EDITORIAL (SEE SIEGELAAR ET AL., P. 855)

Glycemic Variability: Can We Bridge the Divide Between Controversies?

What does it take to put glucose variability into or out the heart of glycemic disorders in type 2 diabetes? By analyzing the database of the Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus) HEART2D trial, a premonitory acronym, Siegelaar et al. (1) have reported in this issue of *Diabetes Care* that glycemic variability cannot be placed at the heart of the risk factors implicated in the progression of cardiovascular diseases in people with type 2 diabetes. The HEART2D trial (2) was initially designed to know whether control of basal hyperglycemia or postprandial hyperglycemia is best for reducing cardiovascular outcomes in patients with type 2 diabetes who had a history of myocardial infarction. In order to answer this question, the investigators of the HEART2D trial have enrolled poorly controlled type 2 diabetic patients who had experienced acute myocardial infarction. Patients were further assigned to either a basal insulin strategy that targeted fasting and interprandial glycemia or an insulin regimen with three daily injections of a rapid insulin analog at premeal times in order to target postprandial glucose excursions. A similar lowering effect on ambient (sustained chronic) hyperglycemia assessed by HbA_{1c} levels was observed with the two insulin regimens. No difference in the incidence of cardiovascular events was detected between the two regimens despite that the prandial group had lower postprandial glycemia compared with the basal group at interim analysis, when the study was halted after a mean follow-up of 2.7 years. Even though the authors of the HEART2D trial did not perform any specific assessment of glycemic variability, a rapid glance at the 7-point glycemic profile seems to indicate that the range of glycemic variability was different between the prandial and basal insulin regimens at study end. The analysis by Siegelaar et al. (1) was designed for quantifying these differences. Unfortunately, the results indicate that glycemic variability did not differ between the two groups when classical well-recognized markers of within-day glycemic variability—SD around the mean glucose value and the mean amplitude of glycemic excursions (MAGE) (3)—were used. Significant differences were only observed when using a new marker, the mean absolute glucose (MAG) change, which calculates the slopes of the absolute increments and decrements from peaks to nadirs (1). However, it should be noted that this marker, which includes time as x-axis coordinate, is more a reflection of the kinetics of glycemic changes per unit of time than a true assessment of the magnitude of absolute glucose fluctuations. In addition, it should be noted that this marker was never validated elsewhere. Therefore, before detailing the pros and cons arguments for the possible impact of glycemic variability on the development or progression of micro- or macrovascular complications in type 2 diabetes, we are left with a mixed impression that the analysis by Siegelaar et al. (1) is not appropriately designed for drawing any firm conclusion and for permitting to gain further insight into the debate whether glycemic variability is an important risk factor of diabetes complications. Therefore, such results should be discussed and integrated in a broader context.

Consider that glycemic disorders can be separated into two independent components: the sustained chronic or ambient hyperglycemia and the glycemic variability characterized by acute glucose swings from peaks to nadirs. At present, there is cogent evidence for the deleterious effect of the former glycemic disorder (4–6). As a consequence, the pathogenesis of vascular complications in type 2 diabetes can be depicted by a very simple "catenary model," in which cardiovascular outcomes result from an excess of glycation caused by a sustained glucose exposure that in turn can be assessed and quantified by using quarterly determinations of HbA_{1c} levels (7,8). Ambient glucose exposure results not only from basal hyperglycemia but also from postprandial hyperglycemia. The latter parameter can participate in the development of diabetes complications at least because its absolute impact on HbA_{1c}, expressed as percentage points of HbA_{1c}, is constant at approximately 1% across the HbA_{1c} continuum in non–insulin-treated diabetic patients who have an HbA_{1c} level >6.5% (9,10). Postprandial glucose excursions can exert deleterious pathophysiological effects through other mechanisms. For instance, besides their role in glycation, postprandial glucose excursions can be a cause for vascular diseases through the activation of oxidative stress (11). More generally, in people with type 2 diabetes, it has been demonstrated that the oxidative stress is activated by acute glucose fluctuations (12,13). According to these observations, the pathophysiology of diabetes complications can be extended from a simple catenary model to a "parallel catenary model," in which the two parallel arms correspond to the sustained chronic hyperglycemia and the glycemic variability with their two subsequent consequences: the excess of glycation and the activation of oxidative stress, respectively. Unfortunately, the data of the HEART2D trial (1,2) do not seem to support such a model since the apparent improvement in glycemic variability as observed in the prandial group has no significant impact on the progression of macrovascular complications. These results are in agreement with those reported in two retrospective analyses of the Diabetes Control and Complications Trial (DCCT) datasets (14,15). These reports concluded that glucose variability has only a minor contribution to microvascular complications of type 1 diabetes. The data obtained by the HEART2D trial investigators extend this concept to macrovascular complications of type 2 diabetes treated with insulin. Such results raise new questions. A few years ago, we have shown that glycemic variability exerts a strong trigger effect on oxidative stress in type 2 diabetic patients who were treated with oral hypoglycemic agents alone (12). In addition, several studies seem to indicate that activation of oxidative stress is probably one of the key factors in the pathogenesis of diabetes complications (6). As the results of the HEART2D trial suggest that glucose variability is not a risk factor for cardiovascular diseases in patients with type 2 diabetes treated with insulin (1,2), several "burning" questions can be raised, why could glucose variability be a risk factor for cardiovascular diseases in patients

with type 2 diabetes who are treated with oral hypoglycemic agents alone, but not in those who are treated with insulin, and does insulin per se neutralize the deleterious effects of glycemic variability on oxidative stress in patients treated with it?

A piece of evidence in favor of the latter hypothesis was provided by the results that we have recently reported in *Diabetologi*a (16). In a cross-sectional study that compared three groups of patients with type 1 diabetes and with type 2 diabetes treated either with oral hypoglycemic agents alone or in combination with insulin, we demonstrated that insulin therapy per se exerts an independent inhibitory effect on activation of oxidative stress. In a setting of induced endotoxinemia, Dandona et al. (17) have confirmed these results. From a pathophysiological point of view, these observations seem to provide a unifying explanation for the discrepancies that have been previously reported between insulin-treated type 1 (18) and non–insulin-treated type 2 diabetes (12) in terms of oxidative stress. In addition, the inhibitory effect of insulin could help to explain why smaller glucose fluctuations with prandial insulin regimens in the HEART2D trial did not improve cardiovascular outcomes compared with basal insulin regimens (1,2). These considerations and observations lead to the suggestion that glucose variability does not contribute significantly to vascular complications of patients with type 2 diabetes as soon as they are treated with insulin. Therefore the negative results of the HEART2D trial demand special attention, and the lessons from this study are probably more important than the conclusions that were initially drawn. This type of situation evokes the famous Sherlock Holmes' remark to his assistant, Doctor Watson, that in a certain case it was the dog's behavior that had attracted his attention. When Watson replied that the dog had done nothing, Sherlock Holmes explained that that, in fact, was the important clue. This lesson can be relevant to many clinical studies such as the HEART2D trial.

Returning to the initial question, what does it take to put glucose variability into or out of the heart of glycemic disorders in type 2 diabetes? there is "consensus" that total glucose exposure as reflected by HbA_{1c} levels represents a major risk factor for the development or progression of diabetes complications. However, there is continuing dissent ("dissensus") on glycemic variability. At present, there is no evidence-based data that permit to have a clear opinion on its exact role, but despite inconsistencies across the results of the different studies, the "nonsensus" would be to systematically exclude the glycemic variability from the list of potential risk factors for diabetes complications. In conclusion, further studies are warranted for confirming or refuting the role of glycemic variability. For the moment, we are not certainly at the end of the glucose variability story, but it is difficult to know whether we are at the beginning of the end or at the end of the beginning (19–21).

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