**Original article:**

# Efficacy and safety of voglibose as an add-on triple drug in patients of type two diabetes mellitus uncontrolled with glimepiride and metformin in punjabi population

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**ABSTRACT**

**Introduction**: Type 2 Diabetes mellitus 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 produce additive effects, allows the use of submaximal doses of individual agents, less side effects and have complementary benefits on cardiovascular risk factors.

**Methods:** The present study was designed to study the effect of voglibose on glycaemic and lipid profile as an add-on drug (agent) in patients with DM whose glycaemic status was uncontrolled with glimepiride and metformin. The present open study was conducted over a six months period. Thirty patients of type 2 DM of either sex in the age group of 30- 75 years who were on maximum doses of glimepiride 2 mg BD and metformin 500 mg BD with FBG> 126 mg/dl and HbA1c between 7- 10 % were selected at random. They were given voglibose 0.2 mg TDS as- add on triple drug.

**Observations and Results:** The effect of triple drug combination was then observed on various parameters i.e. FBG, PPBG, HbA1c and lipid profile (Total cholesterol, TG, LDL, VLDL and HDL). At the end of 6 months it was observed that voglibose reduced FBG, PPBG and $HbA_{1C}$ significantly ($p < 0.001$).

**Conclusion:** There was beneficial effect of voglibose on all the parameters of lipid profile ($p < 0.01$). The side effects like pain abdomen, headache, diarrhea, flatulence, sweating and hot flushes were also observed. Though voglibose had beneficial effect on glycaemic and lipid profile as-add on triple drug but it was associated with side effects.

**Key words:** Diabetes mellitus, Voglibose, Glimepiride, Metformin

## INTRODUCTION

Diabetes mellitus is one of the most common non - communicable diseases globally. The prevalence of diabetes is steadily increasing worldwide, particularly in the developing countries like India [1]. India had 32 million diabetics in 2000 and it is expected to increase to 80 million by 2030 [2]. According to the study conducted by the Jalandhar diabetic society, 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 which 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 health care system.

The key management goals in Type 2 DM are the relief of acute symptoms and prevention of long term complications, whilst avoiding hypoglycaemia. The relationship between the degree of glycaemic control and microvascular complications in Type 2 DM is well established. Aggressive, tight control of serum glucose reduces risk of microvascular disease. However, for prevention of macrovasular disease improving glycaemic control is necessary but not sufficient [5]**.** According to UKPDS 38 **,** treating other risk factors like dyslipidemia and hypertension have been shown to be effective in reducing macrovascular disease [6].Dietary and lifestyle modifications form the mainstay of therapy for Type 2 DM [7]. Pharmacological therapy is advocated when treatment goals are not achieved with lifestyle modifications. Several oral antihyperglycaemic agents are available to optimize the management of Type 2 DM. Based on their mechanism of action, they are subdivided into agents that increase insulin secretion like sulfonylureas, meglitinides, GLP-1agonists, DPP-4 inhibitors, reduce glucose production like biguanides, increase insulin sensitivity like thiazolidinediones and reduce carbohydrate absorption like α-glucosidase inhibitors.Sulfonylureas have been in use since 1950s. They increase insulin levels acutely and thus should be taken shortly before a meal [8]**.**They require the presence of functioning ß cells for their action. Meglitinides are non sulfonylurea insulin secretagogues. They are relatively rapidly acting agents helps in reducing postprandial hyperglycaemia [9].

Metformin acts by decreasing hepatic glucose production and increasing sensitivity of peripheral tissues to insulin. It improves glycaemic control and has been shown to lower both total and LDL cholesterol and serum TG in Type 2 DM [10].

Pioglitazone is an insulin sensitizer which act by improving insulin sensitivity at the cellular level. It reduces insulin resistance by binding to PPAR γ which results in change of expression of genes involved in regulating glucose and lipid metabolism, insulin signal transduction and other tissue differentiation.

Voglibose is a competitive inhibitor of α - glucosiadse enzyme present in brush border of small intestine. It inhibits the cleavage of complex carbohydrates into simple sugars and inhibit their absorption from small intestine.

Although all the oral antidiabetic agents are reasonably effective as monotherapy in improving glycaemic control but due to progressive nature of type 2 DM, monotherapy is often associated with inadequate control of glycaemia and loss of efficacy over time [11]**.** Combining agents with different modes of action produce additive effects on glycaemic control, allows the use of submaximal doses of the agents, thereby decreasing the unwanted side effects and have complementary benefits on cardiovascular risk factors[12].

Therefore, the present study was designed to study the effect of voglibose on glycaemic and lipid profile as an add-on drug in patients with DM whose glycaemic status was uncontrolled with glimepiride 2 mg BD and metformin 500 mg BD.



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## MATERIALS AND METHODS

The present study was open study evaluating the efficacy and safety of voglibose in combination with sulfonylurea (glimepiride 2 mg BD) and biguanide (metformin 500 mg BD) on glycaemic and lipid profile in diabetic patients over a period of six months. The study was conducted after obtaining approval from institutional ethical committee and was conducted from January 2010 to December 2010. Written informed consent was obtained from all the patients prior to their enrollment. Previously diagnosed type 2 diabetes mellitus (DM) patients on sulfonylurea (glimepiride 2 mg BD ) and biguanide (metformin 500 mg BD ) for at least one year and whose FBG >126 mg/dl, PPBG > 200 mg/dl and $HbA_{1C}$ between 7-10% were included in the study. Patients with history of Type 1 DM, with acute medical emergencies like diabetic ketoacidosis, renal failure, liver failure and cardiac failure, who are likely to undergo surgery during the study period, with history of laparotomy and ileus, with chronic intestinal disease, with history of hypersensitivity to the test drug, pregnant and lactating women .This study recruited thirty patients of either sex in the age group of 30-75 years suffering from Type 2 diabetes mellitus (diagnosed as per criteria laid down by National Diabetes Data Group and WHO) [8] attending the medicine Outpatient department of tertiary care hospital of Amritsar. After meeting the inclusion entry criteria, patients were given additional third drug i.e tab. Voglibose 0.2 mg TDS orally for 6 months.Two patients dropped and two patients discontinued the treatment due to adverse events like pain abdomen, diarrhea and flatulence. On the start of the study, (Day 0), after taking the history of the patients and doing the clinical examination, routine investigations were sent. The baseline FBG, PPBG, $HbA_{1C}$ and lipid profile were obtained after 12 hour overnight fasting. Patients were given a 15 day supply of drugs with proper directions and asked to report back after 15 days. Initially patients were followed after 15 days and subsequently every month up to 6 months. FBG and PPBG were recorded monthly while $HbA_{1C}$ and lipid profile were recorded at 3 months intervals. The results were tabulated as mean ± standard deviation (SD) and analyzed using paired t test. The level of significance was determined as its 'p' value with $p > 0.05$ taken as not significant, $p < 0.05$ taken as significant at 5% significance level, $p < 0.01$ taken as significant at 1% significance level and $p < 0.001$ taken as highly significant.

## RESULTS

Thirty patients (17 females and 13 males) who completed the study were included in the analysis. Maximum number of patients was in the age group of >60-70 years and least number of patients were within 30-40 years of age. Mean age was 56.43 ± 8.49 years.

Body mass index (BMI) of patients indicates that majority of the patients (14 in number) were in the overweight range (25- 29.9 $kg/m^2$) and few (4 patients) were in obese (> 30 $kg/m^2$) category. No obvious change in the BMI was observed after 6 months of treatment.

Fasting blood glucose, postprandial blood glucose and HbA1c levels showed significant reduction over a period of 6 months ($p< 0.001$). (Table 1) There was significant reduction in LDL, VLDL ($p< 0.001$), total cholesterol and triglyceride levels ($p< 0.01$) over a period of 6 months. HDL levels increased significantly ($p< 0.01$). (Table 2)



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**Table 1: Glycaemic profile during treatment with voglibose over six months period**

| Duration | FBG (Mean±SD in mg/dl) | PPBG (Mean±SD in mg/dl) | $HbA1_C$ (Mean±SD in %) |
|---|---|---|---|
| Baseline | 171.73 ± 25.45 | 264.40 ± 48.84 | 9.13 ± 0.48 |
| 1st month | 162.27 ± 26.77*** | 223.27 ± 44.00*** | - |
| 2nd month | 159.37 ± 26.25*** | 205.07 ± 42.51*** | - |
| 3rd month | 157.00 ± 25.98*** | 193.13 ± 40.39*** | 7.96 ± 0.68*** |
| 4th month | 155.07 ± 26.96*** | 184.33 ± 37.46*** | - |
| 5th month | 153.43 ± 26.66*** | 178.37 ± 36.56*** | - |
| 6th month | 150.57 ± 27.14*** | 170.27 ± 33.98*** | 7.17 ± 0.63*** |

***: p<0.0001

**Table 2: Lipid profile during treatment with voglibose over six months period**

| Duration | TC | TG | LDL | HDL | VLDL |
|---|---|---|---|---|---|
| Baseline | 229.47 ± 48.99 | 189.17 ± 45.24 | 178.57 ± 28.67 | 34.37 ± 8.16 | 31.93 ± 11.16 |
| 3rd month | 223.83 ± 48.12** | 180.30 ± 44.04** | 175.90 ± 28.85*** | 35.10 ± 8.22*** | 31.27 ± 10.91*** |
| 6th month | 221.27 ± 47.96** | 178.33 ± 42.53** | 174.07 ± 27.78*** | 35.07 ± 8.34** | 30.97 ± 11.12*** |

***: p<0.0001 **: p< 0.01

**DISCUSSION**

Diabetes mellitus is a group of a metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action or both. The management of DM includes diet control, exercise and pharmacological therapy. The drug therapy is generally initiated either with sulfonylurea or metformin as monotherapy. In the present study 30 patients of DM whose glycaemic status was not controlled with two oral hypoglycaemic agents (metformin and glimepiride) were given third drug voglibose.

The effect of add on therapy with voglibose as a third agent was observed on various parameters. Among the clinical parameters, the BMI of majority of the patients included for the study has been found to be in the range of 25- 29.9 $kg/m^2$ designated as overweight. There was no significant change observed in BMI at the end of study. This is in accordance with the previous studies[14][15]**.** There was no significant change in body weight throughout the study period.

A significant reduction in FBG, PPBG and $HbA1_C$ was found with voglibose. The reduction in these parameters was observed in chronological sequence with duration of study i.e. at 1st, 2nd, 3rd, 4th, 5th and 6th months. Derosa et al also observed significant reduction in FBG, PPBG and HbA1c with combination of sulfonylurea, metformin and acarbose [16].

Addition of voglibose has been reported to have an influence on serum lipids. i.e. TC, TG, LDL and



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VLDL and these were reduced significantly with voglibose.

Reports regarding voglibose on lipids are contrary. In the study conducted by Mughal et al, there was significant reduction in TG and VLDL but there was no significant effect on TC and LDL with voglibose [17]. Voglibose has been reported to cause increase in TC and LDL in type 2 diabetic patients by Iwamoto et al [18].

Among the side effects, weakness, pain abdomen, headache, diarrhea, flatulence, sweating and hot flushes were observed with voglibose.

**CONCLUSION**

Though voglibose had beneficial effect on glycaemic and lipid profile as-add on triple drug but was associated with side effects.

**REFERENCES**


1. King H, Aubert RE, Herman WH . Global burden of diabetes, 1995-2025: prevalence, numerical estimates and projections. Diabetes Care.1998; 21: 1414-1431.
2. Ramchandran A, Snehlata C, Vijay V. Burden of type 2 diabetes and its complications – The Indian scenario. Current Sciences. 2002; 83: 1471-1476.
3. Zafar J, Bhatti F, Akhtar N, Rasheed U, Humayun S, Waheed A et al. Prevalence and risk factors for diabetes mellitus in a selected urban population of a city in Punjab. J Pak Med Assoc 2011;61:40-7.
4. Nathan DM, Meigs J, Singer DE. The epidemiology of cardiovascular disease in type 2 diabetes mellitus: how sweet it is...or is it? Lancet. 1997; 350 (1): 4-9**.**
5. Hu FB, Manson JE, Stampfer MJ. Diet, Lifestyle and the risk of type 2 diabetes mellitus in women. NEJM. 2001; 345: 790-797.
6. Guillausseau PJ, Massin P, Charles MA. Glycaemic control and development of retinopathy in type 2 diabetes mellitus: a longitudinal study. Diabetes Med. 1998; 15: 151-155.
7. Grundy SM . Dietary therapy in diabetes mellitus. Diabetes Care. 1991; 14: 796- 808.
8. Powers AC. Diabetes Mellitus. In: Fauci AS, Braunwald E, Kasper DL, Stephen LH, Dan LL, Jameson LL, Loscalzo J. Harrison's principles of internal medicine. 17th ed. New York: Mc Graw Hill 2008; 2275- 2304.
9. Tripathi KD. Insulin, oral hypoglycaemic drugs and glucagon. In: Tripathi KD. Essentials of medical pharmacology. 6th ed. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd 2008; 254-274.
10. Bailey CJ, Turner RC. Metformin. NEJM.1996; 334: 574-579.
11. Mudaliar S. New frontiers in the management of type 2 diabetes. Indian J Med Res. 2007;125: 275-96.
12. Lebovitz HE. Insulin resistance: definition and consequences. Exp Clin Endocrinol Diabetes. 2001; 109 (2): 135-148.
13. Inzucchi SE.Oral antihyperglycemic therapy for type 2 diabetes: scientific review. JAMA.2002; 287: 360-372.
14. Pinol. C, B. Costa. Diabetes Research and clinical practice. 1997; 38: 33-40.

15. Kazuya S, Masaaki S, Junya H, Yasushi H, Yutaka H. Improvement of insulin sensitivity and dyslipidemia with a new glucosidase inhibitor, Voglibose in nondiabetichyperinsulinemic subjects. Metabolism.1996; 45 (6): 731-737.
16. Derosa G, Salvedeo S, Angelo A, Ferrari I, Moreu R, Palumbo I et al. Metabolic effect of repaglinide or acarbose when added to a double oral antidiabetic treatment with sulphonylureas and metformin: a double blind, cross over, clinical trial. Informa Healthcare. 2009; 25 (3): 607-615.
17. Mughal MA, Memon MY, Zardari MK, Tanwani RK, Ali M. Effect of acarbose on glycaemic control, serum lipids and lipoproteins in type 2 diabetes. J Pak Med Assoc. 2000; 50 (5): 152-156.
18. Iwamoto Y, Kashiwagi A, Yamada N, Terao S, Mimori N, Suzuki M et al. Efficacy and safety of vildagliptin and voglibose in Japanese patients with type 2 diabetes; a 12 week, randomized, double blind, active controlled study. Diabetes obes metab.2010; 12 (8): 700-708.
19. .United Kingdom Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ. 1998; 317: 703-713.

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