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ARAŞTIRMA / RESEARCH

Effect of switching insulin treatment to exenatide based therapy in uncontrolled type 2 diabetes mellitus patients

Kontrol altında olmayan tip 2 diyabetes mellitus hastalarında insülin tedavisinden eksenatid bazlı tedaviye geçişin etkinliği

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Abstract

Purpose: In patients with uncontrolled type 2 diabetes mellitus (T2DM) on insulin therapy, increasing the insulin doses is most commonly preferred as the first choice to achieve glycaemic control. We evaluated the efficacy of initiating exenatide combination with oral antidiabetics (OAD) instead of insulin therapy.

Materials and Methods: We examined all 61 uncontrolled T2DM patients had greater than 2 ng/ml C-peptide levels and were switched from insulin and metformin therapy to exenatide combination with OAD in the period of 2015 – 2017. For examination, the patients were divided into 3 groups according to their insulin regimen as basal insulin alone, biphasic insulin and basal-bolus insulin groups. The fasting blood glucose (FBG), HbA1c and C-peptide levels of the patients were recorded before and at the 6th month of treatment.

Results: After the 6th month of the exenatide-based treatment, results show that the HbA1c levels were significantly lower than which had been evaluated before this treatment. By the end of the study, 14 of the 61 patients treated with exenatide and OAD achieved to decrease the HbA1c levels under 7.0%. FBG also decreased with the exenatide and OAD treatment.

Conclusion: We demonstrated that in order to achieve glycaemic control, exenatide-based therapy could be a better therapeutic option than increasing insulin doses with insulin and metformin treatment in patients who have uncontrolled T2DM with insulin regimens.

Keywords:. Type 2 diabetes mellitus, exenatide, insulin treatment, c-peptide

Öz

Amaç: İnsülin tedavisi altındaki kontrolsüz tip 2 diyabetes mellitus hastalarında glisemik kontrolü sağlamak için en sık tercih edilen yöntem insülin dozlarını arttırmaktır. Bu çalışmada, bu grup hastalarda insülin tedavisi yerine eksenatid ile oral antidiyabetik (OAD) kombinasyonunun etkisini değerlendirdik.

Gereç ve Yöntem: 2015-2017 arasında, C-peptid düzeyleri 2 ng/ml'nin üzerinde olan, insülin ve metformin tedavisi altında kontrolsüz seyrederken eksenatid ve OAD tedavisine geçilen 61 hasta çalışmaya alındı. Hastalar kullandıkları insulin rejimlerine göre, sadece bazal insülin, bifazik insülin ve bazal-bolus insülin grubu olarak 3 gruba ayrıldı. Hastaların tedavi değişikliği öncesi ve tedavinin 6. ayında açlık kan şekerleri, HbA1c ve C-peptid düzeylerine bakıldı.

Bulgular: Eksenatid bazlı tedavinin 6. ayında HbA1c düzeylerinde tedavi değişikliği öncesine göre anlamlı azalma görüldü. Çalışmanın sonunda, eksenatid ve OAD tedavisi alan 61 hastanın 14'ünde HbA1c değeri %7'nin altına düştü. Eksenatid ve OAD tedavisiyle açlık kan şekerinde de azalma görüldü.

Sonuç: Bu çalışmada insülin ve metformin tedavisi altındayken kontrolsüz seyreden T2DM hastlarında eksenatid bazlı tedaviye geçişin glisemik kontrolü sağlamakta insülin dozunu arttırmaktan daha iyi bir tedavi seçeneği olduğunu gösterdik.

Anahtar kelimeler: C-peptid, eksenatid, insülin tedavisi, tip 2 diyabetes mellitus

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is the most common form of diabetes resulting from insulin resistance and inadequate insulin secretion, affecting approximately 85%–90% of diabetic individuals. Many treatment options have been developed to regulate blood glucose homeostasis[1]. When insulin regimens fail to provide the adequate glycaemic target, increasing the insulin doses is the appropriate treatment choice depending on the patients' needs[2]. However, increasing the insulin levels causes weight gain and obesity[3], and high levels of insulin cause insulin resistance. Nevertheless, despite the usage of high doses of insulin, many patients do not achieve their glycaemic goals and suffer from the unpleasant effects of insulin treatment such as hypoglycaemia and weight gain[4]. The combination of glucagon-like peptide-1 receptor agonist (GLP-1RA) and oral antidiabetics (OAD) represents an encouraging method of glycaemic control because of the complementary mechanisms of action of these therapies[5]. A meta-analysis of clinical trials reported by Eng et al. showed that the GLP-1RA-based therapies resulted in a potent glycaemic goal without increased risk of hypoglycaemia or weight gain[6,7].

Conversely, some reports showed that ongoing therapy with GLP-1RA alone could result in inadequately controlled T2DM and adding insulin to GLP-1RA or switching to insulin therapy could improve glycaemic control in individuals who fail to respond to GLP-1RA therapy[8,9].

According to the scientific reports, there are controversial situation that which method among GLP-1RA combination with OAD and insulin therapy are more beneficial for the glycaemic control. Thus, we examined retrospectively the efficacy of GLP-1RA combination with OAD compared to insulin therapy. The primary aim of our study is evaluating the possible benefits of the altering insulin treatment to GLP-1RA treatment on plasma glucose and glycosylated haemoglobin (HbA1c).

MATERIALS AND METHODS

For the study, the data of 77 patients with poorly controlled T2DM whose treatments have been switched from insulin and metformin to exenatide based therapy in Selçuk University Endocrinology and Metabolism clinic between 2015-2017 are gathered and analyzed retrospectively.

As exenatide was a new treatment experience for our clinic, the informations and complaints about the treatment of each patient whose exenatide therapy was initiated during in this two-year period was recorded for follow-up and the patients who were switched from insulin and metformin treatment to exenatide based therapy were included in this study. This study was carried out by the approval of the Ethics Committee of Selçuk University Faculty of Medicine dated 15.02.2018 and numbered 2018/02.

As routine in our clinic, exenatide-based therapy is applied for the patients whose fasting C-peptide levels are above 2 ng/ml. Therefore, the population for the study includes patients whose fasting C-peptide levels were at least 2 ng/ml. Moreover, because of the contraindications of the glucagone-like peptide-1 receptor agonist (GLP-1RA) therapy, the patients had no history of pancreatitis, malignancies or chronic kidney disease. Furthermore, the patients who were elder than 18 years old and applied at least six months of insulin and metformin therapy before switched to the exenatide-based treatment were included in the study population.

Since 10 of 77 patients did not continue to follow-up under the exenatide-based treatment and 6 of 77 patients were unable to continue treatment due to adverse events –all of them complained nausea and vomiting- of the treatment, we excluded them from the population and so the analysis. Hence, in our study, data of the 61 patients were used. For examination, the patients were divided into 3 groups according to their insulin regimen as basal insulin alone, biphasic insulin and basal-bolus insulin groups.

As our clinic procedure, exenatide is applied at a dose of 5 mg twice a day and increased, if tolerated, to a maximum of 20 mg/day. For the 61 patients in our study, at the point of GLP-1RA treatment starts after insulin therapy, all of them were prescribed with 2000 mg/day of metformin, 30 mg/day of pioglitazone and 60 mg/day of gliclazide. At the third month of the follow-up, the gliclazide dose was increased to 120 mg/day for the patients whose HbA1c and fasting blood glucose (FBG) at above target levels. FBG, lipid profile and HbA1c values were extracted before and six months after the GLP-1RA-based treatment.

Statistical analysis

The Kolmogorov–Smirnov normality test was used to determine the distribution pattern of the variables. Parametric tests were used for the normally distributed variables results, and the data were presented as the mean±SD. The normally distributed variables were compared using the chi-square test and one-way ANOVA, and the post hoc Bonferroni test was used for multiple comparisons. Comparisons between groups of continuous variables were performed using Student's t-test or the Mann–Whitney U test. A paired sample t-test was used for comparing the treatment effects on the variables. The relationships among the variables were analysed using Pearson's or Spearman's rank correlation coefficients. Significance was assessed at $P<0.05$.

RESULTS

Our retrospective analysis included 61 patients (37 female/24 male, mean age 52.2±10.1 year old, body mass index (BMI): 37.7±4.8 kg/m²). Disease duration of the patients was 13.04±7.7 years. Nine patients were prescribed with basal insulin medications, 20 with biphasic insulin and 32 with basal–bolus therapy. The nine basal insulin users were treated with an average dose of 42.8±12.6 units; the 20 biphasic insulin patients were prescribed with an average dose of 62.7±14.8 units; and the 32 basal–bolus therapy patients were prescribed with an average dose of 68.5±16.2 units. HbA1c, FBG, lipid profile, C-peptide concentrations, weight and BMI values were not significantly different between the groups ($p > 0.05$; Table 1). After six months of exenatide-based therapy, a statistically significant decrease was observed in HbA1c in the bolus insulin alone group (−2.6%), biphasic insulin group (−0.8%) and basal–bolus insulin group (−1.5%) (Table 2). Among the patients who received basal–bolus therapy at their baseline and changed to exenatide-based therapy, approximately 21.9% had an HbA1c level less than or equal to 7% at the sixth month of follow-up (Table 3). The exenatide-based therapy also showed a statistically significantly decrease in FBG level compared to the level which was evaluated before the treatment (Table 3).

Table 1. Laboratory characteristics and metabolic features of the patients before GLP-1-based therapy.

(mean±SD)	Basal insulin (n=9)	Biphasic insulin (n=20)	Basal-bolus (n=32)	p
Age	53.8±5.0	51.1±10.8	52.5±10.7	0.4
Weight (kg)	90.0±17.2	103.4±15.4	96.1±14.0	0.1
BMI (kg/m²)	36.2±4.9	39.2±5.9	37.3±3.5	0.3
FBG (mg/dl)	192±80	231±80	245±82	0.2
HbA1c (%)	9.6±1.7	9.7±1.9	10.1±1.8	0.7
LDL-c (mg/dl)	114.9±41.4	116.8±37.2	113.5±32.3	0.9
HDL-c (mg/dl)	39.2±5.8	40.3±10.9	43.3±9.9	0.4
Triglyceride (mg/dl) Median (Q1-Q3)	228 (145-407)	288 (68-1718)	377 (55-1240)	0.8
C-Peptide (ng/ml)	3.1±1.1	2.8±0.6	3.4±1.1	0.1

BMI: body mass index, FBG: fasting blood glucose, GLP-1: glucagon like peptide-1, HbA1c: glycosylated haemoglobin, HDL-c: high density lipoprotein cholesterol, LDL-c: low density lipoprotein cholesterol.

Table 2. Laboratory characteristics and metabolic features of the patients after GLP-1-based therapy

(mean±SD)	Basal insulin (n=9)	Biphasic insulin (n=20)	Basal-bolus (n=32)	p ANOVA
Weight (kg)	87.8±17.7	102.0±17.4	95.5±15.4	0.2
BMI (kg/m²)	35.8±4.7	37.3±5.6	36.7±3.2	0.7
FBG (mg/dl)	150±30*	186±87	186±76	0.001
HbA1c (%)	7.0±0.9*	8.9±2.5	8.4±2.5	0.001
LDL-c (mg/dl)	98±49	109±28	114.8±31.9	0.6
HDL-c (mg/dl)	41.5±8.8	40.8±9.9	39.8±8.7	0.5
Triglyceride (mg/dl) Median (Q1-Q3)	221 (145-407)	201 (68-1718)	241 (55-1240)	0.1
C-Peptide (ng/ml)	3.1±1.1	2.8±0.6	3.4±1.1	0.1

FBG: fasting blood glucose, HbA1c: glycosylated haemoglobin, HDL-c: high density lipoprotein cholesterol, LDL-c: low density lipoprotein cholesterol. BMI: Body mass index

Among the 20 patients in the biphasic insulin group who switched to the exenatide-based therapy, 25% were at the HbA1c target (≤ 7.0%) at the sixth month of follow-up (Table 3). FBG level showed a significant decrease after exenatide-based therapy compared to the level which was evaluated before the treatment (Table 3).

Six months after exenatide-based therapy, 22.2% of the patients who switched from the basal insulin treatment achieved an HbA1c level less than or equal to 7% (Table 3). FBG level decreased 42 mg/dl after exenatide-based therapy compared to the level which was evaluated before the treatment (Table 3; p=0.01).

Because of the retrospective nature of the study, weight and BMI records of 33 out of 61 patients at the beginning and six months after exenatide-based treatment could be gathered (7 of 9 patients in basal insulin group, 7 of 20 patients in biphasic insulin group and 19 of 32 patients in basal-bolus insulin group). Records showed that only basal-bolus insulin group had a significant decrease in weight and BMI after switching to exenatide-based therapy (Table 3; p=0.01).

Table 3. Changes in HbA1c and FBG after switching from insulin treatment to GLP-1-based therapy.

	FBG (mg/dl)	**HbA1c (%)**	**Weight (kg)**	**BMI (kg/m2)**	**p^**	**p***	**pβ**	**p¥**	**pµ**
Pre- Post treatment response with GLP-1 agonist based therapy in basal insulin group	192±82 versus 150.3±29.8	9.6±1.7 versus 7.0±0.9	90.0±17.2 versus 87.8±17.7	36.2±4.9 versus 35.8±4.7	0.2	0.2	0.01	0.07	2/9 (22.2%)
Pre- Post treatment response with GLP-1 agonist based therapy in biphasic insulin group	230.5±79.8 versus 186.87±69.8	9.7±1.9 versus 8.9±2.5	103.4±15.4 versus 102.0±17.4	39.2±5.9 versus 37.3±5.6	0.8	0.7	0.003	0.035	5/20 (25%)
Pre- Post treatment response with GLP-1 agonist based therapy in basal-bolus insulin group	245.0±81.6 versus 185.69±75.5	10.1±1.8 versus 8.4±2.5	96.1±14.0 versus 95.5±15.4	37.3±3.5 versus 36.7±3.2	0.01	0.01	0.018	0.027	7/32 (21.9%)

FBG: fasting blood glucose, GLP-1: glucagon like peptide-1, HbA1c: glycosylated haemoglobin, OAD: oral anti diabetic.
p^ Pre vs. Post GLP-1 based therapy for weight; p* Pre vs. Post GLP-1 based therapy for BMI pβ Pre vs. Post GLP-1 based therapy for FBG p¥ The percentage of patients at HbA1c target (≤7.0%) after sixth months of GLP-1 based therapy

DISCUSSION

In this study, after six months from exenatide-based treatment starts in patients with uncontrolled T2DM resulted in reduced HbA1c and FBG levels and it is found that the switch from biphasic insulin, basal alone, or basal–bolus therapy to the exenatide-based therapy was associated with improved glycaemic control. The efficacy of the GLP-1RA-based therapy in this study is more promising than the study of Bruinstroop et al[10] that 60 patients were followed-up for 12 months after the insulin-to-liraglutide switch. The researchers found that switching from insulin to the GLP-1RA-based therapy showed no improvement in glycaemic control[10]. The reason for this result could be the low C-peptide levels of the selected patients because the clinical markers of the low beta cell function were associated with the reduced glycaemic response to the GLP-1RA-based therapy[11]. In Bruinstroop et al. study, most of the patients' C-peptide levels were less than 2 ng/ml. In another report, Davis et al. observed no improvement in glycaemic control in a 16-week study after the patients' treatments were switched from

insulin to exenatide[12]. The researchers reported a deteriorated glucose control in the patients who had a low endogenous β-cell function after switching from insulin therapy to exenatide[12] because the C-peptide is a good marker of the remaining beta cell capacity in diabetic patients[13]. In contrast to these studies showing that the GLP-1RA-based therapy is not effective[10,12], other studies demonstrated the augmentation of glycaemic control when switching from insulin treatment to the GLP-1RA-based therapy[14-16]. Only one of these studies emphasised the usefulness of C-peptide levels[16]. Iwao et al. argued that fasting C-peptide and postprandial C-peptide levels could be useful markers in predicting the success of switching from insulin therapy to liraglutide therapy[16]. Switching from insulin therapy to liraglutide monotherapy was found to be successful in achieving good glycaemic control when fasting C-peptide levels were at least 1.8 ng/ml[16]. In our study, we began the GLP-1RA-based therapy in uncontrolled T2DM patients who had greater than 2 ng/ml of C-peptide levels. Our findings are generally consistent with Iwao et al.'s[16] and we achieved good glycaemic control (HbA1c < 7%) in 21.9%–25% of the study population. Currently, the amount of glucose level reduction when the GLP-1RA-based treatment is given instead of insulin therapy cannot be predicted. Nevertheless, Kawata et al. investigated this issue and found that a below the daily insulin dose of 19 units and a disease duration of nine years at most could be predictors of the advisability of switching from insulin therapy to GLP-1RA-based medication[15]. In our study, the disease duration of the patients was 13.0±7.7 years, and the patients received insulin doses of over 40 units per day. For this reason, the results showed that only 21.9%–25% of the participants reached to HbA1c target during follow-up. Although our study found that the rate of achieving glycaemic targets with the GLP-1RA-based therapy was lower than expected, a statistically significant change was found in HbA1c and FBG level after switching from insulin treatment to the GLP-1RA-based therapy. Finally, this study revealed that switching to the GLP-1RA-based therapy significantly lowered the HbA1c levels of uncontrolled T2DM patients who had at least 2 ng/ml of C-peptide levels.

Liraglutide exhibits a greater than 97% amino acid sequence homology with human GLP-1, whereas exenatide exhibits only 53%[17]. Although exenatide is parallel in its nature to liraglutide, the differences in its pharmacokinetic and pharmacodynamic features resulted in different anti-hyperglycaemic effects in our study.

The main advantage of the injectable GLP-1 analogues like exenatide, liraglutide, lixisenatide is weight loss[18]. In Deng et al. study with the exenatide monotherapy, there was a significant weight loss in both obese and non-obese T2DM patients[19]. In our study, the only significant weight loss was realized in basal-bolus inulin group whose weight reduced from 96.1 to 95.5 kg (p=0.01) and BMI reduced from 37.3 to 36.7 kg/m^2 (p=0.01). In the basal and biphasic insulin groups, there were also reduction in weight and BMI at the 6th month of the GLP-1RA-based therapy but reduction amounts were not statistically significant. We thought that this difference occurred because the number of patients' weight records was different in accessibility manner among the 3 groups. Besides, we could not see the expected weight loss in the basal and biphasic insulin groups because of the effects of pioglitazone and gliclazide on weight gain which we used in therapy combination[20].

This study did not show any reduction in the lipid profile at the sixth month of follow-up in the patients treated with the GLP-1RA-based therapy. Normally, favorable changes in lipid profiles are expected with GLP-1RA-based treatment[21]. These contradictory outcomes in our study may be due to the differences in treatment duration or study population.

The most common adverse effects of GLP-1RA treatment are gastrointestinal adverse events, predominantly nausea, vomiting and diarrhea[22]. In the Horowitz et al. study, mild, moderate and severe gastrointestinal adverse events are reported at the rate of 38.6%, 12.4% and 1.7% of exenatide twice-daily-treated patients, respectively[22]. In the same study, discontinuation of the medication because of gastrointestinal adverse events is reported at the rate of 6% of the patients who were treated with exenatide twice-daily. In our study, there were 6 of 77 patients (7.7%) who discontinued the GLP-1RA due to nausea and vomiting despite anti-emetic treatment. Twenty eight of the remaing patients (46%) who continued the GLP-1RA-based treatment had nausea in the first week of the treatment but after that this complaint regressed. There were no other adverse events recorded in our study due to GLP-1RA-based therapy.

This work had some limitations. First, this study was a retrospective and single-centre analysis with a limited sample size. Second, we were not able to

access all of the patients' weight records. Third, although postprandial serum C-peptide level is a useful parameter in predicting the success of the GLP-1RA therapy in patients with T2DM, we could not evaluate the postprandial C-peptide levels in this study.

In conclusion we suggest that the change from insulin treatment to the GLP-1RA-based therapy may be a better option for uncontrolled T2DM patients who have an adequate β-cell reserve. Prospective studies with an adequate sample size are necessary to confirm the current findings.

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