GLUCOSE METABOLISM DISTURBANCES IN ACUTE MYOCARDIAL INFARCTION

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Abstract

The enormous impact that diabetes mellitus has on health systems worldwide is especially determined by a greater prevalence of coronary heart disease, an increased incidence of acute coronary syndromes and a worse prognostic during the recovery phase after an acute coronary event, by comparison to non-diabetic population. Hyperglycemia is a frequent finding in patients admitted with acute myocardial infarction (AMI) and carries an increased risk of mortality, in both known diabetics and patients not previously diagnosed with diabetes. The risk excess is evident even in the "pre-diabetic" states, characterized by disregulation of glucose metabolism (like impaired glucose tolerance). The stimulation of inflammatory processes in AMI seems to be the link between acute hyperglycemia and worse outcome. Recent data has shown that insulin has an anti-inflammatory effect on a cellular level. Clinical research has proved that aggressive glycemic control improves prognosis in AMI. The means of achieving tight glucose control are more controversial.

Keywords: diabetes, myocardial infarction, hyperglycemia, insulin infusion.

The prevalence of diabetes mellitus has reached epidemical proportions throughout the world, as the current population of approximately 140 millions adults affected by this condition will have doubled by 2025, reaching a value of 300 millions. The enormous impact upon health systems worldwide is especially determined by an increased prevalence of coronary heart disease (CHD), a greater incidence of acute coronary syndromes (ACS), and, moreover, a worse prognostic in the period following a coronary event by comparison with the non-diabetic population, after adjustment for relevant clinical variables (12). The risk for CHD is 1,5 times greater in diabetics compared to non-diabetics after adjustment for the other known risk factors. This excess of risk is more obvious in women.

The results of Framingham trial after 18 years of follow up, have shown that all types of CHD and sudden death were more prevalent in men and women with diabetes aging between 45 and 75 years, by comparison with non-diabetics (6).

Information obtained in a recent retrospective study, on a cohort of patients from the United Kingdom Prospective Diabetes Study (UKPDS), has shown that the fatality of myocardial infarction in known diabetics could be predicted by variables related to the quality of glucose control (especially HbA1c). This was confirmed by the analysis of 674 cases of AMI (351 of which were fatal) in diabetics included in

UKPDS, showing that patients who died of MI had greater HbA1c levels (measured 1-2 years after the diagnosis of diabetes had been established) than the survivors (OR 1,17 for every increase with 1% of HbA1c, p=0,014). The AMI was defined as fatal when death occurred in the first 6 months after the diagnosis. Other variables associated with increased mortality were age, blood pressure and urinary albumin excretion (17).

Increased values of fasting glucose are a common finding in patients admitted with an AMI (in up to 50% of the patients) and are associated with an increased risk of death in diabetic patients as well as in those patients not previously diagnosed with diabetes (19).

A recent retrospective study, with prospective follow up, by Stranders et al, has investigated the prognostic value of increased fasting glucose blood levels at admittance, in terms of long time evolution in a cohort of 846 patients (109 of whom were known diabetics). After a median follow-up of 50 months, 208 non-diabetics (28,2%) and 47 diabetics (43,1%) died (p=0,002). Each increment of 18 mg/dl (1 mmol/l) in fasting glycemia brought about an excess risk of 4% in non-diabetics and 5% in diabetics (p=0,05). Even if diabetes mellitus cannot be diagnosed based on a single glycemic value, the threshold of 200 mg/dl will be highly sensitive for this disease. Considering the 737 patients without previously known diabetes, 101 had a fasting glycemia at admittance greater than 200 mg/dl, and the mortality of this subgroup was similar to that of the known diabetics (42,6% vs. 43,3%). Moreover, the incidence of heart failure was especially high in this subgroup of patients (40,6%). The authors conclude that glycemia at admittance can be useful in stratifying post-AMI risk, especially in patients not previously diagnosed with diabetes (18).

A number of trials has shown that this excess of risk is obvious even in the "pre-diabetic" stages characterized by altered homeostasis of glucose metabolism, like the impaired glucose tolerance (IGT). Data from literature shows that cardiovascular mortality and morbidity are increased at glycemic levels under the diagnostic threshold for diabetes mellitus. A recent study has shown that, among the patients admitted for an AMI, who were non-diabetic and having a fasting glycemia under 200 mg/dl, up to 40% were diagnosed with IGT, and up to 25% with overt diabetes at 3 months after the acute event, by means of an oral glucose tolerance test (OGTT). The study protocol included measurement of fasting glucose and HbA1c during hospitalization, and performing an OGTT that included measurement of initial glycemic value, and after 1 and 2 hours from the oral loading with 75 g of glucose. OGTT was performed both at discharge, and 3 months later. According to the result of the OGTT, the patients were divided in three sub-groups: normal glucose tolerance (NGT), impaired glucose tolerance (IGT), or overt diabetes. Insulin resistance was calculated using HOMA-R index at admittance and three months later. This study has shown that insulin resistance is prevalent among people with AMI, without known diabetes. The HOMA-R index didn't change significantly after 3 months. The plasma insulin level 2 hours after the oral glucose loading didn't change during the period between the initial moment and the 3 months follow-up in the patients with IGT or diabetes, but decreased in

the NGT group, and that is indicative of a more adequate acute phase insulin response in these patients. Discharge OGTT was a useful tool for prediction of subsequent diagnosis of diabetes at 3 months, glycemia measured at 1 h being the most powerful prediction variable for the positive diagnosis of IGT or diabetes at 3 months. At a threshold value of 8,6 mmol/l (155 mg/dl), 1 hour glycemia indicated subsequent assignation at 3 months as NGT or IGT/diabetes in 70% of the patients. Therefore, the glucometabolic state investigation prior to discharge would be useful for prognostic purposes. Other variables like age, body mass index, current antihypertensive treatment, fasting glycemia, HbA1c, plasma lipids, insulinemia, proinsulinemia, PAI-1 levels, were also analyzed, but conferred no additional prediction power (2, 13, 14).

A Romanian trial carried out in the period between January and December 2002, was designed to estimate the frequency of hyperglycemia and its associations with cardiac function parameters in patients admitted with an AMI. 347 consecutive cases were included, of which 71 were previously diagnosed with diabetes. According to glycemia at admittance (designated as "random") and fasting glycemia measured in the first 24 hours, the patients who have not already been diagnosed with diabetes were classified as having: "diabetic" hyperglycemia ("random" glycemia > 200 mg/dl and/or basal glycemia > 126 mg/dl), "prediabetic" hyperglycemia (basal glycemia 110-126 mg/dl and/or "random" glycemia 140-200 mg/dl) or normoglycemia (fasting glycemia < 110 mg/dl and "random" glycemia < 140 mg/dl). According to these values 78 subjects (22,5%) were normoglycemic, 80 (23,1%) had "diabetic" hyperglycemia and 89 (25,6%) "prediabetic" hyperglycemia. The remainder of the patients were either known diabetics or not included in this analysis due to the unavailability of fasting glycemia in the first 24 hours. The prevalence of glucose intolerance in this cohort was 69,2%: 20,5% diabetic patients and 48,7% patients with various types of hyperglycemia. Statistically significant, independent and inverse correlations were established between left ventricular ejection fraction and age ($r=-0,218$, $n=259$, $p<0,01$), fasting glycemia ($r=-0,238$, $n=259$, $p<0,001$), and "random" glycemia ($r=-0,272$, $n=259$, $p<0,001$). At a similar distribution of STEMI and NSTEMI, and similar triglycerides, LDH, AST and CKMB values among the groups defined by means of glycemic values, the risk of death by heart failure (frequently associated with death in this study: 41,1%) gradually increased from the normoglycemic group, to "prediabetic", "diabetic" groups and was the greatest in known diabetics. The incidence of heart failure was greater only in the "diabetic" hyperglycemia group. The relative risk of death, by comparison with the normoglycemia group, was greater in the diabetic population as well as in the "diabetic" hyperglycemia group, surprisingly greater in the latter (RR 5,85, CI 2,13-16,09, $p<0,001$ vs. RR 3,85, CI 1,33-11,4, $p<0,015$, both RR by comparison to normoglycemic group). This apparently paradoxical finding is supported by other data in the literature (Marfella et al, 11). The trial also demonstrated that although aggressive therapeutic approach of hyperglycemia in AMI patients is supported by many findings,

only a small number of patients with hyperglycemia were insulin-treated (9).

A growing body of clinical evidence shows that AMI is associated with local and systemic inflammatory phenomena. The activation of immune cells is paramount in the initiation of the inflammatory response. The atheromatous plaques, especially those related to an acute coronary event, contain a large number of activated T cells. This finding suggests that the T cells activation could play a major role in the destabilization of the plaques and, eventually, in the acute clinical manifestations of atherosclerosis, like AMI. Although some biochemical markers of subclinical chronical inflammation are also present in patients with stable coronary heart disease, a true flare of T cell activation occurs only in acute coronary syndromes.

An Italian study has examined the association between glycemic levels, inflammation markers, T cell activation and heart function prognosis in 108 AMI patients. Levels of IL-18, C reactive protein (CRP), cell expression of CD16-CD56, CD4/CD8 ratio, CD152 and HLA-DR were measured. The trial has shown that cardiac function parameters (dimension of the infarcted area, myocardial performance index, transmitral Doppler flow, left ventricular ejection fraction) were more severe affected in patients with hyperglycemia, as compared to normoglycemics, especially in newly discovered diabetic patients (fasting glycemia > 126 mg/dl). IL-18 and CRP plasmatic levels were more elevated in hyperglycemic patients ($p<0,005$), especially in those with newly discovered diabetes ($p<0,05$). The patients with hyperglycemia also had larger percents of CD16-CD56 positive cells, larger CD4/CD8 ratio ($p<0,01$), and reduced expression of CD152 (with inhibitory effects on the T lymphocytes activation) ($p<0,001$). In conclusion, the stimulation of inflammatory mechanisms seems a likely link between acute hyperglycemia and worse prognosis in AMI (11).

The myocardium is an obligate aerobic tissue, which, unlike skeletal muscle, cannot metabolize substrate in the absence of oxygen. The preferred fuel for the myocardium is free fatty acids (FFA) in the fasting state, glucose in the postprandial state and FFA and lactate in effort conditions. In anaerobic metabolic conditions, as ischemia, the balance between the utilization of these substrates is broken, and the FFA and their anaerobic catabolism by-products accumulate in the myocardium, and can lead to cardiomyocites' death (6).

Cathecolamine secretion is another factor that contributes to AMI as this condition is an inflammatory, hypercatabolic state, generating hyperglycemia and increased levels of FFA. Via their inhibitory effects on the endothelial production of nitric oxide (NO), prostacycline, and prostacycline stability in plasma, the FFA bring about the deterioration of vascular reactivity. Moreover, increased levels of FFA generate insulin-resistance by induction of proteinkinase C (PKC) and inflammation by suppression of κB inhibitor in the skeletal muscles. Proinflammatory processes are also generated in the mononuclear immune cells via induction of nuclear transcription factor κB (NF-κB) (important proinflammatory factor), increased generation of oxygen radicals, and increased expression of p47phox (a NADPH-oxidase subunit, responsible for generation of superoxyde radical) (1).

The oral loading with 75 g of glucose has proved to have an increasing effect on the generation of reactive oxygen species by the immune cells, and lipid peroxidation, with a decrease in the level of plasma α-tocopherol (4, 5).

All these processes could be theoretically prevented by the restoration of physiological energy substrate and utilization using glucose-insulin infusion. Recent data has shown that insulin has a profound, rapid anti-inflammatory effect at cellular and molecular levels similar to that of corticosteroids, both in vitro, and in vivo. Insulin suppresses the transcription of NF-κB and expression of certain adhesion molecules, like ICAM-1 and MCP-1, in endothelial cells. The blocking of endothelial cells expression of adhesion molecules is critical for a potent anti-inflammatory effect, because one of the initial phenomena in inflammation is the adhesion of immune cells to the vascular endothelium. One in vivo study has shown that low-dose insulin infusion determines a reduction in CRP, and circulatory ICAM-1 and MCP-1 levels in only 2 hours (4, 5). Moreover, the suppression of NF-κB can lead to the inhibition of other mediators of inflammation like: AP-1, Egr-1, VEGF, TNF-α and IL-6. Egr-1 (early growth response-1) controls the expression of tissue coagulation factor and of PAI-1, and its inhibition could play a role in insulin facilitating spontaneous thrombolysis in AMI (4, 5, 11, 15).

There must be also mentioned here that thiazolidindione class agents probably produce similar effects by favoring insulin action. In an experimental model of AMI, even a single dose of rosiglitasone reduced myocardial damage with as much as 50% (7).

The DIGAMI (Diabetes Mellitus, Insulin-Glucose Infusion in Acute Myocardial Infarction) Trial, published in 1997, arose the interest regarding the use of insulin in AMI. The trial was multicentric (19 centers in Sweden), randomized, prospective. The randomization criterion was an admittance glycemic value greater that 11 mmol/l, which included in the analysis, apart from known cases of diabetes, a percent of 13% newly discovered diabetic patients. The patients were randomized to treatment with insulin-glucose infusion followed by a regimen of three months of multiple daily injections of insulin (n=306), or to the control group which consisted of patients treated with insulin only when required by the clinical circumstances (n=314). Both groups received standard medical care for AMI, with no differences in the utilization of thrombolysis, ASA, β-blockers or ACE-inhibitors between them. The most important result of the DIGAMI Trial was the notice of a 30% reduction in 1-year mortality in the insulin-glucose infusion arm (18,6% vs. 26,1%, p<0,027). The trend was consistent after a medium 3,4 years of follow-up (44% vs. 33%, p<0,011). The absolute risk reduction was 11%, which means one life saved for every 9 patients treated with the DIGAMI protocol. Advanced age, heart failure at randomization, the duration of diabetes, fasting glycemia and HbA1c were independent factors that predicted mortality in the entire cohort, while other traditional risk factors, like history of MI, female sex, smoking and arterial hypertension didn't independently increased the prediction power (10). The most important benefit was observed in the low-risk group of patients, and in the patients not treated with insulin prior to their

admission for AMI. B-blocking therapy did improve prognosis in the control group, but was not independently associated with survival in the active treatment group. This observation indicates the partial superposition of the positive effects of β-blockers and insulin in diabetic patients with AMI. A possible common effect would be the reduction in FFA oxidation and promotion of glucose utilization (6). The absolute risk reduction obtained by glucose-insulin infusion is comparable with that of other interventions presently considered standard care in AMI : thrombolysis (3,7% absolute risk reduction in mortality at 35 days), ASA (3,8%), β-blockade (acute 3,5%, chronic 9,3%), statin therapy (10,4%) (6).

Much criticism was expressed regarding this trial. One problem was that the study protocol didn't allow the discrimination between benefits attributable to the glucose-insulin infusion in the acute setting and the ones attributable to the multiple daily injection regimen used after discharge (although the study protocol stipulated insulin therapy to be used for only three months, many of the patients were in fact insulin-treated for as long as 12 months). Other voices disputed the claiming that the benefit was obtained by insulin treatment per se, but in fact by withholding sulfonylureics (glyburide) therapy, agents that interfere with the process of ischemic preconditioning (8).

It is important that the DIGAMI 2 Trial, designed to address these problems, had equivocal results. The participants were randomized in three groups. Patients in the first group received glucose-insulin infusion for at least 24 hours and then were switched to subcutaneous insulin. The second group received the same glucose-insulin infusion in the acute setting (at least 24 hours) and then returned to conventional treatment, and the third group received only conventional treatment. No difference in mortality was observed between the first two groups, and in the third mortality was slightly decreased. The rate of strokes and reinfarctations was similar in groups 2 and 3, and an ascendant, marginally significant (p=0,07), trend in reinfarctations was seen in group 1 (3, 6). As a consequence of these results the DIGAMI protocol of glucose-insulin infusion is currently not indicated in AMI.

Nevertheless, a general consensus exists regarding the necessity of aggressive therapeutical approach in diabetic patients, concerning glycemic control and cardiovascular interventions. This is based on findings in many large trials on diabetic patients (including UKPDS), with beneficial effects on cardiovascular events and mortality. To support this view we cite a single example: a retrospective trial carried out in Germany by Schnell et al, published in 2003, and based on the Munchen myocardial infarction registry, which saw into the prognostic markers in patients admitted with AMI, with or without diabetes. Patients admitted between 1999 and 2001 were included in the analysis. The results showed that percutaneous transluminal angyoplastic procedures were less used in 1999 as compared to 2001 (p<0,001). In this period, the total in-hospital mortality (29% vs. 16%, p<0,01) and the mortality in the first 24 hours after admittance (14% vs. 5%, p=0,01) were greater in diabetics than in non-diabetics. During 2001 the frequency of invasive cardiologic procedures on patients with diabetes increased to a level comparable to

those performed on non-diabetics (p<0,001 vs. 1999). Glucose-insulin infusions were given to 46% of diabetics. The total mortality in diabetic patients during 2001 decreased to 17% (p=0,028 vs. 1999), and the 24 hours mortality to 4% (p=0,027 vs. 1999). The analysis showed that the addition of therapeutical approaches (adjusted for clinical variables) was directly linked to this reduction in mortality (OR 0,14, p<0,0001) (16).

Research has shown that a tight glycemic control must be obtained in order to improve prognosis. The means of achieving a tight glycemic control remain more controversial. Insulin does seem to have some advantages, probably linked to its anti-inflammatory effect. As mentioned above, glucose-insulin infusion (the DIGAMI protocol) is presently not considered to play a role in the management of AMI, but continuous intravenous insulin infusion is the preferred approach to significant hyperglycemia in AMI, as well as in other acute illnesses, as it is the most effective, fastest, and safest way of obtaining and maintaining relative normoglycemia. All the data point out that the benefits of insulin-glucose infusions are related to their ability to obtain adequate glycemic control, and are only marginal if hyperglycemia isn't corrected.

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