EDITORIAL (SEE CAVALOT ET AL., P. 2237)

Postprandial Glucose: Marker or Risk Factor?

Postprandial glucose (PPG) has a noxious effect on the vascular endothelium, which is mainly mediated by oxidative stress. This condition leads to endothelial activation and dysfunction, two prerequisites for the onset of cardiovascular disease (CVD) (1). The importance of PPG is reflected in the creation of guidelines by the International Diabetes Federation (IDF) for the management of postmeal glucose (http://www.idf.org/guidelines/postmeal-glucose). In these guidelines, the statement "Postmeal and postchallenge hyperglycaemia are independent risk factors for macrovascular disease" was rated as Level 1+, i.e., the data were derived from well-conducted meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a low risk of bias. The relationship between postchallenge hyperglycemia and CVD has been addressed by several studies. In the Honolulu Heart Program, the risk of coronary heart disease was increased in Japanese American men aged 45–68 years who had an abnormal oral glucose tolerance test (2). Comparable results were observed in the Chicago Heart Association Detection Project in Industry Study (3), the Paris Prospective Study (4), the Baltimore Longitudinal Study of Aging (5), and the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study (6). Furthermore, two meta-analyses provided evidence that hyperglycemia in the nondiabetic range was associated with a higher risk of fatal and nonfatal CVD. They also showed that CVD events increased linearly, with no threshold, along with 2-h postmeal plasma glucose levels (7,8).

Relatively few studies have analyzed postmeal hyperglycemia as a risk factor in CVD development. In the Diabetes Intervention Study (DIS), in type 2 diabetic patients who were monitored for 11 years, postbreakfast glucose levels, rather than fasting glucose, were related to myocardial infarction and death (9). In this issue of *Diabetes Care*, Cavalot et al. (10) add further evidence of the harmful relationship between postmeal glucose levels and CVD events. They present 14 years of follow-up data from the San Luigi Gonzaga Hospital, located near Turin in northwest Italy. They assessed whether PPG was predictive of cardiovascular events and all-cause mortality. On a day close to their scheduled visit to the outpatient clinic, 505 type 2 diabetic patients obtained daily glucose profiles either in the clinic or at home by self-monitoring. Blood glucose levels from 2 h after breakfast, 2 h after lunch, and before dinner were tested. No blood glucose data were available from after dinner. Using appropriate corrections for confounders, the authors found that HbA_{1c} and blood glucose levels measured 2 h after lunch, but not fasting glucose, predicted cardiovascular events and all-cause mortality. They also made another important observation: they did not see a U-shaped relationship between HbA_{1c} levels and mortality. The strengths of this report include the long follow-up period and the information provided by the authors regarding both the fasting and nonfasting glucose levels. In contrast to the DIS and Baltimore studies, Cavalot et al. also assessed the predictive role of HbA_{1c}, which, incidentally, was not significant in their first report on 5 years of follow-up data (11). In addition, their patients were carefully assessed for macro- and microvascular complications. However, this study also has some important limitations: *1*) it does not provide the postdinner glucose values, which is important because, at least in Italy, dinner is usually the largest meal; 2) not all of the patients had daily glucose profiles performed at the hospital, where such tests are usually more accurate; *3*) although HbA_{1c} values are presented, the results were based on the glucose profiles from a single day, which may not be representative of the patients' normal metabolic control, especially for those who were monitored inside the hospital; and *4*) there was no information on therapeutic changes implemented during this long follow-up period. Antidiabetic therapies, independent of their hypoglycemic effects, may have a potentially confounding effect on the findings. The authors do not even report hypoglycemic events.

To their credit, Cavalot et al. state that their study does not allow them to state that postprandial blood glucose is not only a predictor but also a risk factor for cardiovascular events and death. This is an important point that needs to be clarified. In the IDF guidelines, question 2 was the following: "Is treatment of postmeal hyperglycemia beneficial?" The guidelines' response, "Treatment with agents that target postmeal plasma glucose reduces vascular events," was rated 1-; i.e., the data were derived from meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias. Only the DCCT (Diabetes Control and Complications Trial) and the UKPDS (UK Prospective Diabetes Study) were cited in the guidelines, and in the UKPDS specifically, the target glucose level was the fasting level rather than the postprandial level (12). In 2007, when the guidelines were published, important studies that were specifically designed to target PPG were still ongoing. The results of these trials have been disappointing. The HEART2D (Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus) study concluded that in diabetic survivors of acute myocardial infarction, the treatment of postprandial versus basal glucose led to similar HbA_{1c} levels and no difference in the risk of cardiovascular events (13). The NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research) study showed that among patients with impaired glucose tolerance and CVD or risk factors for CVD, the use of nateglinide for 5 years did not reduce the incidence of the coprimary composite cardiovascular outcomes (14). The only evidence for a beneficial effect of a specific therapy against PPG comes from the STOP-NIDDM (Study to Prevent Non-Insulin-Dependent Diabetes Mellitus) study, in which patients with impaired glucose tolerance who were randomized to acarbose had significantly fewer CVD events than those randomized to placebo (15). A post hoc analysis of the HEART2D study has demonstrated that targeting postprandial versus fasting/premeal glycemia with insulin in older type 2 diabetic patients may be associated with a lower risk of subsequent cardiovascular events (16). In light of these trials, a more critical rating for the statement "Treatment with agents that target postmeal plasma glucose reduces vascular events" would now be, at best, 2+; i.e., data were derived from

well-conducted case-control or cohort studies with a low risk of confounding bias or chance and a moderate probability that the relationship was causal.

Why is targeting PPG not so effective in reducing cardiovascular events? There are several likely reasons: *1*) PPG may merely be a marker of CVD events; *2*) PPG is simply a surrogate of a much more complex series of metabolic events occurring in the postprandial period; and *3*) the available assessments of PPG postprandial glucose, i.e., the use of a reflectance meter, may not be adequate. It is well established that there is a link not only between insulin resistance and atherosclerosis but also between insulin resistance and other risk factors for CVD. Therefore, PPG may simply mirror a metabolic condition in which several risk factors converge to affect the CVD burden. One of the risk factors that is usually overlooked in the postprandial phase is the concentration of lipids. In the general population, elevated nonfasting triglycerides are associated with an increased risk of myocardial infarction and coronary heart disease (17). The postprandial phase also alters the inflammatory milieu, such as the levels of tumor necrosis factor-α and interleukin-6 (18). It is not known whether a better PPG curbs the prandial proinflammatory state or whether the control of iterative bouts of proinflammatory molecules has any role in the development of CVD. We can also hypothesize that the correction of PPG late in the natural history of the disease is ineffective. Indeed, PPG hits the cardiovascular system early in the course of the disease. Nondiabetic, insulin-resistant subjects show a shorter duration of vasodilatation after a meal with increased fasting vascular resistance (19). In type 2 diabetic patients with no coronary artery disease, elevated PPG is associated with altered myocardial perfusion that is readily corrected when the PPG is controlled (20). Prospective studies are definitively needed in which PPG is specifically corrected early in the course of the disease. As an example, in the HEART2D study, in which the patients had suffered from an acute myocardial infarction, the improvement in PPG might not have been as relevant in terms of CVD prevention as it would be in patients either without CVD or with early-onset type 2 diabetes. Another crucial issue is establishing definitions for PPG and the means of assessing it. Both the San Luigi Gonzaga and the HEART2D studies relied upon glucose levels that were measured with reflectance meters; in addition to the potential problems related to the precision and accuracy of this method, we need PPG metrics that allow clinicians to obtain more robust criteria for both the glycemic quality and variability throughout the day and over a period of several days (21). The methodological limitations of glucose metrics in the published reports may represent another important reason why PPG still may be considered a marker rather than a risk factor for CVD.

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