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EDITORIAL COMMENT

Blood Glucose Variability

A New Metric for Interventional Cardiology?*

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Extensive research has been committed to improving outcomes after coronary percutaneous intervention (PCI). Over the past 2 decades, there has been a great deal of attention committed to the study of elevated low-density lipoprotein (LDL) and blood pressure as major determinants of progression of coronary artery disease (CAD) (1). But what about blood glucose?

With the advent of the PROSPECT trial, novel imaging of patients with acute coronary syndrome (ACS), identified large plaque burden and thin-cap fibroatheromas (TCFA) as determinants of nonculprit lesions that were responsible for subsequent major adverse cardiovascular events (MACE) (2). The availability of imaging technology to identify the percent necrotic core (NC) is at the heart of identifying pathological features of the vulnerable plaque.

In stable CAD, hyperglycemia in the form of chronic blood sugar elevation with abnormal hemoglobin A_{1c} is associated with worse outcome after PCI. As a result, patients are treated for hyperglycemia only when a diagnosis of diabetes is established by an oral glucose tolerance test or by a chronic A_{1c} elevation above 6.5%. Diabetic patients are treated with insulin when they have a longer duration of diabetes or with oral hypoglycemic agents or diet when they have a reduced duration of diabetes. The main problem with antidiabetic therapies is the side effects, mainly weight gain, hypoglycemia, and heart failure (3).

In recent years, epidemiological studies have suggested that glycemic variability (GV) may be a marker of increased progression of coronary disease and plaque vulnerability. Glycemic variability as measured by the mean amplitude of glycemic excursions (MAGE) underscores the vulnerability of a single patient to develop large excursions of blood glucose over repeated measurements over a relatively short measure of time. This has been made possible by the advent of continuous blood glucose monitoring.

There have been multiple studies that document that increased GV is associated with worse outcome both for surrogate and clinical outcome measures and this has been documented, not only in diabetic, but also nondiabetic, patients. In type 2 diabetic patients with and without CAD, GV correlated with increased brachial artery endothelium-dependent flow-mediated dilation, increased C-reactive protein and increased insulin resistance as measured by homeostatic model assessment-insulin resistance (4). A positive association of GV with increased carotid intima-medial thickness in type 2 diabetic patients has been shown to be independent of hemoglobin A_{1C} levels (5).

Glycemic variability have also been associated with worse short-term prognosis for acute myocardial infarction (MI) after primary PCI (6). In a study of 237 patients with ST-segment elevation MI, a higher MAGE level was associated with higher peak creatine kinase-myocardial band ($p < 0.01$) and, when classified by terciles, a higher composite rate of MACE (7.5% vs. 14.0% vs. 22.7%, $p = 0.025$). Overall, MAGE was an independent predictor of composite MACE in ST-segment MI patients undergoing primary PCI. In acute MI patients, MAGE, along with the inflammatory mediators CD-14 and CD-16, has been shown to be significantly and negatively correlated with the myocardial salvage index (7).

With regard to the question of coronary plaque vulnerability, Teraguchi et al. (8) studied the impact of glucose fluctuation on plaque vulnerability in 37

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acute MI patients undergoing optimal coherence tomography. Elevated MAGE levels were more likely in those patients with documented plaque rupture.

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In this issue of *JACC: Cardiovascular Interventions*, Kuroda et al. (9) from Japan reported on an elegant study in stable coronary artery disease. This study is important because the research to date on GV has pertained largely to the ACS population. The question was whether GV was also a predictor of plaque vulnerability in patients undergoing elective PCI. There are a number of important aspects to this study in addition to its excellent design. First, the trial has patients under reasonable LDL control. This is important because we know the importance of LDL cholesterol in the outcome of patients undergoing PCI with stable CAD. Second, they were able to identify new diabetic patients on the basis of an oral glucose tolerance test. These results are important because they underscore the fact that one-third of diabetic patients are unaware of their diagnosis at the time of PCI.

Their findings indicate a strong correlation between increasing MAGE and a higher percent NC, regardless of diabetic status. Interestingly, a longer duration of diabetes, which is a strong marker for the need for insulin therapy, was also associated with a higher percent NC. Similarly, when performing individual plaque analysis, MAGE was the only independent predictor of TCFA. As a result, this single study has brought us greater knowledge of the importance of GV as a marker of plaque vulnerability as well as reinforcing the utility of novel imaging strategies to measure TCFA and percent necrotic core.

Glycemic variability holds promise as a predictor of future cardiovascular events likely through a mechanism of influencing plaque vulnerability. The real challenge, however, is demonstrating that modifying GV can actually improve clinical outcomes. A number of studies have attempted to address this, but perhaps the most widely recognized is the HEART2D (Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus) study in the setting of close to 1,000 acute MI patients and type 2 diabetes (10). Patients were randomized to a strategy of targeting post-prandial blood glucose versus one targeting fasting hyperglycemia. The post-prandial strategy lowered absolute GV by 18% but did not improve cardiovascular endpoints. Clearly, this study requires further validation.

In the current evaluation of patients with stable CAD, much can be learned from the ACS population when dealing with optimizing medical care. However, when it comes to optimizing glycemic control, it is important that we study these 2 populations independently and that we have well-powered prospective trials to address the question of GV and plaque vulnerability. Although it is premature to adopt MAGE measurements in all our patients undergoing PCI, it may be a proof of concept for studying novel mechanisms for plaque instability. It is time for "out of the box" thinking in the management of stable CAD. The rates of residual risk post-PCI are too high even for patients prescribed evidence-based therapies.

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