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Pioglitazone/Exenatide/SGLT-2 inhibitor combination therapy versus insulin therapy in patients with poorly controlled type 2 diabetes

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ABSTRACT

Aims: We aimed to investigate the changes in glycemic status and beta cell function in type 2 diabetes mellitus (T2DM) patients with poor glycemic control despite receiving basal/bolus insulin therapy when switched from insulin therapy to combination therapy [exenatide/pioglitazone/sodium glucose cotransporter 2 inhibitor (SGLT-2i)].

Methods: A retrospective examination was made of the data of 64 patients, aged >18 years, diagnosed with T2DM, who were being followed up in the endocrinology outpatient clinic and were switched from basal/bolus insulin therapy to triple combination therapy. At the time of the patients changing to combination therapy, the glycosylated hemoglobin (HbA1c) value was ≥8.5% and fasting c peptide value was within the normal reference range. The anthropometric data of the patients, and glycemic and biochemistry values with modified homeostastis model assessment β (HOMA-β) levels were compared before the combination therapy and at 6 months after.

Results: Compared to the baseline values, a decrease was seen after 6 months in the values of body weight (89.6±5.8 vs. 83.8±3.6, p=0.015), body mass index (BMI) (38.3±2.7 vs. 33.5±1.9, p=0.011), and waist circumference (105.6±8.8 vs. 99.7±6, p=0.027). A decrease was determined in fasting blood glucose (FBG) (197±27.3 vs. 129±13.1, p<0.01) and HbA1c (9.8±1.6 vs. 8.1±1.1, p<0.01) values, and an increase in the HOMA-β value [233 (187.5, 282.3) vs. 318 (272.1, 365.2), p<0.001].

Conclusion: T2DM is a complex metabolic disease with more than one disorder in the pathogenesis, so it is difficult to control the disease in the long term with a single drug class. The use of drugs in a combined form, which will allow weight loss, have a positive effect on insulin resistance and improve beta cell function, without causing hypoglycemia, can achieve a better and sustainable glycemic and metabolic status.

Keywords: Diabetes mellitus, exenatide, piogitazone, SGLT-2

INTRODUCTION

Insulin resistance and beta cell dysfunction are the main defects in Type 2 diabetes mellitus (T2DM).[1] Hyperglycemia-induced glucotoxicity exacerbates these two major defects.[2,3] Therefore, by improving beta cell function, good glycemic control prevents disease progression.[4]

In T2DM patients with poor glycemic control, it is recommended to start insulin treatment when more than one oral agent has not been successful.[5] Insulin therapy is extremely effective in lowering blood glucose levels but there are disadvantages such as the treatment being parenteral, it requires glucose follow-up at home, causes hypoglycemia, and leads to weight gain.[5] In particular, the continuation of beta cell loss together with hypoglycemia and weight gain are the most important obstacles to strict glycemic control.[6]

Pioglitazone is a potent insulin sensitizer and improves beta cell function, does not cause hypoglycemia and achieves sustained A1c reduction.[7-9] Exenatide is a glucagon-like peptide-1 receptor agonist (GLP-1 RA). GLP RAs are drugs that reduce insulin resistance by obtaining weight loss, improving beta cell function and not causing hypoglycemia.[10] Sodium glucose co-transporter 2 inhibitors (SGLT-2i) are drugs that reduce plasma glucose by forming glucosuria.[11] These anti-diabetic drugs have the properties of improving glycemic control, correcting glucotoxicity, and providing weight loss, while not causing hypoglycemia. Therefore,

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combination therapies with drugs that reduce insulin resistance and improve beta cell function would seem to be rational.[11,12]

The aim of this study was to examine the changes in metabolic parameters, glycemic status and beta cell function with transition to exenatide/pioglitazone/SGLT-2i combination therapy in T2DM patients who could not obtain sufficient glycemic control despite basal/bolus insulin treatment.

METHODS

This retrospective study was conducted in Kilis Prof. Dr. Alaeddin Yavaşca State Hospital with the written permission of the Non-interventional Clinical Research Ethics Committee of Gaziantep Islam Science and Technology University (Date: 19.12.2023, Decision No: 339.33.05). All the study procedures were in compliance with the Helsinki Declaration.

The study included 64 patients who presented at the Endocrinology Outpatient Clinic between June 2022 and April 2023, were diagnosed with T2DM, received basal/bolus insulin treatment, and were determined with glycosylated hemoglobin (HbA1c) value ≥8.5% and fasting C-peptide value within the normal reference range. Patients who had taken any of the drugs in the combination therapy (pioglitazone, exenatide, SGLT-2i) within the last 3 months were excluded from the study. All the patients met the diabetes diagnostic criteria defined by the World Health Organization (WHO) in 1999.[10,11] The information of patients age, gender, body mass index (BMI), waist circumference, duration of diabetes and diabetes-associated microvascular and macrovascular complications was recorded from the medical records.

From a blood sample taken in the morning after overnight fasting, the blood glucose, HbA1c, serum lipids, c-peptide, and estimated glomerular filtration rate (eGFR) values were measured and recorded. Pancreatic beta cell function was evaluated with the modified homeostasis model assessment-β (HOMA-β). The modified HOMA-β was calculated using the formula of 270×fasting c-peptide (ng/ml)/fasting blood glucose (mmol/l)−3.5)×0.333.[13] The basal (glargine or detemir) and bolus (aspart) insulin treatment of the patients was stopped and the switch was made to the triple combination therapy of pioglitazone 30 mg/day, exenatide (first month 2x5 mg/day, and in the following months 2x10 mg/day) and dapagliflozine 10 mg/day or empagliflozine 10 mg/day.

In Türkiye, exenatide treatment can be started for patients with BMI ≥35 kg/m², and therefore, all the patients in the study met this condition. The blood glucose, HbA1c, modified HOMA-β values, and other biochemical variables of the patients before treatment and after 6 months of treatment were compared.

Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS 28.0 software. Quantitative data were stated as mean±standard deviation values and categorical data as number and percentage. Conformity of the data to normal distribution was assessed with the Kolmogorov-Smirnov test. In the analysis of categorical variables, the Chi-square test and Fisher's Exact test were used. Normally distributed continuous variables were analyzed with the Student's t-test whereas the Mann-Whitney U Test was applied to non-normally distributed variables. The variables measured before and 6 months after treatment were compared by Paired Samples t-test when the distribution of the data was normal, and by Wilcoxon test when the data were not normally distributed. The effect of basal-bolus insulin-only and basal-bolus plus oral anti-diabetic (OAD) therapy groups, as well as the effect of baseline total daily insulin doses on outcomes at 6 months of combination therapy was evaluated by one-way analysis of variance (ANOVA). A value of $P<0.05$ was considered statistically significant.

RESULTS

Evaluation was made of 64 patients with T2DM, comprising 67% females, with a mean age of 48.7±9.9 years. The mean duration of diabetes was 9.3±5.1 years, fasting blood glucose (FBG) was determined as 188±27.3 mg/dl, and HbA1c as 9.8%±1.6%. Of the 64 patients, 43 received basal/bolus insulin treatment alone, 12 received basal/bolus insulin + dipeptidyl peptidase 4 inhibitor (DPP-4i) + metformin treatment, and 9 received basal/bolus insulin + metformin treatment. The BMI value of the patients was mean 38.3±2.7 kg/m², and waist circumference was measured as 105.6±8.8 cm.

Microvascular complications were recorded as microalbuminuria at the rate of 28.1%, retinopathy at 20.3%, and neuropathy at 42.1%. Hypertension was present in 62.5% of the patients and ischaemic heart disease in 21.8%. The lipid profile results of the study cohort are also shown in **Table 1**. The comparisons of the glycemic values, modified HOMA-β, and other metabolic parameters of the patients who switched from basal/bolus insulin treatment to triple combination treatment measured before the change and at 6 months after are shown in **Table 2**.

Table 1. Baseline characteristics of participants (n=64)

Age, years	48.7±9.9
Sex: female, n, (%)	43 (67)
BMI, kg/m²	37.3±2.7
WC, cm	105.6±8.8
Diabetes duration, years	9.3±5.1
Diabetes therapy	
Basal/bolus insulin only, n, (%)	43 (67)
Basal/bolus insulin + metformin, n, (%)	9 (14)
Basal/bolus insulin + metformin + DPP4i, n, (%)	12 (19)
Total daily dose of insulin	
<0.5 units/kg/day, n, (%)	13 (20)
0.5-0.8 units/kg/day, n, (%)	40 (63)
>0.8 units/kg/day, n, (%)	11 (17)
FBG, mg/dl	188±27.3
HbA1c, %	9.8±1.6
Triglycerides, mg/dl	276 (248, 305)
Total cholesterol, mg/dl	231 (213, 245)
LDL cholesterol, mg/dl	143 (121, 159)
HDL cholesterol, mg/dl	41 (35, 48)
eGFR, ml/min/1.73 m²	78.8±16.1
Microalbuminuria, n, (%)	18 (28.1)
Diabetic retinopathy, n, (%)	13 (20.3)
Diabetic neuropathy, n, (%)	27 (42.1)
Hypertension, n, (%)	40 (62.5)
Ischemic heart disease, n, (%)	14 (21.8)

Data are presented as the mean±SD or prevalence (%). Measurement data for skewed distribution are expressed as median (interquartile range)

Table 2. Comparison of patients switched from basal/bolus insulin therapy to combination therapy (n=64)

	Basal/bolus insulin therapy	Combination therapy (6th month)	P value
Weight, kg	89.6±5.8	83.8±3.6	0.015
BMI, kg/m²	37.3±2.7	33.8±1.9	0.011
WC, cm	105.6±8.8	99.7±6	0.027
SBP, mmHg	136 ±4.5	130.9±4.3	<0.01
DBP, mmHg	92±3.1	85±2.8	<0.01
FBG, mg/dl	197±27.3	129±13.1	<0.01
HbA1c, %	9.8±1.6	8.1±1.1	<0.01
Modifiye HOMA-β	233 (187.5, 282.3)	318 (272.1, 365.2)	<0.01
Triglycerides, mg/dl	276 (248, 305)	249 (235, 266)	0.034
Total cholesterol, mg/dl	231 (213, 245)	219 (209, 231)	0.061
LDL cholesterol, mg/dl	143 (121, 159)	133 (116, 148)	0.066
HDL cholesterol, mg/dl	41 (35, 48)	48 (43, 50)	0.029

Counting data were expressed as number (percentages, %). Measurement data for normal distribution were expressed as (mean±SD). Measurement data for skewed distribution are expressed as median (interquartile range)
BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HOMA, homeostasis model assessment

Compared to the baseline values, a decrease was seen after 6 months in the values of body weight (89.6±5.8 vs. 83.8±3.6, p=0.015), BMI (38.3±2.7 vs. 33.5±1.9, p=0.011), and waist circumference (105.6±8.8 vs. 99.7±6, p=0.027). A decrease was observed in systolic blood pressure (SBP) (136±4.5 vs. 130.9±4.3, p<0.001) and diastolic blood pressure (DBP) (92±3.1 vs. 85±2.8, p<0.001). A decrease was determined in FBG (197±27.3 vs. 129±13.1, p<0.01) and HbA1c (9.8±1.6 vs. 8.1±1.1, p<0.01) values, and an increase in the HOMA-β value [233 (187.5, 282.3) vs. 318 (272.1, 365.2), p<0.001]. At 6 months after the change in treatment, in the lipid profile there was seen to be a decrease in triglycerides (TG) value [276 (248, 305) vs. 249 (235, 266), p=0.034], and an increase in the HDL cholesterol level [41 (35, 48) vs. 48 (43, 50), p=0.029]. In addition, **Table 3** shows the comparison of the values at 6 months of combination therapy between patients receiving insulin alone at baseline and those receiving insulin plus OAD combination. Accordingly, although both groups showed improvement in glycemic values and metabolic parameters at 6 months of combination therapy, there was no significant difference between the two groups. Total daily insulin doses administered at baseline were also not associated with glycemic status, weight, BMI and WC values 6 months after switching to combination therapy (**Table 4**).

Table 4. Comparison of variables according to baseline insulin doses at 6 months of combination therapy

	Baseline insulin doses			P
	<0.5 units/kg/day (n=13)	0.5-0.8 units/kg/day (n=40)	>0.8 units/kg/day (n=11)	
ΔWeight, kg	4.7±1.1	4.7±1.2	4.9±1.2	0.071
ΔBMI, kg/m²	3.5±9	3.5±1	3.6±1.1	0.12
ΔWC, cm	5.6±1.4	5.8±1.5	5.9±1.5	0.065
ΔFBG, mg/dl	64±6.8	65±7.2	67±7.5	0.092
ΔHbA1c, %	1.7±0.4	1.7±0.3	1.7±0.4	0.234

Δ: refers to the change from baseline at the 6th month of treatment; all changes are in the negative direction
BMI, body mass index; WC, waist circumference; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin

Table 3. Comparison of patients in the 6th month of combination therapy according to their initial treatment patterns

	Only insulin therapy (n=43)		P	Insulin + OAD therapy (n=21)		P	ANOVA
	Baseline	6th month		Baseline	6th month		
Weight, kg	90.7±5.6	84.1±3.4	0.011	87.7±4.9	82.9±3.3	0.02	0.277
BMI, kg/m²	37.8±2.8	34.6±1.9	0.009	36.7±2.7	33.1±1.8	0.015	0.31
WC, cm	106.4±8.5	100.8±5.9	0.022	104.1±8.2	98.9±5.5	0.031	0.11
SBP, mmHg	137±4.6	131.7±4.2	<0.01	135.3±4.4	130±4.3	<0.01	0.078
DBP, mmHg	92±3.1	86.1±2.7	<0.01	92±2.7	84.6±2.7	<0.01	0.092
FBG, mg/dl	201±31.3	132.6±13.1	<0.01	193±28.9	127.5±13.1	<0.01	0.51
HbA1c, %	9.9±1.7	8.2±0.9	<0.01	9.6±1.7	8±1	<0.01	0.23
Modifiye HOMA-β	224 (181.5, 273.4)	311 (268, 361.1)	<0.01	239 (181.5, 273.4)	324 (258.1, 360)	<0.01	0.088

Counting data were expressed as number (percentages, %). Measurement data for normal distribution were expressed as (mean±SD). Measurement data for skewed distribution are expressed as median (interquartile range)
OAD, oral anti-diabetic; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HOMA, homeostasis model assessment; ANOVA, one-way analysis of variance

DISCUSSION

In this study, which evaluated patients who could not achieve good glycemic control with basal/bolus insulin treatment and therefore changed to triple combination (exenatide/pioglitazone/SGLT-2i) therapy, the results showed that there were improvements in glycemic control and beta cell function.

The majority of patients who start insulin treatment for T2DM continue to express residul insulin.[14] A precondition of the transition from basal/bolus insulin treatment to combination treatment in the current study was that the patients had sufficient beta cell function.

As T2DM is generally a progressive disease, there is a continuing decrease in beta cell capacity because of glucotoxicity developing, especially when glycemic control cannot be achieved.[15] Therefore, good glycemic control protects beta cell function. With the combination therapy in the current study, there was seen to be a significant decrease in fasting blood glucose and HbA1c values. Many experimental studies have shown that thiazolidine and incretin effective drugs protect beta cell function and mass.[16,17] This effect is not only the result of the improvement in glycemic status but can also be explained by other mechanisms. Pioglitazone has been shown to protect beta cells against proinflammatory cytokines and prevent the formation of islet amyloid.[18,19] Of SGLT-2 inhibitors, dapagliflozine and empagliflozine have been reported to be effective in protecting beta cell survival and improving beta cell function.[20,21] However, the majority of these studies have shown the results of examining diabetes in the early stages. Kimura et al.[22] reported that pioglitazone and liraglutide increased beta cell function and mass in the early stage of diabetes but these effects weakened as diabetes progressed. Even though patients with a relatively longer duration of diabetes were included in the current study, an increase was seen in the HOMA-β values with the combination therapy. Therefore, it can be said that the efficacy of pioglitazone and GLP-1 analogs continued when there was a beta cell reserve in the pancreas, irrespective of the duration of diabetes.

In another meta-analysis that compared the glycemic efficacy of insulin with GLP-1 analogs, there was reported to be a minimal difference in terms of glycemic efficacy and this difference was in favour of GLP-1.[23] In this respect, for patients who are planned to transition to injectable treatment, it would seen to be reasonable to start GLP-1 analogs, which increase the incretin effect and provide weight control without causing hypoglycemia, before insulin treatment. There is also greater patient compliance to GLP-1 analogs compared to insulin treatment. This is because in treatment with GLP-1 analogs, standard increasing dose titration is made at the beginning, whereas in insulin use, dose titration is made more personalised and in a wider range.[24]

One of the reasons that good glycemic control cannot be achieved in patients receiving insulin treatment is hypoglycemia. Reactive and exaggerated hyperglycemia developing after hypoglycemia causes glucotoxicity. In addition, the feeling of hunger caused by hypoglycemia leads to weight gain. "Confirmed hypoglycemia" was not seen in any of the patients in the current study after transition to combination therapy, and a significant decrease was seen in the weight, BMI, and waist circumference values of the patients. This change is due to the positive effects on weight of exenatide and SGLT-2 inhibitors in addition to eliminating the hypoglycemic effect of insulin. Moreover, the negative effects of pioglitazone such as oedema and weight gain seem to be neutralised when it is included in combination therapy.

Another important result of the current study was that a decrease in TG level and an increase in HDL cholesterol level were seen with combination therapy. When the insulin resistance status and metabolic disorders of patients with T2DM are taken into consideration, dyslipidemia is a common comorbidity.[25] Many patients with T2DM have an abnormal lipid profile characterised by increased TG and decreased HDL cholesterol.[26] In studies of many different monotherapies and combination therapies in patients with T2DM, the use or addition of pioglitazone has been shown to improve fasting and satiated TG metabolism, increase HDL cholesterol levels, and have a positive effect on lipoprotein particle size.[26] In another meta-analysis, GLP-1 RAs were shown to be associated with moderate decreases in LDL cholesterol, total cholesterol, and TG, but no significant improvement was seen in HDL cholesterol.[27] In a meta-analysis that examined the effect on lipids of SGLT-2 inhibitors, it was reported that SGLT-2 inhibitors significantly increased total cholesterol, LDL cholesterol, and HDL cholesterol, and decreased the TG level.[28]

After 6 months of combination therapy in the current study, there was seen to be a significant decrease in systolic and diastolic blood pressure values. Dapagliflozine is known to obtain a decrease of approximately 4 mmHg in systolic blood pressure.[29] This effect can be explained by a decrease in volume contraction and sympathetic nerve system activation.[30] The decrease in blood pressure provided by GLP-1 agonists can be explained by the decrease in vascular resistance, natriuresis, and weight loss.[31] Van Ruiten et al.[32] reported that combination therapy of dapagliflozine and exenatide provided a greater decrease in blood pressure than the effect of either drug alone.

Limitations

To the best of our knowledge, this is the first study in literature to have evaluated the results of exenatide/pioglitazone/SGLT-2i triple combination therapy in T2DM, and this can be emphasised as a strong aspect of the study. However, there were also some limitations, primarily the retrospective design and relatively low number of patients. In addition, the study was conducted in a second-level hospital and the results only represent a single centre.

CONCLUSION

T2DM is a progressive disease, in which several factors play a role in the pathogenesis. It is difficult to achieve sustainable glycemic control with a single drug class. The findings of this study demonstrated that the combined use of drugs with different effect mechanisms resulted in better glycemic control and beta cell function. In patients with beta cell reserve, rather than treatments which patients find difficult to adhere to such as insulin therapy, the combined use of drugs that do not cause hypoglycemia, provide weight loss, and improve cell function can provide a better and sustainable glycemic and metabolic status.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Non-interventional Clinical Researches Ethics Committee of Gaziantep Islam Science and Technology University (Date: 19.12.2023, Decision No: 339.33.05).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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