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REVIEW ARTICLE

Voglibose: Focus on beneficial role in glycemic variability

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INTRODUCTION

According to thepublished data, the number of people diagnosed withdiabetes worldwide has more than doubled since 1980 to nearly 350 million.Glycaemia and diabetes are rising globally, driven both by population growth and ageing and by increasing age-specific prevalence.[1]Despite the availability of a number of anti-diabetic medications,Post-Prandial Hyperglycemia (PPG) still remains a problem in the management of type2 diabetes mellitus.[2]Fasting plasma glucose (FPG), postprandial hyperglycemia, and glucose variability all contributeto the net balance of the long-term glycemic parameter HbA1c (glycated hemoglobin).[3]According to the 2012 American Diabetes Association guidelines, lowering HbA1c to ≤ 7% has been shown to reduce microvascular and neuropathic complications of diabetes. However, many times, even if an adequate HbA1c is reached, PPG can occur. Post-prandial hyperglycemia significantly contributes to the development of chronic diabetic complications, particularly cardiovascular disease, and microvascular complications of diabetes, even more than fasting hyperglycemia. Published data reveal that amongst all the available antidiabetic drugs, α-glucosidase inhibitors are the most effective in reducing PPG.[2]

This is confirmed by the International Diabetes Federation (IDF), which has published a treatment algorithm for people with type 2 diabetes, where α-glucosidase inhibitors play an important role both as first line and second or third line therapy (Figure 1).[4]

Acarbose and voglibose are α-glucosidase inhibitors that typically reduce PPGconcentrations by delaying carbohydrate digestion and therefore absorption in the gut. These drugs can be useful as first-line treatment in the patients who have a combination of slightly raised

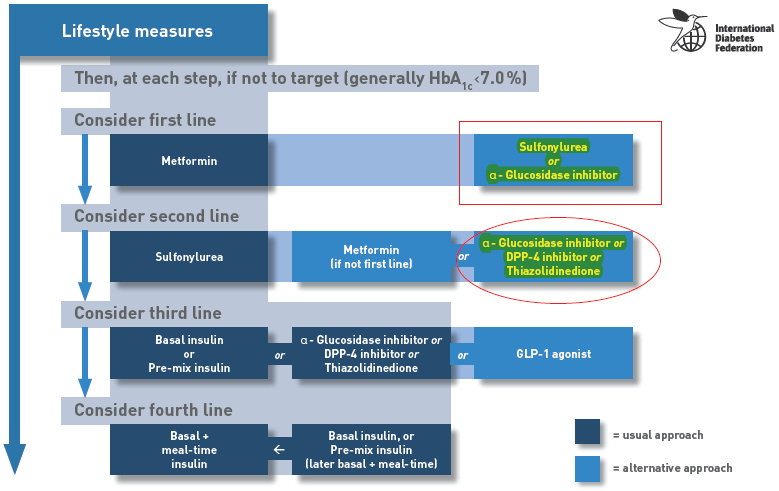

Figure 1. IDF Treatment algorithm for people with Type 2 Diabetes

basal glucose concentrations and marked PPG.[5]

This article highlights the efficacy of Voglibose on glycemic variability.

PPG and Glycemic variability

Glycemic variability (GV) means swings in blood glucose level. The broad definition of GV takes into account the intraday glycemic excursions including episodes of hyper and hypoglycemia. The postprandial hyperglycemic excursions too contribute to GV. Glycemic variability is one more tool to explain relation between hyperglycemia and increased cardiovascular risk in diabetic patients.

The hypothesized etiological factors for these glycemic bumps include diminished or absent glycemic auto regulation or short falls of insulin availability.[6]

Assessment of Glycemic variability- *Is it a confusion?*

Normally, plasma glucose levels are kept within a narrow range, of 80-120 mg/dL, throughout the day in people with normal glucose tolerance (NGT) (Figure 2). The glycemic swings become greater once glucose intolerance develops. As there are various definitions or concepts of GV, there is a great confusion about GV assessment. Generally, GV refers to intra-day GV or day-to-day GV, but it also may refer to visit-to-visit GV over months to

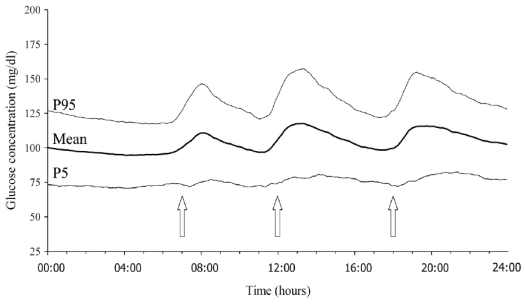

Figure 2. Daily glucose profile in healthy subjects assessed by continuous glucose monitoring. The central line is the mean, and the two outer lines represent the 5th and 95th percentiles (P5 and P95, respectively). Arrows indicate the times of three meals during a day.

years. Furthermore, although GV usually refers to overall glycemic variation including hyper and hypoglycemia, GV is often also used to refer to postprandial glycemic excursion, especially in patients with T2DM. Thus, data interpretation should take into account different definitions and concepts of GV.[7]

For the management of GV, it is important to clarify factors associated with GV in patients with diabetes. Factors that associate with GV are summarized in Table 1.[7]

Voglibose and glycemic variability

α-Glucosidase inhibitors can be used as a first-line drug in newly diagnosed type 2 diabetes 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 PPG.[2]

Voglibose one of the α-glucosidase inhibitors (α-GIs) discovered in Japan in 1981 and has become

Reduced β cell function
Older age
Liver failure
Renal impairment
Reduced lean mass
Autonomic neuropathy
Anti-diabetic medication
Polypharmacy
Cognitive impairment/dementia
Poor compliance with treatment
Intake of food with higher glycemic index and/or glycemic load
Amount of vegetables/fiber intake
Irregular timing of meals
Physical inactivity

Table1. Factors associated with greater glycemic variability[7]

commercially available for the treatment of DM since 1994.Theaction of voglibose results from a reversible inhibition of membrane bound intestines α-glycosidase hydrolyze enzymes which hydrolyze oligosaccharides and disaccharides to glucose and other monosaccharides in the brush border of the small intestine.[8]

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 PPG (Figure 3).[8]

Voglibose may also facilitate α endogenous glycogen-like peptide 1 (GLP-1), which has an inhibitory action on glycogen, thus lowering fasting glucose levels too.

Voglibose is used in DM for reduction in PPG, only when diet and/or exercise with lifestyle modification or oral hypoglycemic agents or insulin preparations, in addition to diet and/or exercise, do not result in an adequate glycaemic control.[8]

Pharmacokinetics

Voglibose is poorly absorbed after oral administration. However, systematic adverse effects have been observed.

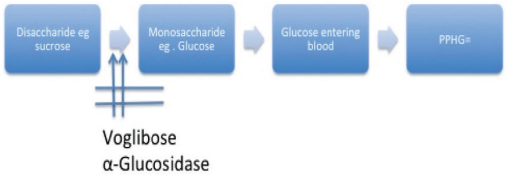

Figure 3.Mechanism of action of Voglibose

The metabolism of voglibose in liver is negligible. The renal excretion is negligible and plasma concentrations after oral dose have been undetectable.[8]

Voglibose lowers the daily glycemic excursions and inhibits overwork of the pancreatic beta-cells

An open, prospective study investigated the effects of voglibose on daily glycemic excursions, insulin secretion, and insulin sensitivity in non-insulin-treated NIDDM patients. The study included 27 NIDDM patients receiving diet therapy alone or treatment with a sulfonylurea drug. Of the study subjects, 14 patients were treated with voglibose; the remaining 13 patients served as the control group. The metabolic parameters were evaluated before treatment and at week 4 of treatment as follows: glycemic excursions by M-value and 1,5-anhydro-D-glucitol (1,5-AG), insulin secretion by area under the curve of daily serum insulin ($AUC_{insulin}$), and insulin sensitivity by the K index of the insulin tolerance test (KITT).

The study results demonstrated that HbA1c and plasma glucose in the patients who had received voglibose were comparable to those of patients in the control group after the study treatment. Voglibose treatment lowered the M-value compared to the control subjects (5.7 ± 0.9 *vs.* 9.8 ± 1.2, p< 0.05). 1,5-AG was higher in the patients treated with voglibose than in the control subjects. A statistically significant increase in $AUC_{insulin}$ occurred after treatment with voglibose but no change occurred in the control group (p=0.60). Insulin sensitivity (KITT) was improved to a statistically significant level in both the patients treated with voglibose and the patients in the control group. KITT in the patients after voglibose treatment was comparable to that of the control group (Table 2).[9]

Fluctuations in plasma glucose were larger in the control patients than in the patients on the voglibose treatment, especially after meals (Figure 4).

The results suggest that voglibose lowers the daily glycemic excursions and inhibits overwork of the pancreatic beta-cells but has little effect on insulin sensitivity in NIDDM patients.[9]

	Voglibose-treated patients		Control patients	
	Before	After	Before	After
HbA_{1c}	9.7 ± 0.5	7.9 ± 0.2*	9.8 ± 0.7	8.0 ± 0.4*
1,5-AG (μg/ml)	3.8 ± 0.9	12.2 ± 1.0*†	4.0 ± 1.0	8.2 ± 0.7*
M-value	25.4 ± 2.9	5.7 ± 0.9*‡	30.0 ±4.4	9.8 ± 1.2*
$AUC_{glucose}$ (mmol · l⁻¹ · h)	168.9 ± 6.7	105.5 ± 3.6*	173.7 ± 10.7	106.3 ± 5.3*
$AUC_{insulin}$ (pmol · l⁻¹ · h)	2,223.5 ± 390.6	1,546.7 ± 303.4‡§	2,364.5 ± 315.4	2,464.2 ± 269.3
K_{ITT} (%/min)	2.47 ± 0.28	3.18 ± 0.30*	2.75 ± 0.23	3.21 ± 0.23§
Body weight (kg)	64.9 ± 3.1	63.0 ± 2.8§	65.5 ± 1.2	63.6 ± 1.0*

Data are means ± SE. *P < 0.01 vs. before treatment; †P < 0.01 vs. without voglibose; ‡P < 0.05 vs. without voglibose; §P < 0.05 vs. before treatment.

Table 2. Glycemic control, glycemic excursions, insulin secretion, and insulin sensitivity in NIDDM patients before and after the study treatment9

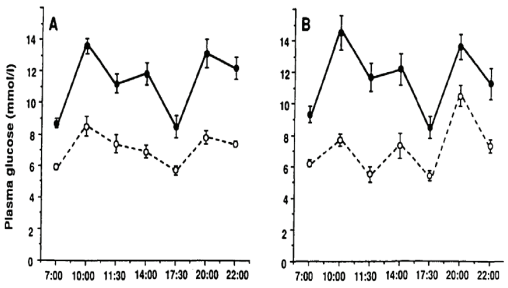

Figure 4. Changes in daily plasma glucose levels before (—●—) and after (- - -O- - -) treatment. Data are presented as means ± SE. A: Plasma glucose levels in patients treated with voglibose. B: Plasma glucose levels in control patients receiving diet therapy alone or treatment with an SU drug.

Comparative efficacy on glycemic variability with sitagliptin

A study bySeo et al., compared glycemic variability in patients with type 2 diabetes given sitagliptin or voglibose. The study included 17 type 2 diabetes patients who were given sitagliptin 50 mg/day or voglibose 0.9 mg/day for 2 months. They were hospitalized for a 4-day evaluation by continuous glucose monitoring (CGM). On discharge, they were crossed over to the other regimen for 2 months of treatment/4 days of evaluation. The CGM data were used to compare each parameter for glycemic variability.

The study results showed significantly different average glucose levels with sitagliptin and voglibose at 138.6 and 152.6 mg/dL for 24 h (p=0.014) and 147.2 and 160.9 mg/dL for during daytime (p=0.050), respectively. The patients' glucose levels with sitagliptin and voglibose were significantly different at 125.3 and 139.7 mg/dL before breakfast (p=0.015) and 112.7 and 131.4 mg/dL before lunch (p=0.049), respectively. The time from

before meal to postprandial peak glucose levels was significantly longer after dinner with voglibose than with sitagliptin (91.5 and 122.3 min, respectively; p=0.012). All of the slopes of glucose elevation were significantly lower with voglibose after each meal, with that after breakfast, lunch, and dinner being 1.16 and 0.86 mg/dL/min (p=0.031), 0.70 and 0.45 mg/dL/min (p=0.048), and 1.06 and 0.73 mg/dL/min (p=0.028), respectively.[10]

This CGM-based pilot study revealed that sitagliptin significantly lowered 24-h and daytime mean glucose levels and glucose levels before breakfast and lunch compared with voglibose. However, the time from before dinner to peak postprandial glucose levels was significantly longer, and the slope of postprandial elevation of glucose level was significantly lower after each meal, with voglibose compared with sitagliptin.[10]

Summary

The number of people diagnosed with diabetes worldwide has more than doubled since 1980 to nearly 350 million.

Despite the availability of a number of anti-diabetic medications, Post-Prandial Hyperglycemia (PPG) still remains a problem in the management of type 2 diabetes mellitus.

Fasting plasma glucose (FPG), PPG, and glucose variability all contributeto the net balance of the long-term glycemic parameter HbA1c.

Amongst all the available antidiabetic drugs, α-glucosidase inhibitors are the most effective in reducing PPG.

Voglibose delays the absorption as well as digestion of dietary polysaccharides by reversibly inhibiting carbohydrate digestive enzymes like sucrose, maltose, zomaltase, etc. thus resulting in a reduction in PPG.

Voglibose lowers the daily glycemic excursions and inhibits overwork of the pancreatic beta-cells.

Voglibose lowers the slope of postprandial elevation of glucose level significantly compared to sitagliptin.

Table 3. *Comparative Efficacy of Voglibose and Sitagliptin on Different Parameters* [10]

Parameters	Sitagliptin	Voglibose	p value
Average glucose levels for 24 h	138.6 mg/dL	152.6 mg/dL	0.014
Daytime Average glucose levels	147.2 mg/dL	160.9 mg/dL	0.050
Glucose levels before breakfast	125.3 mg/dL	139.7 mg/dL	0.015
Glucose levels before lunch	112.7 mg/dL	131.4 mg/dL	0.049
Slopes of glucose elevation after breakfast	1.16 mg/dL/min	0.86 mg/dL/min	0.031
Slopes of glucose elevation after lunch	0.70mg/dL/min	0.45mg/dL/min	0.048
Slopes of glucose elevation after dinner	1.06mg/dL/min	0.73mg/dL/min	0.028

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