Postprandial state is defined as a 4-hour period that immediately follows ingestion of a meal with respect to glucose. During this period, dietary carbohydrates are progressively hydrolyzed through several sequential enzymatic actions. Even though the insulin response rapidly reduces the postprandial glucose excursion with a return to baseline levels within 2 hours, the overall period of absorption has approximately a 4-hour duration corresponding to the postprandial state. Therefore, in subjects who consume 3 meals per day at fixed hours, it appears that the 24-hour period of the day can be divided into 3 periods corresponding to fasting, postprandial, and postabsorptive states. Thus, the real fasting period is only limited to a 3 to 4-hour period of time at the end of the night. That is, the postprandial state occurs during most of the daytime.

Epidemiological studies have revealed that postprandial hyperglycemia is a more powerful predictor of future cardiovascular events than fasting hyperglycemia. Glucose spikes after meals induce oxidative stress. In combination with soluble advanced glycation end products and lipid peroxidation products, these act as key activators of upstream kinases and lead to endothelial dysfunction (Figure). Ultimately, this may cause cardiovascular events. Abnormal glucose homeostasis can be seen in 2 of 3 cardiovascular disease patients. Not increased fasting glucose levels but rather increased postprandial glucose levels are better predictors of cardiovascular disease. Even in the setting of good HbA1c fasting glucose control, postprandial hyperglycemia often occurs. Even when fasting glucose and HbA1c are within normal limits, postprandial hyperglycemia causes myocardial infarction and stroke in patients with newly diagnosed type 2 diabetes. Postprandial hyperglycemia, but not fasting hyperglycemia, is an independent predictor of cardiovascular events.

Postprandial hyperglycemia induces endothelial function

Endothelial dysfunction, well recognized as the initial stage of atherosclerosis, is characterized by a reduction in the production and bioavailability of endothelium-derived relaxing factors. In particular, a reduction of nitric oxide (NO), generated from L-arginine by endothelial NO synthase (eNOS), is the key determinant of endothelial function. On the other hand, endothelial activation includes proinflammation, proliferation, and procoagulation activated in the vessel wall. Endothelial function is impaired not only in patients with diabetes but also in patients with impaired glucose tolerance (IGT). Recent in vivo and in vitro studies demonstrated that glucose spikes induce endothelial dysfunction. Flow-mediated vasodilatation (FMD) was attenuated after meals in patients with type 2 diabetes. Both the level and change in postprandial FMD significantly correlated with postprandial changes in blood glucose levels. Postprandial hyperglycemia is a determinant of FMD reduction. Accordingly, hyperglycemia may be linked with reduced production and/or reduced bioavailability of NO. Hyperglycemia-induced endothelial dysfunction is counterbalanced by increased production of arginine. The inter-relationship between NO production and bioavailability has not yet been established. During an oral glucose tolerance test (OGTT), a rapid decrease in FMD has been demonstrated in patients with IGT, and this decrease was correlated with the degree of glycemia measured at 2 hours.
How do glucose spikes increase oxidative stress?

Since the postprandial state occurs during most of the daytime, interventions that aim to reduce postprandial endothelial dysfunction are essential for the prevention of cardiovascular events. Also, oscillating glucose levels have more deleterious effects than constant high glucose levels on endothelial function.17

Oxidative stress, defined as redox state imbalance, appears to be the key player of endothelial dysfunction. The precise mechanism of the increase in oxidative stress through glucose spikes remains unidentified. However, in vivo and in vitro studies have shown that protein kinase C, NADPH, inducible NO synthase, or inflammatory markers are activated in response to glucose spikes.17 Through the activation of these pathways, glucose spikes generate free radicals at the level of mitochondria, the major source of superoxide anion production.18 Another possible mechanism is that glucose spikes induce the attenuation of superoxide dismutase induction as antioxidant defenses.19 Additionally, glucose spikes induce global down-regulation of gene expression involved in free radical detoxification.20 Oxygen free radicals react with NO to form a powerful oxidant peroxynitrite, which produces nitrotyrosine.17 Glucose spikes promote over-generation of this strong oxidant nitrotyrosine, which directly damages endothelial cells and damage DNA.21 Thus, glucose spike-induced nitrotyrosine over-generation has been shown to be followed by development of endothelial dysfunction.

Which is more effective to prevent postprandial endothelial dysfunction?: α-GIs or glinide drugs?

Currently, there is no gold standard for treatment of postprandial endothelial dysfunction, however, several pharmacological therapeutic approaches have been suggested. Potential drugs to target postprandial hyperglycemia in patients with type 2 diabetes include α-glucosidase inhibitors (α-GIs), glinide drugs.

Acarbose, an α-GI, reduces or delays carbohydrate digestion by competitive and dose-dependent inhibition of α-glucosidase enzymes located in the brush border of the small intestine. The α-glucosidase enzymes metabolize non-absorbable oligosaccharides into absorbable monosaccharides. Thus, acarbose significantly reduces the postprandial rise in glucose without increasing circulating insulin levels. Recent clinical trials have shown that acarbose treatment can prevent cardiovascular complications not only in patients with type 2 diabetes but also in those with impaired glucose tolerance.21,22 Thus, acarbose may be an effective therapeutic modality in patients with postprandial hyperglycemia. In contrast, the D-phenylalanine derivative nateglinide is an insulinotropic agent with rapid effects and a short duration of action which acts as an insulin secretagogue in the treatment of type 2 diabetes.23,24 Thus, acarbose may be an effective therapeutic modality in patients with postprandial hyperglycemia. In contrast, the D-phenylalanine derivative nateglinide is an insulinotropic agent with rapid effects and a short duration of action which acts as an insulin secretagogue in the treatment of type 2 diabetes.

In that study, we used a recently developed commercially available ultrasound machine equipped with online computer-assisted semi-automatic analysis software to measure FMD of the brachial artery (EX, Unex Corporation, Nagoya, Japan) to evaluate endothelial function.25,26 We measured plasma glucose and insulin levels before and at 30 minutes, 60 minutes and 120 minutes after the cookie load: which consisted of 75 g carbohydrate (85% flour starch, 15% maltose), 25 g butter and 7 g protein for a total of 553 kcal. (ABILIT Corp, Osaka, Japan). FMD of the brachial artery was measured using established and validated methods27,28 in the fasting state before cookie ingestion and 120 minutes after the cookie load as the postprandial state.

Our study demonstrated that 12-week treatment with acarbose or nateglinide improved postprandial endothelial dysfunction in newly diagnosed type 2 diabetic subjects and that acarbose was more effective than nateglinide.

Acarbose reduces both postprandial hyperglycemia and hyperinsulinemia, and thereby may improve sensitivity to insulin and alleviate stress on pancreatic β-cells. In contrast, nateglinide, a glinide compound, selectively enhances early meal-induced insulin secretion and thus improves mealtime glucose control. In our study, both acarbose and nateglinide similarly inhibited postprandial hyperglycemia as assessed by the area under the curve (AUC) for glucose levels. While nateglinide increased the AUC for insulin, acarbose did not increase postprandial insulin secretion. Therefore, acarbose may improve postprandial endothelial function by inhibiting postprandial hyperglycemia without increasing postprandial insulin secretion, while nateglinide may improve postprandial endothelial function less significantly by inhibiting postprandial hyperglycemia with an increase in postprandial insulin secretion.

Recent studies have shown that α-GIs, which reduce postprandial hyperglycemia without postprandial hyperinsulinemia, successfully reduced cardiovascular events.22,22 Meanwhile, the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial showed that treatment with nateglinide, which improves postprandial hyperglycemia through transient postprandial hyperinsulinemia, failed to show the reduction of cardiovascular events.23
Sawada, et al\textsuperscript{32}) conducted a randomized study in diabetic patients with coronary artery disease to compare the effects of an \(\alpha\)-GI miglitol and nateglinide on metabolic parameters, oxidative stress, and endothelial function. They assessed insulin resistance using the homeostasis model assessment ratio (HOMA-R: fasting plasma insulin x fasting plasma glucose /405). They also calculated the ratio of triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) as a marker of atherogenic dyslipidemia which has been reported to be associated with cardiovascular events.\textsuperscript{33, 34} In the study, an oxidative stress assessed by serum diacron-reactive oxygen metabolites (d-ROMs) and endothelial function was assessed by FMD. Although both miglitol and nateglinide improved glycemic control, oxidative stress and endothelial function were improved only in patients treated with \(\alpha\)-GI miglitol but not in those treated with nateglinide. In addition, the HOMA-R and the TG/HDL ratio improved only in those treated with miglitol. Therefore, they speculated that an ameliorating effect of \(\alpha\)-GI miglitol on postprandial hyperglycemia without postprandial hyperinsulinemia might improve atherogenic dyslipidemia by improvement of insulin resistance. They also speculated that an ameliorating effect of \(\alpha\)-GI miglitol on oxidative stress might improve endothelial dysfunction.

Hyperinsulinemia increases coronary artery disease independent from the other risk factors.\textsuperscript{35} Recently, Arcano, et al\textsuperscript{36}) reported that insulin may cause endothelial dysfunction in humans. Although the mechanisms through which insulin might impair endothelial function are not well clarified, the hyperinsulinemia-induced increase in oxidative stress appears to be involved. Since vitamin C completely reversed insulin-induced endothelial dysfunction without affecting the vascular endothelium-independent response, they speculated that oxidative stress was one of the intermediate steps in insulin-induced endothelial dysfunction. Another recent study showed that insulin activates both the nitricergic and the endothelinergic systems.\textsuperscript{37} Endothelin-1 induces NAD(P)H oxidase expression in human endothelial cells, with increased generation of superoxide anions.\textsuperscript{38} It is also known that exogenous hyperinsulinemia activates NAD(P)H in the rat aortic endothelium.\textsuperscript{39} Thus, insulin may also cause endothelial dysfunction through increased endothelin-1 availability and through downstream effects on NAD(P)H oxidase and superoxide anion production. Our results may provide evidence that both hyperglycemia and hyperinsulinemia cause endothelial dysfunction. Acarbose improves postprandial endothelial dysfunction in both the short-term (single dose) and in the long-term (12-week) administration. In conclusion, when comparing acarbose and nateglinide to target post-meal flow-mediated dilatation in new-onset, type 2 diabetic patients with mean HbA\textsubscript{1c}, acarbose was superior to nateglinide in restoring postprandial endothelial dysfunction. Our findings appear to support the results of the STOP-NIDDM trial\textsuperscript{40} and a meta-analysis of several clinical studies.\textsuperscript{41}

\textbf{\(\alpha\)-GIs are more effective in Asian than Western populations}

A recent systematic meta-analysis has shown that patients consuming Asian diets achieve a superior blood glucose lowering effect while on treatment with acarbose\textsuperscript{40} compared to those consuming Western diets. Mean HbA\textsubscript{1c} levels were reduced to a significantly greater extent (1.02%\%) in the Asian diet group than in the Western diet group (\(P < 0.001\)). This may be partially because the Asian diets contain higher starch, which might substantially augment the postprandial hypoglycemia effect of acarbose in these populations.\textsuperscript{42} Optimal weight management is a key of successful diabetes therapy aiming at the prevention of cardiovascular complications.\textsuperscript{43} Unlike treatment with insulin, sulfonylureas, glinides, and thiazolidindiones, treatment with acarbose has been shown to associate with a moderate weight loss of about 1 kg, on average, compared to placebo, alongside improved glycemic control in most randomized controlled trials.\textsuperscript{44-46} A recent meta-analysis has confirmed this,\textsuperscript{44,45} as did a head-to-head comparison with a dipeptidyl peptidase (DPP)-4 inhibitor, where acarbose demonstrated significantly greater weight reduction. Administration of acarbose together with initiation of insulin therapy has been found to largely ameliorate the weight gain seen in the placebo control group.

\textbf{Incretin-like effects of \(\alpha\)-GIs}

A gradual declining effect of incretin is a generalized, specific, and slowely emerging characteristic in the pathophysiology of type 2 diabetes disease progression.\textsuperscript{47} Emerging evidence has shown that \(\alpha\)-GIs increase circulating postprandial active glucagon-like peptide-1 (GLP-1) levels and act synergistically to the effect of DPP-4 inhibitors; at the same time, glucose-dependent insulino tropic polypeptide (GIP) is decreased.\textsuperscript{48} The GLP-1 enhancing effect is particularly seen in type 2 diabetic patients during standardized meal tests, when administration of \(\alpha\)-GIs generates significantly lower plasma glucose, serum insulin and total GIP levels. Concentrations of active GLP-1, the key incretin hormone, are significantly higher – up to 50\%.\textsuperscript{49} A recent study demonstrated that 24-week acarbose monotherapy in newly diagnosed type 2 diabetic patients was associated with increased levels of both fasting and postprandial GLP-1, NO levels, and NOS activity.\textsuperscript{50}) Therefore, ated that inding thats, kie ingestion and 120 min after the cookie load as the postprandial state. software to measure f the benefits of acarbose on cardiovascular risk may be related to its stimulation of GLP-1 secretion. Combination studies with \(\alpha\)-GIs on top of DPP-4 inhibitors showed further increase of the concentration of plasma GLP-1 concentrations after a meal, compared to monotherapy with the DPP-4 inhibitor\textsuperscript{51} in type 2 diabetic patients. It seems to be reasonable to conclude that \(\alpha\)-GIs might enhance the potentially beneficial effects of GLP-1 on the cardiovascular system by increasing GLP-1 levels in a physiological manner.\textsuperscript{52,53}

Improvement in postprandial hyperglycemia on \(\alpha\)-GIs is clearly associated with a risk reduction of cardiovascular diseases. However, this may not be a class effect.

As described above, \(\alpha\)-GIs have incretin-like effects. Hiki, et al\textsuperscript{54}) studied the different effects on postprandial endothelial function and on incretin secretion between miglitol and voglibose. In that study, dramatic changes were observed in incretin secretion due to miglitol treatment but not to voglibose treatment. Miglitol strongly stimulates endogenous GLP-1 secretion and inhibits GIP secretion. Miglitol, but not voglibose, is absorbed in the upper small intestine.\textsuperscript{55,56} Accordingly, miglitol is absorbed by a relatively higher amount of carbohydrate in the lower intestine, where GLP-1 secreting L-cells exist. This may explain the strong GLP-1 secretion action of miglitol. A recent study reported that intravenous administration of GLP-1 improves endothelial dysfunction in diabetic patients with CAD, suggesting that incretin should be associated with en-
endothelial function. As previously described, this may, in part, be associated with the unique pharmacokinetics of miglitol, which involves rapid and almost complete absorption in the small intestine.

**Conclusion:** In this review, we described perspectives and expectations of α-GIs not only as glycemia-controlling drugs but also as cardiovascular event-preventing drugs. Glucose spikes after meals induce oxidative stress which leads to vascular inflammation and endothelial dysfunction. This may progress atherosclerosis and may cause cardiovascular events such as myocardial infarction. Controlling postprandial hyperglycemia should be the potential target for preventing cardiovascular events. Among α-GIs, acarbose and miglitol could well be strong future players in the treatment of cardiovascular disease in terms of not only secondary but also primary prevention.

**References**

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