

Comparison of The Efficacy of Sitagliptin With Pioglitazone on Blood Glucose Control in Type 2 Diabetic Patients

Nasser Aghamohammadzadeh ^{1,2}, Vahideh Sadra ², Amir Mehdizadeh ², Sarvin Dalil ¹, Jalil Houshyar ², Akbar Aliasgarzadeh ², Mostafa Najafipour ^{3,4}, Farzad Najafipour ^{1,2*}

¹ Department of Internal Medicine, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran. ² Endocrine Research Center, Tabriz University of Medical Sciences, Tabriz, Iran. ³ Young Researchers and Elite Club, Ardabil Branch, Islamic Azad University, Ardabil, Iran. ⁴ Department of Internal Medicine, Faculty of Medicine, Azad Ardabil University of Medical Sciences, Ardabil, Iran.

Abstract

Background: Type 2 diabetes mellitus (DM) is a progressive chronic disorder that necessitates appropriate treatment and management in order to prevent complications. Thiazolidinediones such as pioglitazone and Dipeptidyl peptidase-4 inhibitors (DPP4i) such as sitagliptin have recently been used for type 2 DM control. The aim of this study was to compare the effects of sitagliptin or pioglitazone on the treatment of diabetic patients with poor control of glycemic status following metformin and sulfonylurea administration. **Methods & Materials:** In this randomized clinical trial, 90 patients with uncontrolled type 2 DM under treatment with full-dose metformin (1500 to 2000 mg/day) and sulfonylureas (glibenclamide 15 to 20 mg/day) were enrolled. The patients were allocated into two groups with equal numbers. One group received a single dose of pioglitazone (30 mg/day) and the other received a single dose of sitagliptin (100 mg/day) as the third medication. Fasting blood sugar (FBS), two hours postprandial blood sugar (2hpp), and HbA1c were assessed before and after three months of treatment. **Results:** FBS level in the sitagliptin group was higher than the pioglitazone group; however, this difference was not statistically significant (131.27 ± 39.18 versus 123.47 ± 36.73 , $p=0.234$, respectively). No significant differences were also observed in HbA1c (7.18 ± 0.86 versus 7.23 ± 1.03 , $p=0.572$, respectively) and 2hpp (193.56 ± 63.02 versus 198.58 ± 51.5 , $p=0.992$, respectively) after treatment between sitagliptin and pioglitazone groups. Mean weight in the sitagliptin group was lower compared to the pioglitazone group after treatment, however, this difference was not statistically significant ($p=0.902$). **Conclusion:** Both sitagliptin and pioglitazone as a third oral agent had similar efficacy in the control of the glycemic state. Considering the possible higher risk of weight gain after pioglitazone treatment, sitagliptin administration especially in overweight type 2 DM patients with poor glycemic control may be beneficial rather than the other oral agents.

Keywords: Pioglitazone, Sitagliptin, Type 2 Diabetes Mellitus

INTRODUCTION

Type 2 diabetes mellitus (DM) is a chronic progressive disease with complex pathophysiology including insulin resistance, decreased insulin secretion, and increased hepatic glucose production ^[1]. Thiazolidinediones are PPAR- γ (Peroxisome Proliferator-Activated Receptor γ) receptor agonists ^[2, 3] and improve insulin resistance in adipose, muscle, and liver tissues ^[4]. Pioglitazone is also a medication belonging to the thiazolidinedione class of drugs that increases glucose uptake in skeletal muscle and adipose tissue and reduces hepatic glucose production ^[5]. Additionally, it affects glycemic control and improves some of the disruptive elements of fat in diabetes mellitus ^[3]. Pioglitazone can cause side effects including bladder cancer, bone loss, bone fractures, weight gain, painful lower extremity edema, and congestive heart failure ^[6].

DPP-4 inhibitors, including sitagliptin, improve glucose metabolism by stimulating GLP-1 receptors. GLP-1 receptor stimulation causes insulin secretion stimulation and inhibits

glucagon secretion in the pancreas and ultimately improves postprandial blood sugar ^[7, 8].

Despite the favorable efficacy of both drugs, insufficient studies have been conducted to compare the use of sitagliptin

Address for correspondence: Farzad Najafipour, M.D., Endocrine Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
E-mail: farzadnajafipour @ gmail.com

This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work noncommercially, as long as the author is credited and the new creations are licensed under the identical terms.

How to cite this article: Aghamohammadzadeh, N., Sadra, V., Mehdizadeh, A., Dalil, S., Houshyar, J., Aliasgarzadeh, A., Najafipour, M., Najafipour, F. Comparison of the efficacy of Sitagliptin with Pioglitazone on blood glucose control in type 2 diabetic patients. Arch Pharma Pract 2019;10(3):52-5.

and pioglitazone. On the other hand, the reported results on the effects of these two drugs are contradictory [9-11]. Therefore, this study was designed to evaluate the effects of sitagliptin and pioglitazone administration on the treatment of diabetic patients with glycemic status poor control following metformin and sulfonylurea therapy.

METHOD AND MATERIAL

Patients

This randomized clinical trial study was performed on 90 patients referred to Imam Reza Medical Research & Training Hospital at Tabriz University of Medical Sciences from March 2018 to March 2019. The age range of patients was 30 to 65 and treated with a full dose of metformin (1500 to 2000 mg/day) and one dose of sulfonylurea (glibenclamide 15 to 20 mg /day), and their diabetes was not controlled (HbA1c > 7%).

Inclusion criteria were Type 2 diabetic, taking a full dose of metformin (1500-2000 mg) and one dose of sulfonylurea (15-20 mg), the age range of 30-65 years, HbA1c \geq 7%, reluctance to take insulin and willingness to participate in the study. Pregnancy, heart failure, renal failure, history of bladder cancer, severe glycemic complications including diabetic ketoacidosis (DKA), unwillingness to participate or continue the study were also considered as exclusion criteria.

Patients were then randomly allocated into two groups with equal numbers. One group received a single dose of pioglitazone 30 mg/day and the other received a single dose of sitagliptin 100 mg/day as a third medication. Fasting blood sugar and HbA1c levels were assessed before and after three months of treatment. This study was approved by the Ethics Committee of Tabriz University of Medical Sciences (Code: IR.TBZMED.REC.1395.397) and registered in the Iranian Registry of Clinical Trials (IRCT code: IRCT201704246712N3)

Statistical Analysis

Statistical analyses were performed by statistical package for social science (SPSS) software version 22. After checking the normality of data distribution, the mean level of the parameters was compared using t-test and chi-square analysis. A paired t-test was used to compare the mean changes in each drug group before and after taking the drug. The independent t-test was used to compare the mean changes between the two groups. $P \leq 0.05$ was considered as statistically significant.

RESULTS

Table 1 shows the general characteristics and frequency of comorbidities in studied groups. Of 90 patients involved in the study, 32 (71.11%) and 28 (62.22%) were female in sitagliptin and pioglitazone groups, respectively. The mean age of sitagliptin and pioglitazone groups was 53.26 ± 6.68 and 54.75 ± 6.27 , respectively. The frequency of comorbidities analysis including hypertension (HTN),

hyperlipoproteinemia (HLP), toxic adenoma, and breast cancer showed no statistical differences between groups.

Table 2 also represents the variations in measured parameters Before and after intervention among or between groups. A significant reduction in FBS (178.48 ± 41.42 versus 131.27 ± 39.18 , $p < 0.0001$ and 189.64 ± 49.24 versus 123.47 ± 36.73 , $p < 0.0001$, respectively), 2hpp (272.6 ± 66.01 versus 193.56 ± 63.02 , $p < 0.0001$ and 304.75 ± 87.58 versus 198.58 ± 51.5 , $p < 0.0001$, respectively) and HbA1c (8.55 ± 1.31 versus 7.18 ± 0.86 , $p < 0.0001$ and 8.42 ± 1.0 versus 7.23 ± 1.03 , $p < 0.0001$, respectively) were observed in sitagliptin or pioglitazone groups. No significant differences were observed in parameters after intervention between groups.

DISCUSSION

Type 2 diabetes mellitus is a chronic, progressive disease that requires appropriate treatment and management in order to prevent complications [1, 2]. Various drugs have been introduced for diabetes treatment. Thiazolidinediones (such as pioglitazone) and DPP-4 inhibitors (such as sitagliptin) are the most recent therapeutic agents [4, 7, 8]. In this study, the effects of the addition of sitagliptin and pioglitazone to the treatment of those patients whose glycemic status was not controlled by metformin and sulfonylurea were investigated. The results of the present study showed no significant differences between the two groups regarding the comorbidities frequency, weight, and BMI, as well as glycemic tests including FBS, 2hpp, and hemoglobin A1C. After treatment, both drugs significantly reduced fasting blood sugar, 2hpp, and hemoglobin A1C among groups. However, no significant differences were observed between the two groups regarding the FBS, 2hpp, and hemoglobin A1C levels, indicating the equal glycemic control status in the studied population. In the side effects evaluation of drugs, patients taking pioglitazone showed a higher but not significant weight gain compared to the sitagliptin group. Additionally, BMI also showed no significant differences between groups after intervention.

The efficacy of pioglitazone in the present study was in line with the results of previous studies. Goldberg *et al.* [12] in a double-blind clinical trial showed that pioglitazone significantly decreased the FBS and HbA1c levels and improved the lipid profile of patients.

The efficacy of sitagliptin was also in line with the results of previous studies. Aschner *et al.* [13] in a study reported that sitagliptin as a monotherapy in type 2 diabetic patients significantly reduced FBS, 2hpp, and HbA1c levels compared to the placebo group. This study also showed no significant difference in the weight of patients taking sitagliptin compared to pre-treatment status. Goldstein *et al.* [14] in a placebo-controlled double-blind clinical trial also showed a significant decrease in HbA1c levels in patients receiving sitagliptin compared to placebo. Chawla *et al.* [10] evaluated the effect of sitagliptin or pioglitazone in patients with uncontrolled type 2 diabetes mellitus and reported no

significant differences in FBS levels between two groups. However, BMI and weight were significantly decreased in the sitagliptin group. Additionally, pioglitazone administration resulted in a significant weight gain.

Regarding the action mechanism of two drugs, pioglitazone is a medication belonging to the thiazolidinedione class increasing glucose uptake in skeletal muscle and adipose tissue and reduces hepatic glucose production^[5]. In contrast, sitagliptin is a DPP-4 inhibitor leading to glucose metabolism improvement through GLP-1 receptor stimulation. GLP-1 receptor stimulation causes insulin secretion and inhibits glucagon secretion in the pancreas and ultimately improves postprandial blood sugar^[7,8]. Although the two drugs control blood sugar with different mechanisms, as shown in this study and most of the studies mentioned above, the two drugs have similar efficacy.

The present study had some limitations. According to many previous studies on drug side effects, the most emphases were on weight changes in this study and the other side effects were not evaluated in both groups. Additionally, the placebo group and the different doses of the drug were not evaluated because of the limitation in the number of admitted patients.

CONCLUSION

The results of the present study showed that both pioglitazone and sitagliptin have a similar effect on glycemic control status type 2 diabetic patients. However, for side effects (especially weight gain) evaluation of the used drugs, further studies with larger sample sizes are still required.

ACKNOWLEDGMENTS

This work has been done as part of the specialty Dissertation for Dr. Sarvin Dalil. This study was supported by the Endocrine Research Center at Tabriz University of Medical Sciences, Iran [Grant No: 58420].

Conflict of interest

Authors declare no conflict of interest.

REFERENCES

1. Derosa G, Cicero A, Franzetti I, Querci F, Carbone A, Piccinni M, D'Angelo A, Fogari E, Maffioli P. A comparison between sitagliptin or glibenclamide in addition to metformin+ pioglitazone on glycaemic control and β -cell function: the triple oral therapy. *Diabetic Medicine*. 2013;30(7):846-54.

2. Qaseem A, Barry MJ, Humphrey LL, Forciea MA. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline update from the American College of Physicians. *Annals of internal medicine*. 2017;166(4):279-90.
3. Olefsky JM. Treatment of insulin resistance with peroxisome proliferator-activated receptor γ agonists. *The Journal of clinical investigation*. 2000;106(4):467-72.
4. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ. The diagnosis and management of non-alcoholic fatty liver disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology*. 2012;55(6):2005-23.
5. Derosa G, Maffioli P. Peroxisome proliferator-activated receptor- γ (PPAR- γ) agonists on glycemic control, lipid profile and cardiovascular risk. *Current molecular pharmacology*. 2012;5(2):272-81.
6. Vinodraj K, Nayak IN, Rao JV, Mathai P, Chandralekha N, Nitasha B, Rajesh D, Chethan TK. Comparison of the efficacy of liraglutide with pioglitazone on dexamethasone induced hepatic steatosis, dyslipidemia and hyperglycaemia in albino rats. *Indian journal of pharmacology*. 2015;47(2):181-4.
7. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *The Lancet*. 2006;368(9548):1696-705.
8. Ellis S, Moser E, Snell-Bergeon JK, Rodionova A, Hazenfield R, Garg S. Effect of sitagliptin on glucose control in adult patients with Type 1 diabetes: a pilot, double-blind, randomized, crossover trial. *Diabetic Medicine*. 2011;28(10):1176-81.
9. Takihata M, Nakamura A, Tajima K, Inazumi T, Komatsu Y, Tamura H, Yamazaki S, Kondo Y, Yamada M, Kimura M, Terauchi Y. Comparative study of sitagliptin with pioglitazone in Japanese type 2 diabetic patients: the COMPASS randomized controlled trial. *Diabetes, Obesity and Metabolism*. 2013;15(5):455-62.
10. Chawla S, Kaushik N, Singh NP, Ghosh RK, Saxena A. Effect of addition of either sitagliptin or pioglitazone in patients with uncontrolled type 2 diabetes mellitus on metformin: A randomized controlled trial. *Journal of pharmacology & pharmacotherapeutics*. 2013;4(1):27.
11. Liu S-C, Chien K-L, Wang C-H, Chen W-C, Leung C-H. Efficacy and safety of adding pioglitazone or sitagliptin to patients with type 2 diabetes insufficiently controlled with metformin and a sulfonylurea. *Endocrine Practice*. 2013;19(6):980-8.
12. Goldberg RB, Kendall DM, Deeg MA, Buse JB, Zagar AJ, Pinaire JA, Tan MH, Khan MA, Perez AT, Jacober SJ; GLAI Study Investigators. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. *Diabetes care*. 2005;28(7):1547-54.
13. Aschner P, Kipnes MS, Lunceford JK, Sanchez M, Mickel C, Williams-Herman DE. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes care*. 2006;29(12):2632-7.
14. Goldstein BJ, Feinglos MN, Lunceford JK, Johnson J, Williams-Herman DE. Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. *Diabetes care*. 2007;30(8):1979-87.

Table 1. General characteristics and frequency of comorbidities in studied groups.

General characteristics	sitagliptin	pioglitazone	p
Sex, women (No., %)	32 (71.11%)	28 (62.22%)	-
Age (year)	53.26±6.68	54.75±6.27	-
Height (Cm)	163.68±10.08	163.98±8.89	-
HTN (%)	30 (66.7%)	29 (64.4%)	0.824
HLP (%)	23 (52.3%)	28 (62.2%)	0.343
Hypothyroidism (%)	4 (8.9%)	2 (4.4%)	0.398
Toxic adenoma (%)	0	1 (2.2%)	0.315
Breast cancer (%)	2 (4.4%)	0	0.153

Data are presented as mean±standard deviation (SD), number or percent. p<0.05 was considered as statistically significant. HTN: hypertension; HLP: hyperlipoproteinemia; IHD: ischemic heart disease; AF: atrial fibrillation

Table 2. Changes of parameters before and after the intervention.

Parameter	Sitagliptin		p	Pioglitazone		p	p*
	Before	After		Before	After		
Weight (Kg)	82.71±12.92	83.14±13.44	0.877	81.9±14.78	83.52±15.8	0.616	0.902
BMI (kg/m ²)	31.11±5.4	31.26±5.46	0.896	30.94±5.52	31.68±6.0	0.544	0.816
FBS (mg/dl)	178.48±41.42	131.27±39.18	<0.0001	189.64±49.24	123.47±36.73	<0.0001	0.234
2hpp (mg/dl)	272.6±66.01	193.56±63.02	<0.0001	304.75±87.58	198.58±51.5	<0.0001	0.992
HbA1c (%)	8.55±1.31	7.18±0.86	<0.0001	8.42±1.0	7.23±1.03	<0.0001	0.572

Data are presented as mean±standard deviation (SD), number or percent. p<0.05 was considered as statistically significant. P: p-value before and after intervention in sitagliptin and pioglitazone groups. P*: p-value after intervention between sitagliptin and pioglitazone groups. BMI: body mass index; FBS: fasting blood glucose; 2hpp: 2 hours postprandial; HbA1c: hemoglobin A1c.