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*Atta Muhammad Khan, Nowsherwan, Muhammad Abbass, Amjad
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¹Atta Muhammad Khan, ²Nowsherwan, ³Muhammad Abbass, ⁴Amjad Ali, ⁵Hussain Afridi, ⁶Wali Gul, and ⁷Shah zaib.

¹Assistant Professor of Medicine, MTI, LRH, Peshawar, Pakistan.

²Associate Professor of Medicine, M.T.H Hospital Peshawar, Pakistan.

³Associate Professor of Medicine, MMC hospital mardan, Pakistan.

⁴Professor of Medicine, MMC, Hospital Mardan, Pakistan.

⁵Assistant professor Diabetes and endocrinology HMC Hospital Peshawar, Pakistan.

⁶Consultant Medical sp DHQ hospital batkhala, Pakistan.

⁷Assistant Professor of Medicine, MMC hospital mardan, Pakistan.

[²nowsherwandr@gmail.com](mailto:nowsherwandr@gmail.com), [³docabbas1@hotmail.com](mailto:docabbas1@hotmail.com), [⁵Mhussainafd@gmail.com](mailto:Mhussainafd@gmail.com)

Abstract

Introduction: Diabetes Mellitus (DM) is one of the leading causes of morbidity and mortality around the world and is responsible for 3.8 million deaths per year. Its prevalence had shown an exponential rise worldwide in the last two decades, from 30 million cases in 1985 to 177 million in 2000

Objective: To compare the efficacy of the combination of Metformin plus modified-release Gliclazide with a variety of Metformin plus Sitagliptin in patients with type-2 diabetes mellitus.

Methodology: This study was conducted at the Department of Medicine, Lady Reading Hospital Peshawar. The study design was a randomized controlled trial conducted for one year from May 2017 to May 2018, in which 62 patients in each group were observed. All patients with type 2 Diabetes Mellitus with baseline HbA1c $\geq 8\%$ and duration >1 year, either gender with age range 35 to 65 years, were included. All patients were subjected to detailed history and clinical examinations. All patients were randomly allocated in two groups by lottery method. Patients in Group A were subjected to the combination of Metformin (1gm twice daily) with modified-release Gliclazide (60mg), and patients in Group B were subjected to the variety of Metformin (1 gm twice daily) with Sitagliptin (50 mg twice daily). All patients were followed up after three months, and blood samples for HbA1c levels were obtained. The analysis was done in SPSS version 20.

Results: The Study showed that the mean age in Group A was 58 years \pm 12.78, and the mean age in Group B was 55 years \pm 13.12. In Group A, 44% of patients were male, and 56% of patients were female, while in Group B, 45% of patients were male, and 55% of patients were female. Moreover, Group A (Metformin (1gm twice daily) + Gliclazide (60mg) was effective in 45% of patients while Group B Metformin (1 gm twice daily) + Sitagliptin (50 mg twice daily) was effective in 71% of patients.

Conclusion: Our study concludes that Metformin plus Sitagliptin is more effective than Metformin plus modified-release Gliclazide.

Keywords: *Efficacy, Metformin plus modified-release Gliclazide, Metformin plus Sitagliptin, type-2 diabetes mellitus.*

INTRODUCTION

Diabetes Mellitus (DM) is one of the leading causes of morbidity and mortality around the world and is responsible for 3.8 million deaths per year. Its prevalence has shown an exponential rise in the last two decades from 30 million cases in 1985 to 177 million in 2000.¹ The estimated number of people with diabetes worldwide for 2010 is 285 million, which is projected to increase to 439 million by 2030. The International Diabetes Federation ranks Pakistan 7th in the list of prevalence of diabetes.² Diabetes mellitus is associated with a 10 to 30% decrease in life expectancy.³

The management of type 2 diabetes mellitus is based on lifestyle changes like dietary modifications, weight reduction and moderate exercise, medications, and insulin. Biphasic insulin is found to be most effective in reducing HbA1c. The major disadvantages with insulin are significant hypoglycemia, relatively complex administration, insulin allergy, and lipodystrophy at the injection site.⁴ In oral medications, Sulfonylureas have been effectively used in managing type 2 diabetes, especially modified-release Gliclazide, but they are associated with side effects of hypoglycemia and weight gain.⁵ In the USA, they were the most common oral anti diabetic prescribed in 1999-2000, but this trend shifted towards Thiazolidinediones in 2003-2001.^{6,7} Recently, Sitagliptin, a DPP-4 inhibitor, proved to be effective in achieving better diabetic control when added to Metformin.^{8,9}

In the United Kingdom Prospective Diabetic Study (UKPDS), Metformin proved to be as effective as sulfonylureas and insulin in reducing blood sugar and microvascular complications. Still, it proved to be more beneficial in reducing cardiovascular risk.¹⁰ This study makes Metformin the first line therapy in newly diagnosed type 2 diabetics, especially in obese patients, because of its weight reduction effect. The choice for the best second-line oral antidiabetic agent is not that clear.^{11,12} Department of Medicine MTi Hospital LRH Peshawar, 320 type two diabetic patients were given Sulfonylurea in combination with Metformin. The mean reduction of 1.36% was seen in HbA1c, and 40% of patients achieved the target HbA1c (pre-treatment mean 8.80 ± 0.97 and post-treatment was 7.45 ± 0.06). When Sitagliptin was used with Metformin in 178 Type 2 diabetic patients, a mean HbA1c reduction of 1.9% (2.06 to 1.74) with a baseline mean HbA1c of 8.76 ± 1.09 , with 66 % of patients achieving target HbA1c.¹⁶ In a recently published meta-analysis of 39 randomized control trials involving 17,860 patients, when used with Metformin, sulfonylureas have shown a 0.82% reduction in HbA1c vs. 0.69% with DPP-4 inhibitors.¹³

The HbA1c is a recognized tool for monitoring the response to treatment in diabetes and corresponds with the probability of long-term complications. In Diabetes Control and Complication Trial, after a seven-year follow up, the group which achieved a mean HbA1c of 7.2% had approximately 60% reduction in risk of microvascular complication and 41% reduction in the risk of macrovascular complications as compared to the group which achieved the mean HbA1c of 8.9%.¹⁴

No significant differences were found between the Metformin plus Sitagliptin and Metformin plus Sulfonylurea groups regarding HbA1c or the proportion achieving <7% HbA1c, while the metformin plus Sitagliptin group experienced fewer hypoglycemic events ($P < 0.00001$) and a more significant reduction in body weight ($P < 0.00001$). Metformin plus Sitagliptin therapy may decrease HbA1c values in patients with type 2 diabetes mellitus who are not achieving their glycemic targets with metformin

monotherapy like Metformin plus Sulfonylurea treatment while posing a lower risk of hypoglycemia and yielding a more beneficial effect on body weight.¹⁵

This study aimed to compare the efficacy of modified-release Gliclazide with Sitagliptin when used in combination with Metformin. It will be able to recommend which one of these two commonly available drugs can be used as add-on therapy to Metformin to achieve adequate diabetic control. Also, the published literature showed a bit of controversy as RCTs showing Sitagliptin-Metformin combination having better diabetic control. In contrast, another meta-analysis shows less reduction in mean HbA1c levels with a similar combination compared to Metformin-Sulfonylurea.

OBJECTIVE

To compare the efficacy of Metformin plus modified-release Gliclazide with a variety of Metformin plus Sitagliptin in patients with type-2 diabetes mellitus.

METHODOLOGY

This study was conducted at the Department of Medicine, Lady Reading Hospital Peshawar. The study design was a randomized controlled trial which was conducted for the period of one year from May 2017 to May 2018 in which 62 patients in each group were observed keeping 40% proportion of efficacy of Metformin plus Gliclazide and 66% proportion of efficacy of Metformin plus Sitagliptin¹⁶ with 95% confidence interval and 90% power of the test under WHO sample size calculations. Non-probability consecutive sampling technique was used for sample collection. More overall patients with type 2 DM with baseline HbA1c $\geq 8\%$ and duration >1 year, either gender with age range 35 to 65 years were included and patient with chronic kidney disease as per medical record, patients with chronic liver disease as per medical record, patient with acute myocardial infarction in last one month, as per medical record. These patients are known to be allergic to Metformin, Gliclazide, and Sitagliptin. Based on clinical assessment, patients using insulin as per medical records were excluded.

All patients were randomly allocated in two groups by lottery method. Patients in Group A were subjected to the combination of Metformin (1gm twice daily) with modified-release Gliclazide (60mg), and patients in Group B were subjected to the variety of Metformin (1 gm twice daily) with Sitagliptin (50 mg twice daily). All patients were followed up after three months and blood samples for HbA1c level were obtained. Those patients who lost to follow-up were excluded from the study. Compliance was checked by interviewing the attendant/patient, while bias in the results was controlled by regular laboratory tests which include random blood sugar (RBS), fasting blood sugar (FBS). Strict exclusion criteria had been followed to control confounders and bias in the study results. All the data were analyzed in SPSS version 20. Mean \pm SD was calculated for numerical variables like age, duration of diabetes follow-up HbA1c level. Frequencies and percentages were calculated for categorical variables like gender and efficacy. A Chi-square test was used to compare the effectiveness in both groups while keeping a p-value of ≤ 0.05 as significant. Effectiveness in both the groups was stratified among age and gender to see the effect modifications. Post-stratification chi-square test was applied, keeping p-value ≤ 0.05 was taken as significant.

RESULTS

The study shows that in Group A, 11(18%) patients were in the age range 35-45 years, 18(29%) patients were in the age range 46-55 years, 33 (53%) patients were in the age range 41-50 years. Mean age was 58 years \pm 12.78 while in Group B, 13(21%) patients were in the age range 35-45 years, 19(30%) patients were in the age range 46-55 years, 30(49%) patients were in the age range 41-50 years. The mean age was 55 years \pm 13.12.

In Group A, 27(44%) patients were male, and 35(56%) patients were female. While in Group B, 28(45%) patients were male, and 34(55%) patients were female. In Group A, 24(38%) patients had diabetes from 1-10 years, and 38(62%) patients had diabetes 11-20 years. The mean duration of diabetes was ten years \pm 8.73. In Group B, 25(40%) patients had diabetes from 1-10 years, and 37(60%) patients had diabetes 11-20 years. The mean duration of diabetes was ten years \pm 8.21. The mean age was ten years with SD \pm 8.21.

Efficacy among two groups was analyzed as Group A (Metformin (1gm twice daily) + Gliclazide (60mg) was effective in 28(45%) patients and was not effective in 34(55%) patients. In comparison, Group B Metformin (1 gm twice daily) + Sitagliptin (50 mg twice daily) was effective in 44(71%) patients and was not effective in 18(29%) patients.

Table 1: Efficacy

Efficacy	(n=124)	
	Group A	Group B
Effective	28(45%)	44(71%)
Not effective	34(55%)	18(29%)
Total	62(100%)	62(100%)

Group A: Metformin (1gm twice daily) + Gliclazide (60mg)

Group B: Metformin (1 gm twice daily) + Sitagliptin (50 mg twice daily)

Chi-Square test was applied in which P-value was 0.0035

Table 2: Stratification of efficacy concerning age distribution

Age	Efficacy	Group A	Group B	P-value
35-45 years	Effective	5	9	0.2391
	Not effective	6	4	
Total		11	13	
46-55 years	Effective	8	13	0.1411
	Not effective	10	6	
Total		18	19	
56-65 years	Effective	15	22	0.0247
	Not effective	18	8	
Total		33	30	

Group A: Metformin (1gm twice daily) + Gliclazide (60mg)

Group B: Metformin (1 gm twice daily) + Sitagliptin (50 mg twice daily)

Table 3: Stratification of efficacy for gender distribution

Gender	Efficacy	Group A	Group B	P-value
Male	Effective	12	20	0.0425
	Not effective	15	8	
Total		27	28	
Female	Effective	16	24	0.0363
	Not effective	19	10	
Total		35	34	

Group A: Metformin (1gm twice daily) + Gliclazide (60mg)

Group B: Metformin (1 gm twice daily) + Sitagliptin (50 mg twice daily)

Table 4: Stratification of efficacy concerning duration of disease

Duration	Efficacy	Group A	Group B	P-value
1- 10 years	Effective	11	18	0.0624
	Not effective	13	7	
Total		24	25	
11-20 years	Effective	17	26	0.0254
	Not effective	21	11	
Total		38	37	

Group A: Metformin (1gm twice daily) + Gliclazide (60mg)

Group B: Metformin (1 gm twice daily) + Sitagliptin (50 mg twice daily)

DISCUSSION

Diabetes Mellitus (DM) is one of the leading causes of morbidity and mortality around the world and is responsible for 3.8 million deaths per year. Its prevalence had shown an exponential rise worldwide in the last two decades, from 30 million cases in 1985 to 177 million in 2000. The estimated number of people with diabetes worldwide for 2010 is 285 million, projected to increase to 439 million by 2030. The International Diabetes Federation ranks Pakistan 7th in the list of prevalence of diabetes.² Diabetes mellitus is associated with a 10 to 30% decrease in life expectancy.³

This study shows that the mean age in Group A was 58 years with SD \pm 12.78 while the mean age in Group B was 55 years with SD \pm 13.12. In Group A, 44% of patients were male, and 56% of patients were female. Whereas in Group B, 45% of patients were male, and 55% of patients were female. Moreover, Group A (Metformin (1gm twice daily) + Gliclazide (60mg) was effective in 45% of patients and Group B, metformin (1 gm twice daily) + Sitagliptin (50 mg twice daily) was effective in (71%) patients.

Sulfonylurea in combination with Metformin, the mean reduction of 1.36% was seen in HbA1c, and 40% of patients achieved the target HbA1c (pre-treatment mean 8.80 ± 0.97 and post-treatment was 7.45 ± 0.06). When Sitagliptin was used with Metformin in 178 Type 2 diabetic patients, a mean HbA1c reduction of 1.9% (2.06 to 1.74) was observed with a baseline mean HbA1c of 8.76 ± 1.09 , with 66 % of patients achieving target HbA1c.

Goldstein BJ et al.¹⁷ had reported that in a recently published meta-analysis of 39 randomized control trials involving 17,860 patients, when used with Metformin, Sulfonylureas had shown 0.82% reduction in HbA1c vs. 0.69% with DPP-4 inhibitors. Maharani U¹⁸ had reported that the HbA1c is a recognized tool for monitoring the response to treatment in diabetes and also corresponds with the probability of long-term complications. In Diabetes Control and Complication Trial, after seven year follow up, the group which achieved a mean HbA1c of 7.2% had approximately 60% reduction in risk of microvascular complications and 41% reduction in the risk of macrovascular complications as compared to the group which achieved the mean HbA1c of 8.9%.

CONCLUSION

Our study concludes that Metformin plus Sitagliptin is more effective than Metformin plus modified-release Gliclazide.

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