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Evaluation of glycemic control by metformin + glitazone + DPP-4 inhibitor + SGLT-2 inhibitor combination in patients with type 2 diabetes quitting basal/bolus insulin therapy

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Abstract

Type 2 diabetes mellitus is one of the most common chronic diseases worldwide and one of the highest morbidity factors. Lowering the levels of Hemoglobin A1c (HbA1c) by strict glycemic control is the most important predictor of preventing complications. Insulin, one of the long-term drugs used to achieve this goal, however adherence and persistence to insulin therapy is not so high due to some barrier such fear of injections, fear of hypoglycaemia, obesity risk etc. This study designed to retrospectively evaluate change in glycemic control of patients with type 2 diabetes who had been on insulin therapy and wanted to quit or unwilling to use insulin therapy for any reason, and given oral antidiabetic combination therapy (metformin + glitazone + DPP-4 inhibitor + SGLT-2 inhibitor). A total of 76 patients met the inclusion criteria's were retrospectively analyzed from hospital records. HbA1c, body mass index, and fasting plasma glucose levels were evaluated while using basal/bolus insulin therapy and after oral anti diabetic combination therapy. After antidiabetic combination therapy all glycemic control parameters significantly improved. 39.5% of the patients reached the glycemic target (HbA1c< 7%), and mean HbA1c level decreased 1.9%. The study suggested that metformin + glitazone + DPP-4 inhibitor + SGLT-2 inhibitor combination may be effective to maintain glycemic control in some type 2 diabetic patients who could not keep up insulin therapy and/or who developed clinical inertia.

Keywords: DPP-4, glitazone, insulin, HbA1c, SGLT-2

Introduction

Diabetes mellitus is a chronic disease caused by an inherited and/or acquired deficiency in insulin production by the pancreas or the ineffectiveness of the insulin produced. Type 2 diabetes is caused by the body's inability to respond appropriately to the effect of insulin secreted by pancreas [1]. Progressive β-cell failure and insulin resistance are the main nuclear defects responsible for the development and progression of hyperglycemia in individuals with T2DM [2]. Hyperglycemia is the main factor responsible for retinopathy and nephropathy, and each 1% decrease in HbA1c is associated with a 35% reduction in the risk of microvascular complications [3-6]. Therefore, the American Diabetes Association (ADA) recommends that HbA1c be kept at 7.0% to minimize microvascular risk in patients with T2DM [7]. According to the IDF Diabetes Atlas 2017 estimates, 425 million patients have diabetes worldwide and half of them are not even diagnosed [8].

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Diabetes prevalence according to the TURDEP-II study in Turkey is 13.7% [9]. Given this large patient population, all treatment modalities have become increasingly important.

Insulin is very effective in lowering plasma glucose concentration, but requires injection and glucose monitoring at home, causes hypoglycemia, and leads to weight gain [10]. Despite modern injection devices, fear of injections, advanced diseases, and personal failures present significant barriers in various insulin therapy modalities for some people and significantly impair compliance.

In the TEMD-2018 guideline, multiple combined drug therapy is recommended as a secondary choice for patients who cannot keep up with basal/bolus insulin treatment [11]. Progressive β-cell failure, weight gain, and hypoglycemia continue to be major obstacles to the maintenance of HbA1c in the normal range [10] with insulin therapy. In addition, hypoglycemia has been reported to be associated with an increased risk of mortality in recent clinical trials [11]. This is a dilemma for patients with poorly controlled T2DM between avoiding microvascular complications and lowering HbA1c to minimize the risk of hypoglycemia.

Metformin is the only biguanide available in many parts of the world. Its main mechanism of action is to reduce hepatic glucose output and fasting hyperglycemia. Typically, metformin monotherapy reduces HbA1c levels by an average of 1.5% [12,13]. One of its main effects is mild weight loss or maintaining weight balance [14].

Thiazolidinediones (TZDs or glitazones) are PPR gamma receptor agonists. They increase the sensitivity of muscles, fat, and liver to endogenous and exogenous insulin ("insulin sensitizers") [15]. TZDs show a decrease of 0.5%–1.4% in Hb1Ac when used as monotherapy. TZDs appear to have a more stable effect on glycemic control, especially when compared with sulfonylureas [16-18].

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a class of oral antidiabetic agents that increase the glucose-lowering effect of endogenous incretin hormones and prevent their degradation by DPP-4 enzyme [19]. DPP-4 inhibitors are better tolerated compared with many other antihyperglycemic agents, with lower adverse event rates and a better profile for hypoglycemia and weight gain [20-22].

Sodium-glucose co-carriers (SGLTs) are responsible for renal glucose reabsorption, mainly SGLT2 [23]. SGLT2 inhibitors do not target the main pathophysiological defects in T2DM (insulin resistance and impaired insulin secretion) and offer a potentially promising option in treating diabetes [24].

Unlike other blood glucose–lowering drugs, no maximum insulin dose exists at which the therapeutic effect does not occur [25]. However, the development of clinical inertia against insulin may lead to an increase in direct and indirect health care costs and serious preventable complications of diabetes by not being able to determine the appropriate dose and continuously increasing the treatment dose to achieve treatment goals [26].

For all these reasons, the aim of this study was to evaluate glycemic control from medical records and determine the success of treatment in patients who applied to the Mersin City Hospital Internal Medicine outpatient clinic for similar reasons; they did not want to continue basal/bolus insulin therapy, and a combination of only four oral antidiabetic drugs (metformin + DPP-4 inhibitor + glitazone + SGLT-2 inhibitor combination) was started. Thus, this article will provide support view that oral antidiabetic combinations can be used for some patients who couldn't comply with insulin therapy.

Material and Methods

This study was a single-center, retrospective study based on the records of patients admitted to the Internal Medicine Outpatient Clinic of Mersin City Hospital. It included patients with T2DM, aged more than 18 years, who refused treatment with various insulin combinations [(30% aspart + 70% aspart protamine insulin at 2 × 1 or 3 × 1 frequency) or (single-dose aspart or glulicin insulin with glargine or detemir insulin at 2 × 1 or 3 × 1 frequency)] because they were unable to comply with the treatment and/or did not want to use it since 2017, but who accepted combined oral antidiabetic therapy (metformin + glitazone + DPP-4 inhibitor + SGLT-2 inhibitor) without starting insulin therapy on the follow-up. The efficacy and safety of the treatment were investigated.

After obtaining necessary permissions from the Mersin Provincial Health Directorate, the ethics committee approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Çukurova University Faculty of Medicine (numbered 01/02/2019/85).

Participants and Study Design

Patients were followed up for HbA1c, weight, and fasting plasma glucose for an average of 8 months (6–16). They were initially selected from those with poor diabetes control and C-peptide level >1 (1.36–4.47) (HbA1c >7.5%, no upper class). Previous insulin doses were not considered in patient selection. Patients were evaluated according to their medical examination records, including patients who had not started a new diet, those who were in good health, and those who were followed up at least four times during the treatment. Participants' kidney and liver function tests; biochemical results such as sodium, potassium, calcium, amylase, and lipase levels; electrocardiogram results; and urinalysis were within normal limits, and pregnancy tests were negative. Patients with major organ failure, proliferative retinopathy, and albuminuria >300 mg/day were excluded. Fifty-nine (77.6%) of the patients used short-acting (insulin aspart/glulicin) insulin three times a day before meals and long-acting (glargine/detemir) insulin at 21:00 at night; the remaining therapy included premix aspart + 30% aspart protamine.

When the patients were started on the combination of metformin, glitazone, DPP-4 inhibitors, and SGLT-2 inhibitors as metformin (2 g) + sitagliptin (100 mg)/vildagliptin (100 mg)/linagliptin (5 mg)/saxagliptin (5 mg) + dapagliflozin (10 mg)/empaglyphlosin (10 mg) + pioglitazone (15–30 mg) and the insulin was gradually discontinued, the patient's need for insulin decreased to 0.2 units/(kg - day) dose. In each patient, fasting plasma glucose, body weight, and HbA1c values were measured at each follow-up examination. Drug doses were determined to maintain fasting plasma glucose at 110 mg/dL without hypoglycemia, 2-h postprandial plasma glucose at <140 mg/dL, and HbA1c at 7%.

The main criteria for success in treating patients were determined as a decrease in HbA1c. Since every 1-point decrease in the HbA1c level was considered clinically significant, treatment success was not categorized, and a statistically significant decrease was considered successful. Data obtained from the application were analyzed using the Statistical Package for Social Sciences (SPSS) 15.0. Normally distribution analyses were performed, and the nonparametric distribution of the data was determined. Initial characteristic distributions of patients were defined as median and minimum–maximum in accordance with nonparametric distribution. Descriptive statistics of responses were created. The Wilcoxon signed-rank test was used to compare HbA1c, fasting plasma glucose (FPG), body mass index (BMI), and body weight data. The Spearman correlation test was used to investigate the relationship between HbA1c difference and some other factors before and after the treatment. A P value of 0.05 or less was considered significant.

Results

After initiation of oral antidiabetics, the mean follow-up period

was 8 (±2.45) months. The initial characteristics of the study participants are presented in Table 1. The median age of the participants was 57 (36–76) years, the female/male ratio was 4, and the median value of BMI was 35.29 (27.1–52). The initial FPG median was 221.5 (143–361) mg/dL, and the HbA1c median was 9.15% (7.3–14.5). The median duration of diabetes was 14 (2–30) years. All the patients used insulin at the beginning, and the median duration of insulin use was 6 (2–20) years. Initially, 44.7% of the participants used only insulin, 34 (44.7%) used insulin and metformin, and 8 (13.1%) used insulin + metformin + OAD. The main oral antidiabetics used were 60 mg gliclazide, 3 mg repaglinide, 3 mg glimepiride, and 360 mg nateglinide. One (1.3%) of insulin + OAD users took 45 mg pioglitazone + 2 mg repaglinide. In all groups, patients used an average 2 g metformin. The median insulin dose used was 50 (26–119) units.

Table 1. Initial characteristics of study participants

	Under insulin therapy (n = 76)
Age	57 (min: 36 to max: 76)
Female, %	80.3
BMI (kg/m2)	35.29 (min: 27.1 to max: 52)
Diabetes duration (year)	14 (min: 2 to max: 30)
Basal/Bolus insulin treatment duration (year)	6 (min: 2 to max: 20)
HbAlc (%)	9.15 (min: 7.3 to max: 14.5)
FPG (mg/dL)	221.5 (min: 143 to max: 361)
Initial insulin dose (unit)	50 (min: 26 to max: 119)
Current therapy	
Basal/Bolus insulin therapy only (BBIT), %	34 (44.7%)
BBIT+ metformin, %	31 (40.7%)
BBIT+ metformin+ OAD, %	8 (13.1%)
BBIT+ OAD, %	3 (1.3%)

At the end of the study, considering the main goal (glycemic control) at least 6 months later, median HbA1c was 9.1 (7.3–14.5) before treatment, while the median value decreased significantly after the treatment (7.2–9.2) (P = 0.001). Although the initial median value of body weight was 91 kg (68–140), it decreased to 87.75 kg (63–134) with a decrease of 3.25 kg (P = 0.001). A significant decrease in BMI was observed (P = 0.001). FPG underwent one of the biggest changes. The median FPG decreased from 221 mg/dL (134–361) to 121 mg/dL (86–210) after the treatment (P = 0.001). When the same values were grouped and compared according to the insulin combination used before the treatment (premix vs three doses of short-acting insulin + one dose of long-acting insulin), no significant difference was found in glycemic control (P > 0.05). Table 2 presents the glycemic control changes of participants after combined oral therapy. Patients did not report hypoglycemia by clinical or glycemic measurement during the treatment.

HbA1c values of patients before and after treatment are presented in Table 3. The results showed that although none of the HbA1c levels were below 7% before the treatment, metformin + glitazone + DPP-4 inhibitor + SGLT-2 inhibitor combination therapy decreased the HbA1c levels of 39.5% of the patients to 7% and below.

The correlation of some characteristics of patients with HbA1c change after treatment is presented in Table 4. No correlation was found between the efficacy of combination therapy in lowering HbA1c and age and onset. A significant negative correlation was observed with the duration of diabetes and a weak positive correlation with the total insulin dose before OAD.

Table 2. Changes in glycemic control after combined oral therapy

	Under insulin therapy n =76	**After metformin + glitazone + DPP-4 inhibitor+ SGLT-2 inhibitor treatment n =76**	**P***
HbAlc (%)	9.1 (7.3–14.5)	7.2 (5.2–9.5)	0.001**
Body weight (kg)	91 (68–140)	87/75 (63–134)	0.001**
BMI	35.29 (27.14–52.05)	34.18 (25.88–49.82)	0.001**
FPG (mg/dL)	221 (134–361)	121 (86–210)	0.001**

*Probability value
**Wilcoxon signed-rank test

Table 3. HbA1c levels of patients during basal/bolus insulin and combined oral antidiabetic therapy

HbA1c levels	Basal/Bolus insulin *	Combined oral* antidia-betics
Hba1c ≤7%	0% (n = 0)	39.5% (n = 30)
Hba1c 7.1%–7.5%	2.6% (n = 2)	35.5% (n = 27)
Hba1c 7.6%–8%	14.5% (n = 11)	15.8% (n = 12)
Hba1c 8.1%–9%	31.6% (n = 24)	7.9% (n = 6)
Hba1c >9%	51.3% (n = 39)	1.3% (n = 1)

*Column percentage

Table 4. Correlation of HbA1c variation and some characteristics of patients

			Diabetes duration (year)	Age	Initial BMI	Total insulin dose before OAD
Spearman's rho	**HbA1c change**	**Correlation coefficient**	–.249	.121	.090	.260
		P	.030*	.298	.438	.024*
		N	76	76	76	76

*Column percentage

Discussion

Since the main goal of the present study was to evaluate glycemic control, the change in HbA1c level was the main finding. In patients previously under insulin therapy as the main treatment, the median HbA1c level decreased significantly by 1.9% (1.7–5) and decreased from 9.1% to 7.2% (P=0.001) after switching to metformin + glitazone + DPP-4 inhibitor + SGLT-2 inhibitor therapy after at least the 6-month follow-up.

The decrease in the level after cessation of basal/bolus insulin therapy showed that the combination therapy had a higher effect on HbA1c. In a study comparing exenatide + pioglitazone with insulin + sulfonylurea + metformin, oral exenatide + pioglitazone combination [27] achieved an average HbA1c reduction of 3.3% and a significant weight gain. This difference was thought to be due to inadequate medications used (not taking insulin therapy, and so forth).

In a meta-analysis by Esposito et al., 98 randomized controlled trials were examined. The analysis reported that DPP-4 inhibitors showed a statistically significant decrease in HbA1c compared with placebo alone. The average value of HbA1c decreased by 0.77%, the weight remained constant, and the higher HbA1c levels decreased more [28]. The HbA1c decrease was higher in the present study due to the separate effect of combined drug use.

In the present study, the patients lost an average of 3.5 kg (P = 0.001) because metformin and SGLT-2 [29] inhibitors also support weight loss. Since each 1% decrease in HbA1c reduces microvascular complications [3-6], the decrease in the present study was statistically and clinically significant. In a meta-analysis [30] of 45 studies on the use of SGLT-2 inhibitors in T2DM [30], SGLT-2 inhibitors alone could reduce HbA1c by 1.3% and cause weight loss, and these results were consistent with the findings of the present study.

In a meta-analysis by Clar et al. [31] on the use of pioglitazone in T2DM [31], when added to insulin therapy, pioglitazone posed a risk of weight gain and hypoglycemia, resulting in an average HbA1c reduction of 0.58%. In the present study, pioglitazone was not added to insulin. Hence, the combination therapy did not cause weight gain and hypoglycemia and helped in glycemic control. This suggested that pioglitazone was more compatible with other oral antidiabetics than with insulin.

The median fasting blood sugar of the participants decreased from 221 (134–361) to 121 (86–210) (P = 0.001). All drugs used in the present study had a direct or indirect effect on fasting blood sugar [32]. However, their effectiveness might be since patients who did not want to use insulin in the present study could not keep up with regular insulin use. Although none of the participants had HbA1c levels below 7% while under basal/bolus insulin therapy, the level in 39.5% receiving combined oral antidiabetic treatment decreased to below 7%, which is the target of ADA [7]. When the ≤7.5% level is considered, it increased from 2.6% to 70% and it is the target where the mortality related to the complications of diabetes is least seen [33].

Conclusions

In the present study, metformin + glitazone + DPP-4 inhibitor + SGLT-2 inhibitor combination significantly decreased HbA1c in patients who developed clinical inertia for basal/bolus insulin-based therapy, indicating that the glycemic control was achieved in the majority of the patients. The risk of hypoglycemia and side effects was found to be very low. Based on these results, additional conclusions were drawn:

• Metformin + glitazone + DPP-4 inhibitor + SGLT-2 inhibitor

combination may be effective and the safe to maintain glycemic control in some type 2 diabetic patients who could not keep up insulin therapy

• And more importantly; is insulin treatment being given too early? Is insulin administration being started unnecessarily?

Conflict of interest
The authors declare that there are no conflicts of interest.

Financial Disclosure
All authors declare no financial support.

Ethical approval
The study protocol has approved from local ethic committee

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