Liraglutide as Additional Treatment in Type 1 Diabetes

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ABSTRACT

Objective. To determine whether the addition of liraglutide to insulin in patients with type 1 diabetes leads to an improvement in glycemic control and diminished glycemic variability.

Subjects and Methods. Fourteen patients with well controlled type1 diabetes on continuous glucose monitoring and intensive insulin therapy were treated with liraglutide for one week. 8 patients continued therapy for 24 weeks.

Results. In all fourteen patients, mean fasting and mean weekly glucose concentrations decreased significantly after one week from 130 ±10 mg/dl to 110± 8 mg/dl (p <0.01) and from 137.5±20 to 115±12 mg/dl (p < 0.01) respectively. Glycemic excursions also improved significantly at one week. The mean S.D. of glucose concentrations decreased from 56±10 to 26±6 mg/dl (p<0.01) and the CV decreased from 39.6±10 to 22.6±7 (p<0.01). There was a concomitant fall in the basal insulin from 24.5±6 units to 16.5± 6 units (p<0.01) and of bolus insulin from 22.5±4 units to 15.5± 4 units (p<0.01).

In patients who continued therapy with liraglutide for 24 weeks, mean fasting, mean weekly glucose concentrations, glycemic excursions, basal and bolus insulin dose also decreased significantly (p<0.01). HbA1c decreased significantly at 24 weeks from 6.5% to 6.1% (p=0.02), as did the body weight by 4.5±1.5 Kg (p=0.02).

Conclusion. Liraglutide treatment provides an additional strategy for improving glycemic control in type 1 diabetes. It also leads to weight loss.

Introduction

Since the landmark discovery of insulin by Banting and Best in 1921(1), advances in treatment of type 1 diabetes have centered on preparations of insulin with different rates of absorption from the subcutaneous tissue either through the addition of other proteins like protamine or the creation of analogs of human insulin(2). These modifications led to the availability of insulin preparations which have either prolonged bio-availability or a more rapid absorption than human insulin. In addition, the continuous subcutaneous infusion of insulin with the use of pumps has contributed to a more predictable absorption and bio-availability of insulin and thus an improved glucose homeostasis(3). Frequent or continuous glucose monitoring may also contribute to an improvement in glycemic control(3).

Since an adequate control of glucose homeostasis in patients with type 1 diabetes still continues to be a major challenge, novel means to improve it are required. The arrival of GLP-1(glucagon-like peptide-1) analogs and receptor agonists has not only provided a novel way of controlling hyperglycemia in type 2 diabetics, the elucidation of the mechanism involved in their action has also facilitated the understanding of mechanisms involved in the pathogenesis of post prandial hyperglycemia(4, 5). In patients with type 2 diabetes, it has been shown that an increase in glucagon concentrations post prandially contributes to hyperglycemia as hyperglucagonemia results in increased hepatic glucose production (5)7. Normally, the post prandial increase in insulin secretion by the β-cell leads to the suppression of glucagon secretion by the α-cell through paracrine mechanisms (6). The sensitivity of alpha cells to insulin is maintained in patients with type 2 diabetes(7). However; hyperglucagonemia occurs possibly due to inadequate post prandial secretion of insulin, or as a result of a possible glucotoxic effect of hyperglycemia on alpha cell function(6,8) .It is possible that a similar pathophysiological disturbance occurs in type1 diabetes since the lack of insulin secretion by the β-cell is more severe.

One study showed that native GLP-1 improves postprandial hyperglycemia in type 1 diabetics, possibly by the suppression of glucagon (9). Another study demonstrated reduction in postprandial glucose after a single exenatide injection in adolescents with type 1 diabetes (10). In view of this and the need of an additional therapeutic strategy in type 1 diabetics, we hypothesized that the use of a GLP-1 analog, liraglutide may help in controlling hyperglycemia and the oscillations in glucose concentrations in this condition. This study describes our experience in 14 patients with type 1 diabetes who were given liraglutide.

Subjects and Methods

This study was conducted at Diabetes-Endocrinology Center of Western New York at the State University of New York at Buffalo. Fourteen patients (9 males and 5 females) with type 1 diabetes (plasma C-peptide concentrations of <0.10 nmol/liter; positive GAD antibodies) on continuous subcutaneous insulin infusion (CSII, n=13) or multiple (four or more) injections of insulin per day (n=1) and using a continuous glucose monitoring device (CGM) were included in the study. All patients who agreed to try liraglutide were included in the study. They were all required to be on a continuous glucose monitoring device. Eight patients were on CGM as a part of their long term management while six others were provided with a CGM for three weeks for the study.

Age of subjects ranged from 25–52 yr (mean: 39.5±4.8 yr), their body mass index (BMI) from 19.5–29.9 kg/m^2 (mean: 24.0 ± 2.0 kg/m^2) and the duration of diabetes from 12–46 yr (mean: 24 ± 4

years). The insulin doses ranged from 12–54 U/d (24.5 ± 6 U/d) for the basal and from 14–59 U/d (22.5 ± 5

U/d) for the meal time (bolus). The mean HbA1c was 6.6±0.5%.

All the patients were well versed with carbohydrate counting and self adjustments of insulin dose on the basis of carbohydrate intake and blood glucose. However, all patients were asked to try

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and further improve their glycemic control by paying a greater attention to their blood glucose concentrations, dietary intake, carbohydrate counting, adjustment of insulin dose and the regularization of exercise. Intensification of control was attempted as part of a regular clinic follow up visit to target preprandial glucose of 80-120mg/dl and 2 hr post prandial glucose of <140 mg/dl and minimize hyperglycemic excursions in order to achieve a mean blood glucose of < 130mg/dl .

As a result of the intensification prior to the administration of liraglutide, there were small increases in the basal insulin dose and in insulin boluses, reductions in carbohydrate intake and the regularization of exercise. There was no increase in the frequency of hypoglycemic (BG < 60mg/dl) episodes.

All patients were instructed to inject 0.6 mg liraglutide subcutaneously daily for 1 week. Patients were asked to reduce their basal insulin by 25% and bolus by 33% of their usual dose at the start of liraglutide treatment to avoid hypoglycemia. This reduction was decided after our initial experience with 2 patients, in whom a reduction of 10% each for basal and bolus doses had resulted in hypoglycemia. HbA1c was measured within 1-3 weeks prior to starting liraglutide therapy.

CGM data on all patients were collected one week prior to treatment with liraglutide (after the patients had intensified their glucose control and were on stable dose of insulin), and for one week on liraglutide after a stable dose of insulin had been achieved following the initiation of liraglutide therapy. It took an average of 3±1 days to achieve stable insulin doses. In 6 out of 14 subjects, liraglutide (0.6 mg daily) was discontinued after one week since subjects were not able to continue CGM due to cost. In these subjects, CGM was continued for one week after the cessation of treatment. Eight out of 14 patients continued liraglutide for a mean duration of 24 weeks. In these patients, the dose of liraglutide was increased to 1.2 mg daily after one week and subsequently to 1.8 mg daily after 2 weeks. Patients who discontinued liraglutide were allowed to adjust their insulin doses upwards as appropriate immediately after the cessation of liraglutide.

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Patients continuing on liraglutide for the longer duration were allowed to reduce their insulin doses further as appropriate during the course of their treatment under our guidance.

All subjects were advised about the possibility of hypoglycemia and the suppression of appetite after the addition of liraglutide and were provided guidance about expected changes in insulin dose after the initiation of liraglutide. Patients were informed about side effects of liraglutide including nausea and vomiting. They were asked to contact the physician on call if they had any side effects. The side effects were evaluated at each visit. An approval was obtained for the retrospective review of the data from the patients' case records from the Human Research Committee of the State University of New York at Buffalo.

Statistical Analysis:

Data are presented as means ± S.D (standard deviation). Paired *t*-tests were used to compare the change in insulin doses, weight and fasting and weekly mean blood glucose concentrations prior to and after liraglutide. To evaluate the oscillations in glucose concentrations, SD and co-efficient of variation (CV) of the mean weekly blood glucose concentration of each patient were also compared using paired t-test. $p < 0.05$ was considered significant. SPSS software (SPSS Inc, Chicago, Illinois) was used for analysis.

Results

CGM data from patients prior to liraglutide treatment are presented in Table 1. They show that there was no significant change in the mean fasting and weekly glucose concentrations, SD and co-efficient of variation (CV%) of weekly mean glucose concentration, and insulin doses before and after intensification of efforts to improve glycemic control.

Effect of liraglutide on glycemic indices at 1 week

Fasting mean glucose concentrations fell significantly within 24 hrs and mean glucose concentrations fell significantly within 48 hrs (figure 2) after the institution of liraglutide. During

one week of therapy with liraglutide in all 14 patients, the mean fasting glucose concentrations and weekly mean glucose concentrations decreased significantly (p<0.01) (Table 2 and figure 4). The mean S.D. of glucose concentrations decreased from 56±10 to 26±6 mg/dl (p<0.01) and the CV from 39.6±10% to 22.6±7% (p<0.01) .The duration of time spent at a glucose concentration of >150 mg/dl, >200 mg/dl and >250 mg/dl decreased significantly (p for all< 0.05). There was a concomitant fall in the basal insulin (p<0.05) and bolus insulin doses (p<0.05) within one week (Table 2 and figure 1).

In the 6 patients who stopped liraglutide after one week, the insulin requirements increased and returned to baseline at the end of the one week of withdrawal of liraglutide. The mean fasting blood glucose increased to 130±10 mg/dl and the mean weekly blood glucose concentration, increased to 143±18 mg/dl while the mean weekly SD of glucose concentration increased to 56±8 mg/dl. These values were almost identical to those prior to treatment (table 3 and Figure 5).

The effect of liraglutide on glycemic indices at 24 weeks

In the 8 patients who continued on liraglutide for a mean duration of 24 weeks, the mean fasting glucose fell significantly (p<0.05) and the weekly mean glucose fell significantly (p<0.01) (table 4). The S.D. of mean glucose concentration, CV, the time spent at >250 mg/dl, >200 mg/dl, and >150 mg/dl in these patients decreased significantly. (P< 0.01) (table 4). The mean HbA1c fell significantly from 6.5% to 6.1%. There was a reduction in the total daily insulin dose from 0.65 U/Kg to 0.47 U/Kg (p <0.05).

The effect of liraglutide on body weight

There was a mean fall in body weight of 0.5±0.2 Kg at 1 week for all 14 patients. This was not significant. For those patients who continued Liraglutide for a mean duration of 24 weeks, the body weight fell by 4.5±1.5 Kg (p=0.02) (figure 3). The weight loss was maximal in the first 12 weeks of starting treatment, 3.5±1.5 kg; it was 1.0±0.5 kg in the next 12 weeks. The decrease in

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weight was not related to the change in HbA1c (r=0.27, P=0.18). The patients reported a reduction in appetite with a concomitant reduction in food intake following liraglutide. Unfortunately, we do not have records of their dietary intake.

The effect of liraglutide on hypoglycemic episodes

There was no significant increase in the duration of hypoglycemia following liraglutide treatment in all 14 patients: time spent at <70 mg/dl and time spent at <40 mg/dl (see table 2). In patients on liraglutide for 24 weeks, the time spent at <70 mg/dl and <40 mg/dl prior to liraglutide and after liraglutide was not significant. Approximately 75% of recorded hypoglycemia was nocturnal at both (<70 and <40 mg/dl) blood glucose levels. Perceived hypoglycemia was reported more frequently early after the initiation of liraglutide but it diminished with further appropriate reductions in the insulin dose. There was no severe hypoglycemic episode requiring intervention by others.

The effect of liraglutide on C-peptide

Fasting C-peptide concentrations were measured in 8 patients after 24 weeks of treatment. They were still undetectable (<0.10 nmol/L). Two patients experienced nausea, constipation and headache after starting liraglutide but all the side effects resolved after 2-3 days of treatment.

Discussion

Our data show that the mean fasting glucose and the mean weekly glucose concentrations and the time spent with hyperglycemia decreased after the addition of liraglutide in spite of the reduction in the dose of insulin in subjects with type 1 diabetes. The oscillations of blood glucose concentrations also diminished significantly as reflected in the reduction in mean SD and CV of blood glucose concentrations. As visualized in the figures, both the peaks and troughs of glucose concentrations diminished. In association with these improvements, there was a marked reduction in the dose of insulin required and a simultaneous reduction in body weight. Those patients in

whom liraglutide was discontinued, the original doses of insulin had to be restored and the glycemic excursions observed prior to liraglutide also returned.

These improvements were observed within 1-2 days of the initiation of liraglutide and they reversed within a similar period after the discontinuation of the drug. The rapid return of the glucose concentrations, the SDs and the insulin doses to pre-liraglutide levels also indicate that they have most likely occurred as a result of the effects of treatment with lirgalutide. Furthermore, since the improvement in glycemic control occurred within one week, this improvement cannot be attributed to the weight loss that followed. Even though the intensification of treatment regimen prior to starting liraglutide may have contributed to beta cell rest and glycemic control in itself, data obtained from CGM following the intensification regimen still showed significant oscillations in glucose concentration which improved significantly following initiation of treatment with liraglutide.

Those patients in whom the treatment with liraglutide was continued, the improvement in the glycemic pattern was persistent. Although there was no further improvement either in the glucose concentrations or in SDs following longer period of treatment, there was a further reduction in insulin dose. The reductions in carbohydrate and food intake and body weight following liraglutide may have contributed to this.

These observations raise questions about the mechanisms underlying such rapid changes in glucose homeostasis following liraglutide in type 1 diabetics. The first possibility is that liraglutide may have suppressed the increase in glucagon concentration after meals(11). The near total absence of β-cell function in type 1 diabetics would suggest that there is no inhibition of glucagon secretion post prandially through the local paracrine inhibitory effect of insulin. Therefore, it is likely that there is a significant increase in glucagon secretion in these patients after meals. It is possible that liraglutide suppresses this. There are recent data demonstrating that GLP-1 infusion induces a significant suppression of the basal and arginine induced increase in the plasma concentration of glucagon in type 1 diabetics(12).

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Another mechanism to explain the reduction in the duration of hyperglycemia could be the decrease in post prandial glucose excursion due to the slowing of gastric emptying, which is known to occur with liraglutide (11). However, this does not explain the lowering of fasting glucose in these subjects.

Although patients with long standing type 1 diabetes do not have significant insulin secretion, it has been shown that they have a significant β-cell population which is not fully differentiated(13-15). It is possible that long term treatment may facilitate full differentiation of these cells and restore some insulin secretion. This potential mechanism is probably not relevant following the short term treatment described here, especially since there was no significant change in fasting C-peptide concentration after liraglutide treatment. The study on the effect of exenatide in type 1 diabetics by Rother et al demonstrated an increase in insulin secretion over a period of several months but this was not considered to be clinically significant(16).

The weight loss and the associated suppression of appetite even over the short period of treatment are of interest. Liraglutide is known to exert an appetite suppressive effect(11). This effect of liraglutide is important since 40-50% of patients with type 1 diabetes in the US concomitantly have the metabolic syndrome(17). 30% of patients with type 1 diabetes in Diabetes Control and Complications Trial (DCCT)/ Epidemiology of Diabetes Interventions and Complications (EDIC) trial were obese at 12 years of follow-up (18). A similarly high proportion of children (30%) with type 1 diabetes are either overweight or obese (19). The suppression of appetite by liraglutide may have also contributed to the improved glycemic control and the continued reduction in the dose of insulin required. However, weight loss was not necessary for the reduction in insulin dose since the latter occurred within the first two days of the initiation of liraglutide therapy. The reduction in body weight has implications in terms of cardiovascular complications. In addition, liraglutide has been shown to reduce systolic blood pressure like exenatide. This may also potentially help in the reduction of cardiovascular outcomes (20-24).

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The major weakness of this study is that it was not placebo controlled and not carried out double blind. However this study provides the initial proof of principle on the basis of which future double blind crossover studies need to be carried out to confirm the findings reported in this study. The other limitation of this study is that we cannot generalize our observations to all patients with type 1 diabetes since the patients included in this series were well controlled, based on their HbA1c, meticulous and disciplined who improved significantly following this treatment.

In conclusion, the addition of liraglutide to insulin therapy in well controlled type 1 diabetics resulted in a significant and rapid reduction in glycemic excursions with a concomitant reduction in insulin dose. These glycemic effects were rapidly reversed after the cessation of liraglutide treatment. There was also a reduction in appetite and food intake. Body weight fell significantly in the group followed up for 24 weeks. These observations warrant a detailed investigation into the efficacy of liraglutide and other GLP-1 agonists in the treatment of type1 diabetes and the pathophysiological mechanisms underlying these effects, including prospective randomized double blind trials.

Author Contributions: AV – planning, execution, writing; NB – hypothesis, planning; MV – execution; DR – execution; SD – statistical analysis, interpretation; AM – statistical analysis, interpretation; AC – interpretation, writing; PD – hypothesis, interpretation, writing.

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Legends

Table 1: Results of patients (n=14) one week prior and one week during which they attempted to improve their diabetic control with further intensification of treatment by controlling their diets and adjusting their insulin doses. Note that there was no significant change in any of the indices.

Table2: Effects of liraglutide treatment for one week on 14 patients

Table 3: Results of patients (n=6) one week prior, one week during and one after stopping Liraglutide. Note that there was a reversal of all characteristics to baseline.

Table 4: Effects of liraglutide treatment for mean duration of 24 weeks in 8 patients.

Figure 1: The change in insulin dose over seven- day duration in 14 patients treated with liraglutide for one week.

Open circles: bolus insulin

Closed circles: basal insulin

Figure 2: The change in Mean blood glucose, Fasting blood glucose and Standard Deviation (SD) values at 0, 1, 2, 4 and 7 days in 14 patients who were treated with liraglutide for one week .

Open circles: Mean blood glucose (mg/dl)

Closed circles: Mean Fasting blood glucose (mg/dl)

Closed triangles: Mean Standard deviation (mg/dl)

Figure 3: The change in weight of 8 patients who continued liraglutide for 24 weeks at 0,1,12 and 24 weeks.*p<0.05 as compared to baseline.

Figure 4: Weekly continuous glucose monitoring record (Dexcom) of one patient prior to (panel 1a, 1b) and following liraglutide (panel 2a, 2b). Note the glycemic variability and the frequency of glucose concentrations within the target range prior to and following liraglutide

Figure 5: Weekly continuous glucose monitoring record (Medtronic) on one patient prior to, during and after liraglutide treatment. Note the glycemic variability and the frequency of glucose concentrations within the target range prior to (panel 1), during (panel 2) and following (panel 3) liraglutide

Figure 1
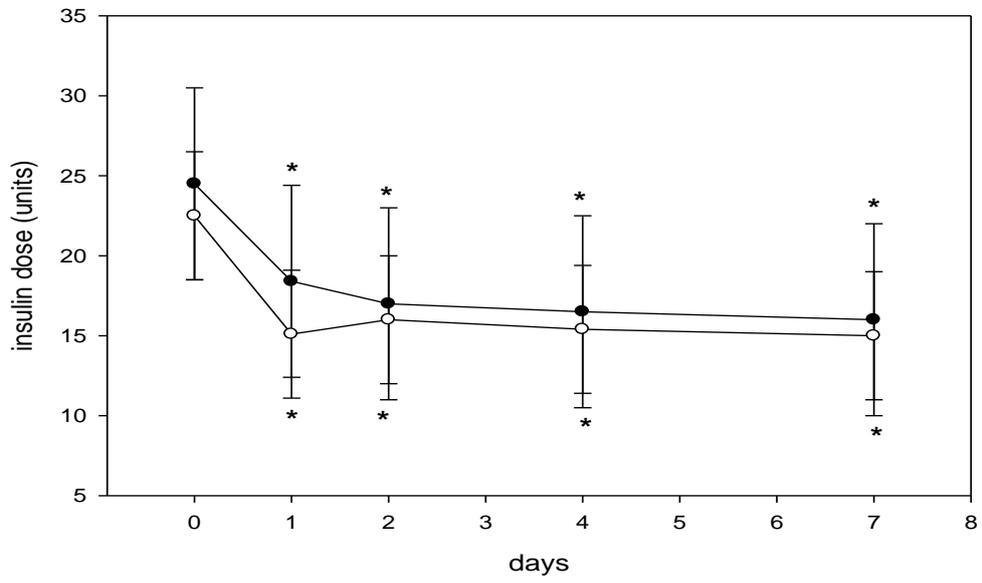
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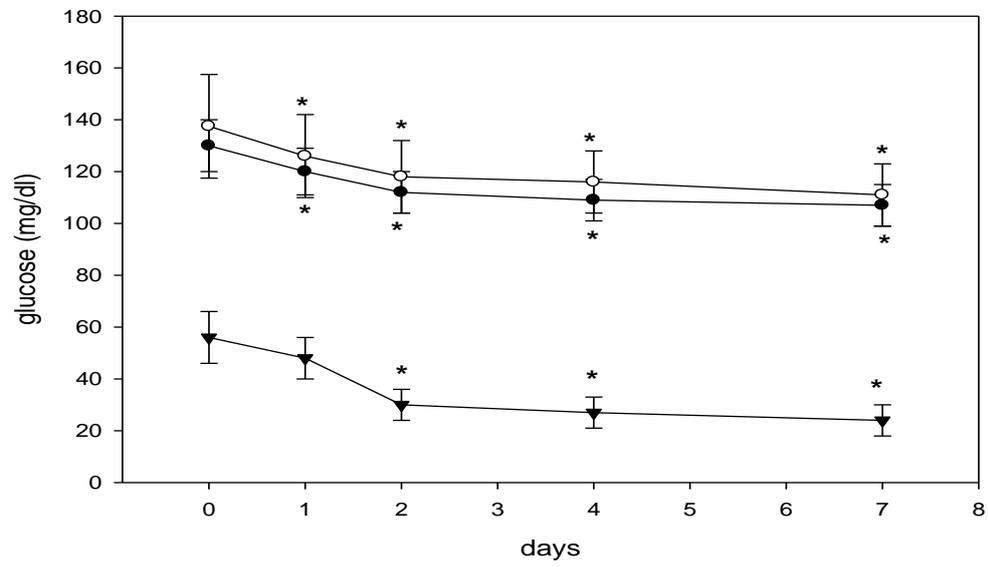
Figure 3

Figure 4

Figure 5

Panel 1

Panel 2

Panel 3
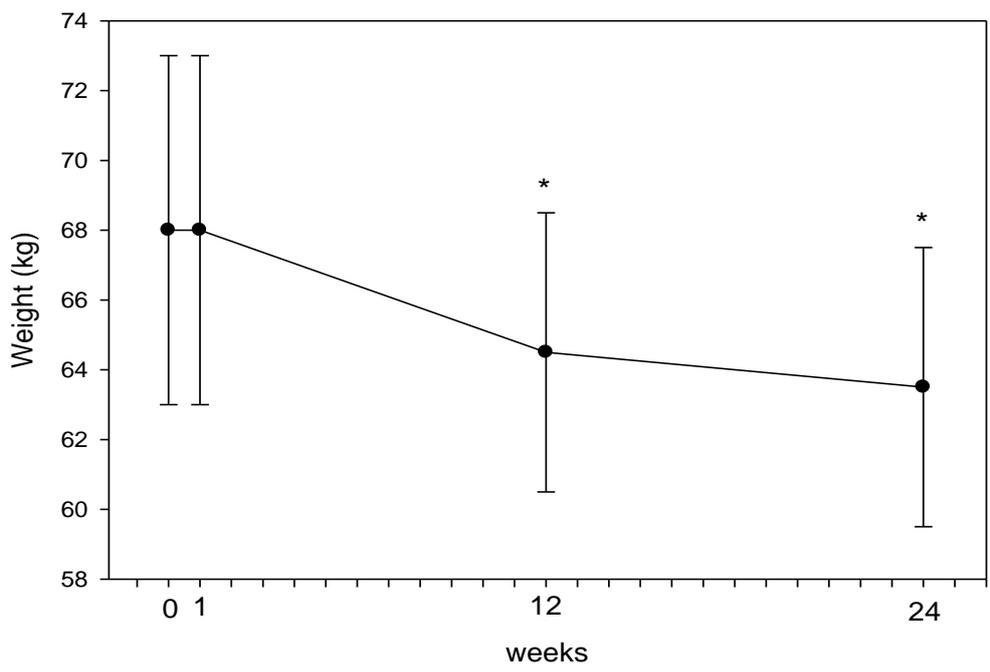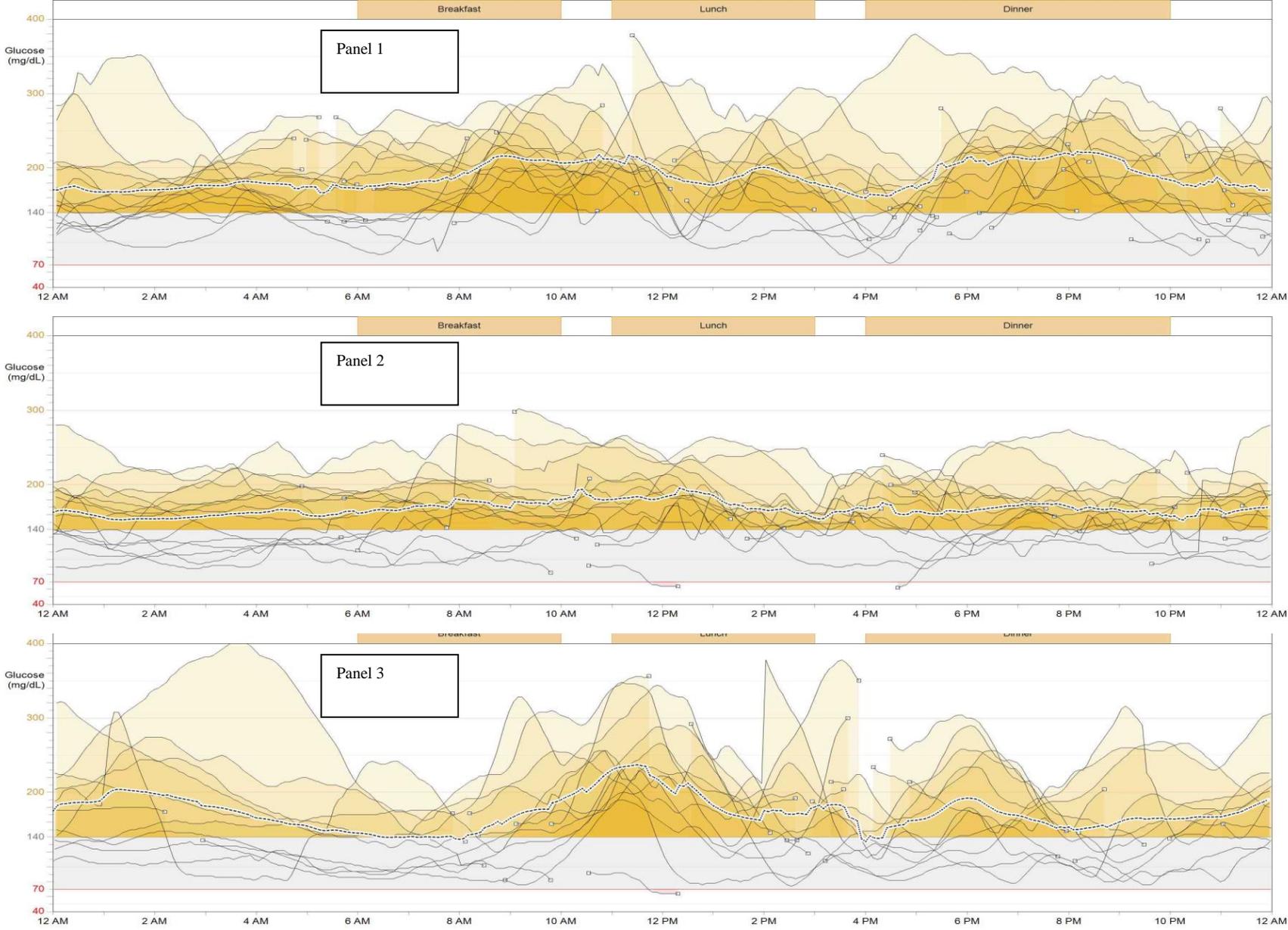
Table 1	First week	Second week	P value
HBA1c %	6.6±0.5		
insulin dose(basal)	24.5 ± 7 U/d	23 ± 6 U/d	0.31
insulin dose(bolus)	22.5 ± 4 U/d	21 ± 4 U/d	0.36
Mean Fasting Blood Glucose (mg/dl)	129.5±10	127.5±8	0.28
Weekly Mean Blood Glucose (mg/dl)	138±20	136.5±12	0.37
Time spent in hyperglycemia > 150 mg/dl(% time)	28±6	26±5	0.34
Time spent in hyperglycemia >200 mg/dl(% time)	18±5	17.5±2	0.41
Time spent in hyperglycemia >250 mg/dl(% time)	7.0±2	7.3±1	0.44
Time spent in hypoglycemia <70 mg/dl (% time)	2.1±2	2.0±2	0.32
Time spent in hypoglycemia <40 mg/dl (% time)	0.1±0.2	0.11±0.3	0.36
Mean SD weekly (mg/dl)	56±10	54±6	0.38
Coefficient of Variation CV (%)	40.5±9	39.6±8	0.38

Table 2 N=14	Before treatment (one week)	On Liraglutide (one week)	P value
Weight(kg)	66 ± 6	65.5± 5	0.42
insulin dose(basal)	24.5 ± 6 U/d	16.5 ± 6 U/d	<0.01
insulin dose(bolus)	22.5 ± 4 U/d	15.5 ± 4 U/d	<0.01
Mean Fasting Blood Glucose (mg/dl)	130±10	110±8	<0.01
Weekly Mean Blood Glucose (mg/dl)	137.5±20	115±12	<0.01
Time spent in hyperglycemia > 150 mg/dl (% time)	28± 6	22.5± 5	0.03
Time spent in hyperglycemia >200 mg/dl (% time)	18± 5	9± 2	<0.01
Time spent in hyperglycemia >250 mg/dl (% time)	8± 2	1.5± 1	<0.01
Time spent in hypoglycemia <70 mg/dl (% time)	2.0±2	2.4±2	0.06
Time spent in hypoglycemia <40 mg/dl (% time)	0.12±0.2	0.14±0.3	0.08
Mean weekly SD (mg/dl)	56±10	26±6	<0.01
Coefficient of Variation CV (%)	39.6±10	22.6±7	<0.01

Table 3 N=6	Before treatment (one week)	On Liraglutide (one week)	P value	Post Liraglutide (one week)	P value	P value before and post liraglutide
insulin dose(basal)	22.0 ± 6 U/d	15.5 ± 6 U/d	<0.01	23 ± 6	<0.01	0.51
insulin dose(bolus)	18.8 ± 4 U/d	14.5 ± 4 U/d	<0.01	20 ± 4U	<0.01	0.36
Mean Fasting Blood Glucose (mg/dl)	132.5±10	113±8	<0.01	130±10	<0.01	0.58
Weekly Mean Blood Glucose (mg/dl)	148±18	118±12	<0.01	143±18	<0.01	0.39
Time spent in hyperglycemia > 150 mg/dl(% time)	28.62± 6	21.5± 5	<0.01	27.6± 6	<0.01	0.54
Time spent in hyperglycemia >200 mg/dl(% time)	18.63± 5	10± 2	<0.01	17.8± 5	<0.01	0.46
Time spent in hyperglycemia >250 mg/dl(% time)	8± 2	2.0± 1	<0.01	7.5± 2	<0.01	0.54
Time spent in hypoglycemia <70 mg/dl (% time)	2.12±2	2.3±2	0.08	2.2±2	0.16	0.36
Time spent in hypoglycemia <40 mg/dl (% time)	0.13±0.2	0.14±0.3	0.13	0.13±0.2	0.12	0.66
Mean SD weekly (mg/dl)	59.75±10	28±6	<0.01	56±8	<0.01	0.39
Coefficient of Variation CV (%)	40.38	23.8	<0.01	39.2	<0.01	0.48

Table 4 N = 8	Before treatment (one week)	On Liraglutide (24 weeks)	P value
Weight (kg)	68±5	63.5±4	0.02
HBA1c %	6.5±0.5	6.1±0.4	0.02
insulin dose(basal)	26.5 ± 7 U/d	13.5 ± 5 U/d	<0.01
insulin dose(bolus)	25.5 ± 6 U/d	14 ± 4 U/d	<0.01
Mean Fasting Blood Glucose (mg/dl)	128±10	108±8	<0.01
Mean Weekly Blood Glucose (mg/dl)	134±20	111±12	<0.01
Time spent in hyperglycemia > 150 mg/dl (% time)	27.5± 6	21± 5	0.02
Time spent in hyperglycemia >200 mg/dl (% time)	17.5± 5	6.5± 2	<0.01
Time spent in hyperglycemia >250 mg/dl (% time)	8.0± 2	2.0±1	<0.01
Time spent in hypoglycemia <70 mg/dl (% time)	2.1.±2	2.3±2	0.08
Time spent in hypoglycemia <40 mg/dl (% time)	0.11±0.2	0.12±0.3	0.12
Mean SD weekly (mg/dl)	53±10	27±6	<0.01
Coefficient of Variation Weekly CV (%)	39.5±10	24.3±8	<0.01