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ORIGINAL ARTICLE

Comparison of the efficacy and safety of Metformin versus Sitagliptin among treatment naive patients of Type-2 Diabetes.

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ABSTRACT… Objective: To compare the efficacy and safety of metformin versus Sitagliptin among treatment naïve patients of type-2 diabetes mellitus (T2DM). **Study Design:** Randomized Controlled Trial. **Setting:** Department of Medicine, Unit-III, Bahawal Victoria Hospital, Bahawalpur. **Period:** September 2021 to August 2022. **Material & Methods:** During the study period, a total of 320 treatment naïve T2DM patients (160 in each group) were randomly enrolled and followed up. Baseline demographics of all patients including gender, age, BMI (kg/m2), fasting plasma glucose (FPG) and baseline HbA1c were recorded. Patients of Group-A were given oral Sitagliptin 100mg once daily whereas patient in Group-B were prescribed oral metformin as 500-2000 mg per day aiming achievement of glycemic goals. Repeat HbA1c and FPG levels were tested at the end of 12th and 24th weeks therapy among both study groups. Side effects related to studied drugs were also observed and recorded. **Results:** Out of a total of 320 patients, 57 patients (27 in Group-A and 30 in Group-B) lost follow up so 263 patients were included in the final analysis. Majority of the patients, 134 (51.0%) were male. Mean age, BMI and duration of diabetes among study participants were 53.07+9.62 years, 29.44+4.74 kg/m^2 and 1.96+2.3 years respectively. No statistically significant difference was noted at zero, 12 or 24 weeks in between both study groups ($p>0.05$) in terms of reduction in HbA1c or FPG levels during the study period ($p>0.05$). **Conclusion:** Both metformin and Sitagliptin effectively reduce HbA1c and FPG levels among treatment naïve T2DM patients with relatively good tolerability and safety. Both study drugs can be used as initial monotherapy among T2DM patients with relatively mild-to-moderate disease.

Key words: HbA1c, Metformin, Type-2 Diabetes Mellitus, Sitagliptin.

INTRODUCTION

To achieve glycemic control among type-2 diabetes mellitus (T2DM) patients, many oral hypoglycemic agents are available. Metformin is considered to be the most endorsed mono-therapy for treating T2D as it provides efficacy along with trusted experience and elaborated safety.[1] Metformin lowers blood glucose due to suppression of hepatic production of glucose while it is also enhancing sensitivity to insulin as well. Metformin also increases peripheral uptake of glucose and lowers insulin induced suppression of fatty acid oxidation while increasing the peripheral utilization of glucose through improving insulin bondage to insulin receptors.[2,3] Despite all these benefits, management of T2DM with metformin is associated with frequent side effects like gastrointestinal disturbance and risk of lactic acidosis in poor perfusion and renal insufficiency.[4]

Sitagliptin is FDA approved highly selective and orally active anti-hyperglycemic drug that belongs to dipeptidyl peptidase-4 (DPP-4) inhibitors. Sitagliptin preserves stimulated circulating incretin hormones and insulin secretion is enhanced while it also suppresses glucagon's production.[5,6] Some researchers have found Sitagliptin to have similar safety profile when compared to placebo while it has lower degree of GI related side effects and no weight gain.[7,8] Among patients having HbA1c round 8%, Sitagliptin 100mg once daily has been noted to provide an overall 0.7% reduction in HbA1c levels.[7,9]

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Around the world, both metformin as well as Sitagliptin are adopted as initial mono-therapy by physicians for managing patients of T2DM but no real data exists about their comparison in Pakistan. This study was aimed to compare the efficacy and safety of metformin versus Sitagliptin among treatment naïve patients of T2DM.

MATERIAL & METHODS

This randomized controlled trial was done at The Department of Medicine, Unit-III, Bahawal Victoria Hospital, Bahawalpur from September 2021 to August 2022. Approval from institutional ethical and research review board was acquired for this study (171/DME/QAMC Bahawalpur).

During the study period, a total of 320 treatment naïve T2DM patients (160 in each group) were randomly enrolled (through computer generated numbers) and followed up. Patients of both genders (male and female), aged 18 to 70 years and having HbA1c between 6.5% to 9.0% were included. All patients of type-1 diabetes or those who had coronary artery disease or renal impairment or elevated hepatic enzymes were excluded. All those patients who were having fasting plasma glucose (FPG) below 100 mg/dl or above 250mg/dl were also not enrolled. All enrolled patients were advised to follow recommended diet and exercise plans throughout the study course. Those patients who did not complete a minimum follow up period of 6 months were not included in the final analysis. Written consent was sought from all study participants.

Baseline demographics of all patients including gender, age, BMI (kg/m2) and baseline HbA1c were recorded. Patients of Group-A were given oral Sitagliptin 100mg once daily whereas patient in Group-B were prescribed oral metformin as 500-2000 mg per day aiming achievement of glycemic goals. Initially, fortnightly follow-ups were advised to all patients for period of 2 months, while monthly follow ups were advised later on up till 24 weeks of treatment. Any patient having FPG levels of more than 240 mg/dl at any point during the study period was discontinued on previously advised management option labeling as lack of effectiveness. Repeat HbA1c was tested at the end of 12th and 24th weeks therapy among both study groups. Side effects related to studied drugs were also observed and recorded.

SPSS version 26.0 was used for data entry as well analysis. For quantitative variables like age, BMI, baseline and endpoint HbA1c, mean and standard deviation were calculated. Qualitative variables like gender and adverse effects were represented in terms of percentages and frequencies. Student t-test was applied to compare HbA1c levels while chi-square test was applied to compare qualitative variables between study groups.

RESULTS

Out of a total of 320 patients (160 in each group), 57 patients (27 in Group-A and 30 in Group-B) lost follow up so 263 patients (133 in Group-A and 130 in Group-B) were included in the final analysis. Majority of the patients, 134 (51.0%) were male. Mean age, BMI and duration of diabetes among study participants were 53.07+9.62 years, 29.44+4.74 kg/m^2 and 1.96+2.3 years respectively. Table-I shows distribution of baseline characteristics among study participants and there was no significant difference ($p>0.05$).

Characteristics		Group-A (n=133)	Group-B (n=130)	P- Value
Age in years(Mean+SD)		53.81+9.14	52.41+10.08	0.2389
Gender	Male	66 (49.6%)	68 (52.3%)	0.6634
	Female	67 (50.4%)	62 (47.7%)	
BMI kg/m^2 (mean+SD)		29.51+4.27	29.34+4.61	0.7565
HbA1c % (mean+SD)		7.3+0.64	7.2+0.72	0.2347
Fasting Plasma Glucose		145.3+25.4	140.5+27.1	0.1394
Duration of Diabetes in years (mean+SD)		1.9+2.4	2.0+2.2	0.7251

Table-I. Characteristics of patients among both study groups

Figure-1 shows comparison of HbA1c levels between both study groups at baseline and during the study period. No statistically significant difference was noted at zero, 12 or 24 weeks in between both study groups (p>0.05). A net decrease of 0.42% HbA1c levels was reported among Group-A study participants while in Group-B, a net decrease of 0.41% was noted.

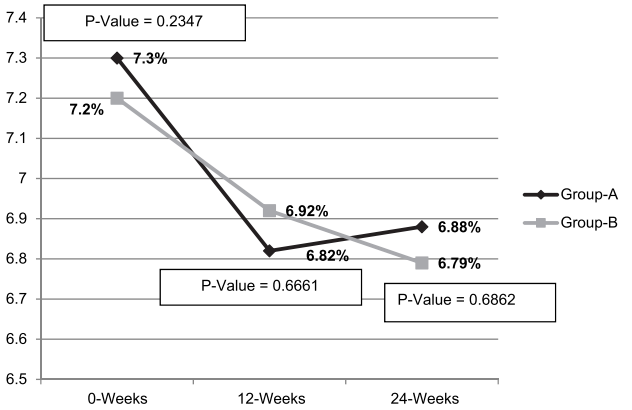

Figure-1. Comparison of HbA1c levels (%) between study groups during the study period

Figure-2 shows comparison of FPG levels (mg/dl) between both study groups at baseline and during the study period. No statistically significant difference was noted at zero, 12 or 24 weeks in between both study groups (p>0.05).

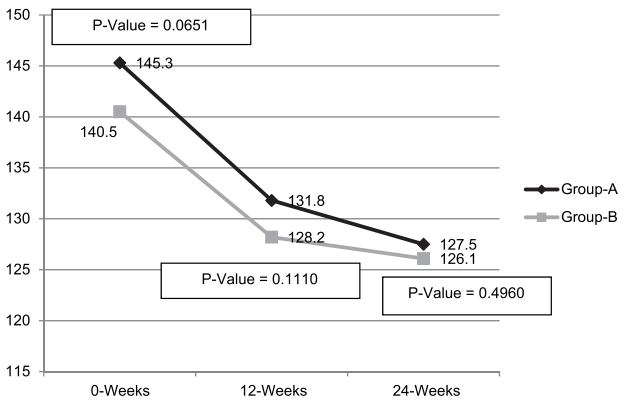

Figure-2. Comparison of fasting plasma glucose levels (mg/dl) between study groups during the study period

In Group-A, 11 (8.3%) patients experienced drug related adverse events while in Group-B, 22 (16.9%) had drug related adverse events. In Group-A, 3 (2.3%) patients discontinued treatment because of adverse events while in Group-B, 6 (4.6%) patients left treatment.

DISCUSSION

Metformin is considered to be the most commonly endorsed antihyperglycemic agent as 1st monotherapy regarding management of T2DM. Weight reduction along with efficacy and an established safety like low risk of hypoglycaemia are some of the major attributes of metformin.[2,3] Other options like sulfonylureas are linked with weight gain as well as hypoglycaemia while alpha-glucosidase inhibitors are commonly induce gastrointestinal adverse effects.[10] Since the approval of DPP-4 inhibitors in the management of T2DM, researchers have found these to be effective and safe.[11]

"American Diabetes Association (ADA)" in their recent guidelines have emphasized the need for individualized treatment for each individual.[12] We had included treatment naïve patients of T2DM who had HbA1c levels between 6.5-9.0% as usually these anti-hyperglycemic agents are used as monotherapy in these patients. So, we tried to include T2DM cases that represent relatively early phases of the disease requiring treatment. Opting for anti-hyperglycaemic options like metformin and Sitagliptin were also considered as these have less chances of hypoglycaemia.[13]

In the present study, no statistically significant difference was noted at zero, 12 or 24 weeks in between both study groups (p>0.05). A net decrease of 0.42% HbA1c levels was reported among Group-A study participants while in Group-B, a net decrease of 0.41% was noted. A study done by Aschner P et al from Colombia USA, comparing efficacy of metformin versus Sitagliptin as initial therapy among patients of T2DM noted that Sitagliptin resulted a net decrease of 0.43% HbA1c level from baseline in comparison to 0.57% with metformin during the 24 weeks study period.[14] The authors found no statistically significant difference among both study groups in terms of net HbA1c reduction which is quite similar to what was noted in the present research. These results highlight that both metformin and Sitagliptin effectively reduce HbA1c levels among treatment naïve T2DM patients. Some researchers have noted a bigger decrease with these anti-hyperglycaemic agents but the reason

could be that we had only included patients with mild-to-moderate T2DM so including patients with relatively higher HbA1c levels might show up bigger decrease.[15] Our results also highlight that decrease in HbA1c levels is quite similar if patients of relatively similar disease profile are considered on these anti-hyperglycaemic agents.

We had also witnessed that reduction in FPG levels (mg/dl) were quite similar during the course of the study. With regards to FPG levels in early weeks, sharp decrease was seen among both study groups but then a relatively stable trend was seen among the study participants which again show that these anti-hyperglycaemic agents, when used as initial monotherapy, are good at decreasing FPG levels among patients with mild-to-moderate disease. Researchers in the past have found monotherapy with Sitagliptin to enhance beta-cell functions.[16] Although, we did not evaluate beta-cell measures in the present study but sitagliptin and metformin, both have been found to have relatively similar improvement in terms of measures of beta-cell functions by other researchers as well. We did not record impact of studied agents on weight reduction/ increase but sitagliptin is known to be weight neutral.[17]

In this study, patients using Sitagliptin had relatively fewer adverse events in comparison to those using metformin so clinically, Sitagliptin has fewer side effects especially those related to gastrointestinal system. Many previous studies have noted metformin and Sitagliptin to have better tolerability and safety profile, we also noted these to have relatively good safety profile during the study course.[9,18]

Our study had few limitations as well. We were unable to note improvement in beta-cell measures like HOMA-beta, proinsulin / insulin ratio as well as insulinogenic index. We were also unable to note effects of study drugs on insulin resistance. We also did not complied data about the other drugs used along with study drugs like statis or renin-angiotensin system blockers which could have altered the glucose metabolism among the study subjects. Being a single center study, our findings cannot be generalized so further multicenter trials involving different study populations are needed to confirm the findings of this study. Still, randomized controlled design and being the 1st study from South Punjab, comparing Sitagliptin and metformin, are some of the major strengths of this study.

CONCLUSION

Both metformin and Sitagliptin effectively reduce HbA1c and FPG levels among treatment naïve T2DM patients with relatively good tolerability and safety. Both study drugs can be used as initial monotherapy among T2DM patients with relatively mild-to-moderate disease.

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2	Ghulam Jilani	Drafting.	
3	M. Waqas Saeed	Data analysis.	
4	Syed Zain Ul Abidin	Literature review, Critical analysis.