A Comparative Evaluation of the Effect of Metformin and Voglibose Individually and in Combination on Serum Insulin of Diabetic Patients

Komal Shivmore[1]   Sukhmeen Kaur Johar[1]

[1] Department of Pharmacology, MGM Medical College, Aurangabad, Maharashtra, India

Int J Health Environ Res 2023;1:6–10.

Address for correspondence Sukhmeen Kaur Johar, MSc, PhD, Department of Pharmacology, MGM Medical College, Aurangabad, Maharashtra 431003, India (e-mail: sukhmeensk13@gmail.com).

Abstract

Background   Type 2 diabetes mellitus (DM) is a heterogeneous group of disorders associated with both microvascular and macrovascular complications. Due to progressive nature of type 2 DM, dual/triple drug therapy produces additive effects, less side effects, and allows the use of submaximal doses of individual agents. Therefore, the present study was designed to study the effect of metformin (500 mg BD) and voglibose (0.3 mg BD) alone and compare it with the effect of the combination (500 mg+ 0.3 mg) of on serum insulin as an add-on drug in patients with DM.

Methods   The present study was open, randomized parallel group comparison of two active treatment groups over a 6 month period. Sixty patients of either sex in the age group of 30 to 75 years, suffering from type 2 DM were selected at random. The effect of metformin, voglibose, and a combination of metformin and voglibose were observed –on serum insulin.

Results   At the end of 6 months, it was observed that though both metformin and voglibose reduced serum insulin levels significantly but their combination caused a significantly greater percentage change in serum insulin levels. A few side effects were observed with voglibose and not with metformin.

Conclusions   Though metformin and voglibose were equally effective in lowering serum insulin levels yet their combination showed better results on serum insulin as compared with metformin and voglibose individually.

Keywords
► diabetes mellitus
► metformin
► voglibose

Introduction

Diabetes mellitus (DM) is one of the most common noncommunicable diseases globally. The prevalence of diabetes is steadily increasing worldwide, particularly in the developing countries such as India.[1] India had 40.9 million diabetics in 2006 and it is expected to increase to 69.9 million by 2025.[2] The incidence of diabetes in urban Punjab is on the rise and the number of diabetics is increasing year by year.[3] The predominant clinical form of DM is type 2 DM that accounts for more than 90% of all cases.[4] Its association with developing complications severely alters the quality of life and imposes an enormous burden on the health care system. Diabetes mellitus has emerged as a major healthcare problem in India. According to the Diabetes Atlas published by the International Diabetes

Federation (IDF), there were estimated 40 million persons with diabetes in India in 2007 and this number is predicted to rise to almost 70 million people by 2025. The World Health Organization (WHO) estimates that diabetes, heart disease, and stroke together will cost about $ 333.6 billion over the next 10 years in India alone. The real burden of the disease is however due to its associated complications, which lead to increased morbidity and mortality.[1] Metformin is an effective oral hypoglycemic agent. It is approved for the management of non–insulin-dependent diabetes mellitus (NIDDM) in several countries, including Canada, although it is still an investigational drug in the United States.[1] Its use has been associated with only minimal toxicity.[2] Lactic acidosis, although a problem with the biguanide phenformin, has rarely been reported with metformin and only in situations in which the drug should not have been used, such as renal impairment.[1] Metformin does not lower blood glucose in nondiabetic individuals,[3] but has direct beneficial effects on serum lipids and lipoproteins.[1] Various beneficial vascular effects of metformin have also been reported, including reduction of micro vascular permeability[4] and vascular cell proliferation in diabetic animal models.[1]

Voglibose is a competitive inhibitor of α-glucosidase enzyme present in brush border of the small intestine. It inhibits the cleavage of complex carbohydrates into simple sugars and inhibits their absorption from the small intestine. Although all oral antidiabetic agents are reasonably effective as monotherapy in improving glycemic control but due to progressive nature of type 2 DM, monotherapy is often associated with inadequate control of glycemia and loss of efficacy over time.[5] Combining agents with different modes of action produce additive effects on glycemic control, allowing the use of submaximal doses of the agents, thereby decreasing the unwanted side effects and having complementary benefits on cardiovascular risk factors.[1] Therefore, the present study was designed to study the effect of metformin and voglibose alone and in combination on serum insulin as an add-on drug (agent) in patients with DM.

Methods

Study design and settings: The present study was an open, randomized, parallel study evaluating the comparative effect of metformin and voglibose individually and in combination on serum insulin in diabetic patients over a period of 6 months in MGM Medical College and Hospital, Aurangabad. The study was conducted after obtaining approval from the institutional ethical committee. Written informed consent was obtained from all patients prior to their enrollment.

Inclusion criteria: Previously diagnosed type 2 diabetes mellitus (DM) patients in the age group of 30 to 75 years of either sex were enrolled in study, provided they were ready to give written informed consent and had a history of type 2 DM for 6 months or more not controlled by dietary measures and exercise.

Exclusion criteria: Patients with history of type 1 DM, with acute medical emergencies such as diabetic ketoacidosis, renal failure, liver failure, cardiac failure, any microvascular complication, who are likely to undergo surgery during the study period,or had history of laparotomy and ileus, with chronic intestinal disease, with history of hypersensitivity to the test drug. Pregnant and lactating women were excluded from the study.

Procedure: The drug regime was explained to the patients and at each follow up visit, patients were assessed for glycemic control (blood sugar level); history pertaining to adverse drug effect was also asked and all patients were given advice about diet and exercise. The Primary efficacy measures for the study were change in serum insulin level by Metformin and Voglibose alone from baseline to end of study (24 weeks) and change in insulin level by the combination of two drugs metformin and voglibose from baseline to end of study. For comparing the effect of Metformin and Voglibose alone and in combination on serum insulin level before and after therapy, Paired "t" test was carried out. For intergroup comparison, unpaired "t" test was carried out. Data was analysed using SPSS software.

Observations and Results

The observations made during the study have been shown graphically (►**Figs. 1–3**). All three graphs along the X-axis (number of patients) and Y-axis (serum insulin levels) show that metformin (►**Fig. 1**) and voglibose (►**Fig. 2**) reduce the serum insulin levels but when both the drugs were given in combination (►**Fig. 3**), the reduction in serum insulin levels was more significant.

Statistical analysis of the observed data was performed and the following inferences were drawn (►**Table 1**):

1) Metformin, voglibose, and their combination at baseline and metformin, voglibose, and their combination after 6 months:
The difference in the reduction of serum insulin levels in all the three above groups was significant with $p < 0.0001$ (paired t-test).
**2)** Voglibose after 6 months and combination after 6 months:
Inter group comparison between voglibose (post) and combination (post) was significant with $p < 0.0316$ (unpaired) using unpaired t–test and was statistically significant with $p = 0.0316$.
3) Metformin after 6 months and combination after 6 months:
Inter group comparison between metformin (post) and combination (post) was not significant with $p < 0.009$ (unpaired) using unpaired t-test and was not statistically significant with $p = 0.009$.
4) Metformin at baseline and voglibose, combination after 6 months:

Intergroup comparison between metformin (at baseline) and voglibose (at baseline) was not significant with
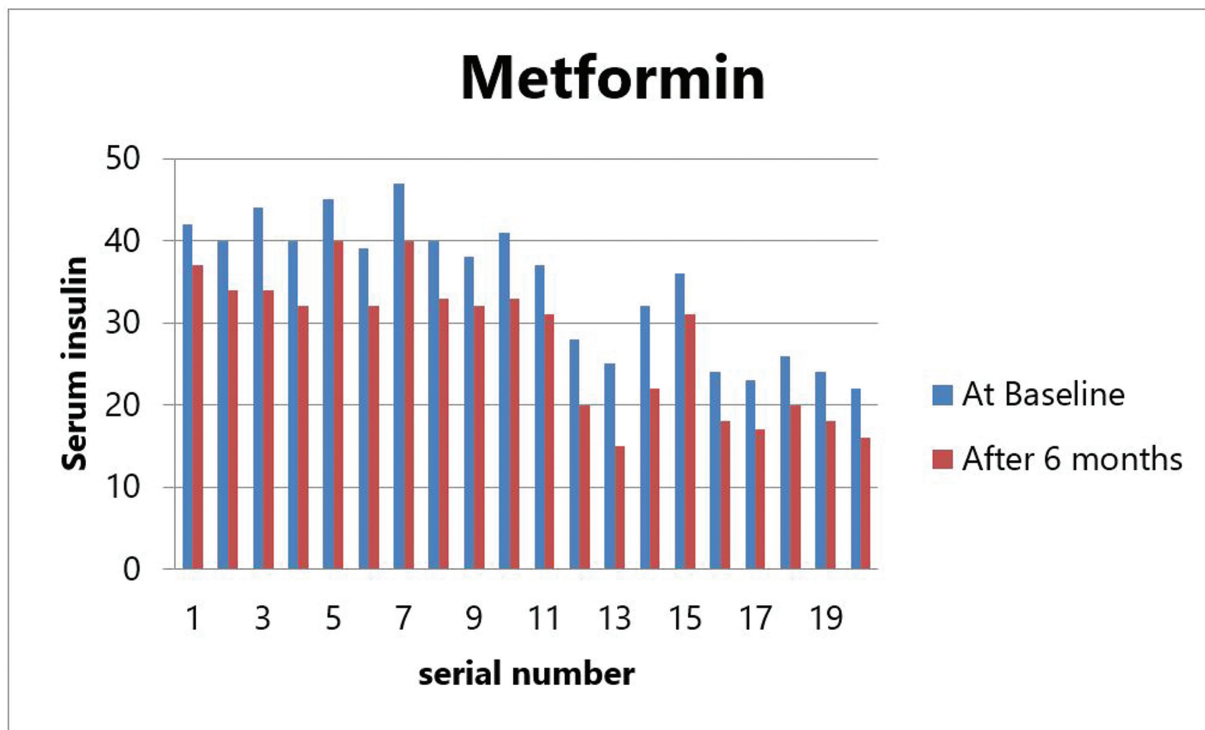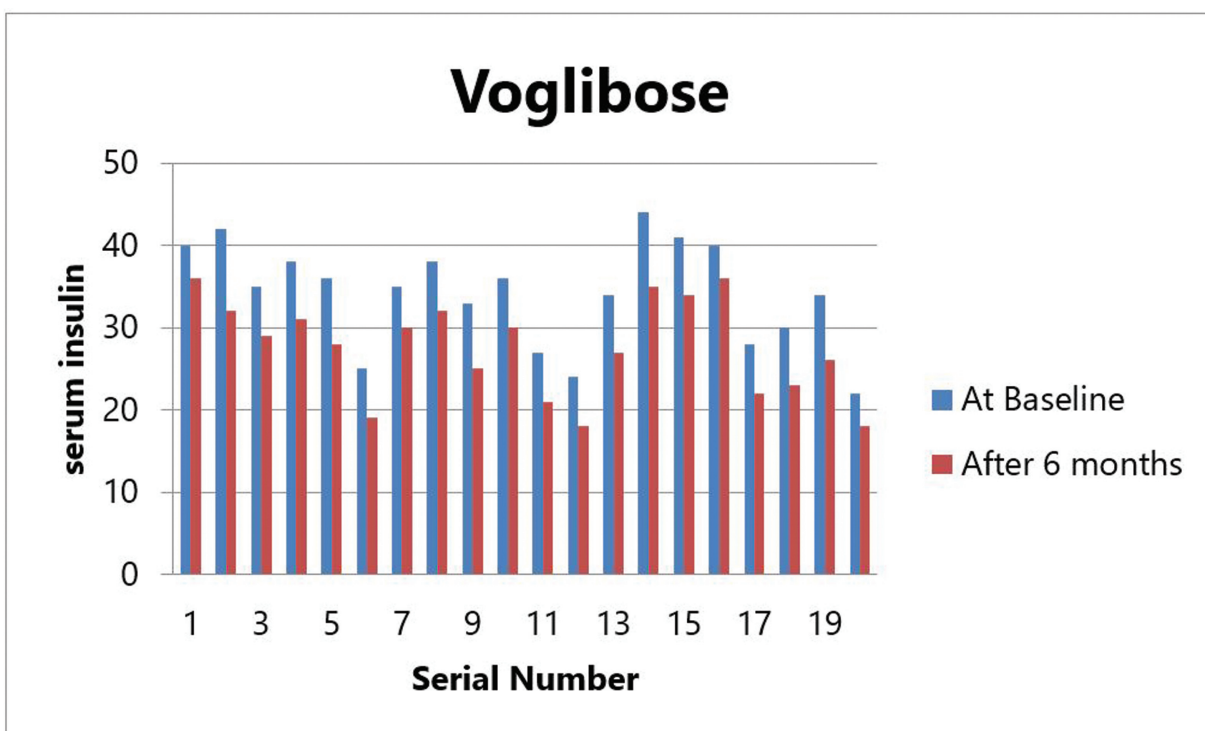
Fig. 1 Graph showing the effect of metformin at baseline and after 6 months of the treatment.

$p < 0.8145$ (unpaired) using unpaired t-test and was statistically not significant with $p = 0.8145$.

Intergroup comparison between metformin (at baseline) and combination (baseline) was not significant with $p < 0.4267$ (unpaired) using unpaired t–test and was statistically not significant with $p = 0.4267$.

Discussion

Diabetes mellitus is a group of a metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.[4] The management of DM includes diet control, exercise, and pharmacological

Fig. 2 Graph showing the effect of Voglibose at baseline and after 6 months of the treatment.
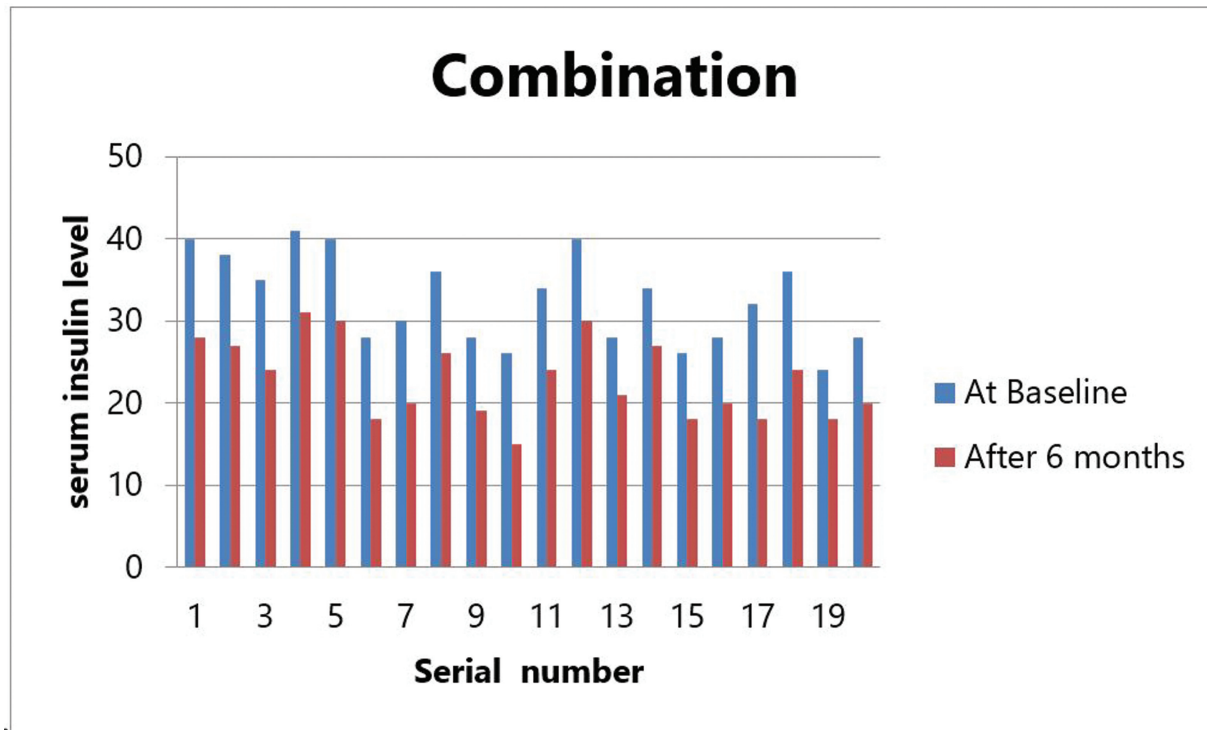
Fig. 3 Graph showing the effect of combination at baseline and after 6 months of the treatment.

therapy.[6] The drug therapy is generally initiated either with sulfonylurea or metformin as monotherapy.[7]

In the present study, 60 patients of DM were administered metformin (500 mg BD), voglibose (0.3 mg) and a combination of both the drugs. The effect of add on therapy with combination therapy was observed on serum insulin. There was no significant change in body weight in both groups throughout the study period.

A significant reduction in serum insulin levels was found with both metformin and voglibose. The reduction in serum insulin levels was significant after 6 months. However, on comparison, the combination of metformin and voglibose resulted in greater reduction in serum insulin levels, i.e., at the end of sixth months, on comparison, statistically significant difference was observed. Similar results have been observed by Oh et al, who, in their study found the combination therapy to be better than metformin alone.[8] Several other studies[9,10] have proven the efficacy of combination

therapy in the management of type II DM and hence the physicians in the current scenario are favoring the same for their patients.

Having said that, it, cannot be ruled out that single drug therapy especially metformin, has been used in the management since several years and has proven to be quite efficient. A recent study has revealed metformin to be significantly associated with reduced mortality in patients with type 2 DM who were admitted to hospital for COVID-19.[11]

Side effects of hypoglycemic drugs cannot be overlooked at any point of time.[12] In our study, among the side effects, weakness was observed with both the drugs, whereas pain in the abdomen, headache, diarrhea, flatulence, sweating, and hot flushes were observed only with voglibose. As expected, most common adverse effect in all three groups was gastrointestinal side effects such as diarrhea, flatulence, nausea, and abdominal pain.

Table 1 *T*-test applied to the treatment given in the study groups (note: $p < 0.005$ statistically highly significant)

	p-Value	Significant difference ($p < 0.05$)
Met (pre)+ met (post)	< 0.0001 (paired)	Yes
Vog (pre)+ vog (post)	< 0.0001 (paired)	Yes
Comb (pre)+ comb (post)	< 0.0001 (paired)	Yes
Met (post) + comb (post)	< 0.009 (unpaired)	Yes
Vog (post) + comb (post)	< 0.0316 (unpaired)	Yes
Met (pre) + vog (pre)	< 0.2302 (unpaired)	No
Met (pre) + comb (pre)	< 0.4267 (unpaired)	No

Conclusion

Though metformin and voglibose were equally effective in lowering serum insulin levels, their combination showed better results in lowering serum insulin levels as compared with metformin and voglibose alone.

Conflict of Interest
None declared.

References

1 Kaveeshwar SA, Cornwall J. The current state of diabetes mellitus in India. Australas Med J 2014;7(01):45–48

2 Mohan V, Sandeep S, Deepa R, Shah B, Varghese C. Epidemiology of type 2 diabetes: Indian scenario. Indian J Med Res 2007;125 (03):217–230

3 Singh A, Shenoy S, Sandhu JS. Prevalence of type 2 diabetes mellitus among urban sikh population of Amritsar. Indian J Community Med 2016;41(04):263–267

4 American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2009;32(01, Suppl 1):S62–S67

5 Mudaliar S. New frontiers in the management of type 2 diabetes. Indian J Med Res 2007;125(03):275–296

6 Fujiwara Y, Eguchi S, Murayama H, et al. Relationship between diet/exercise and pharmacotherapy to enhance the GLP-1 levels in type 2 diabetes. Endocrinol Diabetes Metab 2019;2(03):e00068. Doi: 10.1002/edm2.68

7 Rojas LB, Gomes MB. Metformin: an old but still the best treatment for type 2 diabetes. Diabetol Metab Syndr 2013;5 (01):6

8 Oh TJ, Yu JM, Min KW, et al. Efficacy and safety of voglibose plus metformin in patients with type 2diabetes mellitus: a randomized controlled trial. Diabetes Metab J 2019;43(03): 276–286

9 Murti K, Sethi M, Dey A, Lal C, Pandey K, Das P. Addition of voglibose to glimepiride and metformin have better glucose control in diabetics: a prospective, parallel-group and open-label comparative study. Int J Pharmacol 2016;12:422–428

10 Padhi S, Nayak AK, Behera A. Type II diabetes mellitus: a review on recent drug based therapeutics. Biomed Pharmacother 2020; 131:110708

11 Bramante CT, Ingraham NE, Murray TA, et al. Metformin and risk of mortality in patients hospitalised with COVID-19: a retrospective cohort analysis. Lancet Healthy Longev 2021;2(01): e34–e41

12 Kinaan M, Ding H, Triggle CR. Metformin: an old drug for the treatment of diabetes but a new drug for the protection of the endothelium. Med Princ Pract 2015;24(05):401–415