

The Significance of Hyperglycemia in Acute Coronary Syndrome

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It is thought that in 2025 there will be some 300 million diabetics worldwide, of whom some 90% will have diabetes mellitus type 2 (DM2). The prevalence of DM2 in the adult population varies from 0.7% to 34% depending on the area in question (eg, it is some 6%-15% in most developed countries and in Spain ranges from 5.6% to 18.7%).¹ Its incidence in European countries is 1.24-4.1 cases per 1000 inhabitants/year; in a Spanish study it was reported as 0.8 cases/1000 inhabitants/year.¹ A remarkable fact is that in all the epidemiological studies performed on DM2 (independent of the diagnostic criteria used), some 30%-50% of people did not realize they had the disease.

People with DM2 have a 2-3 times greater risk of developing cardiovascular disease than non-diabetics, and about 70% die from macrovascular complications, especially ischemic heart disease and cerebrovascular disease. Approximately 20% of DM2 sufferers already have vascular complications at the time of diagnosis.

The strong relationship between DM2 and coronary disease risk is well reflected in a study by Haffner et al (1998)² in which these authors compare mortality of coronary cause in 1059 patients with DM2 and 1373 non-diabetics. After 7 years of follow-up the patients with DM2 who had not suffered a prior myocardial infarction had a mortality rate similar to the non-diabetics who had suffered a prior myocardial infarction. Although later works provided discrepant data, the impact of this study

was so great that it served as the basis for considering DM2 as equivalent to cardiovascular disease. A more recent study that involved 77 814 non-diabetic subjects and 2100 diabetics, and that covered a follow-up period of 18 years, showed that coronary mortality in the former was a little over twice that seen in the latter, thus confirming the relationship between diabetes and ischemic cardiomyopathy.³

The protagonism of hyperglycemia and its relationship with ischemic events was well established by the WHO Multinational Study of Vascular Disease in Diabetes Study⁴ and the United Kingdom Prospective Diabetes Study⁵ (UKPDS) (among others). For 12 years the WHO study followed 4743 diabetics with no history of cardiovascular disease and showed a direct relationship between fasting glycemia values and the incidence of myocardial infarction, cerebrovascular accident and cardiovascular mortality. The UKPDS involved 3055 patients with DM2 and no known history of cardiovascular disease who were followed-up for more than 7 years, and found the HbA_{1c} concentration to be an independent predictor of fatal and non-fatal infarction (an increase of 11% was recorded in the risk of cardiovascular mortality for every 1% increase in the HbA_{1c} concentration).

In DM2, chronic hyperglycemia and tissue resistance to the action of insulin leads to a series of functional changes in many types of cell (such as endothelial cells, smooth muscle cells, and platelets), favoring the development of atherosclerosis and coronary thrombosis.⁶ A fundamental change in the vascular endothelium leads to its dysfunction, manifested as vasoconstriction, hyperplasia of the vascular medial layer, and inflammation. A prothrombotic state also exists due to changes in fibrinolysis and platelet function. In addition, metalloproteinases accumulate, favoring the rupture of atheromic plaques.⁶ Chronic hyperglycemia perpetuates the process such that the mentioned vascular changes gradually become worse, and a strong and pernicious relationship develops between hyperglycemia, mid- and long-term coronary events, and the length of time DM2 has been present.

Acute or stress hyperglycemia has a facilitating role in the development of acute coronary syndrome (ACS) and accentuates the consequences of cellular damage

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caused by acute myocardial ischemia.⁷ The excess of free radicals produced (owed to the increase in cellular oxidative stress produced by hyperglycemia) leads to an increase in the concentrations of fibrinopeptide A, factor VII, and active fragments of prothrombin. Also increased is the degree of endothelial dysfunction and the activation and aggregation of the platelets, while the half life of fibrinogen is reduced. All this facilitates the development of the intravascular thrombosis characteristic of ACS. Acute hyperglycemia also produces a significant lengthening of the QT interval, reduces ischemic preconditioning, increases no-reflow, reduces myocardial contractility, and encourages greater local and systemic inflammation.

Given the above, the negative influence of diabetes and hyperglycemia on the prognosis of patients with ACS is hardly surprising. Diabetic patients with ACS have a greater mortality rate than non-diabetics, as indicated by Donahoe et al,⁸ who studied 62 036 patients with ACS (with or without elevation of the ST segment) involved in the 11 different TIMI studies published at that time. Some 17.1% of all these patients were known diabetics. Mortality at 30 days was higher among the diabetic patients, both in those with ACS but with no elevation of the ST segment (hazard ratio [HR]=1.78, 95% confidence interval [CI], 1.24-2.56) and in those in whom the latter was elevated (HR=1.40, 95% CI, 1.24-1.57). Diabetic patients with ACS also show high admission plasma glucose (APG) levels and greater in-hospital mortality, as indicated by the meta-analysis of Capes et al.⁹ The latter work showed that diabetics admitted for acute myocardial infarction with an APG of >10-11 mmol/L have an in-hospital mortality rate 1.7 times that of patients admitted with a lower APG level.

In recent years many studies have focused on the prognostic value of hyperglycemia in ACS, independent of whether the patient is known to be diabetic. In a study involving 662 patients with acute myocardial infarction (all from the Spanish province of Gerona), Sala et al¹⁰ showed that those with an APG concentration of >6.67 mmol/L had a 28-day mortality rate of 4 times that of patients with lower concentrations, independent of any prior diagnosis of diabetes. In a similar study involving 2127 patients with ACS, Foo et al¹¹ stratified APG concentrations above 5.8 mmol/L into quartiles, and reported a relationship between increasing glycemia and ventricular dysfunction, and in-hospital death. The prognostic value of this variable was not affected by the known presence of diabetes at admission, and was similar in patients with ACS with and without ST segment elevation. Even in patients subjected to percutaneous intervention, hyperglycemia was a marker of a poorer short-term prognosis, independent of the presence of diabetes.¹² The results of these and other studies show, without doubt, that hyperglycemia is

associated with a poorer clinical course in both patients with ACS known to have diabetes and in those with no history of this disease. A consequence of this has been the recent understanding of hyperglycemia as an independent risk factor to be taken into account when trying to arrive at a prognosis for patients with ACS.

Although the prognostic value of hyperglycemia is well established, a certain amount of controversy still surrounds the cut-off value that should be used (which commonly differs depending on the paper read) as a predictor of adverse events and as a diagnostic marker of diabetes. Further, it seems unsure whether the value measured should be that of the APG, that of fasting glycemia, that obtained in the oral glucose tolerance test, or the glycohemoglobin level (an indirect measure of glycemia). In this edition of the *Revista Española de Cardiología*, Vivas et al¹³ compare the prognostic values of the APG and first fasting plasma glucose (FPG) concentrations in 547 consecutive patients with a diagnosis of ACS admitted to their coronary unit. The main endpoint was the combined event of death and/or reinfarction during hospitalization. The patients were stratified into 3 glycemia intervals: <126 mg/dL, 126-200 mg/dL, and ≥200 mg/dL (both for their APG and FPG values). As expected, the patients who suffered adverse events had more serious disease profiles (they were older and more were diabetics or smokers, had suffered a previous infarction, had multi-vessel disease, a high Killip class, a high plasma creatinine concentration, a poor left ventricular ejection fraction, or high APG and FPG values). No differences were seen in terms of the treatment the different patients received, which more than met the criteria of current clinical practice guidelines (including a high number of revascularization procedures). In the analysis of the results, increasing APG and FPG concentrations were found to be associated with an increasing proportion of adverse events, but only the FPG value was an independent predictor of death and/or reinfarction (although the OR had wide confidence levels [OR=5.26; 95% CI, 1.09-25.45 for FPG in the 126-200 mg/dL interval; OR=6.6; 95% CI, 2.05-21.63 in the >200 mg/dL interval] and the area under the ROC curve was discrete [0.67; 95% CI, 0.58-0.76]). The authors concluded that the FPG value was a better indicator of in-hospital death and/or reinfarction than the APG value.

The study by Vivas et al¹³ does not resolve current controversies—although it helps. Their results confirm in the Spanish population that indicated by recent studies such as that of Suleiman et al¹⁴ (performed in Israel with 735 patients suffering infarction but with no previously diagnosed diabetes). Using a similar methodology, the latter authors stratified the APG and FPG values into tertiles with intervals even lower than those used by Vivas et al. Nonetheless, they also showed a gradual increase in mortality at 30 days as the APG and FPG concentrations

increased, and that the predictive power of the FPG value was greater.

Although the criteria for establishing a diagnosis of diabetes in the acute phase of ACS are not well defined, about 30% of patients are diagnosed with diabetes when they suffer an ischemic event (similar numbers are diagnosed as prediabetic). This information is important since patients with ACS who are then diagnosed as having diabetes have a poorer diagnosis than known diabetics. Patients admitted for an infarction with previously diagnosed diabetes and an FPG concentration of 110-125 or >125 mg/dL (diabetic range) suffer 4 times and 10 times greater mortality at 30 days than those with a normal FPG concentration; however, for those known to have diabetes mortality is only 2.4 times higher.¹⁴ These data support the hypothesis that stress hyperglycemia is a marker more directly linked to the extent of acute myocardial damage than diabetes itself. The greater the myocardial damage the greater the release of catecholamines and cortisol, with the consequent increase in insulin resistance. The relative deficit of insulin and the excess of catecholamines reduce the utilization of glucose by the ischemic myocardium and promote lipolysis, thus increasing the concentration of circulating fatty acids. These inhibit the oxidation of glucose and are toxic to the ischemic myocardium, resulting in further damage to cell membranes, arrhythmias, and a loss of contractility that might explain the increase in mortality associated with hyperglycemia.^{7,14} The recent work of van der Horst et al¹⁵ supports this hypothesis; these authors indicate that the appearance of adverse events in the month before undergoing primary angioplasty are more related to the persistence of glycemia above 9 mmol/L in the first 2 days after admission rather than to the APG value.

Even when leaving aside other areas of discussion such as the prognostic value of the glycohemoglobin level and the results of the oral glucose overload test, it would appear that the controversy surrounding hyperglycemia in ACS is not yet over. For the clinical cardiologist the message is that it is not enough to know that patients with ACS and known diabetes have a poorer prognosis (which can be improved by treatment that maintains normoglycemia since the time of admission); it is also important to recognize prediabetic patients (who should be strictly monitored in order to reduce future complications) and to understand that initial hyperglycemia in non-diabetic patients is also associated with a poorer prognosis (these patients would also probably benefit from treatment designed to normalize their blood sugar levels).

Finally, the article by Vivas et al should contribute towards Spanish cardiologists becoming aware of their need to know more about diabetes and the metabolic alterations that influence the progress of ACS—a need that was recognized in a survey by

Palma et al¹⁶ published in this same journal not so long ago.

REFERENCES

1. Goday A. Epidemiología de la diabetes y sus complicaciones no coronarias. *Rev Esp Cardiol*. 2002;55:657-70.
2. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med*. 1998;339:229-34.
3. Dale AC, Nilsen TI, Vatten L, Mighthjell K, Wiseth R. Diabetes mellitus and risk of fatal ischaemic heart disease by gender: 18 years follow-up of 74914 individuals in the HUNT 1 Study. *Eur Heart J*. 2007;28:2924-9.
4. Fuller JH, Stevens LK, Wang SL. Risk factors for cardiovascular mortality and morbidity: the WHO Multinational Study of vascular disease in diabetes. *Diabetologia*. 2001 Suppl 2:554-64.
5. Turner RC, Millns H, Neil HAW, Stratton IM, Manley SE, Matthews DR, et al. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom prospective diabetes study (UKPDS:23). *BMJ*. 1998;316:823-8.
6. Palma JL. La diabetes mellitus entendida como una enfermedad cardiovascular de origen metabólico. *Rev Esp Cardiol Supl*. 2007; 7:H12-9.
7. Ceriello A. Acute hyperglycaemia: a new "risk" factor during myocardial infarction. *Eur Heart J*. 2005;26:328-31.
8. Donahoe SM, Stewart GC, McCabe CH, Mohanavelu S, Murphy SA, Cannon CP, et al. Diabetes and mortality following acute coronary syndromes. *JAMA*. 2007;298:765-75.
9. Capes SE, Hunt D, Malmberg K, Herstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: A systematic overview. *Lancet*. 2000;355:773-8.
10. Sala J, Masiá R, González de Molina FJ, Fernández-Real JM, Gil M, Bosch D, et al. Short-term mortality of myocardial infarction patients with diabetes or hyperglycaemia during admission. *J Epidemiol Community Health*. 2002;56:707-12.
11. Foo K, Cooper J, Deane A, Knight C, Suliman A, Ranjadavalan K, et al. A single serum glucose measurement predicts adverse outcomes across the whole range of acute coronary syndromes. *Heart*. 2003;89:512-6.
12. Isihara M, Kagawa E, Inoue I, Kawagoe T, Shimatani Y, Kurisu S, et al. Impact of admission hyperglycemia and diabetes mellitus on short-and long-term mortality after acute myocardial infarction in the coronary intervention era. *Am J Cardiol*. 2007;99:1674-9.
13. Vivas D, García-Rubira JC, González-Ferrer JJ, Núñez-Gil I, Del Prado N, Fernández-Ortiz A, et al. Valor pronóstico de la primera glucemia en ayunas en comparación con la glucemia al ingreso en pacientes con síndrome coronario agudo. *Rev Esp Cardiol*. 2008; 61:458-64.
14. Suleiman M, Hammerman H, Boulos M, Kapeliovich MR, Suleiman A, Agmon Y, et al. Fasting glucose is an important independent risk factor for 30-day mortality in patients with acute myocardial infarction: a prospective study. *Circulation*. 2005;111:754-60.
15. van der Horst JC, Nijsten MW, Vogelzang M, Zijlstra F. Persistent hyperglycemia is an independent predictor of outcome in acute myocardial infarction. *Cardiovasc Diabetol*. 2007;6:2.

16. Palma JL, Hernández Madrid A, Bertomeu Martínez V, González-Juanatey JR, López-García Aranda V, Calderón Montero A, et al. La diabetes mellitus en la práctica de la cardiología en España.

Encuesta del Grupo de Trabajo de Corazón y Diabetes sobre la importancia de la diabetes mellitus en relación con las enfermedades cardiovasculares. Rev Esp Cardiol. 2004;57:661-6.