

## Improvement in Blood Glucose Fluctuations in Type 2 Diabetes Mellitus by Voglibose with or without High Fiber Dietary Intervention

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**Abstract:** Diabetes Mellitus (DM) is a chronic metabolic disorder affecting people worldwide, with significant morbidity and mortality caused by its micro-vascular and macro-vascular complications, affecting various vital organs and structures in humans. Glycemic variability seems to have more deleterious effects than sustained hyperglycemia on the development of diabetic complications. The aim of the present study was to investigate the effectiveness of voglibose with or without high-fiber dietary intervention for 12 weeks on glycaemic variability in type 2 diabetes patients using a continuous glucose-monitoring system (CGMS). This randomized control trial was conducted at Department of General Medicine of a tertiary care centre. Fifty diagnosed T2 DM patients whose HbA1c levels ranged from 7.0% to 10.0% were randomized to voglibose monotherapy and other 50 patients were randomized to receive voglibose in combination of high-fiber dietary intervention therapy. After 12 weeks intervention, overall glycaemic control and blood glucose variability were evaluated by CGMS parameters. Combination therapy using high-fiber dietary intervention and voglibose was more effective in reducing HbA1c and the mean of daily differences (MODD) than voglibose monotherapy ( $P < 0.05$ ), whereas no significant differences were found in the mean amplitude of glycemic excursion (MAGE) and largest amplitude of glycemic excursions (LAGE) between the combination therapy group and the monotherapy group ( $P > 0.05$ ). In conclusion, voglibose alone or in combination with high-fiber dietary intervention can improve overall blood glucose levels and glycaemic variability. But voglibose with high-fiber dietary intervention contributes to the alleviation of glycemic variability via modulating intestinal secretion of GLP-1.

**Keywords:** Voglibose, CGMS, hyperglycemia

## INTRODUCTION

Diabetes Mellitus (DM) is a chronic metabolic disorder affecting people worldwide, with significant morbidity and mortality caused by its micro-vascular and macro-vascular complications, affecting various vital organs and structures in humans. It has been estimated that by year 2030, the diabetic population will rapidly increase from 21.7 million to 79.4 million in India. However, prevalence is much more than this estimation, as many patients are asymptomatic and unaware about this and go undiagnosed. This accounts for nearly another one-third of estimated cases [1]. In diabetic patients, postprandial hyperglycemia (PPHG) is a direct and independent risk factor for development of cardiovascular diseases or stroke caused by premature atherosclerosis [2]. Fasting blood glucose (FBG), if high, also leads to some complications in long run if it is not controlled. Voglibose is an alpha-glucosidase

inhibitor used for lowering post-prandial blood glucose (PPBG) levels in people with DM. PPHG is primarily due to first phase insulin secretion. Alpha glucosidase inhibitors delay glucose absorption at the intestine level and thereby prevent sudden surge of glucose after a meal. The anti-hypoglycaemic action of voglibose results from a reversible inhibition of membrane bound intestines  $\alpha$  glycosidase hydrolize enzymes which hydrolize oligosaccharides and disaccharides to glucose and other monosaccharides in the brush border of the small intestine. Thus, voglibose delays the absorption as well as digestion of dietary polysaccharides by reversibly inhibiting carbohydrate digestive enzymes like sucrose, maltose, zomaltase, etc. This results in a reduction in PPHG. Voglibose may also facilitate mobilisotary  $\alpha$  endogenous glycogen-like peptide 1 (GLP-1), which has an inhibitory action on glycogen, thus lowering FBG levels too. Voglibose treatment has

resulted in an increased release of GLP-1, which is an insulinotropic hormone and it has also increased release of GLP-1, which is known to enhance insulin secretion and insulin sensitivity [3].

Voglibose has no inhibitory activity against lactase and so, it does not cause lactose intolerance and diarrhoea. Glycemic variability seems to have more deleterious effects than sustained hyperglycemia on the development of diabetic complications. The aim of the present study was to investigate the effectiveness of voglibose with or without high-fiber dietary intervention for 12 weeks on glycaemic variability in type 2 diabetes patients using a continuous glucose-monitoring system (CGMS).

## MATERIALS & METHODS

### Study design:

This is a randomized control trial.

### Study setup:

This study is conducted at Department of General Medicine of a tertiary care centre.

### Study duration:

The duration of study was two years; January-2015 to December-2016.

### Sampling:

Purposive sampling technique is used for selection of desired samples according to inclusion criterion.

### Sample size:

One thousand patients of general medicine department of a tertiary care centre were evaluated for possible inclusion in study. Out of these 100 subjects were recruited for the study after fulfilling inclusion criteria.

### Inclusion criteria

All adults with type 2 diabetes mellitus with FBG > 110 mg/dl, PPBG > 180 mg/dl and HbA1c > 7.0% included in this study.

### Exclusion criteria

Patients with history of type 1DM, ketoacidosis, kidney disease, liver diseases, inflammatory bowel diseases and intestinal obstruction were excluded from the study.

### Methods

Fifty diagnosed T2 DM patients whose HbA1c levels ranged from 7.0% to 10.0% were randomized to voglibose monotherapy and other 50 patients were randomized to receive voglibose in combination of high-fiber dietary intervention therapy. After 12 weeks intervention, overall glycaemic control and blood

glucose variability were evaluated by CGMS parameters.

The CGMS sensor (Medtronic, Northridge, CA) was inserted into all subjects by the same specialized technician at day 0 at ~8:00–9:00 AM in hospital. First CGMS calibration by finger stick blood glucose was performed after 1 h of initialization. If no abnormal CGMS situation was observed, the subjects were discharged and continued with CGM at home for 3 consecutive days. Subjects were instructed to input at least four calibration readings per day. At day 3 at ~8:00–9:00 A.M., subjects came to the hospital and had the CGMS removed. The 24-h mean blood glucose (24-h MBG) was calculated as mean blood glucose level from 288 readings measured by a CGMS over 24 h. Daytime and nighttime mean blood glucose levels were defined as blood glucose levels during the time intervals of 6:00 AM to 10:00 PM and 10:00 PM to 6:00 AM, respectively. Postprandial blood glucose levels at 30, 60, 120, and 180 min and the area under the curve within 3 h after each meal were recorded and calculated. For each subject, the proportion of time spent on the blood glucose ranges of 70–140 (3.9–7.8 mmol/l),  $\geq 140$ , and  $\leq 70$  mg/dl were determined from the CGM data. Percentage of time (PT) for blood glucose  $\leq 70$  mg/dl and  $\geq 140$  mg/dl within 24 h were recorded as PT70 and PT140, respectively (13,14). Other CGM parameters, including the area under the curve for blood glucose >100 mg/dl and the SD of blood glucose concentration within 24 h were also calculated (13,14). All of the above parameters were based on the mean values taken on days 1 and 2.

### Statistical methods

CGM parameters were analyzed using CGMS software 3.0. Measurement data was presented as means  $\pm$  SD. Statistical analyses were performed using SPSS software (version 18.0). The t test was used for comparison between two groups when data were normally distributed; otherwise, nonparametric analysis was applied. Pearson and Spearman analytical methods were employed for correlation analysis of two variables.

## RESULTS

None of the subjects complained of discomfort, such as inflammation or allergy at the embedding sites. FBG and PPBG, HbA1c, mean blood glucose (MBG), standard deviation of daily average blood glucose (SDBG), largest amplitude of glycemic excursions (LAGE), mean amplitude of glycemic excursion (MAGE), the mean of daily differences (MODD) and homeostasis model assessment of insulin resistance decreased significantly in both groups (all  $P < 0.01$ ). Combination therapy using high-fiber dietary intervention and voglibose was more effective in reducing HbA1c and MODD than voglibose monotherapy ( $P < 0.05$ ), whereas no significant

differences were found in the mean changes of MAGE and LAGE between the combination therapy group and the monotherapy group ( $P > 0.05$ ).

## DISCUSSION

Acarbose, voglibose, and miglitol are pseudo-carbohydrates that competitively inhibit  $\alpha$ -glucosidase enzymes located in the brush border of enterocytes that hydrolyze non-absorbable oligosaccharides and polysaccharides into absorbable monosaccharides. Voglibose is the most used drug of this family. Voglibose is slowly and poorly absorbed and rapidly excreted in stools, with no metabolites identified to date [4]. Since  $\alpha$ -glucosidase inhibitors prevent the digestion of complex carbohydrates, they should be taken at the start of main meals, taken with the first bite of a meal. Moreover, the amount of complex carbohydrates in the meal will determine the effectiveness of  $\alpha$ -glucosidase inhibitors in decreasing PPBG.

$\alpha$ -Glucosidase inhibitors can be used as a first-line drug in newly diagnosed type 2 DM insufficiently treated with diet and exercise alone, as well as in combination with all oral anti-diabetics and insulin if monotherapy with these drugs fails to achieve the targets for HbA1c and PPBG. As a first-line drug, they are particularly useful in newly diagnosed type 2 DM with excessive PPBG, because of their unique mode of action in controlling the release of glucose from complex carbohydrates and disaccharides.  $\alpha$ -Glucosidase inhibitors may also be used in combination with a sulfonyleurea, insulin or metformin[5].

$\alpha$ -Glucosidase inhibitors are contraindicated in patients with known hypersensitivity to the drug, in patients with diabetic ketoacidosis or inflammatory bowel disease, colonic ulceration, partial intestinal obstruction or in patients predisposed to intestinal obstruction. In addition, they are contraindicated in patients who have chronic intestinal diseases associated with marked disorders of digestion or absorption and in patients who have conditions that may deteriorate as a result of increased gas formation in the intestine. Voglibose should be orally administered in a single dose of 0.2 mg three times a day, just before each meal; if not sufficient, the dose can be up-titrated to 0.3 mg three times a day.

Mori *et al.* [6] conducted a study using CGM to assess MAGE with acarbose. Five of the patients were randomized to acarbose at 300 mg/day on days 1 and 2, but not on days 3 and 4; the remaining five patients were not administered acarbose on days 1 and 2, but were given 300 mg/day on days 3 and 4. During CGM, insulin was administered at the same time and the same dose. When acarbose was administered, the average CGM profile was decreased in almost all patients regardless of the current insulin regimen. The

24-h mean blood glucose level when acarbose was not administered was  $158.03 \pm 32.78$  mg/dl, the 24-h blood glucose fluctuation was  $677.05$  mg/dl, and MAGE was  $97.09$ . The 24-h mean blood glucose level when acarbose was administered was  $131.19 \pm 22.48$  mg/dl ( $p = 0.004$ ), the 24-h blood glucose fluctuation was  $453.27$  mg/dl ( $p = 0.002$ ), and MAGE was  $65.00$  ( $p = 0.010$ ). The mean proportion of time spent in the hyperglycemic range (defined as  $\geq 180$  mg/dl) during CGM was  $29.5 \pm 24.4\%$  when acarbose was not administered and  $16.2 \pm 25.4\%$  when it was administered. The mean proportion of time spent in the hyperglycemic range (defined as  $\geq 140$  mg/dl) during CGM was  $58.7 \pm 29.4\%$  and  $40.4 \pm 36.3\%$ , respectively. The mean proportion of time spent in the hypoglycemic range (defined as  $< 70$  mg/dl) during CGM was  $0.31 \pm 0.63\%$  when acarbose was not administered and  $0.02 \pm 0.5\%$  when it was administered. These data show that hypoglycemia was not increased by concomitant treatment targeting PPG.

A similar study conducted by Wang *et al.* [7,8,] evaluated the effects of acarbose versus glibenclamide on MAGE and oxidative stress in type 2 diabetic patients not well controlled by metformin. Patients treated with metformin monotherapy (1500 mg daily) were randomized to either acarbose (50 mg three times a day for the first month, then 100 mg three times a day), or glibenclamide (2.5 mg three times a day for the first month, then 5 mg three times a day) for 16 weeks. Continuous glucose monitoring for 72 h and a meal tolerance test (MTT) after a 10-hour overnight fast were conducted before randomization and at the end of the study. HbA1c significantly decreased in both treatment groups (from  $8.2 \pm 0.8\%$  to  $7.5 \pm 0.8\%$ ,  $p < 0.001$  with acarbose, and from  $8.6 \pm 1.6\%$  to  $7.4 \pm 1.2\%$ ,  $p < 0.001$  with glibenclamide). The MAGE did not change significantly with glibenclamide, whereas oxidized low-density lipoprotein (ox-LDL) increased significantly (from  $242.4 \pm 180.9$  ng/ml to  $470.7 \pm 247.3$  ng/ml,  $p < 0.004$ ). Acarbose decreased MAGE ( $5.6 \pm 1.5$  mmol/l to  $4.0 \pm 1.4$  mmol/l,  $p < 0.001$ ) without significant change in ox-LDL levels (from  $254.4 \pm 269.1$  ng/ml to  $298.5 \pm 249.8$  ng/ml,  $p < 0.62$ ). Body weight and serum triglycerides decreased (all  $p < 0.01$ ) and serum adiponectin increased ( $p < 0.05$ ) after treatment with acarbose, whereas HDL-C decreased ( $p < 0.01$ ) after treatment with glibenclamide.  $\beta$ -cell response to PPG increments was negatively correlated with MAGE ( $r = 0.570$ ,  $p < 0.001$ ) and improved significantly with acarbose ( $35.6 \pm 32.2$  pmol/mmol to  $56.4 \pm 43.7$  pmol/mmol,  $p < 0.001$ ), but not with glibenclamide ( $27.9 \pm 17.6$  pmol/mol to  $36.5 \pm 24.2$  pmol/ mmol,  $p < 0.12$ ).

## CONCLUSION

In conclusion, voglibose alone or in combination with high-fiber dietary intervention can

improve overall blood glucose levels and glycaemic variability. But voglibose with high-fiber dietary intervention contributes to the alleviation of glycemic variability via modulating intestinal secretion of GLP-1.

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