Editorial

Platelet Function and Hyperglycemia in Acute Coronary Syndrome

Función plaquetaria e hiperglucemia en el síndrome coronario

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The literature provides strong evidence showing that platelet function is altered in patients with diabetes mellitus (DM) and that the platelet hyperactivation associated with hyperglycemia is produced by a number of thromboxane A2–independent pathways, such as those responsible for the release of adenosine diphosphatase, thrombin, epinephrine, and von Willebrand factor, among others. Being that they are independent of thromboxane A2, none of these platelet activation pathways are affected by the potential beneficial effect of the classical antiplatelet therapy with acetylsalicylic acid (ASA) or more modern compounds like clopidogrel. For this reason, the search for novel therapeutic approaches designed to control platelet reactivity, especially in diabetic individuals and not only in atherosclerosis not associated with DM, has been an object of interest in recent years, particularly if we take into consideration that diabetics have a certain resistance to the antiplatelet effect of ASA. Diabetic thrombocytopenia is due to the activation of multiple pathways that play a role in platelet function, the most relevant of which are the modification of platelet membrane components, the alteration of calcium and magnesium homeostasis (increasing and decreasing mobilization, respectively), increases in arachidonic acid metabolism and in thromboxane A2 synthesis, a decrease in prostacyclin and nitric oxide synthesis, and increased expression of certain adhesion molecules such as glycoprotein Iib/IIa (GPIIb/IIa) and P-selectin.

The platelets of patients with DM, both type 1 and type 2, exhibit increased reactivity in early stages of the disease, and these phenomena are relevant because they contribute to the excessive rates of cardiovascular morbidity and mortality associated with this disease. Thus, the knowledge of these platelet-related phenomena from the pathophysiological point of view, and of their eventual normalization, has been of great interest; in fact, the clinical practice guidelines on DM have incorporated, to a greater or lesser extent, recommendations concerning antiplatelet therapy. The platelets of diabetic patients express greater amounts of adhesion molecules such as activated GPIIb/IIIa, lysosomal GP53, thrombospondin, and P-selectin. In addition to supporting greater platelet aggregability, this may play a role in the generation of phenomena such as chemotaxis, leukocyte attraction, and interaction with glycosylated low-density lipoproteins and, in short, intensify the inflammatory mechanisms characteristic of arteriosclerosis in diabetic patients. Although treatment with ASA or clopidogrel can inactivate platelet function for approximately 7 days to 10 days, diabetic patients usually have, in addition, an increased platelet turnover as compared to the nondiabetic population, which decreases the protective effect of antiplatelet therapy in these patients. In recent years, new groups of therapeutic agents have been incorporated into antiplatelet treatments, such as thienopyridines and later the cyclopentyl-triazolo-pyrimidines (adenosine diphosphate receptor inhibitors), compounds that target GPIIb/IIIa, and most recently, agents that act on protease–activated receptor 1 (PAR-1) and thromboxane A2 antagonists; we would expect that their utility will soon be evaluated in diabetic patients, by studies specifically designed for that purpose.

In 2007, the American Diabetes Association and the American Heart Association issued a joint recommendation that therapy with ASA (75–162 mg/day) be utilized as a primary prevention strategy for individuals with DM at higher cardiovascular risk, such as those over 40 years of age or having additional risk factors (family history of cardiovascular disease, hypertension, smoking habit, dyslipidemia, or albuminuria). However, these recommendations are derived from several trials that included a relatively small number of subjects with DM. The results of 2 more recent trials, carried out specifically in diabetics, called into question the efficacy of ASA for the primary prevention of cardiovascular events in DM. Together, the results of different meta-analyses appear to indicate that the protective effect of ASA with respect to myocardial infarction and stroke is moderate. Moreover, there may be sex-related differences in the degrees of protection; in fact, studies focusing specifically on the diabetic population are still being carried out to determine the true efficacy of ASA in reducing atherothrombotic risk in these patients. To be precise, there are hopes that the results of the ACCEPT-D and ASCEND trials will be highly informative in this respect. The current recommendations of the scientific societies advise against primary preventive measures involving antiplatelet therapy unless the cardiovascular risk is as high as 10% at 10 years. In addition, they caution that the individual not have high susceptibility to bleeding for any specific reason, which usually results in the establishment of an age cutoff point (also depending on the particular geographical

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context) at 60 years for women and 50 years for men. Thus, the indication for antiplatelet therapy is highly influenced by the method used to assess cardiovascular risk. This is a very important aspect, especially when the tables used to evaluate potential risk differ widely depending on the geographical context; a clear example of these situations are the evident differences between the population included in the Framingham study and the Spanish cohort in the REGICOR study.\(^\text{12}\)

Despite the fact that many of our diabetic patients, especially those at high cardiovascular risk or those who have had a recent cardiovascular event, are receiving more or less effective antiplatelet therapy, the hyperglycemic phenomenon, in its own right, results in a higher level of platelet hyperreactivity with respect to the nondiabetic population. In fact, the degree of platelet hyperreactivity is related to glycemic control.\(^\text{13}\) In contrast, other aspects of the platelet dysfunction found in diabetes, such as the increase in platelet volume, have not been associated with glycemic control.\(^\text{14}\)

The article published by Vivas et al.\(^\text{15}\) in the Revista Española de Cardiología describes the effect of intensive insulin treatment of hyperglycemia on platelet function in patients with type 2 DM at 12 months after experiencing an acute coronary syndrome. The patients enrolled in the study—a prolongation of the CHIPS (Control de la Hiperglucemia y Función Plaquetaria en Pacientes con Síndrome Coronario Agudo) [Control of Hyperglycemia and Platelet Function in Patients with Acute Coronary Syndrome] study—were randomized to a group receiving intensive insulin therapy, the objective of which was to achieve blood glucose levels of 80 mg/dL to 120 mg/dL, or to a less demanding control group, with target blood glucose levels of < 180 mg/dL. The glycemic control, as measured by HbA\(_{1c}\), was very similar in the two groups, with HbA\(_{1c}\) levels of 6.4% (0.7%) and 6.8% (1.3%), respectively, and, despite the statistically significant difference between the two groups in terms of glycemic control, a large number of the patients in the standard treatment group (with follow-up performed by their family physicians rather than by expert endocrinologists) had HbA\(_{1c}\) levels that were more than acceptable and did not differ in clinical terms from those obtained in the intensive therapy group. At the present time, the general consensus is that the target HbA\(_{1c}\) levels should be established according to the characteristics of the patient,\(^\text{16}\) especially if we accept the premise (currently the subject of debate) that glycemic control may not only serve to protect against microvascular disease, but could also result in cardiovascular benefits. Diabetic patients who have had an acute coronary syndrome have very advanced overall cardiovascular disease and, thus, it is accepted that a glycemic control with a HbA\(_{1c}\) level of around 7.5% achieves maximal beneficial effects in the context of a previous vascular event.\(^\text{17}\) Vivas et al.\(^\text{13}\) found no changes in platelet function in any of the parameters evaluated that correlated with the different approaches to hyperglycemia treatment. Should our diabetic patients who have had recent cardiovascular events be subjected to a less demanding glycemic control? The answer to this question is not and cannot be categorical; diabetic patients should be treated on an individual basis;\(^\text{16}\); good glycemic control, the best glycemic control that can be obtained with drugs that minimize or prevent hypoglycemic episodes, benefits the patient at least in terms of microvascular disease, and probably with respect to macrovascular disease as well. However, in patients with very advanced macrovascular disease, its potential reversibility by means of intensive glycemic control is exceedingly improbable, and any contribution of highly optimized glycemic control to this reversibility (or eventually to the stabilization of its progression) is also questionable (or has not been demonstrated at the present time). Moreover, hypoglycemic episodes are or can be dangerous in these patients with advanced macrovascular disease. However, these events are not the direct cause of the increased mortality observed in the patients participating in large studies involving intensive glycemic control in type 2 DM that have been published in recent years, such as ACCORD,\(^\text{18}\) ADVANCE,\(^\text{19,20}\) and VADT.\(^\text{21}\)

These trials compared highly optimized and less optimized glycemic control in patients with different degrees of macrovascular disease, and concluded that therapy based on intensive lowering of the glucose level is associated with rates of mortality that increase in correlation with macrovascular disease progression. These studies have demonstrated that the frailer the patient and, in cardiovascular terms, the greater the severity of his or her macrovascular disease, the lesser the benefit and the greater the negative impact of the adverse effects associated with intensive treatment of hyperglycemia. In the study reported by Vivas et al.,\(^\text{15}\) the object of the present editorial, the more effective glycemic control obtained in the group treated more intensively (a term that better defines the type of therapy implemented, in contrast to so-called “aggressive therapy”) was associated with an improvement in cystatin C, a prognostic marker independent of acute coronary syndrome. The key to the benefit of the treatment of hyperglycemia in the patient with type 2 diabetes is to start it as soon as possible. In many cases, type 2 DM is discovered years after the initial development of the disease, a circumstance demonstrated by the fact that, at the time of diagnosis, up to 5% to 10% of these patients already have some type of microvascular lesion. Moreover, it is not uncommon that it be the cardiologist who, in the context of a first episode of acute coronary syndrome, informs the patient that he or she has diabetes, a condition of which the patient was unaware until then. When this occurs, we are arriving late, in some way, and many of the already established lesions will benefit less from intensive treatment of hyperglycemia. Thus, the intensive treatment of DM can achieve recognized and preventive benefits, not only in the sphere of microvascular disease, but probably in that of macrovascular disease as well, when DM is detected early and treated immediately with intensive regimens. In fact, in recent years, a highly interesting concept has been introduced, the so-called metabolic memory,\(^\text{22}\) according to which exposure to hyperglycemia that is prolonged over time results in changes at different levels that include genetic alterations, which determine the establishment and progression of diabetic complications, among them, vascular problems, in these patients. The extent of this association is such that the late reestablishment of normal blood glucose levels results in lesser benefits than when it is achieved early in the course of the disease. As a consequence, the role of our colleagues, the family physicians, is crucial both in early detection of DM and in its intensive treatment, adapted to the individual and positing the least possible risk, including hypoglycemia.\(^\text{23}\)

Does the metabolic memory explain why Vivas et al.\(^\text{15}\) found no changes in platelet function after 1 year of follow-up of an acute metabolic syndrome? We could probably find the response in a study involving patients with a recent diagnosis of DM that evaluates their platelet function one year later and compares the findings with those of patients with highly optimized glycemic control, with an HbA\(_{1c}\) level of around 6% the group in which the control was less strict, but nonetheless satisfactory, with an HbA\(_{1c}\) level of perhaps 7%, a level which, on the other hand, is recommended by a number of clinical practice guidelines.

In any case, within the context of acute coronary syndrome, both in recently diagnosed patients and in those with late diagnosis, individualized treatment with good metabolic control, or the best possible control in a given patient, including both the glycemic and nonglycemic aspects, together with the use of compounds that help to effectively modulate platelet hyperreactivity, will undoubtedly contribute to improve the prognosis for the vital status of individuals with DM.
CONFLICTS OF INTEREST

None declared.

REFERENCES