ORIGINAL ARTICLE

Comparison of HBA1C With Sitagliptin Plus Metformin and Pioglitazone Plus Metformin

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ABSTRACT

Background: Hyperglycemia had proven to be a major risk factor in microvascular complication developments in patients with Type II DM. Contrary to this many clinical trails proved the reduction in HbA1c can control the complication development in type II DM patients.
Aim: To compare the HbAicwith sitagliptin + metformin and pioglitaxone + metformin in patients with Type II
Methods: This was an analytical study where the opted design was analytical prospective. All the patients were given the treatments randomly and assigned a group. Group I contained all patients, which were treated with sitagliptin + metformin as of their usual doses for 12 weeks, on the other hand group II was given pioglitazone + metformin for 12 weeks, the dose of treatment was usual as well.
Results: A total of 120 patients were recruited for this study. Both the group contains 60 type II DM patients each. Group I was treated with sitagliptin + metformin and group II was treated with pioglitazone + metformin. In group I the mean age was 51.3 ± 6.8 and in-group II was 54.45±5.2 years. WE observed in our study that HvA1c level has been upgraded in group I from 8.7±0.50 to 7.72+0.80 where the p value was o.oo1, whereas in group II similar improvement were seen with significance value of 0.001.
Conclusion: We may concluded in our study both the treatment options were effective to reduce the HbA1c, fasting blood glucose and blood glucose two hours after a meal and no significant difference was observed between the two treatment groups in improving the outcomes.
Key words: Type II Diabetes Mellitus (Type II DM),Insulin, HbAic, Blood glucose, Hyperglycemia

INTRODUCTION

The hyperglycemia elevated over time in type II diabetes mellitus (type II DM) due to the decline in the pancreatic beta cells function and resistance of insulin[1,2]. Hyperglycemia had proven to be a major risk factor in microvascular complication developments in patients with Type II DM[3,4]. Contrary to this many clinical trails proved the reduction in HbA1c can control the complication development in type II DM patients[5,6]. For example one degree reduction in HbA1c level may reduce the risk to 35% to microvascular complications[7]. There is a recommendation of 7% reduction by lowering HbA1c level in Type II DM patients by the American Diabetes Association (ADA)[8,9]. In attaining the desired results or goals in type II DM patients, a single drug option is limited, that's why a combination therapy may be required in type II DM management[6-12]. The drug Metformin may reduces the Hb1Ac by rising liver and outlying tissue sensitivity to glucose, preclude hepatic gluconeogenesis and glycogenolysis. Thedecrease in Hb1Ac is between 1.2- 3%, but this drug may not prevent beta cells failure[7-15]. Pioglitazone is one of the thiazolidinediones. Thiazolidinediones are Peroxisome Proliferator Activated Receptor γ (PPAR- γ) agonists and are appropriate for use as monotherapy and in combination with metformin and/or a sulphonylurea in patients with Type II DM[16,17]. These drugs deferral the development of Type II DM and can progress beta cell function and create a sustainable reduction in Hb1Ac[7,18,19,20]. The Aim of the study was to compare the two treatment combinations in patients with type II DM.

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MATERIAL AND METHODS

This was an analytical study where the opted design was analyticalprospective. All the patients were given the treatments randomly and assigned a group. Group I contained all patients, which were treated with sitagliptin + metformin as of their usual doses for 12 weeks, on the other hand group II was given pioglitazone + metformin for 12 weeks, the dose of treatment was usual as well. The duration of the study was of one year starting Feb 2015 conducted in abc department of xyz hospital. The exclusion criteria include all the patients with Cardiac disease, ketoacidosis history, nephropathy, impaired hepatic function, impaired renal function whereas all patients of both gender and aged above 30 with type II diabetic Miletus and patients with HbA1c above 8 and less than 9.5 (insufficient glycemic control) were included in this study. Firstly along with treatment patients were asked to increase the time of exercise daily to 30 minutes and a nutrition plan was opted or provided for them. Along side the demographic and diagnostic values were evaluated and noted. Standard operating procedures were followed for the laboratory diagnostic tests.An informed consent was also taken from the patients or attendant of the patient. Ethical considerations were taken in to account by taking approval Hospital ethical Committee.
Statistical analysis: All the collected data was stored electronically & analyzed later by using SPSS version 18. Descriptive statistics were applied to calculate mean and standard deviation. Frequency distribution and percentages were calculated for qualitative variables like gender, body mass indexetc.Over all a P values less than 0.05 was considered statistically significant.

RESULTS

A total of 120patients were recruited for this study. Both the group contains 60 type II DM patients each. Group I was

treated with sitagliptin + metformin and group II was treated with pioglitazone + metformin. In group I the mean age was 51.3±6.8 and in-group II was 54.4±5.2 years. Both the groups have higher number of female participants i.e., 35(58.3%) in group I and 42(70%)in group II. The baseline demographic and diagnostic characteristics for type II DM patients were given in table 1.

WE observed in our study that HvA1c level has been upgraded in group I from 8.7 +0.50 to 7.72+0.80 where the p value was o.oo1, whereas in group II similar improvement were seen with significance value of 0.001. The average FBS levels in the group I enhanced from 170.09±46.41 to 151.60±42.33 (p<0.001), whereas in group II, FBS improved from 169.26±58.144 to 148.72±46.66 (p<0.001). This difference was not statistically significant. The difference in the improvements between both groups before the treatment and after treatment can be observed in table 2.

Table 1: baseline demographic and diagnostic characteristics for HCV patients were given in table 1.

Characteristic/ parameter	Group I	Group II	Signifi-cance
Age (Mean)	51.3+6.8	54.45 + 5.2	0.003
Weight (kg)	75.3+11.3	71.4 +10.34	0.562
BS2hpp	271.5+58.45	242.4+ 78.1	0.003
HbA1c (%)	8.7+0.50	8.62+0.60	0.34
BUN (mg/dl)	09.80±1.99	10.60±2.25	0.18
Creatinin(mg/dl)	0.93±0.17	0.85±0.15	0.78
ALT (U/L)	39.89±26.19	27.60±6.37	0.0001
Chol (mg/dl)	175.0±45.51	176.44±33.99	0.83
HDL (mg/dl	42.16±8.22	42.85±7.67	0.55

Table 2: Comparison among groups before and after treatment

Variables	Group I		P Value	Group II		P Value
	Before treatment	After Treatment		Before Treatment	After Treatment	
FBS (mg/dl)	171.09±46.41	152.60±42.33	0.001	170.26 ± 56.144	149.72 ±46.66	0.000
BS2hpp	271.5 +58.45	228.29 ± 63.18	0.002	242.4 + 78.1	212.49 ±66.56	0.000
HbA1c (%)	8.7 + 0.50	7.74 ± 0.90	0.001	8.62 + 0.60	7.88 ± 1.20	0.000
BUN (mg/dl)	09.80 ± 1.99	10.18 ± 1.99	0.56	10.60 ± 2.25	10.80 ± 2.67	0.55
Creatinin (mg/dl)	0.93 ± 0.17	0.958 ± 0.15	0.43	0.85 ± 0.15	1.005 ± 0.81	0.56
ALT (U/L)	39.89 ± 26.19	38.14 ± 16.83	0.65	27.60 ± 6.37	26.26 ± 6.80	0.22
Chol (mg/dl)	175.00 ± 45.51	153.31 ± 34.91	0.000	176.44 ± 33.99	171.50 ±37.98	0.23
HDL (mg/dl	42.16 ± 8.22	46.35 ± 12.19	0.005	42.85 ± 7.67	44.12 ± 8.28	0.88

DISCUSSION

The study was planned to compare the two treatment options among groups of patients with type II DM that had been ineffectively organized.We observed in our study that various variables that were controlled after treatment for the two treatment regimens vary. We observed no significant difference in the reduction of HbA1c between two groups. Both the treatments have great influence on HbA1c reduction. This finding is well supported by the study finding of sung-Chen Liu et al.where the difference of the treatment was insignificant[21]. We reports our results better than the mentioned study, this may be due to the difference of age (mean) between two studies. Thus older age may reduce the treatment response, with older age the resistance to insulin increased in comparison to younger aged people[22,23]. The findings of another study conducted by Chawla had no statistical difference in HbA1c level reduction between two treatment groups as well[24]. Interestingly, another study conducted in Japan had compared the two treatments and they reported that group I treatment is more effective than the group II treatment, moreover the difference between the groups was also significant[13]. This might be due to the low body weight of the population and the regional differences were also obvious. Insulin may have also act differently, they may have lower levels of insulin excretion and insulin confrontation than other races[25,26]. We observed in our study that the reduction in FBS was significant with the intervention in groups, but this reduction difference was insignificant when comparing the two treatments. Similar findings were available in the literature to support our study[13,24] contrary to our results Sung Chen Liu et al highlighted the treatment in group II has better reduction in FBS from baseline to end point[21]. Studies propose that the influence of pioglitazone on blood sugar is by taming hepatic and outlying insulin resistance[19,24]. Studies also available for comparing the therapies effect on BS2hpp, We observed in our study that treatment given to group I is better and effective in BS2hpp. Treatment I can improve both fasting and postprandial hyperglycemia excellently[26,27,28,29] on the other hand group II treatment may improves the fasting hyperglycemia more effectively[30]. We reported the gain in weight especially the treatment provided in group II was well known consequence[31,32]. An association observed in overweight and insulin resistance, this may conclude that the loss in weight may lead to improve the insulin resistance thus yielding a better response to the drug[33,34]. Thus the weight neutrality of the treatment option I offers better compensations to manage the type II DM. To measure the efficacy and safety of the drugs we reported no side effects such as hypoglycemia and gastrointestinal symptoms due to the two treatment regimens. Fewer studies reported these side effects with the both the treatments combinations[13].

CONCLUSIONS

We may concluded in our study both the treatment options were effective to reduce the HbA1c, fasting blood glucose and blood glucose two hours after a meal and no significant difference was observed between the two treatment groups in improving the outcomes.

REFERENCES

1. Wysham C, Blevins T, Arakaki R, Colon G, Garcia P, Atisso C, et al. Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). Diabetes care. 2014;37(8):2159-67.
2. Razl, Chen Y, Wu M, Hussain S, Kaufman KD, Amatruda JM, et al. Efficacy and safety of sitagliptin added to ongoing

metformin therapy in patients with type 2 diabetes. Current medical research and opinion. 2008;24(2):537-50.
3. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. Bmj. 2000; 321(7258):405-
4. Inzucchi SE, Bergenstal RM, Buse JB et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes care. 2015;38(1):140-9.
5. Chen YW, Wang JS, Sheu WH et al. Hemoglobin glycation index as a useful predictor of therapeutic responses to dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes. PloS one. 2017;12(2):e0171753.
6. Cahn A, Cefalu WT. Clinical considerations for use of initial combination therapy in type 2 diabetes. Diabetes Care. 2016;39(Supplement 2):S137-45.
7. Abdul-Ghani MA, Puckett C et al. Initial combination therapy with metformin, pioglitazone and exenatide is more effective than sequential add on therapy in subjects with new onset diabetes. Results from the Efficacy and Durability of Initial Combination Therapy for Type 2 Diabete: a randomized trial. Diabetes, Obesity and Metabolism. 2015;17(3): 268-75.
8. Derosa G, Maffioli P, Salvadeo SA, Ferrari I, Ragonesi PD, Querci F, et al. Effects of sitagliptin or metformin added to pioglitazone monotherapy in poorly controlled type 2 diabetes mellitus patients. Metabolism. 2010;59(6):887-95.
9. Nathan DM, Buse JB, Davidson MB, Ferrannini Eet al. Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the and Adjustment of Therapy Initiation. Clinical diabetes. 2009; 27(1): 4-16.
10. Goldstein BJ, Feinglos MN, Lunceford JK, Johnson J, WilliamsHerman 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; 30:1979–1987.
11. Jabbour SA, Hardy E, Sugg J, Parikh S, Study 10 Group. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, doubleblind, placebo-controlled study. Diabetes Care. 2014;37(3):740-50.
12. Fonseca V, Staels B, Morgan JD, Shentu Y, Golm GT, Johnson-Levonas AO, et al. Efficacy and safety of sitagliptin added to ongoing metformin and pioglitazone combination therapy in a randomized, placebo-controlled, 26-week trial in patients with type 2 diabetes. Journal of Diabetes and its Complications. 2013;27(2):177-83.
13. Takihata M, Nakamura A, Tajima K, Inazumi T, Komatsu Y, Tamura H, et al. 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.
14. Einhorn D, Rendell M, Rosenzweig J, Egan JW, Mathisen AL, Schneider RL, Pioglitazone 027 Study Group. Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: a randomized, placebo-controlled study. Clinical therapeutics. 2000;22(12):1395-409.
15. Thomas I, Gregg B. Metformin; a review of its history and future: from lilac to longevity. Pediatric Diabetes. 2017;18(1):10-6.
16. Kovacs CS, Seshiah V, Swallow R, Jones R, Rattunde H, Woerle HJ, et al. Empagliflozin improves glycaemic and weight control as add on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: a 24 week, randomized, placebo controlled trial. Diabetes, Obesity and Metabolism. 2014;16(2):147-58.
17. Dobs AS, Goldstein BJ, Aschner P, Horton ES, Umpierrez GE, Duran L, et al. Efficacy and safety of sitagliptin added to ongoing metformin and rosiglitazone combination therapy in a randomized placebo controlled 54 week trial in patients with type 2 diabetes. Journal of diabetes. 2013;5(1):68-79.
18. Abdul-Ghani M, Migahid O, Megahed A, Adams J et al. Combination Therapy With Exenatide Plus Pioglitazone Versus Basal/Bolus Insulin in Poorly Controlled Patients With Type 2 Diabetes on Sulfonylurea Plus Metformin: The Qatar Study. Diabetes Care. 2017:dc161738.
19. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. New England Journal of Medicine. 2006;355(23):2427-43.
20. Ceriello A, Johns D, Widel M, Eckland DJ, Gilmore KJ, Tan MH. Comparison of effect of pioglitazone with metformin or sulfonylurea (monotherapy and combination therapy) on postloadglycemia and composite insulin sensitivity index during an oral glucose tolerance test in patients with type 2 diabetes. Diabetes Care. 2005;28(2):266-72.
21. Liu SC, Chien KL, Wang CH, Chen WC, Leung CH. Efficacy and safety of adding pioglitazone or sitagliptin to patients with type II diabetes insufficiently controlled with metformin and a sulfonylurea. Endocrine Practice. 2013;19(6):980-8.
22. Petersen KF, Befroy D, Dufour S, Dziura J, Ariyan C, RothmanDL, DiPietro L, Cline GW, Shulman GI. Mitochondrial dysfunction inthe elderly: possible role in insulin resistance. Science. 2003;300(5622):1140-2.
23. Scheen AJ. Diabetes mellitus in the elderly: insulin resistanceand/or impaired insulin secretion? Diabetes & metabolism.2005;31:5S27-34.
24. 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 and Pharmacotherapeutics. 2013;4(1):27.
25. Welch S, Gebhart SS, Bergman RN, Phillips LS. Minimal modelanalysis of intravenous glucose tolerance test-derived insulinsensitivity in diabetic subjects. The Journal of ClinicalEndocrinology & Metabolism. 1990;71(6):1508-18.
26. Taniguchi A, Nakai Y, Fukushima M, Kawamura H. Pathogenic factors responsible for glucose intolerance in patients with NIDDM. Diabetes. 1992;41(12):1540-6.
27. Aschner P, Kipnes MS, Lunceford JK, Sanchez M. 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.
28. Watanabe K, Kobayashi K, Takemoto M, Ishibashi R, Yamaga M, Kawamura H, Fujimoto M, Ishikawa T, Onishi S, Okabe E, He P. Sitagliptin improves postprandial hyperglycemia by inhibiting glucagon secretion in Werner syndrome with diabetes. Diabetes care. 2013;36(8):e119.
29. Iwamoto Y, Tajima N, Kadowaki T, Nonaka K, Taniguchi T,. Efficacy and safety of sitagliptinmonotherapy compared with voglibose in Japanese patients with type 2 diabetes: a randomized, double-blind trial. Diabetes, Obesity and Metabolism. 2010;12(7):613-22.
30. Kawamori R, Kadowaki T, Onji M, Practical Study Group. Hepatic safety profile and glycemic control of pioglitazone in more than 20,000 patients with type 2 diabetes mellitus: postmarketing surveillance study in Japan. Diabetes research and clinical practice. 2007;76(2):229-35.
31. Waugh J, Keating GM, Plosker GL. Pioglitazone: A Review of its Use in Type 2 Diabetes Mellitus. Drugs. 2006; 66 (1): 85-
32. Dhillon S. Sitagliptin. Drugs. 2010 Mar 1;70(4):489-512.
33. Derosa G, Carbone A, Franzetti I, Querci F, Fogari E, Bianchi L, Bonaventura A, Romano D, Cicero AF, Maffioli P. Effects of a combination of sitagliptin plus metformin vs metformin monotherapy on glycemic control, β-cell function and insulin resistance in type 2 diabetic patients. Diabetes research and clinical practice. 2012;98(1):51-60.
34. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature. 2006;444(7121):840-