THE EFFECT OF EXENATIDE THERAPY IN PREVIOUSLY INSULIN-TREATED TYPE 2 DIABETIC PATIENTS

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Abstract

Objective. To evaluate the effect of multiple daily injection (MDI) treatment replaced by Exenatide BID as compared with continuation of MDI.

Patients and Methods. A total of 140 patients with type 2 diabetes, taking metformin and multiple daily insulin injections, were randomized to exenatide or insulin group that continued their insulin treatment. Patients were followed-up for 16 weeks. Blood glucose profiles, BMI, waist circumference, HbA1C, serum lipids and side effects were assessed at weeks 0,12 and 16.

Results. There were no significant differences between the two groups with respect to baseline parameters. Glycemic control was similar between the two groups. The mean changes in HbA1C in exenatide group were $-0.66 \pm 0.63\%$ and in insulin group $-0.74 \pm 0.92\%$ ($p=0.594$). In exenatide group, 59.6 % of patients and in insulin group 85.71 % of patients had maintained or improved glycemic control at the end of the study. In insulin group, insulin requirement increased 5.86 ± 4.46 units/day. Body weight and waist circumference decreased significantly in exenatide treatment group with respect to insulin group ($p<0.001$).

Conclusions. Substituting exenatide for insulin might be an option in insulin-treated, type 2 diabetic patients having obesity, and poor glycemic control. However, patients with longer duration of diabetes and insulin treatment and with lower C-peptide levels might not benefit from exenatide therapy.

Key words: Type 2 diabetes mellitus, Exenatide, insulin therapy, glycaemic control, body weight.

INTRODUCTION

Type 2 diabetes is characterized by progressive loss of beta-cell function and insulin resistance (1, 2). Insulin treatment is recommended when diet therapy and oral antidiabetic agents fail to maintain euglycemia. According to the recent guidelines basal insulin is the

first line insulin therapy and with the progression of hyperglycemia insulin treatment becomes intensified. The intensification of insulin treatment leads to more weight gain in type 2 diabetic patients majority of whom are already obese (1-3). Glucagon-like peptide-1 (GLP-1) receptor agonists including Exenatide and analogues which were recently approved for clinical use in the management of type 2 diabetes seem to be promising for the control of hyperglycemia and weight gain (4, 5). They regulate glucose levels by stimulating glucose dependent insulin secretion and biosynthesis, and by suppressing glucagon secretion, delaying gastric emptying and promoting satiety (4-6). Since the action of GLP-1 receptor agonist is glucose-dependent, the occurrence of hypoglycemia is decreased. Most common side effects are gastrointestinal and include nausea, diarrhea, vomiting and injection site reactions (4-6). In the UK, the National Institute for Health and Care Excellence (NICE) guideline, in USA, the ADA and in Europe EASD statement suggested that the GLP-1 receptor agonists and analogues can be used as second line agents (4, 7). There are various reports about the comparison of exenatide with insulin treatment (1, 3, 5, 6, 8) and there is adequate clinical data about the combination of exenatide with insulin (9-15). Generally exenatide was added to basal insulin therapy (9,11,13). Recently, United States Food and Drug Administration (FDA) approved the use of exenatide as add-on treatment to insulin glargine and European Medicines Agency (EMA) approved the use of exenatide as add-on treatment to basal insulin (16). Only Davis and Barthelemy *et al.* studied the effect of substitution of insulin with exenatide in patients with type 2 diabetes and suggested that exenatide was not likely to be effective in patients taking high doses of insulin, with longer duration of diabetes and lower C-peptide levels (2, 17). In this study we aimed to

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evaluate the effect of multiple daily injection (MDI) treatment replaced by Exenatide BID as compared with continuation of MDI.

PATIENTS AND METHODS

This prospective, single-center, block randomized, open-label study was carried out between December 2010 and February 2012. A total of 140 type 2 diabetic patients taking metformin 1gr twice a day and multiple daily insulin injections -at least four injections- as three times premeal insulin lispro or insulin aspart and one or two times insulin glargine were included in the study. The duration of type 2 diabetes was > 1 year and the patients had been treated with multiple daily insulin for > 3 months. The patients with hypertension and/or hyperlipidemia were on stable antihypertensive and/or lipid-lowering therapy. Patients were excluded if they had HbA1c > 10.9 %, BMI < 35 kg/sqm and had a history of weight loss or gain or had used any medication to promote weight loss within six months, had history of acute pancreatitis or had previously received exenatide or glucagon-like peptide-1 analogues. Exclusion criteria also included elevated alanine aminotransferase and/or aspartate aminotransferase > three times of laboratory's upper limit of reference range, serum creatinine > 1.6 mg/dL for men and > 1.4 mg/dL for women and creatinine clearance < 30 mL/min, uncontrolled hypertension or having medication known to affect glucose metabolism.

The patients were randomized to two groups; patients in the exenatide group (n=70) used a multiuse pen injecting a fixed dose of exenatide 5mg b.i.d. for 4 weeks and then 10mg b.i.d. Patients in the insulin group (n=70) continued their insulin treatment as multiple daily injections. All the patients were taking metformin combination therapy. Patients were followed-up for 16 weeks. They were evaluated with 5-point self-monitored blood glucose (SMBG) profiles every week in the first 4 weeks and then every two weeks for the remaining 12 weeks. SMBG profile included measurement of pre-breakfast and pre-supper glucose values and postprandial glucose concentrations after each meal. In insulin group, insulin doses were titrated according to the measured SMBG profiles.

Fasting and postprandial serum glucose levels were measured every 4 weeks. HbA1C levels, blood chemistries and fasting serum lipids were assessed at weeks 0, 12 and 16. Patients were defined as having lost glycemic control, if self-measured blood glucose values or HbA1C levels were found to increase. Patients were defined as having maintained or improved

glycemic control if HbA1C levels and glucose values remained stable or decreased. Adverse events such as gastrointestinal effects and hypoglycemic episodes were assessed at each visit. Hypoglycemia was defined as experiencing a sign or symptom of hypoglycemia or documented having a glucose level of < 60mg/dl during self monitoring, regardless of signs or symptoms of hypoglycemia.

Anthropometric Measurements

The patients were evaluated by weight, height and waist circumference measurements at week 0 and 16. BMI was calculated by the ratio between weight and height squared in kg/m². Waist circumference was measured on bare skin between the tenth rib and the iliac crest in centimeters.

Laboratory Assessments

After an overnight fast of 12 hours, venous blood was collected from the antecubital vein. Baseline, 12th and 16th week fasting and 2-hour serum glucose and fasting lipid levels were measured enzymatically with commercial kits (Synchron LX[®] Clinical Systems Reagent, CA, United States) by use of an automated analyser. HbA1C values were measured by the Beckman Synchron LX system (Beckman Instruments Inc, Fullerton CA, 92834-3100). This utilizes two cartridges, Hb and A1c to determine A1c concentration as a percentage of total Hb. The hemoglobin is measured by a colorimetric method and the A1c concentration by a turbidimetric immunoinhibition method. The normal range for the HbA1c in our lab is 4–6%. C-peptide was measured by immunometric assay with electrochemiluminescence detection (Roche Diagnostics). The study was approved by the local ethics committee of Aydin State Hospital and all patients provided written informed consent.

Statistical Analysis

Results are expressed as means $\pm$ SD. Distribution of the continuous variables was determined by the Kolmogorov-Smirnov test. Continuous variables were expressed as mean $\pm$ SD, and categorical variables are expressed as percentage. For comparison of categorical variables or percentages we used Fisher's exact. Differences between numeric variables of the two groups at baseline and at the end of the study were tested with independent T-test and ANOVA. A paired t-test was used to compare the effect of the two treatment modalities on all the studied variables in each group. General linear model with

repeated measurement was used to compare 5 point SMBG values and HbA1C levels of the two groups. The subjects who responded to exenatide treatment were compared with the subjects that did not respond to treatment, by using independent T-test. Logistic regression analysis was used to determine the variables that predicted the response to exenatide treatment. For all statistics, a two-sided p value < 0.05 was considered statistically significant. All analyses were performed with SPSS 15.0 for Windows.

RESULTS

Clinical characteristics of the two groups at baseline are described in Table 1. Patients were between 38 and 72 years of age. There were no significant differences between the two groups according to age, gender, BMI, waist circumference, diabetes duration, insulin treatment duration, total daily insulin

requirement. The dose of basal and bolus insulin and the proportion of basal and bolus insulin were also similar between the two groups. Basal insulin dose was 53.62 ± 17.52 units/day in exenatide group and 54.55 ± 14.15 units/day in insulin group. Bolus insulin dose was 41.35 ± 13.51 units/day in exenatide and 40.91 ± 11.49 units/day in insulin groups. Basal-bolus ratio was 1.35 ± 0.26 in exenatide group and 1.39 ± 0.31 in insulin group. Likewise, there were no significant differences between the groups with respect to baseline fasting and postprandial glucose values and 5-point SMBG values (Table 2). HbA1C values, C-peptide and lipid levels were also similar between the two groups. A total of 62 patients in the exenatide group completed the study; 3 patients were lost to follow-up and we discontinued the treatment in 5 patients due to severe gastrointestinal side effects. In insulin group all the 70 patients completed the study.

Table 1. Clinical Characteristics and Laboratory Values of the Study Population at baseline

	Exenatide (n= 70)	Insulin (n=70)	P value
Age (years)	53.83 ± 9.40	57.47 ± 6.91	0.403
Sex (M/F)	14/16	13/17	>0.05
Body weight (kg)	105.94 ± 16.90	99.60 ± 11.57	0.328
BMI (kg/m ²)	39.70 ± 3.47	38.37 ± 2.05	0.566
Waist circumference(cm)	119.33 ± 8.57	116.06 ± 4.12	0.182
Diabetes duration (years)	11.29 ± 4.12	11.93 ± 3.75	0.505
Insulin treatment duration (years)	2.67 ± 1.28	3.94 ± 3.03	0.160
Insulin dose (unit/day)	91.55 ± 33.91	92.60 ± 21.22	0.208
Basal insulin dose (unit/day)	53.62 ± 17.52	54.55 ± 14.15	0.595
Bolus insulin dose (unit/day)	41.35 ± 13.51	40.91 ± 11.49	0.682
Basal/bolus insulin ratio	1.35 ± 0.26	1.39 ± 0.31	0.59
Fasting serum glucose (mg/dL)	162.50 ± 11.56	169.10 ± 20.33	0.461
Postprandial serum glucose (mg/dL)	228.11 ± 35.31	224.40 ± 38.01	0.382
HbA1C (%)	8.39 ± 1.01	8.47 ± 1.02	0.430
C-peptide (µg/L)	2.14 ± 1.12	1.96 ± 0.94	0.110
Total cholesterol (mg/dL)	206.33 ± 45.59	214.64 ± 37.28	0.187
LDL-cholesterol (mg/dL)	120.38 ± 37.60	122.26 ± 26.82	0.640
HDL-cholesterol (mg/dL)	49.27 ± 16.32	44.50 ± 10.22	0.287
Triglyceride (mg/dL)	152.94 ± 96.52	135.36 ± 67.34	0.275

Table 2. Five-point self-monitored blood glucose profiles

		Prebreakfast (mg/dL)	Postprandial (after breakfast) (mg/dL)	Postprandial (after lunch) (mg/dL)	Predinner (mg/dL)	Postprandial (after dinner) (mg/dL)
Week 2	Exenatide	164.17 ± 21.08	196.78 ± 26.31	206.65 ± 41.62	163.87 ± 24.11	192.43 ± 21.65
	Insulin	159.62 ± 23.14	187.29 ± 25.67	191.37 ± 29.98	157.59 ± 23.54	205.13 ± 22.46
	P value	0.399	0.121	0.156	0.546	0.290
Week 8	Exenatide	156.59 ± 42.58	187.52 ± 32.14	196.53 ± 34.89	159.62 ± 35.18	196.62 ± 25.18
	Insulin	151.43 ± 31.78	196.37 ± 24.76	182.37 ± 30.79	154.55 ± 25.97	179.33 ± 25.97
	P value	0.645	0.893	0.289	0.713	0.2777
Week 16	Exenatide	155.73 ± 34.02	178.87 ± 23.12	196.44 ± 24.62	157.89 ± 26.86	184.51 ± 31.17
	Insulin	152.37 ± 24.93	181.66 ± 24.62	188.37 ± 25.15	152.19 ± 32.14	181.38 ± 23.52
	P value	0.556	0.560	0.279	0.760	0.552

Changes in glycemic control and insulin requirement

Basal, 12th and 16th week HbA1c levels were 8.39 ± 1.01 , 7.96 ± 0.74 , 7.73 ± 0.38 %, respectively in exenatide group and 8.47 ± 1.02 , 8.01 ± 0.85 , 7.82 ± 0.94 % in insulin group and values were similar between the two groups (p_{basal}= 0.098, p_{12th week}= 0.201, p_{16th week}= 0.473). Similarly, the mean changes in fasting and postprandial serum glucose values were not statistically different between the two groups (p_{fasting}= 0.77 and p_{postprandial}= 0.72). The change in mean fasting serum glucose value was -22.74 ± 33.06 mg/dL in exenatide group and -21.93 ± 17.45 mg/dL in the insulin group. The mean change in postprandial glucose values observed in insulin group was -42.36 ± 43.24 mg/dL and in exenatide group -39.26 ± 35.36 mg/dL (Table 3).

In exenatide group, of the 62 patients who completed the study, 37 of them (59.6 %) had maintained or improved glycemic control at the end of the study. In insulin group 60 out of 70 patients (85.71%) had maintained or improved glycemic control.

When the patients that had not responded to exenatide treatment (who lost glycemic control) were compared with the patients that responded to the treatment (who had maintained or improved glycemic control), it was found out that the duration of diabetes and insulin treatment were significantly longer in non-responders. The duration of diabetes was 9.37 ± 1.90 years (6-14 years) in responders and 15.13 ± 4.78 years (7-23 years) in non-responders (p= 0.001). The duration of insulin treatment was 2.40 ± 1.13 years (1-5 years) in responders and 6.33 ± 2.71 (1-10 years) in non-responders (p=0.001). Also, plasma C-peptide levels were significantly higher in responders (2.09 ± 0.83 µg/L) with respect to non-responders (1.68 ± 0.88 µg/L) (p= 0.031). Logistic regression analysis revealed that the duration of diabetes and insulin

treatment, and plasma C-peptide levels were still predictors of response to therapy (p_{diabetesduration}= 0.021, p_{insulinduration}= 0.034, p_{c-peptide}= 0.007). However, mean age and BMI of the patients did not differ between responders and non-responders in the exenatide group (p>0.05).

In insulin group, insulin requirement increased 5.86 ± 4.46 units/day.

Changes in body weight and waist circumference

Changes in body weight and BMI were significantly different between the two groups (p<0.001). Mean body weight decrease was 5.50 ± 2.52 kg in exenatide group, whereas body weight increased by 0.16 ± 2.46 kg in insulin group. Consistent with these findings, waist circumference decreased significantly in exenatide treatment group (p<0.001).

Change in lipid levels

Change in lipid levels was not statistically significant between the two groups (p>0.05).

Adverse events

Adverse events reported in this study were usually mild to moderate and consisted of gastrointestinal side effects. None of the patients in exenatide group experienced severe hypoglycemia and needed assistance of another person, but 6 patients in the insulin group had severe hypoglycemia. Apart from this, the incidence of mild hypoglycemia reported was 0.33 ± 0.48 per patient and month in exenatide group and 1.10 ± 1.02 per patient and month in insulin group. The incidence of hypoglycemia was significantly lower in exenatide-treated patients with respect to insulin-treated ones (p= 0.007). Gastrointestinal side effects included nausea, diarrhea, vomiting and abdominal pain and observed in exenatide group, but not in insulin

Table 3. Change in anthropometric values and metabolic variables

	Exenatide (n= 62)	Insulin (n=70)	P value
Δfasting glucose (mg/dL)	-22.74±33.06	-21.93±17.45	0.77
ΔPostprandial glucose (mg/dL)	-39.26 ± 35.36	-42.36 ± 43.24	0.72
Δ HbA1C (%)	-0.66 ± 0.63	-0.74 ± 0.92	0.594
Δ Insulin dose (unit/day)	-91.55 ± 5.76	5.86 ± 4.46	<0.001*
Δ Body weight (kg)	-5.50 ± 2.52	0.16 ± 2.46	<0.001*
Δ BMI (kg/m ²)	-1.96 ± 0.23	0.59 ± 0.18	<0.001*
ΔWaist circumference(cm)	-3.88 ± 0.35	0.06 ± 0.27	<0.001*
Δ Total cholesterol(mg/dL)	-12.96 ± 5.10	-4.06 ± 3.95	0.388
ΔLDL-cholesterol (mg/dL)	-10.55 ± 3.31	-2.81 ± 2.56	0.199
ΔHDL-cholesterol (mg/dL)	3.16 ± 1.87	3.63 ± 1.45	0.421
Δ Triglyceride (mg/dL)	-31.44 ± 12.72	-27.11 ± 9.85	0.096

group. Five patients in exenatide group discontinued the study due to severe gastrointestinal side effects (two of them had severe abdominal pain and nausea, the 3 of them had severe nausea and vomiting). Besides, 25 (36 %) exenatide-treated patients experience mild to moderate temporary nausea.

DISCUSSION

It is shown in the United Kingdom prospective diabetes study (UKPDS) that tight glycemic control in type 2 diabetes decreases the risk of diabetes related complications (18). Pharmacological approaches for glycemic control include oral antidiabetic medications, insulin and Glucagon-like peptide-1 receptor agonists and analogues. Glycemic control is cumbersome in type 2 diabetic, obese patients taking very high doses of insulin. Even with the insulin sensitizing agents (metformin) it may not be possible to sustain euglycemia and more weight gain and hypoglycemic episodes are inevitable with the increasing insulin doses. As novel therapeutic agents, GLP-1 analogues and receptor agonists are associated with improved glycemic control and decreased weight and hypoglycemia (19). They are indicated for treatment of Type 2 diabetes mellitus in combination with metformin and/or sulphonylureas in patients who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies (6, 11, 14). As a matter of fact, exenatide treatment was reported to improve glycemic control and B-cell function and decrease body weight compared with insulin glargine in previously metformin-treated patients (1). Exenatide treatment was not only compared to basal insulin treatment, but also to premixed insulin treatment (5, 8, 20). It was found to be non-inferior to biphasic insulin aspart treatment in patients who were previously taking metformin, however, Bergenstal *et al.* reported better glycemic control with premixed insulin (8).

There are several studies about the concomitant use of exenatide and insulin (9, 13-15, 21, 22). Since GLP-1 mimetics act principally to reduce postprandial plasma glucose exposure, they could complement the activity of basal insulin which acts on fasting plasma glucose (7). Rosenstock *et al.* reported that, exenatide added to optimized basal insulin was associated with improved glycemic control and weight loss, including modestly obese patients with a longer duration (>9 years' duration) of diabetes (22). The Association of British Clinical Diabetologists (ABCD) nationwide audit collected data across 126 centers in the UK

(23). In total, 1257 patients in the ABCD study received exenatide treatment as add-on to continuing insulin therapy. Patients treated with a combination of exenatide twice daily and insulin experienced a mean HbA1C reduction of 0.51 %, weight reduction of 5.8 kg, insulin dose reduction of 42 units/day and insulin discontinuation rate of 16.6 %. In the light of expanded clinical data, FDA approved the use of exenatide as add-on treatment for use with insulin glargine. But, the data about the effect of administration of exenatide to patients taking multiple daily insulin injections or substitution of insulin with exenatide therapy is limited. In Nayak's and Lind's studies (14, 15), exenatide was added to multiple insulin therapy. Nayak's prospective study included 174 insulin-treated patients of whom 23 % were taking >2 insulin injections/day. Although there was no improvement in glycemic control, insulin cessation rate was 25% and mean insulin dose reduction was 62% (14). Weight loss was 23% at 6th month and 26% at 12th month. These effects were prominent especially in obese patients taking very high doses of insulin (15). But there were no control groups in these studies.

Davis *et al.* studied the effect of substituting exenatide for insulin in patients with type 2 diabetes using insulin in combination with oral antidiabetes agents (metformin and/or sulfonylurea) (2). The insulin treated patients were randomized to exenatide group or reference group which remained on their insulin regimens. Among 49 patients only 7 of them were taking multiple insulin therapies and 4 were in the exenatide group. They showed that 62% of the exenatide-treated patients maintained glycemic control compared with 81% of the insulin-treated patients. It is suggested that patients with longer disease duration, taking higher doses of insulin may experience deterioration in glucose control if exenatide is substituted for insulin (2). Likewise, in our study 140 patients, taking multiple daily injections, were randomized to exenatide and discontinued insulin treatment or control group which remained on their insulin regimens. Being different from the study of Davis *et al.*, our whole study population were previously taking multiple daily injections. Although the patients were previously taking high doses of insulin, we observed improvement in glycemic control after exenatide treatment. A total of 59.6 % of exenatide-treated patients and 85.71 % of insulin treated patients had improved or maintained glycemic control. Similar to Davis *et al.*, Barthelemy *et al.* studied the substitution of insulin by exenatide in bad controlled type 2 diabetic patients and reported

that patients with diabetes duration shorter than 12 years, fasting C-peptide higher than 2.0 µg/L and mean capillary blood glucose <200 mg/dL after 3 days of exenatide, had improvement in glycemic control (17). However, there was no control group in this study. Consistent with the findings of Davis and Barthelemy *et al*, we observed response to treatment in patients with BMI > 35 kg/m², duration of diabetes < 15 years and duration of insulin treatment <6 years and C-peptide levels higher than 2.0 µg/L.

Our study has some limitations; first it has a short duration of 16 weeks with a small sample size and open label design that might cause possible bias for the lack of blinding. And also we did not evaluate the treatment satisfaction of the participants, because improved glycemic control observed with exenatide treatment might be the result of increased motivation for adherence to diet therapy and exercise programme after the start of weight loss.

Although there is an increasing body of clinical data about the concomitant use of basal insulin and exenatide, the data about substituting exenatide for insulin therapy is limited. To our opinion, adding GLP-1 receptor agonists of short half-life that better mimics endogenous GLP-1, in patients already receiving multiple insulin doses, would be a better approach (24). To our knowledge, this is the first study, which compared the effect of exenatide and insulin treatment in previously insulin treated patients all of whom were taking high doses of insulin as multiple daily injections.

In conclusion, substituting insulin with exenatide therapy might be an option in insulin-treated, type 2 diabetic patients having obesity, and poor glycemic control. The lack of response to treatment suggests that some subjects may have been in an advanced stage of their diabetes and may not have had sufficient beta-cell function for a GLP-1 mimetic to be effective. Therefore, close follow-up is obligatory, since it might cause deterioration in glycemic control, especially in patients with longer duration of diabetes and insulin treatment.

Conflict of interest

The authors declare that they have no conflict of interest.

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