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EDITORIAL COMMENT

Insulin Resistance and Ischemic Myocardial Injury Post-Percutaneous Coronary Interventions*

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The paper by Uetani et al. (1) in this issue of *JACC: Cardiovascular Interventions* reports that a greater degree of insulin resistance is associated with worse short-term and long-term cardiovascular disease (CVD) outcomes in Japanese patients who underwent elective percutaneous coronary interventions (PCI) with a drug-eluting stent (DES). The investigators used the homeostasis model to assess insulin resistance (HOMA-IR), which was calculated by multiplying fasting glucose by fasting insulin and dividing by a constant. Assessment of insulin resistance with this method has typically been highly correlated with the gold standard euglycemic-hyperinsulinemic clamp (2–4); and the HOMA-IR approach is practical in a clinical setting. The investigators also assessed myocardial injury shortly after the procedure by measuring troponin T and creatine kinase myocardial band lysozyme biomarkers.

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Some of the results from this study could easily be anticipated by examining the characteristics of the study participants. Their average age was approximately 70 years, most were men, hypertension was extremely prevalent, and approximately 50% had diabetes mellitus. The participants seemed to generally harbor traits associated with the metabolic syndrome, which is characterized by greater adiposity, impaired fasting glucose or diabetes mellitus, elevated blood pressure, low HDL, and elevated triglycerides. By contrast, body mass index levels in the participants were generally low.

Other results from the study might not have been easily anticipated. The elective PCI procedure was followed by elevated troponin T and creatine kinase levels in many subjects, and evidence of myocardial injury after PCI was found to be present to a greater degree in persons with more insulin resistance.

Many investigators have used metabolic syndrome traits as indicators of insulin resistance and showed greater risk for CVD events in association with a greater burden of metabolic syndrome traits (5). As can be seen in the Uetani data, the standard definition of the metabolic syndrome, even with special provisions for making the diagnosis in an Asian population, might not have identified the persons at high risk for myocardial damage after stent placement or those who experienced CVD events during the 2-year follow-up interval. This study provides convincing evidence that altered glucose and insulin metabolism act in concert to increase the risk for CVD (3). These HOMA-IR data help to identify persons at greater risk for myocardial damage after the procedure and for greater clinical CVD risk during 2 years of follow-up. Similar data have been reported in the past for the development of first coronary artery disease (CAD) events in healthy populations (6,7). Additionally, higher levels of insulin resistance have been shown to be predictive of greater risk for recurrent angina pectoris in persons who have undergone PCI with DES placement (8).

More severe coronary atherosclerosis is associated with insulin resistance (9); and assessments that have been undertaken in subjects who were suspected to have clinical CAD and were studied with quantitative coronary angiography are illustrative. Finnish investigators have compared angiographic findings with a reference group of nondiabetic persons without insulin resistance, and they found more severe distal CAD lesions in nondiabetic subjects with insulin resistance as well as in persons known to be diabetic (10). Intravascular ultrasound was used to undertake these investigations, and remodeling was considered present if there was >5% difference in lumen diameter compared with a proximal coronary artery reference segment (11). Remodeling of coronary vessels has also been associated with insulin resistance, and it has been thought that insulin might affect vascular wall smooth muscle cell proliferation and augment CAD risk synergistically with the renin-angiotensin system.

It has been difficult to identify successful treatment strategies that reduce insulin resistance and concomitantly reduce risk for CVD events. Most oral hypoglycemic agents do not have major effects on insulin resistance. The thiazolidinediones have been shown to reduce insulin resistance and in some cases to reduce atherosclerotic disease but these agents have been associated with increased risk of cardiac failure, and the total CVD risk–benefit ratio has not been favorable (12). Newer therapeutic strategies that might affect glycemia, insulin resistance, and inflammation are being evaluated and include novel agents, such as interleukin-1-beta

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neutralizing antibody and the newer hypoglycemic treatments, such as glucagon-like peptide inhibitors and inhibitors of the enzyme dipeptidyl peptidase IV (9).

The American Heart Association and the American Diabetes Association have issued a joint scientific statement that urges comprehensive risk assessment, lifestyle management, and assiduous attention to risk factor control (13). The prevention efforts have generally focused on reducing risk for first CVD events, but an increasingly large number of insulin-resistant and diabetic patients have prevalent CVD, which places them at extremely high levels of risk for subsequent CVD events (13). Unfortunately, the report by Uetani does not provide information beyond the baseline assessment of cardiovascular risk factors. Post-procedure cigarette smoking, blood pressure control, and lipid levels are important CVD risk determinants in patients who have undergone PCI. Furthermore, it would be of interest to have information on glycosylated hemoglobin (HbA1C) levels in the post-hospital-stay interval. The Uetani study participants had excellent HbA1C control at the time of PCI, but it is possible that such good control was not maintained during the follow-up period. Intensive glucose control and very low HbA1C levels do not necessarily reduce CVD risk, and diabetic patients in the ACCORD and ADVANCE clinical trials with very low HbA1C levels experienced greater risk for adverse CVD outcomes during follow-up (14,15).

Determining the level of insulin resistance helps to characterize persons with moderate-to-severe abnormalities of glucose, insulin, and fat metabolism. Such assessments have generally been reserved for clinical research, and provide clues to improve identification of persons at greater CVD risk over the near-term and longer-term post-PCI. Optimizing such strategies and potentially developing and implementing newer therapeutic approaches might help to improve risk for CVD outcomes in the future for PCI patients.

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