

# Effects of combination therapy with mitiglinide and voglibose on postprandial plasma glucose in patients with type 2 diabetes mellitus

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**Abstract:** Patients with diabetes mellitus are at increased risk from cardiovascular-related morbidity and mortality as compared with healthy individuals. An association between the postprandial metabolic state and atherogenesis has been observed in patients with diabetes mellitus. In the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM), treatment with an  $\alpha$ -glucosidase inhibitor ( $\alpha$ -GI) in patients with impaired glucose tolerance not only reduced the rate of conversion from impaired glucose tolerance to type 2 diabetes mellitus (T2DM), but was also associated with a reduction in the risk of cardiovascular events. These results suggested the importance of treating postprandial hyperglycemia in the early stages of T2DM. Glinides are rapid and short-acting insulin secretagogues that bind to the sulfonylurea receptors on pancreatic  $\beta$ -cells to facilitate rapid insulin secretion, restore postprandial early insulin secretion, and reduce the postprandial glucose spike. Moreover,  $\alpha$ -GIs reduce postprandial hyperglycemia and insulin secretion by delaying the digestion of carbohydrates and polysaccharides in the small intestine. Then, both glinides and  $\alpha$ -GI have beneficial effects for treating patients with T2DM and impaired glucose tolerance. Considering the ameliorating effects of these drugs on postprandial metabolic disorders, combinations of glinides and  $\alpha$ -GI might constitute a promising therapeutic strategy for managing patients with T2DM, and also appear to be suitable for Japanese people, who consume more carbohydrates, such as polished rice, than Caucasians. It has recently been reported that combined use of mitiglinide and voglibose reduces postprandial insulin secretion and blunts diurnal glycemic changes in T2DM patients. This therapy can thus be regarded as being suitable for achieving strict postprandial glycemic control. In this report, we outline the effects of this combination therapy on postprandial plasma glucose and assess its safety.

**Keywords:** mitiglinide, voglibose, combination therapy, type 2 diabetes mellitus, postprandial hyperglycemia

## Introduction

Patients with diabetes mellitus (DM) are at increased risk for cardiovascular disease-related morbidity and mortality as compared with healthy individuals.<sup>1</sup> A relationship between the postprandial metabolic state and atherogenesis has been demonstrated,<sup>2,3</sup> and has also been documented in DM patients.<sup>4,5</sup> It has been suggested that postprandial hyperglycemia may be an independent risk factor for cardiovascular disease.<sup>6</sup> Moreover, large-scale clinical trials, such as the Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) study, have shown that postprandial hyperglycemia is a risk factor for arteriosclerosis, independent of other established risk factors such as hypertension and hyperlipidemia.<sup>7,8</sup> In the Study to

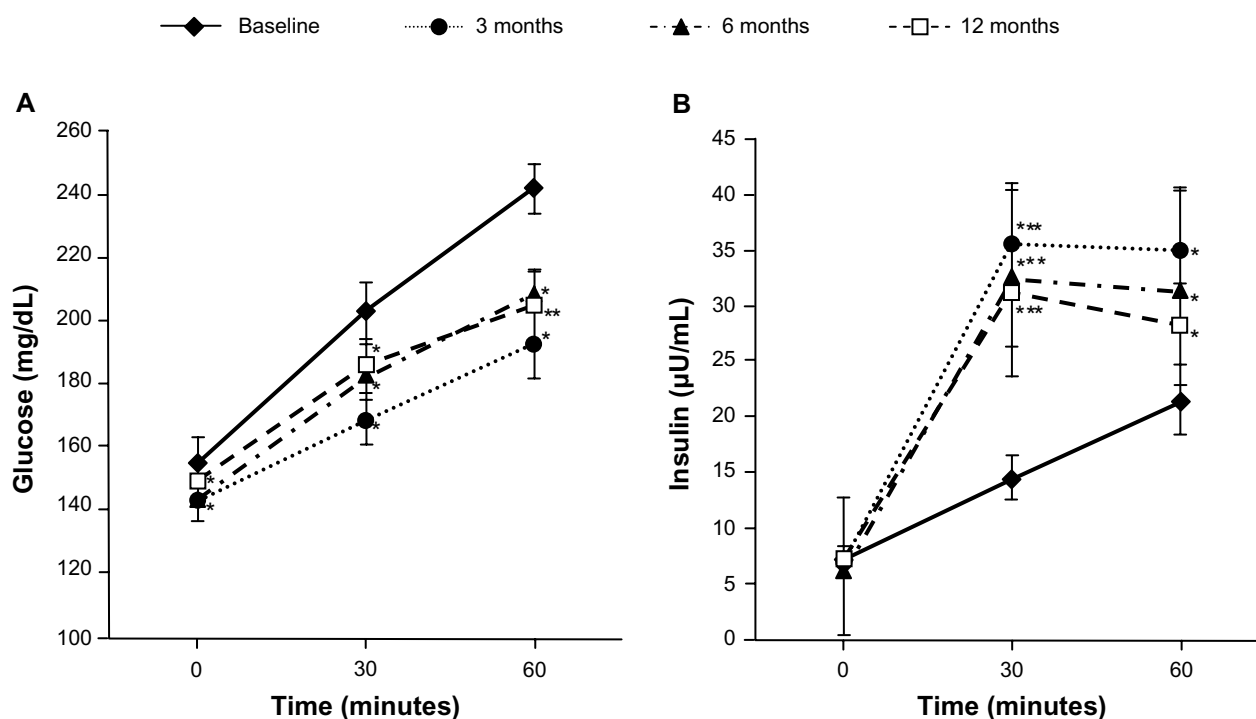
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Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM), treatment with an  $\alpha$ -glucosidase inhibitor ( $\alpha$ -GI) in patients with impaired glucose tolerance (IGT) not only reduced the rate of conversion to type 2 DM (T2DM), but was also associated with a reduction in the risk of cardiovascular events.<sup>9</sup> These results suggested the importance of treating postprandial hyperglycemia in the early stages of DM. Although sulphonylureas (SU) have been widely used for the treatment of DM, they do not act rapidly enough to increase glucose-stimulated insulin secretion after a meal and are, therefore, insufficient to control postprandial hyperglycemia. Since it has been shown that SU can easily cause prolonged hypoglycemia and weight gain, they have to be used with caution in the early stages of T2DM.<sup>10,11</sup>

Although glinides are insulin secretagogues that bind to the SU receptors of pancreatic  $\beta$ -cells as well, they can facilitate rapid insulin secretion, restore postprandial early insulin secretion, and reduce the postprandial glucose spike. On the other hand,  $\alpha$ -GI reduces postprandial hyperglycemia and insulin secretion by delaying the digestion of carbohydrates in the small intestine. Both glinides and  $\alpha$ -GI have beneficial effects for treating patients with T2DM and IGT.

Considering the ameliorating effects of these drugs on postprandial metabolic disorders, combinations of glinides and  $\alpha$ -GI might constitute a promising therapeutic approach for patients with T2DM. Although voglibose exerts a slightly less potent effect in reducing postprandial hyperglycemia than acarbose and miglitol, it has the advantage of fewer gastrointestinal adverse events.<sup>12</sup> Therefore, voglibose is widely used in Japan to reduce postprandial hyperglycemia in both T2DM and IGT patients.<sup>13</sup> Mitiglinide calcium hydrate (mitiglinide) is a glinide that was developed in Japan and is occasionally used as monotherapy or in combination with other oral hypoglycemic agents for the treatment of T2DM in Japan (Figure 1).<sup>14-17</sup>

Several clinical investigations have also confirmed the beneficial effects of combining glinides with  $\alpha$ -GIs.<sup>18-20</sup> A fixed-dose combination tablet consisting of 10 mg of mitiglinide and 0.2 mg of voglibose was recently approved in Japan.<sup>21</sup> A small number of interesting reports on these drugs has recently been published, but the data were obtained from relatively small subject groups. Thus, this review aims to summarize the effects of combined therapy with mitiglinide and voglibose.



**Figure 1** Postprandial plasma glucose levels and postprandial immunoreactive insulin levels with patients with type 2 diabetes mellitus treated with mitiglinide for 12 months.

**Notes:** (A) Postprandial plasma glucose levels and (B) postprandial immunoreactive insulin levels in patients with type 2 diabetes mellitus treated with mitiglinide for 12 months. Wilcoxon signed rank test was used to compare the differences between baseline values and those at 3 months, 6 months, and 12 months posttreatment ( $n = 16$ ). \* $P < 0.05$ ; \*\* $P < 0.005$ ; \*\*\* $P < 0.001$  versus baseline (mean  $\pm$  SE). Copyright © 2009, SAGE Publications. Adapted with permission from Konya H, Miuchi M, Konishi K, et al. Pleiotropic effects of mitiglinide in type 2 diabetes mellitus. *J Int Med Res.* 2009;37(6):1904–1912.<sup>16</sup>

**Abbreviations:** n, number; SE, standard error of the mean.

## Pharmacology, mode of action, and pharmacokinetics of mitiglinide monotherapy

Mitiglinide, a derivative of benzy succinic acid, closes adenosine triphosphate-dependent  $K^+$  channels by selectively binding to the SU receptor on pancreatic  $\beta$ -cells, which leads to opening of the voltage-dependent calcium channels and induces insulin secretion.<sup>22</sup> Mitiglinide has stronger affinity for SU receptors (SUR)1 than other insulinotropic SU receptor ligands, namely, repaglinide and nateglinide.<sup>23</sup> In addition to its glucose-lowering effect, mitiglinide inhibits postprandial hypertriglyceridemia in Otsuka Long–Evans Tokushima Fatty rats, which exhibit insulin resistance and visceral fat accumulation, and are regarded as models of diabetes development with aging.<sup>24</sup> Mitiglinide also improves postprandial hyperglycemia in T2DM patients via both an insulin-mediated indirect effect on the liver and a direct regulatory influence on hepatic glucose metabolism.<sup>25</sup>

Among the pharmacokinetic parameters of mitiglinide administered to healthy adult male subjects in a single dose of 5 mg, 10 mg, or 20 mg immediately before a meal, the time to peak plasma concentration ( $C_{max}$ ) after administration was 0.23–0.28 hours and the half-life ( $t_{1/2}$ ) was about 1.2 hours.<sup>26</sup> On the other hand, for nateglinide, which was similarly administered in a single dose of 20 mg, 40 mg, or 60 mg, the corresponding values were 0.9–1.8 hours ( $C_{max}$ ) and 1.1–1.3 hours ( $t_{1/2}$ ).<sup>27</sup> Similarly, repaglinide administered in a single dose of 0.25 mg, 0.5 mg, or 1.0 mg reached the  $C_{max}$  0.5 hours later with a  $t_{1/2}$  of about 0.8 hours.<sup>28</sup> These data indicate that, whereas an initial rise in blood concentration is more rapid for mitiglinide than for nateglinide and repaglinide, the half-life of mitiglinide is almost the same as those of the other two glinides.

The pharmacokinetic properties of mitiglinide include rapid absorption and elimination. Thus, mitiglinide triggers a rapid and short-acting insulin secretory response that improves postprandial hyperglycemia, mimicking normal physiological insulin secretion and glucose metabolism in healthy individuals. Its preprandial administration controls postprandial hyperglycemia and improves overall glycemic control.<sup>29</sup> Because it is a short-acting agent, mitiglinide is unlikely to exert adverse hypoglycemic effects early in the morning or between meals.<sup>30</sup> Therefore, mitiglinide may become a first choice drug for managing the early stage of T2DM.

Moreover, suppression of postprandial hyperglycemia with mitiglinide has been reported to prevent postprandial increases in oxidative stress and markers of inflammation in DM patients.<sup>31</sup> If mitiglinide even partially regulates oxidative stress and vascular inflammation, it could be used to

prevent the cardiovascular complications of DM. Mitiglinide treatment significantly reduced plasma nitrotyrosine, malondialdehyde, and oxidized low density lipoprotein levels. Additionally, mitiglinide administration preserved the plasma total radical-trapping antioxidant parameter as compared with a placebo. Importantly, mitiglinide decreased the levels of proinflammatory cytokines such as interleukin-6, interleukin-18, and tumor necrosis factor- $\alpha$ . However, the study demonstrating these reductions examined only the effect of acute administration of mitiglinide; it appears that reducing postprandial oxidative stress and inflammation may result in long-term cardiovascular preventive effects in diabetic patients.

Though the use of SU agents in T2DM patients remains quite common, increased risk of cardiovascular complications and increased fatality rates after myocardial infarction have been reported in such patients.<sup>32</sup> SUR, which constitute the adenosine triphosphate-sensitive  $K^+$  channel, have three subtypes with differing distributions: SUR1 (present in pancreatic  $\beta$ -cells), SUR2A (cardiac myocytes), and SUR2B (vascular smooth muscle cells).<sup>33,34</sup> Accordingly, *in vitro* selectivity for insulin secretagogues may have an important impact on cardiovascular outcomes of diabetic patients with coronary artery disease.<sup>33</sup> In isolated perfused rat hearts, mitiglinide (a selective blocker for SUR1) preserved the cardioprotective effect of ischemic preconditioning as compared to glibenclamide (a nonselective SUR blocker).<sup>35</sup> In another study on isolated perfused rat hearts, glibenclamide induced a significant increase in left ventricular end-diastolic pressure and significantly decreased left ventricular systolic/developed pressure, while glimepiride only significantly decreased left ventricular developed pressure.<sup>36</sup> However, mitiglinide had no effects on canine isolated coronary arteries or perfused rat hearts. Therefore, mitiglinide may have more certain benefits in terms of its cardiovascular effects than glibenclamide and glimepiride in DM patients.

Mitiglinide administration also decreased free fatty acids (FFA) at 60 minutes after a meal tolerance test in T2DM patients.<sup>16</sup> Mitiglinide significantly lowered hemoglobin  $A_{1c}$  ( $HbA_{1c}$ ) levels, increased 1,5-anhydroglucitol (1,5-AG) levels after 6 months, and significantly decreased urinary albumin levels after 12 months.<sup>16</sup> These data suggest that mitiglinide clearly improves postprandial hyperglycemia, which is crucial to treating metabolic disorders, including insulin resistance and dyslipidemia, in T2DM patients.

Evidence from previous studies suggests the importance of the association between postprandial hyperglycemia and endothelial dysfunction in diabetic patients. The outcomes

of 12-week interventions with 300 mg/day acarbose, 270 mg/day nateglinide, or no medication were compared among patients with new-onset T2DM.<sup>37</sup> Only acarbose improved postprandial endothelial function, as assessed by the percent of flow-mediated dilation at 0 minutes and 120 minutes after a cookie test.

To investigate whether mitiglinide improves endothelial function, a pilot study on mitiglinide add-on therapy with pioglitazone was conducted on T2DM patients whose blood sugar was insufficiently controlled with pioglitazone monotherapy. In eight patients with T2DM, mitiglinide was administered as add-on therapy with 10 mg/day of pioglitazone for 12 weeks. Endothelial function was measured by the reactive hyperemia peripheral arterial tonometry (Itamar Medical, Ltd, Caesarea, Israel) technique in all patients before and after the intervention.<sup>38,39</sup> Mitiglinide add-on therapy significantly improved the reactive hyperemia peripheral arterial tonometry index in DM patients receiving pioglitazone monotherapy.<sup>40</sup> Significant HbA<sub>1c</sub> reductions were also observed with no other modifications of lifestyle or other drug administration; however, there was no reduction in triglyceride levels, low density lipoprotein cholesterol levels, body weight, or waist circumference. In T2DM patients, combination therapy with mitiglinide and pioglitazone resulted in marked improvements in HbA<sub>1c</sub> levels and endothelial function. In 16 patients with T2DM treated with 30 mg/day of mitiglinide, levels of plasma glucose, FFA, and urinary albumin excretion were significantly decreased.<sup>16</sup> One of the mechanisms underlying the efficacy of this agent might be the reduction in circulating levels of FFA with mitiglinide administration. Recently, the use of Roux-en-Y gastric bypass as bariatric surgery has been increasing. Treatment with mitiglinide before glucose loading in a patient who

received Roux-en-Y gastric bypass resulted in a significant elevation of intact glucagon-like peptide-1 (GLP-1) secretion (9% increase in area under the curve [AUC]<sub>0-180 min</sub>), while total glucose-dependent insulinotropic polypeptide secretion was further decreased (-48% decrease in AUC<sub>0-180 min</sub>). The increased secretion of intact GLP-1 with mitiglinide administration suggested that this agent exerts a direct effect on GLP-1 secretion from GLP-1-secreting L-cells.<sup>41</sup>

## Benefits of combination therapy with voglibose

It should be noted that  $\alpha$ -GI might have other beneficial effects on the secretion of incretins, including GLP-1 and glucose-dependent insulinotropic polypeptide, which have been reported to exert trophic effects on  $\beta$ -cells. In animal models, native GLP-1 stimulates  $\beta$ -cell proliferation and inhibits apoptosis, possibly increasing  $\beta$ -cell mass and function.<sup>42</sup>

When two groups (one in which the subjects received preprandial monotherapy with mitiglinide, 20 mg three times a day [tid], and the other in which the subjects received preprandial combined therapy with mitiglinide 10 mg tid and voglibose 0.2 mg tid for 12 weeks) were compared to assess the beneficial effects, as well as other influences, both groups showed an improvement in 1,5-AG with significant and comparable increases in 1,5-AG levels. In addition, the combined therapy group also showed a significant increase in the AUC<sub>0-120</sub> of active GLP-1 levels (Table 1), as well as a reduction in postprandial insulin secretion. This change was also supported by the study of Ono et al.<sup>43</sup> When mitiglinide was given concomitantly with voglibose for 12 weeks, the active GLP-1 levels at 60 minutes and 120 minutes after a meal were significantly increased (Table 1).<sup>19</sup>

**Table 1** Changes in parameters from week 0 to week 12 in the concomitant voglibose group and the double mitiglinide group

	Concomitant voglibose group (n = 10)		P-value (versus week 0)	Double mitiglinide group (n = 10)		P-value (versus week 0)
	Week 0	Week 12		Week 0	Week 12	
HbA <sub>1c</sub> (%)	8.1 ± 0.6	7.9 ± 0.8	NS	7.4 ± 0.3	7.2 ± 0.4	0.0469
GA (%)	22.3 ± 2.2	21.8 ± 3.4	NS	22.1 ± 2.7	20.5 ± 1.9	0.0078
1,5 AG (µg/mL)	3.5 ± 2.9	6.9 ± 6.6	0.0039	4.1 ± 2.0	5.9 ± 3.6	0.0234
Fasting plasma glucose (mg/dL)	179.5 ± 30.8	168.7 ± 27.6	NS	156.3 ± 18.0	150.5 ± 16.2	NS
Weight (kg)	71.9 ± 12.7	70.8 ± 12.6	0.0039	60.0 ± 14.0	59.8 ± 16.8	NS
Glucose AUC <sub>0-120</sub> (mg hours/dL)	30196.5 ± 5627.4	26044.5 ± 4394.3	0.0098	25363.5 ± 5443.6	24180.0 ± 5366.1	NS
Insulin AUC <sub>0-120</sub> (µU hours/mL)	3741.8 ± 2184.6	3229.8 ± 1551.8	NS	2878.0 ± 1840.5	3221.1 ± 2365.3	NS
GLP-1 AUC <sub>0-120</sub> (pmol hours/L)	648.9 ± 91.6	843.3 ± 336.9	0.0137	604.2 ± 58.8	664.5 ± 103.7	NS
GIP AUC <sub>0-120</sub> (pg hours/mL)	24151.1 ± 9506.3	22856.1 ± 10277.1	NS	24481.2 ± 8888.7	26751.1 ± 12145.2	NS
Glucagon AUC <sub>0-120</sub> (pg hours/mL)	10347.6 ± 2029.6	11090.4 ± 1948.1	NS	10373.0 ± 2590.2	9820.5 ± 2151.4	NS

**Notes:** Data are represented as the mean ± standard deviation. For intergroup comparison, Wilcoxon signed rank test was used. © 2010 Asian Association for the Study of Diabetes and Blackwell Publishing Asia Pty Ltd. Adapted with permission from Katsuno et al.<sup>19</sup>

**Abbreviations:** n, number; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; NS, not significant; GA, glycoalbumin; 1,5-AG, 1,5-anhydroglucitol; AUC, area under the curve; GLP-1, glucagon-like peptide 1; GIP, glucose-dependent insulinotropic polypeptide.

The active GLP-1 level was reported to increase when voglibose was given to ob/ob mice for 3–4 weeks.<sup>44</sup> It appears that continuous administration of voglibose evoked chronic glucose absorption from the small intestine and increased the amount of undigested carbohydrates, which results in constant stimulation of the lower small intestine and the large intestine, thus promoting differentiation and proliferation of GLP-secreting cells.<sup>45</sup>

These findings suggest that concomitant use of mitiglinide and voglibose could minimize excessive insulin secretion, and that the GLP-1 increase might diminish insulin secretory overload. This combination appears to be suitable for Japanese people, who consume more carbohydrates such as polished rice, than Caucasians.

Because impairment of early insulin secretion is closely related to the pathogenesis of T2DM in Japanese patients and the secretory capacity of pancreatic  $\beta$ -cells is lower in Japanese than in Caucasian patients in the USA and Europe,<sup>46–48</sup> concomitant use of mitiglinide with voglibose might be more useful even in fairly well-controlled obese Japanese patients with T2DM, so long as the switch to concomitant treatment is made at an early stage.

### Mitiglinide and voglibose: clinical trial data for combination therapy

The effects of a fixed-dose combination of 10 mg of mitiglinide and 0.2 mg of voglibose on postprandial glycaemic excursions in Japanese T2DM patients were reported. After a 2-week baseline period, eleven T2DM patients were treated with mitiglinide alone for 2 weeks and with the mitiglinide/voglibose combination for 6 weeks. Postprandial glycaemic excursions after all three meals, as assessed by self-monitoring of blood glucose, were significantly lower during the combination than during the baseline period, as well as after lunch and dinner during the combination as compared to the mitiglinide period. The meal tolerance test confirmed that the magnitude of postprandial hyperglycemia was significantly lower, with significantly greater early-phase serum insulin secretion and sustained GLP-1 production, during the combination as compared with the baseline period. Overall glycaemic control parameters also improved significantly during the combination as compared with the baseline period. This study demonstrated that the mitiglinide/voglibose combination therapy can reduce postprandial insulin secretion and blunt diurnal glycaemic changes more markedly than monotherapy with mitiglinide.<sup>43</sup>

The effects of mitiglinide and voglibose, alone and in combination, on metabolic responses after a test meal in

Japanese patients with T2DM were reported. This randomized cross-over study consisted of four periods. During the first period, all patients ( $n = 12$ ) received water only (control period). During the next three periods, the patients received 10 mg of mitiglinide, 0.2 mg of voglibose, or the two combined, in random order. The combination reduced postprandial glucose levels as compared with either mitiglinide or voglibose alone, particularly at 30–90 minutes, which significantly exceeded the effects of mitiglinide only ( $P < 0.05$ ). Mitiglinide and the combination therapy both restored the early insulin response, but the combination provided an insulin-sparing effect as compared with mitiglinide alone. The combination improved postprandial lipid profiles, combining the effects of both drugs.<sup>20</sup>

The efficacy of the combination of mitiglinide and voglibose for diabetic patients on hemodialysis (HD) was reported. An open-label randomized study was performed with 36 T2DM patients with poor glycaemic control on HD and receiving daily doses of voglibose (0.9 mg). The efficacy of this treatment was determined by monitoring plasma glucose, HbA<sub>1c</sub>, and glycated albumin (GA) levels using a homeostasis model assessment of insulin resistance. The final dose of mitiglinide was  $22.9 \pm 8.9$  mg (mean  $\pm$  standard deviation) (0.41 mg/kg) daily. Mitiglinide reduced fasting plasma glucose and GA levels after 4 weeks and HbA<sub>1c</sub> levels after 8 weeks. Triglyceride levels and homeostasis model assessment of insulin resistance values also decreased significantly after mitiglinide treatment. Safety and tolerance were determined by monitoring clinical and laboratory parameters. No significant changes in blood pressure levels or serious adverse effects such as hypoglycemia or liver impairment were observed. This study suggested that combination therapy with mitiglinide and voglibose has potential as a treatment for diabetic patients on HD.<sup>18</sup>

The efficacy of two options in T2DM patients whose blood glucose had not been well controlled with mitiglinide (30 mg/day) alone was evaluated. In total, 20 patients were included in the add-on therapy group and then divided into two subgroups: concomitant voglibose, in which mitiglinide was given concomitantly with voglibose (0.6 mg/day); and double mitiglinide, in which a double dose of mitiglinide (60 mg/day) was given. Table 1 shows the results obtained after the meal tolerance tests (460 kcal; 56.5 g of carbohydrates, 18 g of protein, and 18 g of fat) performed at week 0 (at the initiation of add-on therapy) and at week 12. At week 12, HbA<sub>1c</sub>, GA, 1,5-AG, fasting plasma glucose, weight, glucose, insulin, active GLP-1, total GIP, and glucagon levels were measured. The plasma level of 1,5-AG was improved



at week 12 in both groups. Intragroup comparison of the concomitant voglibose group revealed a significant reduction in the effect on insulin secretion and a significant increase in GLP-1 activity. In the concomitant voglibose group, the plasma insulin level decreased significantly and the plasma active GLP-1 level increased significantly during the meal tolerance test at week 12; thus, body weight decreased significantly only in the concomitant voglibose group. These findings suggested that concomitant administration of mitiglinide with voglibose achieves better glycemic control, particularly in the postprandial period, without weight gain and might have beneficial effects in T2DM patients at risk for macrovascular complications (Table 1).<sup>19</sup>

## Safety and tolerability

The therapeutic options for patients with T2DM and chronic kidney disease (CKD) are limited because the decreased glomerular filtration rate results in an accumulation of certain drugs and/or their metabolites (Table 2).<sup>49</sup> Mitiglinide can also be safely used in CKD patients.<sup>50</sup> However, careful observation should be recommended, especially in HD patients, in whom therapy should be initiated at a low dose with careful attention to hypoglycemia. The same may be

true in the case of combined therapy with mitiglinide and voglibose.<sup>18</sup> In non-HD CKD patients, repeatedly inquiring about hypoglycemic symptoms and adverse events might be the most important and useful means of monitoring these patients for the presence of hypoglycemia.<sup>51</sup>

As described above, combination therapy with mitiglinide and voglibose improved glycemic control in T2DM patients even on HD. There were no significant changes in the levels of the systolic or diastolic blood pressure during the study period. No statistically significant changes were observed in any other parameters with combined data such as the cardiothoracic ratio and dry weight. There were no significant differences in hemoglobin or erythropoietin levels at any time during the treatment period. During the study period, none of the patients exhibited significant increases in adverse effects such as hypoglycemia, liver impairment, skin rash, fluid overload, or edema.<sup>18</sup> This study suggested that combination therapy with mitiglinide and voglibose might have adequate safety and tolerability for the treatment of diabetic patients, even those on HD.

Moreover, in the other study, when mitiglinide (30 mg/day) was given concomitantly with voglibose (0.6 mg/day), body weight decreased significantly, whereas

**Table 2** Dosing adjustment by CKD stage for meglitinides,  $\alpha$ -glucosidase inhibitors, and DPP-4 inhibitors

Class	Drug	Dosing recommendation CKD stage 3, stage 4, or kidney transplant	Dosing recommendation, dialysis
Meglitinides	Repaglinide	No dose adjustment necessary Initiate at 0.5 mg dose when GFR < 40 mL/minute/1.73 m <sup>2</sup>	No dose adjustment necessary Initiate at low dose Not available in Japan
	Nateglinide	Initiate at low dose, 60 mg meglitinides before each meal	Avoid
	Mitiglinide	No dose adjustment necessary Not available in the US	Initiate at low dose of 5 mg before each meal Not available in the US
$\alpha$ -glucosidase inhibitors	Acarbose	Not recommended in patients with sCr > 2 mg/dL in the US No dose adjustment necessary in Japan	Not recommended in the US Caution recommended in Japan
	Miglitol	Not recommended in patients with sCr > 2 mg/dL in the US Caution recommended in Japan	Not recommended in the US Caution recommended in Japan
	Voglibose	Not available in the US No dose adjustment necessary in Japan	Not recommended in the US No dose adjustment necessary in Japan
DPP-4 inhibitors	Sitagliptin	Reduce dose by 50% (50 mg/day) when GFR < 50 mL/minute/1.73 m <sup>2</sup> and $\geq$ 30 mL/minute/1.73 m <sup>2</sup> , and by 75% (25 mg/day) when GFR < 30 mL/minute/1.73 m <sup>2</sup>	Reduce dose by 75% (25 mg/day)
	Vildagliptin	Initiate at low dose Not available in the US	Initiate at low dose Not available in the US
	Alogliptin	Reduce dose by 50% (12.5 mg/day) when GFR < 50 mL/minute/1.73 m <sup>2</sup> and $\geq$ 30 mL/minute/1.73 m <sup>2</sup> , and by 75% (6.25 mg/day) when GFR < 30 mL/minute/1.73 m <sup>2</sup> Not available in the US	Reduce dose by 75% (6.25 mg/day) Not available in the US

**Note:** Data from Abe et al.<sup>49</sup>

**Abbreviations:** CKD, chronic kidney disease; DPP-4, dipeptidyl peptidase-4; GFR, glomerular filtration rate; sCR, serum creatinine.

there was no significant change when a double dose of mitiglinide was given (60 mg/day). No symptoms of hypoglycemia were noted in either group at any time during the study period.<sup>19</sup>

## Clinical application of mitiglinide and voglibose

The potent and selective dipeptidyl peptidase-4 inhibitor (DPP-4), vildagliptin, improves glycemic control in T2DM patients through incretin hormone-mediated increases in both  $\alpha$ -cell and  $\beta$ -cell responsiveness to glucose. Vildagliptin has been evaluated in several subjects with T2DM, including patients on HD three times a week for about 3 years due to diabetic nephropathy. The efficacy and safety of vildagliptin (30 patients) versus controls (21 patients) with T2DM and a mean starting HbA<sub>1c</sub> of 6.0% were demonstrated in a prospective open label study. Criteria for adding vildagliptin included HbA<sub>1c</sub> after either dietary intervention alone, or therapy with mitiglinide or voglibose for 8 weeks, an HbA<sub>1c</sub> level greater than 7%, and a GA level greater than 21%, as levels of HbA<sub>1c</sub> may be underestimated in patients with renal failure on dialysis. Vildagliptin was added to the prior antidiabetic therapy after the 8-week observation period. The treatment was initiated at a dose of 50 mg/day for the first 8 weeks, with an option for up-titration if HbA<sub>1c</sub> targets were not achieved, with a mean final vildagliptin dose of 80 mg/day. Vildagliptin treatment reduced HbA<sub>1c</sub> from 6.7% to 6.1% over 24 weeks. No serious adverse effects such as hypoglycemia or liver impairment were observed in any of the patients. All 30 patients in the vildagliptin group received antidiabetic therapy; 21 patients in the control group received no antidiabetic medications. When subjects were divided into the vildagliptin monotherapy group (n = 9) and the combination therapy group (vildagliptin plus mitiglinide and/or voglibose; n = 21), there were no significant differences in age, sex distribution, body mass index, reductions in HbA<sub>1c</sub> and postprandial glucose levels, or in the vildagliptin dose, but the GA reduction was greater in the monotherapy group. This study suggests that vildagliptin combined with mitiglinide or voglibose has potential, due to its safety and tolerability, for the treatment of diabetics with CKD.<sup>52</sup>

The long-term efficacy and safety of DPP-4 inhibitors remain largely unknown. However, combination therapy with a DPP-4 inhibitor and mitiglinide and/or voglibose is associated with a lower risk of hypoglycemia than SU agents. DPP-4 inhibitors, such as vildagliptin, when combined with

mitiglinide and/or voglibose, appear to be both safe and tolerable treatments for diabetes.

## Conclusion

In conclusion, we reviewed the effects of combination therapy with mitiglinide and voglibose on postprandial hyperglycemia and vascular endothelial function in T2DM patients. The improvement of postprandial hyperglycemia may be crucial to preventing atherosclerosis progression and cardiovascular events. The combined use of mitiglinide and voglibose reduces postprandial insulin secretion and is expected to reduce diurnal glycemic changes while enhancing GLP-1 activity. Therefore, such therapy is considered to be suitable for achieving strict postprandial glycemic control and can also be administered to diabetic patients with CKD. However, the studies presented herein were all conducted in a small number of subjects. Further studies involving a larger number of subjects are required, anticipating future progress in this field.

## Disclosure

The authors report no conflicts of interest in this work.

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