ANATOL J FAMILY MED

Original Article

The Anatolian Journal of Family Medicine

DOI: 10.5505/anatoljfm.2021.87049
Anatol J Family Med 2021;4(2):165–169

Sitagliptin Add-on to Metformin Plus Sulphonylurea Combination Therapy: The Efficacy of Triple Therapy on Metabolic and Glycemic Control in Type 2 Diabetes

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Please cite this article as:
Kısıoğlu SV, Can Ö, Tekin S, Sargın M. Sitagliptin Add-on to Metformin Plus Sulphonylurea Combination Therapy: The Efficacy of Triple Therapy on Metabolic and Glycemic Control in Type 2 Diabetes. Anatol J Family Med 2021;4(2):165–169.

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Received Date: 08.09.2020
Accepted Date: 11.03.2021
Published online: 20.08.2021

ABSTRACT

Objectives: This study aimed to evaluate the efficacy of sitagliptin add-on metformin and sulphonylurea combination therapy in type 2 diabetic patients with insufficient glycemic control.

Methods: This study included who were treated with sitagliptin and continued with sitagliptin for 12 months while receiving metformin-sulphonylurea combination. The fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) levels of the patients were measured at the initial, 3rd month, 6th month and 12th month.

Results: A total of 40 patients were included in this study. The mean age patients was 59.2±9.6 years and initial HbA1c level was 7.6% (7.0-10.5). The HbA1c level of the patients was 6.8% (5.9-8.7) at 3 months, 6.7% (5.3–7.5) at 6 months, and 6.9% (5.4–9.1) at 12 months ($p<0.001$ for 0-3. months, $p<0.001$ for 0-6. months, $p=0.003$ for 0-12. months).

Conclusion: Adding sitagliptin to the treatment is an effective and well-tolerated option in patients with type 2 diabetes who are not able to achieve adequate glycemic control despite metformin–sulphonylurea combination treatment.

Keywords: Blood glucose, glycated hemoglobin A1c, sitagliptin, metformin, drug combination

INTRODUCTION

Diabetes is a complex, chronic entity that requires strategies to reduce multiple risk factors and continuous medical care well beyond glycemic control.[1] Oral antidiabetic drugs (OAD) are continuously being approved for the treatment of type 2 diabetes, leading to more diverse combination possibilities before treatment intensification and forefront combination therapies. The American Diabetes Association (ADA) Standards of Medical Care in Diabetes 2019 guideline advises a combination therapy of two drugs if hemoglobin A1c (HbA1c) levels are >1.5% of the aimed rate. Meanwhile, The American Association of Clinical Endocrinologists and The American College of Endocrinology (AACE/ACE) 2019 guidelines advise for double drug treatment as a first-line approach in patients with ≥7.5% HbA1c.[1,2] Data on the outcomes of adding a third OAD into the double treatment, including metformin,

continues to be scarce according to ADA 2019 guidelines even though diversity in combination therapies greatly varies.[1]

Dipeptidyl peptidase-4 (DPP-4) is an enzyme that plays a role in the inactivation of active incretin hormones, glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic peptide (GIP).[3] Both GLP-1 and GIP are secreted into the bloodstream by the intestine as a result of oral food intake and both insulin secretion dependent on glucose intake. Furthermore, GLP-1 suppresses glucagon release and inhibits active incretins for degradation. However, sitagliptin raises active incretin concentration and enhances their glycemic control ability.

The combination of DPP-4 inhibitors and GLP-1 analogs was found in effective.[4] Therefore, DPP-4 inhibitors can be used in combinations aside from GLP-1 analogs. Sulfonylureas (SU) can cause hypoglycemia, weight gain, and, in progress, HbA1c elevation even though they can provide short-term glycemic control.[5] Thus, effectiveness depends on suitable patients although this group is one of the most used OAD worldwide.

The aim of study was to evaluate the effect of adding sitagliptin on the glycemic change of patients who had >7% HbA1c while both on metformin and SU therapy.

METHOD

Type 2 diabetes patients who applied to Kartal Lutfi Kırdar Training and Research Hospital Family Medicine Diabetes Unit and Endocrinology and Metabolic Diseases Clinic between May 2011 and October 2012 and were sitagliptin added to combination treatment metformin and SU were included in this retrospective study. All patients had >7% HbA1c when sitagliptin (100 mg) was commenced. Age, weight, body mass index (BMI), fasting plasma glucose (FPG), HbA1c, creatinine, low-density lipoprotein (LDL) cholesterol and alanine transaminase (ALT) parameters were included.

The fasting blood samples of all patients were taken from the antecubital vein after overnight fasting (at least 8 h). Moreover, biochemical parameters were studied from plasma samples. FPG levels were measured using the enzymatic reference method with hexokinase (Beckman Coulter AU5800, Brea, CA, USA), and plasma HbA1c levels were measured by high-performance liquid chromatography and mass spectroscopy method (Trinity Biotech Premier HB9210, Kansas, MO, USA). Moreover, plasma creatinine was assessed using the kinetic Jaffé method (Beckman Coulter AU5800, Brea, CA, USA).

Data were analyzed using SPSS 23.0 for Windows (Armonk, NY: IBM Corp.). Normal distribution of data was assessed using Kolmogorov-Smirnov test and Shapiro-Wilk test. Descriptive data were expressed as frequency and percentage for categorical variables and as mean, standard deviation, median, minimum, and maximum for continuous variables. Paired sample t test was used for variables with a normal distribution, and Wilcoxon signed-rank test was used for variables without a normal distribution. A p value of <0.05 was considered significant.

RESULTS

This study included 40 patients who had added sitagliptin on their treatment while on metformin–SU combination and the mean age was 59.2±9.6 years. The metabolic and anthropometric features at the initial of the treatment are summarized in Table 1.

The initial HbA1c and FPG levels were determined as 7.6% (7.0–10.5) and 170.0 mg/dL (74.0–257.0), respectively. The changes in HbA1c and FPG levels with sitagliptin therapy are summarized in Table 2.

When other metabolic parameters were evaluated between the at initial and end of the study, the mean LDL cholesterol, ALT, and creatinine values at the end of the study were found 105.1±25.8 mg/dl, 24.5±10.1 IU/L, and 0.8±0.3 mg/dl, respectively (p=0.738, p=0.237, p=0.563, respectively).

Table 1. The metabolic and anthropometric features at the initial of the treatment

	Mean±SD
Age (years)	59.2±9.6
Height (cm)	161.3±9.3
Weight (kg)	80.3±14.4
BMI (kg/m^2)	30.8±5.7
LDL cholesterol (mg/dl)	107.0±32.4
Creatinine (mg/dl)	0.8±0.2
ALT (IU/L)	22.6±10.0
	n (%)
Sulfonylurea	
Glimepride	24 (60.0)
Gliclazide	16 (40.0)
	Median (Min-Max)
FPG (mg/dL)	170.0 (74.0–257.0)
HbA1c (%)	7.6 (7.0–10.5)

ALT: Alanine transaminase; FPG: Fasting plasma glucose; LDL cholesterol: Low-density lipoprotein cholesterol; SD: Standard deviation.

Table 2. The changes in HbA1c and fasting plasma glucose levels with sitagliptin therapy

	HbA1c (%)	p	FPG (mg/dl)	p
3rd month	6.8 (5.9–8.7)	<0.001*	142.0 (90.0–279.0)	0.001*
6th month	6.7 (5.3–7.5)	<0.001*	146.0 (105.0–224.0)	0.036*
12th month	6.9 (5.4–9.1)	0.003*	142.0 (83.0–218.0)	0.002*

FPG: Fasting plasma glucose.
Data are presented as median (min-max) value.
Wilcoxon test.
*HbA1c and FPG levels were compared with the initial of treatment.

DISCUSSION

This study evaluated sitagliptin, a DPP-4 inhibitor, for 12 months which showed as an effective treatment option for patients using both metformin and SU. In a study by Hermansen et al. in 2007, the patients who had glimepiride monotherapy and metformin–glimepiride combination therapy was evaluated by adding sitagliptin into their treatment.[6] In this 511-patient group, placebo-controlled 24-week-long trial, the initial HbA1c level was 8.4%. Of the patients, 364 completed the trial. After 24 weeks, the glimepiride–sitagliptin group had a 0.3% and 0.88 mg/dL decrease in HbA1c and FPG levels, respectively. Meanwhile, 0.59%, 7.8 mg/dL, and 21.3 mg/dL were the decrease in the HbA1c, FPG, postprandial plasma glucose (PPG) (2nd hour) in the metformin–SU–sitagliptin group, respectively. Furthermore, adding sitagliptin to the combination therapy proved to be more effective than adding it to the glimepiride monotherapy for glycemic control. Moreover, the combination group gained weight from the initial recordings. Another study, Jianming et al. evaluated 440 patients who had gliclazide or glimepiride treatment whether combined with metformin or not.[7] In that study, 230 patients had added sitagliptin in their treatment and 210 patients are placebo. In the subgroup analysis, 111 patients were treated with metformin–SU and had added sitagliptin with 0.86%, 22.2 mg/dL, and 33.4 mg/dL decline in HbA1c, FPG, and PPG levels after 24 weeks of treatment, respectively. Those two placebo-controlled 24-week long studies reported statistically relevant HbA1c level decrease similar to the current study.

Owens et al. evaluated the 774-stable metformin–SU treated patient group in a placebo-controlled study using linagliptin for 24 weeks.[8] In addition, a 0.72% decline was found in the initial HbA1c level at 24 weeks. The FPG decline was reported as 5.4 mg/dL as the mean weight gain of patients was 0.27 kg. In another placebo-controlled study by Moses et al., a 127-patient group who had stable doses of metformin–SU combination had saxagliptin for 24 weeks.[9] After 24 weeks, a 0.74% decline was reported in the initial mean HbA1c level. The FPG and PPG decline were 5.2 and 11.7 mg/dL, respectively. The mean weight gain during the study was reported as 2.2 kg. In a 24-week randomized controlled study comparing the addition of sitagliptin or telegliptin to the treatment of 201 patients who had insufficient blood glucose control despite receiving treatment with metformin plus glimepiride, both groups achieved significant reductions from baseline in HbA1c.[10] These suggested that DPP-4 inhibitors had a group effect in HbA1c reduction in combination therapy.

However, when baseline FPG was compared to final FPG, the decrease in FPG was not statistically significant by Hermansen, Owens, and Moses, but relative FPG was found to be statistically significant when placebo was evaluated.[6,8,9] These studies have insignificant results regarding FPG decline while having statistically relevant HbA1c decline. The study by Jianming et al. found that FPG decline was statistically relevant.[7] In a previous study, adding sitagliptin to metformin therapy showed a 0.86% decline in HbA1c on month 6 while the pre-prandial glycemic decline was 26.07 mg/dL.[11] This study found a visible sitagliptin effect on HbA1c levels starting on month 3, becoming most prominent on month 6, and decreasing in month 12, which was found to be statistically relevant. Taking both studies into consideration, sitagliptin statistically decreases both FPG and HbA1c significantly in Turkish society.

In another study by Moses et al., sitagliptin add-on for the metformin–SU treatment was evaluated for 52 weeks.[12] The decreases on week 24 were 0.84%, 12.6 mg/dL, and 36 mg/dL on HbA1c, FPG, and PPG, respectively. Moreover, the decreases on 52 weeks were 0.65%, 5.4 mg/dL, and 28.8 mg/dL on HbA1c, FPG, and PPG, respectively. Similar to this study, glycemic-control effectiveness decreased at the end of the current study.

In a randomized, open-label, parallel-assignment clinical trial, patients who had in adequate glycemic control despite a minimum 6-month active treatment with metfor-

min plus gliclazide were enrolled in a study to compare the efficacy of sitagliptin versus pioglitazone as add-on drugs in patients with poorly controlled diabetes with metformin and SU.[13] The mean HbA1c changes from baseline to week 52 were −1.9% and −1.8% for the pioglitazone and sitagliptin groups, respectively. However, no significant difference in HbA1c reduction was observed between the treatment groups during the study. Both pioglitazone and sitagliptin decreased FPG during the study, but the FPG changes from the baseline were greater in the pioglitazone group. In a 52-week, randomized, double-blind, active-controlled, phase-3 study, subjects using stable metformin plus SU received canagliflozin or sitagliptin daily.[14] The primary endpoint was the change from baseline in HbA1c at 52 weeks. At 52 weeks, canagliflozin (300 mg) and sitagliptin (100 mg) both reduced HbA1c. In studies comparing combination therapies, sitagliptin gave positive results.[13,14] Thus, sitagliptin is an effective treatment option when compared with different OAD.

This study has some limitations. This study was retrospective and cross-sectional. The PPG levels of the patients were not evaluated. The change in BMI could not be evaluated since regular body weight measurements were not performed in all patients. The frequency of hypoglycemia could not be evaluated in our study. Sample size analysis was not conducted prior to the study.

CONCLUSION

The current study confirmed that sitagliptin is an effective treatment option in patients treated with metformin and SU who require more intensive therapy. Moreover, sitagliptin has a success rate in decreasing FPG and HbA1c both in adding on metformin–SU combinations.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Funding: No funding was received for this study.

Ethics Committee Approval: The study protocol was approved by Kartal Lutfi Kırdar Training and Research Hospital Ethics Committee (Approval date: October 10, 2012, and Approval number:10.09/87).

Authorship Contributions: Concept – M.S.; Design – M.S.; Supervision – M.S.; Materials – M.S., S.T.; Data collection &/or processing – S.V.K., O.C.; Analysis and/or interpretation – S.V.K., S.T.; Literature search – S.V.K., O.C.; Writing – S.V.K.; Critical review – S.T., M.S.

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