients who do not achieve recommended glycaemic control with lifestyle modifications [11, 12]. The purpose of our study was to see the effect of Liraglutide alone and in combination with Glimepiride on body weight in obese-diabetic rabbits. The limited studies with respect to the response of liraglutide on body weight in obesity associated with diabetes triggered us to take up this study to find out the influence of these drugs on body weight.

2.Material And Methods

2.1 Animals

The study was conducted in New Zealand white adult rabbits weighing approximately 2-2.5 kg of either sex which were housed individually in standard cages at natural light/dark condition and room temperature maintained at 26±2 °C. The animals were obtained from Lala Lajpat Rai University of Veterinary & Animal Sciences, Hisar. They were provided with food and water ad libitum. The animals were acclimatized to the laboratory conditions for at least 7 days prior to the experiments. After a week of acclimation period, the animals were fed with standard rabbit's chow having composition of all dietary elements appropriate for maintaining normal rabbit [15]. The experimental protocols were approved by the Institutional Animal Ethics Committee (IAEC), Pt. Bhagwat Dayal Sharma, Post Graduate Institute of Medical Sciences, Rohtak.

2.2 Experimental Obesity

To induce obesity, the rabbits were given high fat diet (HFD) constituting 10% fat (2/3 corn oil and 1/3 animal lard) to a standard normal rabbit chow for 10 weeks [14]. Food consumption by rabbits was measured for a period of 24 hours daily at a fixed time of the day. Weekly body weight was recorded throughout the period of 10 weeks. The skin fold thickness (SFT) lateral to umbilicus, measured in mm was recorded. The rabbits were considered obese which showed approximately 25% gain in body weight and 37% increase in skin fold thickness (SFT) at the end of 10 weeks of high fat diet intake [13].

2.3 Experimental Diabetes

To induce diabetes, the rabbits were given single injection of dithizone 5mg/kg body weight intraperitonealy. Seventy-two hours was allowed for full development of diabetes [15]. Rabbits showing blood glucose levels ≥ 250 mg/dl were considered diabetic.

2.4 Body Weight And Sft Measururement

Body weight was measured before and after pretreatment and weekly for three weeks, and at the end of treatment. The body weight was recorded using a standard animal weighing machine and skin fold thickness (SFT) was measured with the help of vernier caliper.

2.5 Drugs And Chemicals

Liraglutide was purchased from Novo Nordisk, India Pvt. Limited, Bengaluru and was used in doses of 7µg/kg, s.c. Glimepiride obtained from Med Care Remedies Pvt. Ltd, Una, Himachal Pradesh and was used in doses of 2mg/rabbit/oral [16]. Dithizone was purchased from Keminova India chemicals Pvt. Ltd. Thane, Mumbai and was used in doses of 5mg/kg, i.p. for inducing diabetes [15]. Rabbit chow and HFD was purchased from the market.

2.5 Experimental Design And Protocol

The obese diabetic rabbits were divided into following four groups containing 6 rabbits in each to receive various treatments as follows:

Group 1: Rabbits received vehicles of inj. Liraglutide and /or Glimepiride daily for 3 weeks.

Group 2: Rabbits received inj. Liraglutide 7µg/kg/daily s.c. for 3 weeks.

Group 3: Rabbits received Glimepiride 2mg /Rabbit/daily orally for 3 weeks.

Group 4: Rabbits received inj. Liraglutide 7µg/kg/daily s.c. and Glimepiride 2mg /Rabbit/daily orally for 3 weeks.

2.7 Statistical Analysis

The data was collected from various study groups and expressed as Mean ± Standard Error of Mean (m ± SEM). The data were analyzed using Repeated Measures Analysis Of Variance (RM-ANOVA) with Bonferroni's correction. P value less than 0.05 was considered to be statistically significant. All statistical calculations were performed with SPSS software package.

3. Results

3.1 Effect of Liraglutide alone and in combination with Glimepiride on body weight in obese-diabetic rabbits

Liraglutide (7µg/kg/day, s.c.) decreased the body weight from 2.85±0.01 to 2.55±0.02 kg at the end of treatment significantly ($p<0.05$). The weight loss that occurred with liraglutide over a period of time is depicted in figure 1.

The combination of Liraglutide and Glimepiride decreased the body weight from 2.85±0.01 to 2.74±0.02 kg at the end of treatment. However, the decrease in body weight with this combination of drugs in all these rabbits was not significant ($p>0.05$) as shown in figure 1.

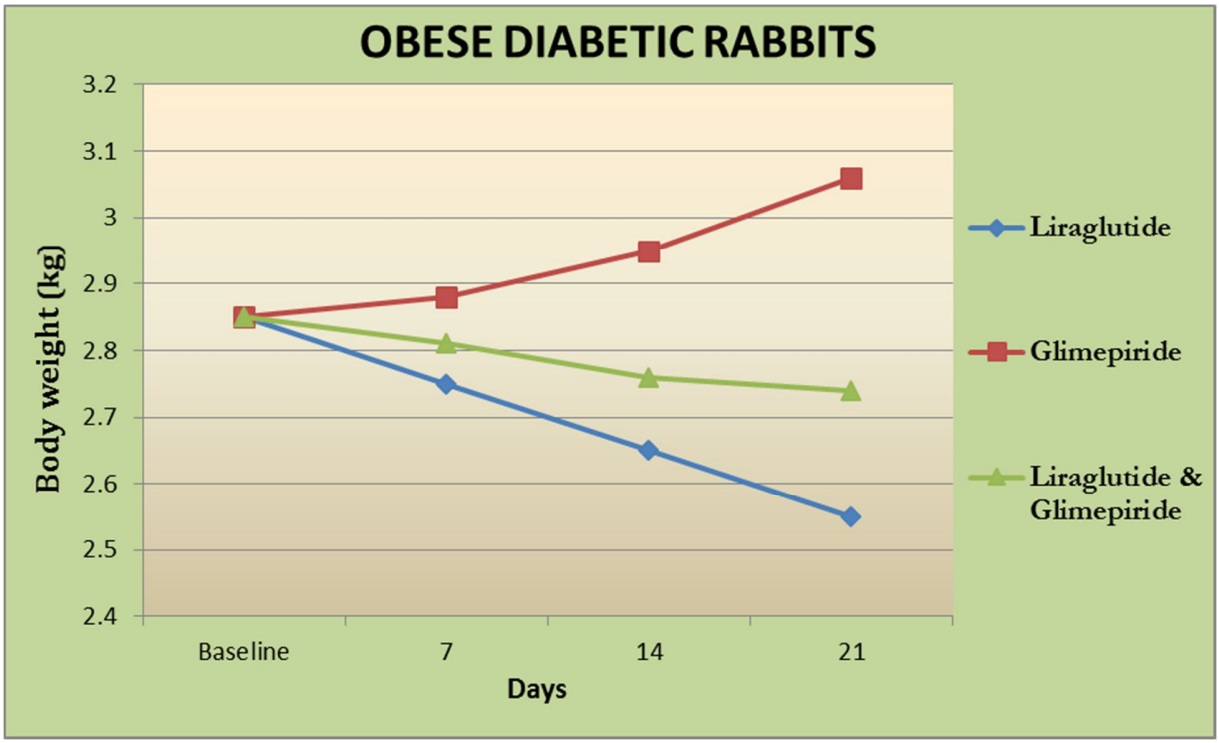

Fig 1: Effect of various drugs on body weight at different time intervals

3.2 The percentage (%) change in body weight

In obese diabetic rabbits the reduction in body weight with liraglutide and in combination with glimepiride was 10.5% and 3.8% respectively. However, with glimepiride the body weight was increased by 7.3%. Furthermore, the vehicle treated control group did not show any significant change. Hence the weight loss that occurred with liraglutide is more compared to its combination with glimepiride as shown in figure 2.

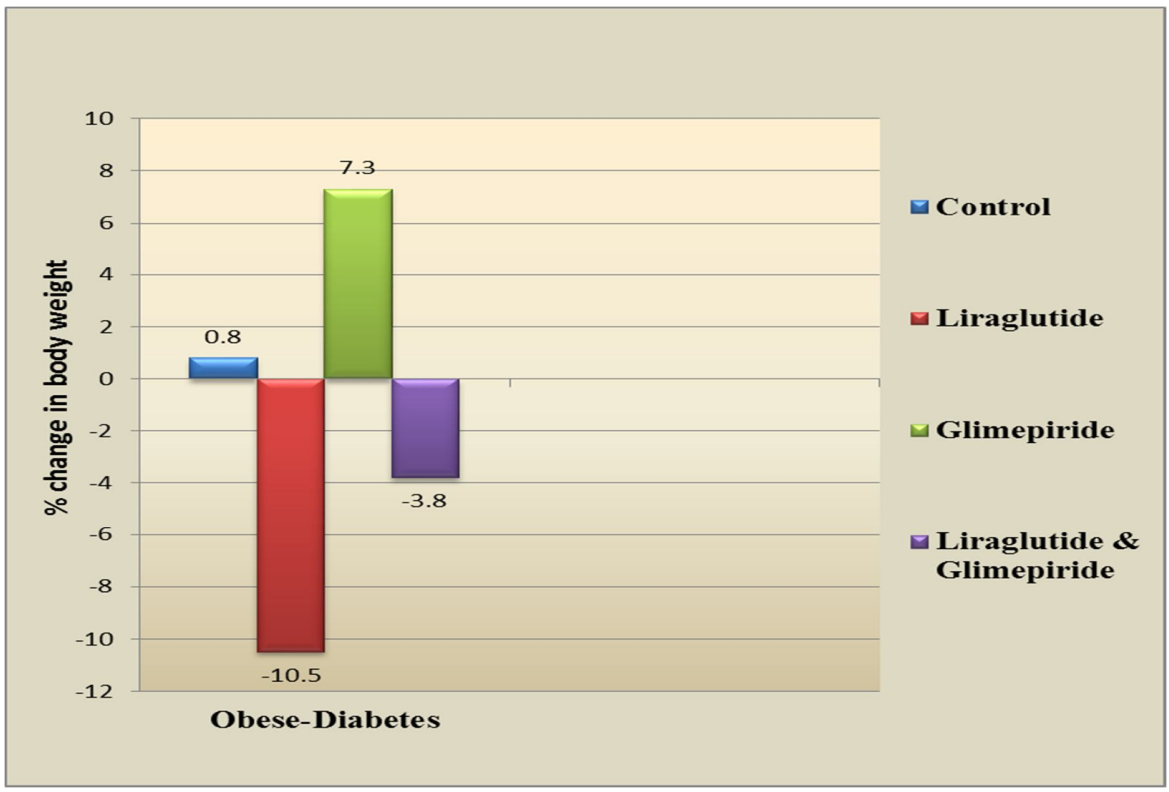

Fig 2: Effect of drugs on Body weight in obese diabetic rabbit

4. Discussion

Liraglutide is a novel human GLP-1analogue approved for treatment of type 2 diabetes mellitus. It is effective in reducing body weight, decreasing visceral fat and improving lipid profile as well as other cardio vascular risk markers [17]. In our study, liraglutide decreased the body weight in all the obese-diabetic rabbits markedly. Whereas glimepiride increased the body weight. Hyperglycaemia in obese-diabetic was significantly decreased with liraglutide and glimepiride individually as well as in combination. All though the combination of liraglutide and glimepiride decreased the body weight in obese-diabetic rabbits to some extent but it was not significant ($p>0.05$). Studies done by others observed that liraglutide had many predicted therapeutic properties including blood glucose lowering efficacy with a low risk of hypoglycaemia and a concomitant decrease in body weight [5, 6]. The possible reasons for decreasing body weight with liraglutide in our study may be attributed to the effects of

liraglutide including delay in gastric emptying, promoting satiety and decreasing food intake. This is probably related to the combined effect of liraglutide on the gastrointestinal tract and brain, leading to decreased food intake and simultaneously weight reduction. Liraglutide in combination with glimepiride could not exert its complete effect on body weight. The probable reason could be attributed to the effect of glimepiride which has the tendency to cause weight gain and thus counteracted the effect of liraglutide to some extent. Our observations support the findings of the effect of liraglutide and glimepiride on body weight demonstrated in the studies conducted by Vilsboll *et al.* [6]. and Nauck *et al.* [18]. Vilsboll *et al.* compared subcutaneous liraglutide once daily with oral glimepiride 8 mg once daily in 746 subjects of type 2 diabetes, body weight fell by 2 kg with 1.2

mg and 2.5 kg with 1.8 mg of liraglutide, but increased by 1.1 kg with glimepiride group. In the other study conducted by Nauck *et al.* compared addition of liraglutide to glimepiride or placebo on a base of metformin, liraglutide 0.6 mg showed a 2.8 kg difference, liraglutide1.2 mg had a 3.6 kg difference and liraglutide 1.8 mg had 3.8 kg difference with respect to glimepiride. All these differences were significant ($P<0.01$).

5. Conclusion

Liraglutide alone reduced the body weight in all the obese-diabetic rabbits significantly. The body weight was also reduced even with the combination of Liraglutide and glimepiride but it was not statistically significant. This study was conducted only for 3 weeks duration and requires more and long term studies to establish the clinical efficacy of liraglutide in management of obese-diabetic patients. Hence Liraglutide alone but not in combination with glimepiride become the choice for reduction of the body weight in obese diabetics.

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