

Counterpoint: Postprandial Glucose Levels Are Not a Clinically Important Treatment Target

The recently published randomized controlled Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study evaluated the effect of nateglinide in people with impaired glucose tolerance (IGT) who also had cardiovascular disease (CVD) or CVD risk factors (1). After a median of five years, there was no effect on either incident diabetes or CVD. In five studies (2–6) in which the development of diabetes in subjects with IGT was delayed by lifestyle intervention or drugs, the beneficial effect was postulated to be mainly due to decreasing insulin resistance with resulting less demands on β -cell insulin secretion. On the other hand, subjects with IGT in an older small study treated with tolbutamide (a first-generation sulfonylurea agent) (7) or in the more recent Study To Prevent Non-insulin-Dependent Diabetes Mellitus (STOP-NIDDM) given acarbose (8), there was significantly less incident diabetes than in their control groups. (The STOP-NIDDM study, however, has been severely criticized [9]). Neither tolbutamide nor acarbose are thought to primarily affect insulin resistance. It is very possible, of course, that all of these drugs were simply masking the development of diabetes by treating hyperglycemia (10). If so, nateglinide was unable to accomplish this.

The rationale for the CVD end point in the NAVIGATOR study might have been that glucose levels after a glucose challenge, extending all the way down into the midnormal range, are associated with CVD (11). It is important to point out that in many articles postprandial glucose is used mistakenly to describe glucose levels after the nonphysiologic large amount of glucose ingested for the oral glucose tolerance test. In the only study I could find in which CVD events were related to postprandial glucose concentrations, i.e., after meals, these levels were more predictive than fasting plasma glucose (FPG) concentrations in a bivariate analysis (12). In a multivariate analysis, only the value after lunch remained sig-

nificant. Since nateglinide has a more profound effect on postprandial glucose concentrations than on fasting ones in people with diabetes, it was chosen to test the hypothesis that lowering postprandial glucose levels might have a beneficial effect on people at risk for CVD and the development of diabetes. That it did not might not be too surprising because day-to-day glucose levels in people with IGT on weight maintaining diets (35 kcal/kg) were not increased (13–15). On the other hand, the perhaps problematic STOP-NIDDM study showed that acarbose was associated with decreased incidents of CVD and hypertension (16).

However, in contrast with people with IGT, postprandial glucose concentrations are certainly increased in diabetic patients. There is much speculation that specifically targeting these levels might be beneficial for both the microvascular and macrovascular complications of diabetes (17). Brownlee (18) laid out an intricate theoretical framework of how postprandial hyperglycemia might cause the whole gamut of diabetic complications. This involves increasing glucose concentrations causing oxidative stress reflected in altered mitochondrial function, which causes inhibition of glyceraldehyde phosphate dehydrogenase. This, in turn, leads to increased activity of four biochemical pathways associated with the complications of diabetes, i.e., the polyol, hexosamine, protein kinase C, and advanced glycation end product pathways. Could this be the mechanism whereby the rise in postprandial glucose concentrations leads to diabetic complications? Let's examine the evidence for this intriguing hypothesis.

In vitro incubations of various tissues and cell lines with increasing concentrations of glucose lead to products that reflect oxidative stress (19). One study (20) did show that mitochondrial function in biopsies from the muscle of diabetic subjects was impaired while three other studies (21–23) could not confirm this finding.

Increased variability of daily glycemia is often taken as a surrogate measure for higher postprandial glucose excursions (24). Yet retinopathy was unrelated to this variability, although it remained related to mean glycemia (25). Urinary excretion of free 8-iso-PGF_{2 α} is postulated to reflect oxidative stress, and its excretion is inhibited by vitamin E, an antioxidant (26). One study did find that glucose variability, measured by the mean amplitude of glycemic excursions, was positively correlated with urinary free 8-iso-PGF_{2 α} (27), but this could not be confirmed in two other studies (28,29). Rather, urinary free 8-iso-PGF_{2 α} levels were increased in diabetic patients and lowered by improved diabetic control (26).

Endothelial dysfunction is an early manifestation of atherosclerosis (30). Endothelial function, measured by flow-mediated dilation, decreased in people with diabetes after eating in association with rising postprandial glucose levels but did not change in healthy subjects who have much less of a postprandial rise (31). Artificially raising glucose concentrations with intravenous glucose also decreased flow-mediated dilation and increased oxidative stress, as reflected in increased plasma nitrotyrosine, in both healthy subjects and type 2 diabetic patients (32). Both of these responses to intravenous glucose were blocked by an infusion of vitamin C, also an antioxidant, in healthy subjects but not in those with diabetes (33).

Carotid artery intima-medial thickening (CIMT) reflects coronary artery disease (34). In a cross-sectional study, CIMT correlated with the postprandial rise in glucose concentrations (35). In a prospective study, CIMT did not change in patients treated for three years with voglibose, an α -glucosidase inhibitor, compared with a 0.1 mm increase in those given a placebo with a significant difference between the two groups (36). In another prospective study in drug-naïve patients, there was a small but significant 0.03 mm decrease in CIMT over 1 year in a large number of patients treated with

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