Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Research Article

J Exp Clin Med
2022; 39(3): 798-802
doi: 10.52142/omujecm.39.3.39

Fasting plasma c-peptide level predicts the response of glucagon-like peptide-1 agonist (exenatide) add on to metformin monotherapy in obese type 2 diabetics

Kağan GÜNGÖR[1,*] Serkan ÖZTÜRK[2] Bülent CAN[1] Mehmet SARGIN[1]

[1] Department of Endocrinology and Metabolic Diseases, İstanbul Medeniyet University Göztepe Training and Research Hospital, İstanbul, Turkey

[2] Department of Family Medicine, İstanbul Medeniyet University Göztepe Training and Research Hospital, İstanbul, Turkey

Received: 17.04.2022 • **Accepted/Published Online:** 20.07.2022 • **Final Version:** 30.08.2022

Abstract

We aimed to evaluate the ability of serum C-peptide levels to predict glycemic control in obese type 2 diabetes (T2DM) patients in which a glucagon-like peptide-1 receptor agonist (GLP1-RA), an exenatide, was added to metformin monotherapy. This was a retrospective study, in which we enrolled 44 consecutives obese, type 2 diabetic patients receiving metformin monotherapy and have inadequate glycemic control (HbA1c >7% and <10%). Twice daily GLP1-RA (10 mcg exenatide injection) was added to the treatment. Weight, height and body mass index (BMI), in addition to fasting plasma glucose, hemoglobin A1c (HbA1c), and C-peptide levels measured baseline and at the sixth months post treatment. Regardless of the initial HbA1c level, treatment success was considered a HbA1c level below 7%. Predictors of successful glycemic control were assessed by a regression analysis. The fasting plasma C-peptide level was used as a marker of β cell function. After adding the GLP-1 RA, fasting glucose, C-peptide, BMI, and body weight decreased significantly ($p < 0.01$ for all). 27 (61.4%) patients were achieved treatment success, who have HbA1c level < 7% at the sixth month. The baseline C-peptide level was correlated with the HbA1c level 6 months post-treatment (r: 0.4, p: 0.01). Multivariate logistic regression analysis showed that the baseline fasting plasma C-peptide level was an independent predictor of successful glycemic control [exp.B: 6.6 (1.63-26-9) p: 0.008]. In a receiver operating characteristics (ROC) curve analysis, a baseline plasma C-peptide level of 2.56 ng/mL was the best cut-off value. Initial fasting plasma C-peptide levels can predict the treatment response of the GLP1-RA (exenatide 10 mcg, twice daily) add on to metformin monotherapy in obese type 2 diabetics.

Keywords: C-peptide, type 2 diabetes, GLP-1 RA, exenatide

1. Introduction

The prevalence of T2DM continues to increase worldwide mainly due to obesity, which is one of the biggest health problems today. Unless there is a contraindication to its use, metformin is recommended as the first-line drug in pharmacological treatment of T2DM. Due to the progressive nature of T2DM, many patients require treatment with additional anti-diabetic drugs including injectables and insulin at some point in their disease course (1). There is no consensus on which drug should be added to metformin monotherapy.

All drugs in diabetes treatment are aimed reducing blood glucose levels. Some drugs, such as thiazolidinediones, sulfonylureas, and insulin have side effects of weight gain and hypoglycemia (2). When considering potential drug candidates to be added to metformin monotherapy, potential adverse reactions that could further complicate T2DM treatment must be taken in to account.

Glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1 RAs) are effective glucose-lowering drugs chosen for second or third line therapy in the treatment of type 2 diabetes and prescribed in combination with metformin, other oral antidiabetic drugs and insulin (1–3). These drugs are also associated with weight loss and have a low risk of hypoglycemia in comparison to other therapies (4).

Exenatide was approved in 2005 as the first GLP-1 RA drug for the treatment of T2DM (5). Exenatide is available as a short-acting formulation for administration twice daily (BID) before meals. Exenatide BID is effective therapy for glycemic control in patients with T2DM, both as monotherapy and as a component of combination therapy (5).

The glycemic response to treatment with GLP-1 RAs is

*Correspondence: kagang@msn.com

highly variable. In the treatment of T2DM with GLP-1 RA drugs, some patients have a very effective treatment response while others may have an inadequate decrease in HbA1c (3, 6, 7). Since C-Peptide is secreted equal amounts with insulin from the pancreas, it is used to evaluate the endogenous insulin reserve in patients using insulin therapy (8, 9). Clinical markers of low β-cell function are also associated with reduced glycemic response to GLP-1 RAs therapy (10).

In the present study, we aimed to investigate the ability of serum fasting C-peptide levels predict to treatment response in obese type 2 diabetic patients in which a glucagon-like peptide-1 agonist (exenatide) was added to metformin monotherapy.

2. Materials and methods

2.1. Study subjects and design

This was a retrospective study in which 283 consecutive obese type 2 diabetic patients aged between 30 and 70 years were screened for inclusion in the study in an outpatient obesity clinic. All the included patients were receiving metformin monotherapy and they have inadequate glycemic control (HbA1c >7% and <10%). Patients who had a history of type 1 diabetes mellitus, malignancies, chronic kidney disease, chronic liver disease, pancreatitis, previous bariatric surgery were excluded from the study in addition to patients using glucocorticoids or insulin. Of these 283 patients, 44 patients were included in the present study and treated with the exenatide GLP-1 RA (injection). There were no other treatment changes during treatment changes during a 6 month follow up. The study was performed in accordance with the Declaration of Helsinki 2000. The study protocol was approved by ethnics committee of University Hospital (2020/0632) Informed consent was not required because of the retrospective nature of our study.

2.2. Data collection

The patient history, physical examination findings and anthropometric measurements (body weight and height) were obtained from the patient's charts. Other data including, weight measurements, concomitant medications and laboratory results were obtained from standard forms used in the obesity clinic. Regardless of the initial HbA1c level, treatment success was considered a HbA1c value below 7% at the sixth month. Weight was measured by Tanita (Name of Manufacturer, City, and Country) using bioelectric impedance analysis method. Blood tests were performed after 12 hours overnight fasting. Plasma C-peptide was measured using radioimmunoassay method (Immunotech). The HbA1c level was measured by high performance liquid chromatography. Fasting blood glucose was determined using the hexokinase method. At every visit, the patients were advised of the importance of diet and exercise. The body mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared (kg/m2). A BMI value larger than 30 kg/m2 was considered as obesity. Weight measurements and laboratory tests were repeated after 3 and 6 months.

2.3. Statistical analysis

Statistical analyses were carried out using SPSS, version 21.0. Normality of the data distribution was evaluated by the Kolmogorov-Smirnov test. Non-normally distributed variables were analysed by Wilcoxon's-signed-ranks test for repeated measurements. The McNemar test was used for comparisons of repeated categorical measurements. Data were expressed as mean ± standard deviation (SD) for continuous variables and frequency (percentage) for categorical variables. To determine the correlation between C-peptide and HbA1c levels Pearson's correlation coefficient was used. Predictors of treatment success 6 month post-treatment we were analysed by multivariate regression analysis. A receiver operating characteristics (ROC) curve was used to determine the appropriate cut-off value for the prediction of treatment success. The sensitivity and specificity of the best cut-off value were calculated by the areas under the curve (AUC).

3. Results

In total 44 obese T2DM patients (33 females and 11 males) were included in the study. The mean age was 51.4±8.9 years at the time of the first visit. Table 1 shows that the addition of the GLP-1 RA (exenatide 10 mcg twice daily) to metformin monotherapy resulted in statistically significant decrease in fasting blood glucose and serum C-peptide levels and HbA1c, BMI and body weight (all p<0.01).

Table 1. Average measurements and laboratory values of the patients at baseline and 6 months post-treatment

Parameter	Baseline	6 month	P value
Fasting glucose (mg/dL)	166.0±54.9	148.5±62.4	<0.001
C-peptide (ng/mL)	3.67±1.43	3.31±1.24	0.002
HbA1c (%)	7.82±1.43	6.85±1.45	<0.001
BMI (kg/m^2)	43.05±6.33	40.39±6.28	<0.001
Body weight (kg)	111.64±16.66	104.70±16.24	<0.001

BMI: body mass index, HbA1c: Hemoglobin A1c; Data are given as mean ± standard deviation

The 6-month HbA1c value of 27 (61.4%) of 44 patients who had a baseline value 7%. The frequency of HbA1c in target range was statistically increased at the 6-month follow up as compared to the baseline (p<0.001). Baseline fasting C-peptide level was correlated with HbA1c level at the 6-month follow up (r: 0.4, p: 0.01). Parameters, which could be a predictor for treatment success, were evaluated with simultaneous multiple regression analysis in Table 2. Multivariate logistic regression analysis showed that baseline fasting plasma C-peptide level was an independent predictor of successful glycaemic control [exp.B: 6.6 (1.63-26-9) p: 0.008].

Table 2. Multivariate logistic regression analysis of independent parameters of treatment success (HbA1c <7%) at sixth month

	Exp (B)	95%CI	P value
Age (years)	1.0	(0.91-1.14)	0.718
Fasting glucose (mg/dl)	1.0	(0.97-1.02)	0.908
Fasting C-peptide (ng/ml)	**6.6**	**(1.63-26.9)**	**0.008**
HbA1c (%)[1]	3.2	(0.88-11.5)	0.077
BMI (kg/m^2)[1]	1.0	(0.79-1.07)	0.326

[1]BMI: body mass index, HbA1c: hemoglobin A1c; Data are given as mean ± standard deviation

In the ROC curve analysis, 2.56 ng/mL was the best cut-off value of initial fasting plasma C-peptide for indicating the specificity (100%) and sensitivity (63.1%) of the treatment success (HbA1c<7% at 6-month) (Fig**.** 1 **and Table 3**).

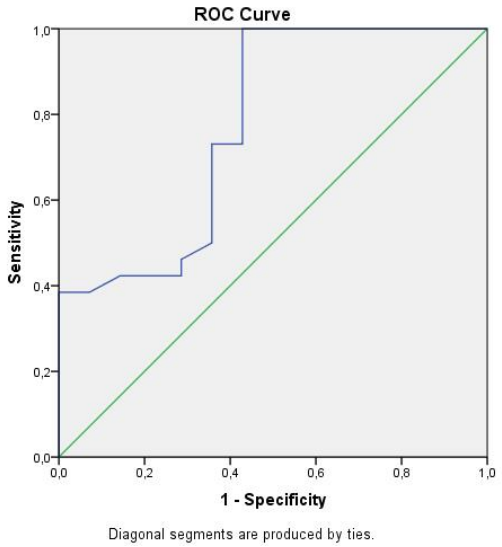

Fig.1. ROC curve showing the serum c-peptide value specificity and sensitivity for the treatment success (HbA1c<7% at the sixth month).

Table 3. Area under the curve; Test Result Valuable: Fasting c-peptide

Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.775	0.083	**0.005**	0.613	0.937

4. Discussion

The goal of this study was to determine whether the C-peptide level was a predictor of treatment success after the addition of GLP-1 RA to treatment regimen in obese type 2 diabetic patients receiving metformin monotherapy. After adding GLP-1 RA, fasting glucose, C-peptide, BMI and weight decreased. The baseline fasting plasma C-peptide level was correlated with the HbA1C level at the 6-month follow-up and the baseline fasting plasma C-peptide level was an independent predictor of glycemic control.

T2DM is associated with a progressive loss of ß-cell mass and function, which result in progressive increase in blood glucose values. Successful treatment requires understanding the disease pathogenesis. GLP-1 concentrations are reduced in patients with type 2 diabetes mellitus. GLP-1 increases insulin secretion from ß-cells, decreases glucagon release from pancreatic α-cells, promotes satiety in the brain, and slows gastric emptying.

In the literature, there are several studies reporting the safety and efficacy of exenatide. Exenatide significantly reduced HbA1c in patients with diabetes not adequately controlled by maximally effective doses of metformin (11–14). DeFronzo et al., Apovian et al. and Derosa et al. showed that exenatide 10 µg BID add on to metformin reduced HbA1c of 0.8%, 0.9% and 1.2% respectively (11,15,16). Results of our study, that showed 1.0% reduction of HbA1c at sixth month, are in concordance these results reported.

In the study of DeFronzo et al., 40% (n:41) of subjects in the 10µg exenatide arm reached an HbA1c ≤7%. In that group, change in body weight was -2.8±0.5 kg from baseline weight 101±2 kg (11). Our data demonstrated that when exenatide at dose of 10 µg twice daily is added to metformin monotherapy for 24 weeks in a group of obese type 2 diabetic patients with less than-optimal glycemic control (baseline HbA1c 7.8%), there was an overall improvement in glycaemia (end of study HbA1c 6.8%), with 61.4% of patients able to reach an HbA1c treatment goal of below 7%. In our study, as patients of the study group (baseline body weight: 111.64±16.66 kg and BMI: 43.05±6.33 kg/m2) lost 6.94 kg (6.3%) on average, it is likely that the improvement in glycemic control resulted from both the treatment and the weight loss, because a 5–10% body weight reduction in overweight/obese type 2 diabetics improve blood glucose measurements (6). Similar with our results, Appovian et al. reported that exenatide BID also showed reductions in weight (–7.3 kg) in a 24-week study in 194 overweight or obese patients with T2DM (baseline body weight: 91.4 kg and BMI: 32.9 kg/m2) on stable metformin therapy. In that study, 65% of participants on metformin plus exenatide BID achieved HbA1c goal ≤6.5% at endpoint (15).

C-peptide is a biomarker for testing and also provides support for the classification of diabetes subtypes, and assists in the staging of T2DM and its clinical management (9,17). In insulin-treated T2DM, clinical markers of low β-cell function are associated with reduced glycemic response to GLP-1RA therapy (18). C-peptide and islet autoantibodies represent potential biomarkers for the stratification of GLP-1RA therapy in insulin-treated diabetes. However, higher C-peptide levels do seem to predict response to GLP-1 agonists (10).

On the other hand, there is limited and variable evidence

to support the use of C-peptide to predict treatment response to non-insulin treatments for T2DM (10, 19). High fasting C-peptide is associated with response to the thiazolidinediones, rosiglitazone and pioglitazone, which is in keeping with their action of reducing insulin resistance (20, 21). In two cohort studies of mixed DPP4 inhibitor use has shown that initial higher fasting C-peptide predicts reduction of HbA1c (8, 22). Better insulin response to glucose is seen in those patients taking Liraglutide with higher GST c-peptide levels (23). The clinical relevance of this finding is confirmed by studies showing that fasting c-peptide predict reduction of HbA1c following initiation (10, 19).

Iwao et al. reported outcomes in 39 type 2 diabetes patients with successful glucose control and 30 type 2 diabetes with unsuccessful glucose control who were converted from the insulin therapy to monotherapy with GLP-1 RA liraglutide. Urinary, fasting and postprandial C-peptide levels were measured to assess the β-cell function (24). Unlike our study, the fasting plasma C-peptide level was not predictive of treatment success in their study. The reason for this discordance might be the differences in the BMI values between the two study cohorts (43.05±6.33kg/m2 vs. 25.4±4.2 kg/m2) and difference in the baseline C-peptide levels. Additionally, the initial fasting C-peptide values of our study, the group with treatment success and the group without treatment success, are also divergent (3.67±1.43 ng/mL, 1.8±0.9 ng/mL, 0.8±0.5 ng/mL; respectively). Furthermore, the mean BMI of the patients in the treatment success group in the study by Iwao et al. (14) was significantly higher than that of the unsuccessful treatment groups. Similar to our study, they used C-peptide levels to assess ß-cell reserves in their study. The GLP-1 RA liraglutide treatment provided weight loss and helped meet treatment targets in patients with adequate ß-cell reserve (24).

The limitations of our study are that being retrospective, have the limited number of patients, and the study population consists mostly of class 2-3 obese T2DM patients.

In conclusion, initial fasting plasma C-peptide level can predict the treatment success of the GLP1-RA (exenatide 10 mcg, twice daily) add on to metformin monotherapy in type 2 diabetics. In the future, prospective studies with larger patient populations should attempt to further elucidate the effect of fasting plasma C-peptide levels on the treatment response in T2DM.

Conflict of interest

The authors declared no conflict of interest.

Funding

No funding was used for the study.

Acknowledgments

None to declare.

Authors' contributions

Concept: K.G., Design: M.S., Data Collection or Processing: S.Ö., Analysis or Interpretation: B.C., M.S., Literature Search: B.C., Writing: M.S., K.G.

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