

Original Article



Glycemic Control by Combination Therapy of Sitagliptin-Metformin Versus Metformin Alone

Misu Rani Saha¹, Shahin Ara², A. k. M. Shahidur Rahman³, Shakilur Rahman⁴,
M Iqbal Hossain⁵, Nazia Mahmud Badhon⁶.

Abstract

Background: Type 2 diabetes is a chronic disease characterized by various metabolic defects. Uncontrolled diabetes mellitus gives rise to a number of life-threatening complications that can increase mortality and morbidity. **Objectives:** This study was carried out to compare the effectiveness of glycemic control between combined therapy of sitagliptin-metformin and metformin monotherapy. **Materials and Methods:** Total data of 40 newly diagnosed type-2 diabetic patients were compiled in the study. Those patients having HbA1c more than 6% were considered as uncontrolled diabetes. The total subjects were randomly divided into two experimental groups, treated by metformin alone and treated by sitagliptin-metformin combination. Both groups were treated for three consecutive months and they were followed up after 12 weeks of treatment. Fasting blood sugar (FBS), blood sugar 2 hours after breakfast (2-ABF) and glycated hemoglobin A1c(HbA1c) were estimated in both experimental groups before starting of treatment and after 12 weeks of treatment. **Results:** HbA1c change from baseline was 0.82% with metformin and 1.83% with sitagliptin-metformin combination. Fasting blood glucose changed from 9.41 ± 1.34 mmol/l to 8.04 ± 1.10 mmol/l with metformin and from 9.75 ± 1.40 mmol to 7.25 ± 0.80 with sitagliptin-metformin therapy. Blood sugar 2 hours after breakfast changed from 12.68 ± 1.07 mmol/l to 10.34 ± 1.68 mmol/l with metformin and from 12.65 ± 1.90 mmol to 8.74 ± 0.68 with sitagliptin-metformin therapy. The results showed that though both experimental groups reduced FBS, blood sugar 2-ABF, HbA1c at an acceptable level the combined therapy was found to be superior in terms of effectiveness. **Conclusion:** The administration of sitagliptin-metformin combined therapy to control hyperglycemia uniquely is preferable.

Key words: Type-2 Diabetes mellitus, Glycemic control, Sitagliptin, Metformin.

Date of received: 20.04.2020.

KYAMC Journal.2020;11(3): 150-153.

Date of acceptance: 20.08.2020.

DOI: <https://doi.org/10.3329/kyamcj.v11i3.49874>

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia, glycosuria which is due to either reduced production or reduced response to insulin by cells. Prevalence of DM in Bangladesh is about 6.1% (5.6 million) and it will hold the 8th position in the world by the year 2030.²⁻³ DM is incurable, may produce complications like diabetic neuropathy, retinopathy, and peripheral vascular diseases if remains uncontrolled.⁴ Type-2 diabetes mellitus is resulting from several pathogenic abnormalities, such as inadequate insulin secretion by pancreatic cell and insulin resistance in target tissue.⁵ Initially, type-2 diabetes is treated

by oral antidiabetic medicine along with lifestyle modification.⁶

After the diagnosis of type-2 DM, metformin is one of the commonly prescribed oral antidiabetic medicines.⁶ Metformin increases insulin sensitivity, decreases glucose output through the suppression of gluconeogenesis and glycogenolysis. It also increases glucose uptake in peripheral tissues.⁷⁻⁸ Sitagliptin inhibits dipeptidyl peptidase 4 (DPP-4) enzyme resulting in prolonged activation of glucagon-like peptide (GLP-1) and gastric inhibitory polypeptide (GIP). These hormones enhance insulin release and also reduce glucagon secretion.⁹⁻¹⁰ Monotherapy is often unsuccessful

1. Lecturer, Department of Pharmacology & Therapeutics, Rajshahi Medical College, Rajshahi, Bangladesh.
2. Professor, Department of Pharmacology & Therapeutics, and HOD, Rajshahi Medical College, Rajshahi, Bangladesh.
3. Professor Department of Pharmacology & Therapeutics and HOD, Khwaja Yunus Ali Medical College, Sirajganj, Bangladesh.
4. Associate Professor, Department of surgery, Barind medical College, Rajshahi, Bangladesh.
5. Assistant Professor, Department of Pharmacology & Therapeutics, Rajshahi Medical College, Rajshahi, Bangladesh.
6. Assistant Professor, Department of Pharmacology & Therapeutics, MH Samorita Medical College, Dhaka, Bangladesh, Bangladesh.

Correspondence: Dr. Misu Rani Saha, Lecturer, Department of Pharmacology & Therapeutics, Rajshahi Medical College, Rajshahi, Bangladesh. Email: iqbalpor06@gmail.com

in achieving glycemic control of type-2 diabetic patients due to the progressive nature of this disease.¹¹ Initial combination therapy is thought worthwhile as an alternative approach for getting adequate glycemic control and to avoid diabetes related complications. In this context, sitagliptin-metformin combination possesses an excellent option for patients having undiagnosed hyperglycemia.¹² Sitagliptin-metformin acts on both beta cell function and gut hormone level. So, this combination therapy provides effective and potentially additive glycemic control.¹²

Glycated hemoglobin (HbA_{1c}) is an important marker of glycemic control and it indicates blood glucose status over the previous 3 months prior to the measurement.¹³ Normal HbA_{1c} should be <7%. Every 1% drop in HbA_{1c} causes 37% reduction of diabetes related complications.¹⁴ No such study has been done in our country by comparing glycemic control using single therapy of metformin and combination therapy of sitagliptin-metformin. So, this study was done to observe and compare glycemic control of newly diagnosed diabetic patients who were treated either sitagliptin-metformin combination or metformin alone. Here glycemic control was observed based on HbA_{1c} but at the same time fasting blood sugar (FBS), blood sugar 2 hours after breakfast (2-ABF) were also determined.

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Materials and Methods

This experimental study was carried out in the department of Pharmacology and Therapeutics, in collaboration with Diabetic Association, Rajshahi. Purposive sampling was employed for this study. Clinically diagnosed 40 patients of type-2 DM were included in the study. The patients were randomly divided into two groups: Group A (20 patients who were treated with metformin 500mg twice daily for 3 consecutive months) and Group B (20 patients who were treated with sitagliptin-metformin 50/500mg combined drug twice daily for 3 consecutive months). Before starting treatment, FBS, blood sugar 2-ABF and HbA_{1c} were estimated. The patients of both groups were advised to follow up in the diabetic center after 12 weeks. After 12 weeks of treatment FBS, blood sugar 2 ABF and HbA_{1c} were estimated again. All the data were analyzed with the help of SPSS (Statistical Package for Social Science) software program as

per objectives. All values were expressed as Mean±SD (Standard deviation). Results presented by appropriate table, chart, diagram with relevant interpretation and by using paired "t" test in the case of before and after treatment groups and unpaired "t" test in the case of both experimental groups. The "p" value of 0.05 or less was considered statistically significant.

Results

Before starting treatment, the mean fasting blood sugar of group A was 9.41±1.34mmol/l and group B was 9.75±1.40mmol/l. But after administration of metformin (Group A) and sitagliptin-metformin (Group B) for 12 weeks blood sugar was significantly reduced (8.04±1.19mmol/l in group A and group B was 7.25±0.80mmol/l) in both groups which are shown in Table-I.

Table I: Effects of metformin (Group A) and sitagliptin-metformin (Group B) combination on fasting blood sugar.

Group	FBS before Treatment (mmol/l)	FBS after 12weeks treatment (mmol/l)	P value
Group A	9.41±1.34	8.04±1.19	SoP<0.05 Significant
Group B	9.75±1.40	7.25±0.80	So, P<0.05 Significant

Before starting of treatment, mean blood sugar level 2 hours after breakfast in group A was 12.68±1.07 mmol/l and in group B was 12.65±1.90mmol/l. After administration of drug for 12 weeks blood sugar was reduced to 10.34±1.68mmol/l in group A and 8.74±0.68mmol/l in group B. (Figure-1) In both cases, a significant reduction was observed (p<0.05).

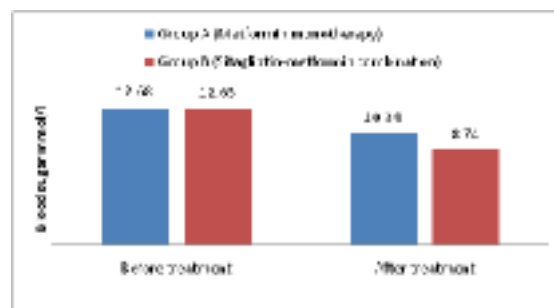


Figure 1: Bar diagrams showing blood sugar level 2 hours after breakfast in experimental groups-A and B.

In experimental group A, before treatment, mean HbA_{1c} level was 8.30±0.64% and after 12 weeks of medication with metformin (500 mg twice daily) it was decreased to 7.48±1.00%. In experimental group B, before treatment, mean HbA_{1c} level was 8.39±0.99% and after 12 weeks of medication with sitagliptin-metformin (50/500 mg twice daily) it was decreased to 6.56±0.52%. (Figure-2) In both cases, a significant reduction of HbA_{1c} was observed (P<0.001). The mean reduction of HbA_{1c} from baseline was 0.82% in metformin and 1.83% in the sitagliptin-metformin combination group.

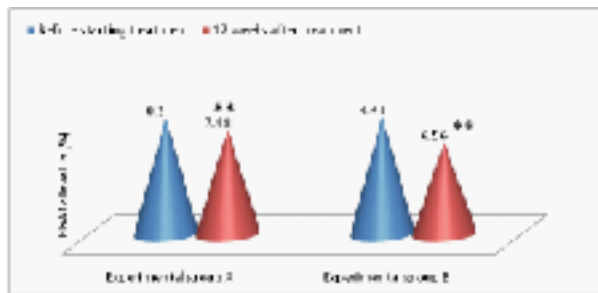


Figure 2: Diagrams showing HbA_{1c} level in both experimental groups-A and B (*Statistically significant, **Statistically highly significant)

Discussion

In this study, determination of glycemetic control was assessed based on HbA_{1c}. FBS and blood sugar 2 ABF were also measured during the study. The present study showed significant reduction of FBS and blood sugar 2 ABF by both monotherapy with metformin and combination therapy with sitagliptin-metformin. In the present study, FBS was reduced from 9.41 ± 1.34 to 8.04 ± 1.19 mmol/l with metformin (500 mg twice daily) monotherapy and from 9.75 ± 1.84 to 7.25 ± 0.80 mmol/l with sitagliptin-metformin (50/500 mg twice daily) combined therapy after 12 weeks of treatment. In a similar study, conducted among 1250 patients showed a greater reduction of FBS with combination therapy than metformin alone within 18 weeks.¹⁵ In another similar study performed among 701 patients for 24 weeks also reported good control of FBS with sitagliptin-metformin (50/500 mg twice daily).¹⁶

In the present study, a significant reduction of blood sugar 2 ABF was also observed. Mean reduction of blood sugar 2 ABF was from 12.68 ± 1.07 to 10.34 ± 1.68 mmol/l with metformin (500 mg twice daily) and from 12.65 ± 1.80 to 8.74 ± 1.97 mmol/l with sitagliptin-metformin after 12 weeks of treatment. The findings were supported by several researchers.¹⁷ Similar observations also reported by a study done among 117 patients who found significant improvement of blood sugar 2 ABF level after 24 weeks of treatment by both sitagliptin-metformin combination and metformin monotherapy.¹² However, a better improvement was observed by the combined therapy.

On the other hand, the present study showed a reduction of HbA_{1c} from $8.30 \pm 0.64\%$ to $7.48 \pm 1.00\%$ with metformin alone and from $8.39 \pm 0.99\%$ to $6.56 \pm 0.52\%$ with sitagliptin-metformin combination after 12 weeks. The findings of this study were in strong agreement with several studies.¹⁸ In another study, researchers found a 2.3% reduction of HbA_{1c} with the combination therapy of sitagliptin-metformin and 1.8% with metformin monotherapy among 1250 patients after 44 weeks of treatment.¹⁹ Whereas a study was done among 906 patients for 24 weeks showed a 0.99% reduction with metformin (500 mg twice daily), 1.30% with metformin (1000 mg twice daily), 1.57% with sitagliptin-metformin (50/500 mg twice daily), and 2.07% with sitagliptin-metformin (50/1000

mg twice daily). The researchers found the largest reduction of HbA_{1c} in a short duration with appropriate diet control and regular exercise along with sitagliptin-metformin combined therapy. They showed the maximum reduction of HbA_{1c} with the sitagliptin-metformin combination was 1.5% to 2.9%.¹²

The observed reduction of HbA_{1c} in the present study was less than earlier studies. It might be due to shortness of study duration or minimum sample size than others. There might be another cause, that the patients of our country could not maintain appropriate diet control and regular exercise along with the drug therapy. But our comparative effect was quite satisfactory. The difference of HbA_{1c} reduction level between group A and group B was 1.01%. With the overall discussion, the present study showed that, the combined therapy of sitagliptin-metformin causes better improvement of FBS, blood sugar 2 ABF, HbA_{1c} level than that of metformin alone. In fact, the combination therapy produces better glycemetic control within a short duration of treatment. Though sitagliptin-metformin fixed-dose combination is more costly than metformin, it produces better glycemetic control in NIDDM patients.

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Conclusion

This study concluded that the medicine sitagliptin was combined with the insulin sensitizing medicine metformin was better in reduction of blood sugar and HbA_{1c} level than metformin alone. The use of both medications, either metformin alone and sitagliptin-metformin in a combined therapy also affect many underlying metabolic abnormalities associated with NIDDM. Furthermore, the effects of these antidiabetic medicines on hepatic and renal functions were not evaluated. So long-term research is recommended to assess the definite effectiveness of sitagliptin-metformin combination on glycemetic control, lipid profile, hepatic and renal function.

Acknowledgement

We are grateful to the Diabetic Association, Rajshahi for helping in data collection. We are also thankful to the participants of this study for their kind cooperation.

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