Diabetes Mellitus and Coronary Artery Bypass

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Diabetes mellitus (DM) constitutes an independent risk factor for developing coronary artery disease (CAD), with which it often coexists. The incidence of CAD is double in diabetic men compared to non-diabetics and three times higher in diabetic women compared to non-diabetics[1]. Moreover, women that are insulin treated (who mainly have a more severe form of DM) have more frequently CAD and higher mortality from the disease. Generally, most of diabetic patients –it is reported up to 80%– die from cardiovascular diseases[2], with CAD to be responsible for the 2/3 of these deaths[3]. Despite the fact that modern techniques in the treatment of CAD have improved the prognosis, whether DM is present or not, diabetic patients (and particularly diabetic women) still have double mortality rates compared to non-diabetics[4]. The percentage of diabetic patients among patients with CAD that undergo coronary artery bypass grafting (CABG) is 7-20%[5-8].

Pathogenesis of coronary artery disease in diabetics

All the known risk factors of atheromatosis contribute in the pathogenesis of CAD in diabetics, in higher, however, degree[9,10]. Diabetes promotes the atheromatosis even in an indirect way through its various metabolic disturbances[11,12]. According to others, asymptomatic hyperglycemia constitutes itself an independent risk factor for cardiovascular mortality[13,14].

Diabetics have more often compared to the general population the following risk factors of atheromatosis: hypertension, increased body mass index, increased triglycerides, low HDL-cholesterol, coagulation disturbances due to increased platelet adhesion, increased fibrinogen, increased PAI-1 and von Willebrand factor[15]. In diabetics that have hyperglycemia, there is a disturbance of the metabolism of arachidonic acid, which is the main factor of improper platelet function[16]. Moreover, a lot of diabetics continue to smoke. Smoking causes damage to vascular endothelium[17], it creates atheromatous changes in lipoproteins[18,19] and increases the tendency for thrombogenesis[20,21].

During last years the role of hyperinsulinemia in the atheromatosis after the theory of Reaven has been extensively discussed. However, Reaven's opinion despite its frequent reference did not enjoy general acceptance[22-27]. Moreover, in epidemiologic studies, cross-correlations between the amount of insulin in diabetics and CAD have not been not found[28,29].

The atheromatous changes in diabetics do not have pathological differences from the changes that are present in non-diabetics, but they are diffused and they are also located even in small arteries[30]. DM also accelerates the development of these atheromatous changes[31]. The myocardial infarction in diabetics is generally more extensive and the subsequent heart failure or cardiogenic shock are more frequent[32].

Therapeutic options in diabetic patients with coronary artery disease

Large randomised trials compared the results of balloon angioplasty with CABG as the first choice in the treatment of CAD. BARI study, which is the largest of them, showed that hospital mortality after balloon angioplasty and CABG in diabetic patients was 0.6% and 1.2%, five-year survival was 65.5% and 80.6%, five-year survival without reintervention was 22.1% and 75.0%[33,34], while seven-year survival was 55.7% and 76.4%, respectively[35]. EAST study found that the diabetics with pharmacologically treated diabetes (tablets or insulin) had eight-year survival of 60.1% after balloon angioplasty compared to 75.5% after CABG[36]. Similar results have been also showed in the CABRI study[37]. According to this study (at a four-year follow-up) the mortality in diabetic compared to non-diabetic patients after balloon angioplasty was 22.6% versus 9.4% and after CABG was 12.5% versus 6.8%[38].

With regard to the effect of the different ways of treatment of DM (diet, tablets, insulin) in prognosis, the BARI study showed higher five-year mortality after balloon angioplasty compared to CABG in the insulin-dependent patients, while there was no difference in the patients that received antidiabetic tablets[39]. In other large series of patients, the late survival after balloon angioplasty was less compared to CABG in patients with pharmacologically treated diabetes (46% versus 60% in 10 years)[40], while generally the need for insulin was associated with worse survival after balloon angioplasty (68% and 36% in 5 and 10 years, respectively), as well as after CABG (75% and 47% in 5 and 10 years, respectively)[41].

Trials regarding balloon angioplasty (ARTS, SOS)[42], as well as other revascularization techniques with intensive glycemic control[43] are in progress and is expected to be published soon. Until then, it is considered that CABG, as first choice in diabetic patients with multivessel CAD, is superior to balloon angioplasty.

The use of internal thoracic artery

The use of Internal Thoracic Artery (ITA) contributes significantly in the improvement of the postoperative result of CABG in diabetic patients[8,34,41,44,45]. The better postoperative late prognosis in the large studies BARI and EAST concerning balloon angioplasty in diabetic patients can be attributed in the use of ITA, whose patency can last for years and may be able to decrease the incidence of myocardial infarction[46,47]. The use of two ITAs does not appear to be associated with increased operative mortality, while it contributes to the improvement of late prognosis in diabetic patients, with or without pharmacologically treated DM[44]. On the contrary, there is a decrease in postoperative mortality and total morbidity from the use of two ITAs in the general population, as well as in diabetic patients specifically[48,49].

With regard to the incidence of sternal wound infection from the use of ITA in diabetic patients, there is no agreement in the literature. In a series, use of ITA did not increase incidence of this complication, even though sternal wound infection in this series was generally more frequent concerning the non-diabetic patients[68]. In another study it appeared that the use of ITA doubles the risk of this complication[84]. In some studies the rate of sternal wound infection is similar in diabetics and non-diabetic patients, whether one or two ITA are utilized[87,50]. With regard to the use of two ITAs, this increases five-fold the above mentioned risk according to a study[51]. This policy may increase the sternal wound infections, but it appears that this complication has in total low incidence (2.5% in patients with use of two ITAs versus 1.4% in those with use of one)[52]. It is suggested that skeletonization of ITA improves the sternal wound infection rates[93,53,54], while according to other authors the utilization of two ITAs should not necessarily be avoided in diabetic patients with CAD, provided that there is concern for the proper perioperative control of glucose[78.] In any case, it appears that the obese female diabetic patients are those that have the higher risk to present this complication[94].

Losing control of glycemia due to surgery

Surgery and cardiopulmonary bypass machine are related to a tendency of plasma glucose increase. The body responds to the operative stress (catabolic condition) with increased excretion of catecholamines, cortisol, ACTH, growth hormone, vasopressin and glucagon. At the same time, insulin excretion is decreased and insulin resistance is increased. These are followed by increased gluconeogenesis and glucogonolysis, protein catabolism, lipolysis and ketogenesis. The final result is plasma hyperglycemia and hyperosmosis[55]. Apart from the

induction to the anaesthesia and the surgical stress, use of cardiopulmonary bypass in CABG contributes even more in the suspension of insulin excretion. In the phase of hypothermia there is higher insulin resistance of the tissues, which is particularly increased in the rewarming phase. Moreover, use of hypothermia suspends temporarily the hepatic glucose production, which restarts at the rewarming phase[56,57]. Administration of catecholamines (inotropic agents) immediately after the operation in patients with low cardiac output, causes excessive insulin resistance, thus resulting to the need of excessively high doses of insulin for the regulation of glycemia (up to 20 U/h). As a consequence, there is an increase of the existing, due to the low cardiac output, metabolic acidosis and the base deficit, resulting to a difficulty of the inotropic agents to act in the low pH that evolves. The needs in insulin are probably increased as well due to the sulfhydrilic parts of its molecule that render it to be absorbable from the membrane of the oxygenator of the cardiopulmonary bypass machine[58,59]. Use of glucose solutions for priming the circuits of the extracorporeal circulation –a technique that was used in the old days– it is best avoided because it causes severe hyperglycemia[60,61]. The stabilization of the cardiovascular status of the patient is usually accompanied by lowering of the needs in insulin.

Control of hyperglycemia

In a diabetic patient that undergoes CABG we aim to maintain the blood glucose levels perioperatively between 90-180 mg/dl (5-10 mmol/l). When the intervention is scheduled, the perioperative management of these patients is easier. The insulin-dependent diabetics should receive their regular dose of insulin the evening before the operative day. In past days, the experts recommended a decrease in the dose of insulin the previous evening for the fear of hypoglycemia during surgery. However, according to our experience, such a policy usually results to an increase of blood glucose the next morning. Currently, there are facilities for the measurement of glucose rapidly, so the fear of hypoglycemia during the anesthesia is unjustifiable.

In major operations, only rapid action insulin is used, which should be given intravenously in a continuous infusion mode, because its absorption is not reliable when it is given subcutaneously[62]. With the slow infusion pump, administration of the exact dose is guaranteed. The intermittent intravenous infusion is not recommended[63]. Due to the increased urine production from the osmotic diuresis that it caused by the hyperglycemia and from the action of catecholamines to the cells, there is often the tendency for hypokalemia. The bolus intravenus insulin infusion can lead to abrupt lowering of potassium, which potentially increases the risk of dangerous arrhythmias[64].

The morning of the operative day, the insulin should not be given subcutaneously, unless the planning of the time of surgery allows the patient to eat breakfast. Generally, diabetics should be planned to be among the first patients that will be operated in the morning. A drip of dextrose 5% (150 cc/h) is placed and at the same time rapid acting insulin is given with a pump. Blood glucose levels should be measured hourly and it is necessary to adjust the dose of insulin, if plasma glucose falls out of the acceptable range of 90-180 mg/dl. Insulin dose infusion of 4-6 U/h is the rule during the operation. In obese patients and in operations with complications the doses that are required to control the blood glucose levels can reach the level of 10 U/h. Non-insulin dependent diabetics almost always need insulin during the perioperative period. If, however, the preoperative plasma glucose is in acceptable levels, then the insulin infusion may start with the beginning of the operation[65].

The initial hourly dose of insulin infusion in the non-insulin dependent diabetics is usually 2-3 units (basic hourly need of insulin), with an hourly check for the maintenance of its level <200 mg/dl[55]. If the glucose value is above 300 mg/dl, e.g. in emergency operations, the infusion starts with 0.1 U/Kg/h, which is equal to 5-10U/h[54]. For the insulin dependent patients the daily insulin dosage divided by 24 should be added in the initial hourly insulin dosage. With sufficient insulin infusion the expected decrease in blood glucose should be 60-120 mg/dl/h. With satisfactory hydration and good blood circulation, part of the excessive blood glucose can be cleared by the kidneys. If the insulin dose that is given causes marked decrease in blood glucose, then the hourly infusion of insulin should be doubled. On the contrary, if the value of plasma glucose is decreased excessively, then the insulin infusion should be decreased by 1-2 U/h. During the postoperative period in the ICU, the intravenous continuous insulin infusion should be continued, while the regulation of the hourly dose depends on the blood

glucose levels every two hours[52,54,55]. This policy should be followed for the insulin dependent, as well as for the non-insulin dependent patients until the late postoperative period, when the regular feeding of patient (usually the second postoperative day) begins. Postoperatively, in the ICU, as well as in the ward, the measurement of the blood glucose of the patient should be taken four times a day (before the main meals and at bed-time) or even more often.

Before the discharge, this regime is stopped and the patient returns to the regime that was followed preoperatively, provided that with this there was good glucose regulation. Otherwise a more flexible regime is recommended, e.g. three or four insulin injections a day[66]. In cases of postoperative infections, regulation of DM becomes difficult and particular care is required. In such cases, we have found effective the regime of continuous intravenous insulin infusion (3-5 U/h) in combination with subcutaneous doses of 15-20 U of rapid action insulin 20 min before the three main meals.

Continuous intravenous insulin infusion appears to result in the decrease of the risk of sternal wound infection. With "Portland CII Protocol", which aimed at plasma glucose <200 mg/dl, the risk of deep sternal wound infection was decreased considerably (2.5 fold) in the group with continuous intravenous insulin infusion. In this study, glucose level <200 mg/dl was achieved in 85% of patients with intravenous insulin infusion versus 47% of patients with the use of an algorithm for subcutaneous insulin infusion[80].

Glucose measurements

It should be stressed that blood glucose measurements can be done either with venous blood analyzed in the laboratory that has a coefficient of variation roughly ±2%, or with the use of small portable meters that have coefficient of variation roughly ±5-10%. Of course, the staff that uses these devices must be properly trained[54].

Treatment of electrolytes disturbances

Particularly important in diabetic patients perioperatively is the regulation of the electrolytes disturbances that probably coexist or can be caused from it. Generally, a poorly regulated diabetic patient has a lack of potassium and magnesium, which is aggravated if insulin is administered without administering electrolytes at the same time, thus leading to increased risk of serious arrhythmias postoperatively[67]. Moreover, the lack of magnesium, contributes to the increased insulin resistance of the tissues[68].

Solutions of glucose-insulin-potassium

The theory of improved myocardial function during CABG and decreased postoperative morbidity with the use of continuous infusion of glucose-insulin-potassium solution (GIK) perioperatively can be applied even in diabetic patients, resulting to a faster recovery from surgery. The technique includes administering a solution consisting of 500 ml DW 5%, 80 units of actrapid insulin and 40 mEq KCl in administration rate of 30ml/h, from the induction to anesthesia up to 12 hours postoperatively, ceasing only during the aortic cross-clamp time. The benefit from the use of these solutions in the ischemic perioperatively myocardium is based on the offer of ATP from the glucolysis of the exogenous glucose and the reduction of the free fatty acids, as well as on the effect of insulin via the L-arginin-NO route in the coronary circulation, resulting to vasodilation and to decreased vascular resistance[69].

Postoperative morbidity

Most researchers consider that DM is responsible for increased postoperative morbidity in CABG operations, such as neurological complications[6,62,65,70-72], renal complications[65,73], reopenings, increased need for blood transfusion65, arrhythmias, respiratory failure, use of intra-aortic balloon pump[74] and surgical wound infection[72,75,76].

As for the postoperative infections, it appears that even the short-term hyperglycemia can suppress the immune system, via non-enzymatic glucosyliosis of the circulating immunoglobulin[77]. Moreover, the hyperglycemia can cause decreased chemotaxis and reduced phagocytic ability[78]. Protein glucosyliosis in diabetics is related with increased collagenase activity and decreased content of the wound in collagen, resulting to the delay of the surgical wound healing[79]. On the contrary, the continuous intravenous insulin infusion improves significantly the decreased phagocytic ability of the neutrophil leukocytes of diabetics and improves the resistance to the postoperative infections[80,81]. Generally, DM has been proved to constitute an independent risk factor of postoperative surgical wound infection, which is 2 to 5-fold

more than that in non- diabetic patients[82]. The mean glucose value the first two postoperative days after open heart operations was found to be the most potent factor for sternal wound infection. Glucose levels more than 200 mg/dl in the two first postoperative days are related with increased incidence of sternal wound infection[83].

Moreover, combination of DM and obesity appears to be linked with increased postoperative morbidity, particularly surgical wound infections[80,84,85]. Some authors suggest that DM is not a prognostic factor of sternal wound complications, contrary to obesity and specifically with BMI (body mass index=weight/height^2) >27 that these autors consider as independent prognostic factors of infections after CABG[86].

Diabetic patients have longer duration of staying in the Intensive Care Unit after CABG compared to the non-diabetics[65]. Insulin-treated diabetics appear to have longer in-hospital stay compared to the non-insulin dependent diabetics and non-diabetic patients that undergo CABG. There is no difference in the in-hospital stay and in the cost of hospitalization in the non-insulin treated diabetics compared with the non- diabetics[87,88].

Early and late mortality

CASS study showed that the diabetic patients with CAD have higher mortality than the non-diabetics, while CABG has a protective result[89]. CABRI study showed better prognosis in diabetic patients who underwent CABG[90]. Nevertheless, from the first decade of establishment of CABG as a method of treatment for CAD, diabetics have higher operative mortality[91], a finding also confirmed by most of the recent studies, in which the total mortality in diabetic patients is 2.8-6.7% versus 1.6-3.0% in non-diabetics[5,6,92-94]. However, in other studies there is no difference between the groups[95-97].

Postoperative prognosis concerning the treatment of diabetes before surgery

The preoperative level of blood glucose was found to constitute an independent prognostic factor of late survival after CABG. The survival is worse in the insulin dependent patients[6,42,98,99], better in those who receive tablets and even better in those who are in diet control. Of course, the non-diabetic patients have the best prognosis[97]. According to another study, patients with DM and CAD appear to have higher mortality with the use of metformin alone or in combination with soulfonylurias[100]. The use of soulfonylurias is related to bad prognosis after balloon angioplasty[41,101] and to better late prognosis after CABG, while there is no survival difference between the insulin dependent diabetics and those who are in diet control[41]. In the UKPDS 33 study, the possibility of increased mortality after myocardial infarction in patients that receive soulfonylurias was not confirmed; in the UKPDS 34 study the use of metformin had higher benefit, with regard to the incidence of CAD in diabetic patients, while its use in diabetic patients with already established CAD worsened their prognosis[102]. Blockage of ATP-sensitive potassium channels (K-ATP) that it is caused from soulfonylurias prevents myocardial "preconditioning" in ischemic periods. However, why this phenomenon is important after balloon angioplasty and not after CABG is unknown[103]. Generally, because the evidence for this observation is limited, currently and until further clarification of the subject, the replacement of soulfonylurias with insulin some days before cardiac surgery is proposed[104].

Postoperative quality of life

With regards to the quality of life after CABG, DM appears to be a factor that has negative influence to it, despite the obvious postoperative improvement in the symptoms of the diabetic patient[105,106]. Generally, diabetic patients who underwent coronary bypass had longer survival and longer period free of symptoms compared to those who did not undergo surgery, while they had similar survival[l6,62] and they had more frequent recurrences of angina rather compared to the non-diabetic patients who underwent surgery. Moreover, survival was less in diabetics who did not undergo surgery compared to the non-diabetics who did not undergo surgery[107].

The worse morbidity and mortality after CABG in diabetic patients can be also be attributed to diabetic myocardiopathy. The latter is due to the long-lasting hypertension and hyperglycemia, that cause cellular changes –e.g. deficit in calcium transport and in fatty acids metabolism– and lead to myocell hypertrophy and myocardial fibrosis. This in turn results initially to diastolic and later to systolic dysfunction[108]. Moreover, the sudden deaths that occur in these patients may be also be due to the often coexisting diabetic neuropathy of the autonomous

nervous system[109]. The increased endothelin (ET-1) concentrations that have been found in diabetic patients who undergo CABG may contribute to the increased morbidity that they present[110,111]. Generally, the long-lasting effect of hyperglycemia causes endothelial dysfunction (even in coronary arteries), with the following consequences: decreased endothelial production of NO, decreased maximum coronary vasodilation and defective adaptation of the vasculature in increased myocardial needs. The above mentioned mechanisms most likely contribute to worse postoperative prognosis[6]. Endothelial dysfunction which exists when microalbuminuria is present, is an important prognostic indicator, not only of a possible future nephropathy, but also of cardiovascular morbidity and mortality[112-114].

Postoperatively, not only hyperglycemia but also for other cardiovascular risk factors should be treated. To treat hypertension in diabetics with CAD, ACE inhibitors appear to be superior, since they contribute to the prevention and treatment of left ventricular hypertrophy and the congestive heart failure. ACE inhibitors stabilize the atheromatous plaques in the coronary vessels and the prognosis of the patients is improved. Moreover, they contribute to the improvement of the vascular endothelial function[113,115,116]. B-blockers can also help in the treatment of hypertension and in the improvement of prognosis[117]. Finally, calcium antagonists, particularly dihydropyridines, can be used postoperatively especially in patients with arterial grafts, because they contribute to the prevention of the spasm of grafts[118,119].

After surgery, the regulation of LDL-cholesterol levels and other lipids is the main target[120]. As for the choice of the suitable treatment, it is accepted that statins decrease cardiovascular risk and the atheromatous dyslipidemia in diabetic patients, while as for fibrates –even though they perhaps increase the mortality that is due to non-cardiovascular reasons– the benefit that comes from their use in diabetic patients compensates their disadvantages[3].

Disturbances of platelet function and fibrinolysis are frequently present in diabetic patients, resulting to an imbalance between formation and lysis of clot and, thus to an increased tendency for thrombogenesis[121,122]. The benefit from the use of aspirin after surgery for the graft, as well as for the coronary artery patency is established[123]. The good long-term glucose control after surgery (low HbA1 levels), contributes to the minimization of hypercoagulable predisposition of diabetic patients[124].

Conclusions

Surgical revascularization as the first therapeutic option in at least patients with multivessel disease appears to be the best approach and is associated with very good results. The extensive literature that exists on the subject suggests that when CAD coexists with the DM, proper attention should be given during the surgical treatment of patients with such combination. These patients that constitute a high-risk group should be led, if possible, to an elective operation only when the level of glucose control is very good. Strict control of preoperative glycemia and avoidance of hyperglycemia during the perioperative period, are prerequisites for a successful surgical result. The frequent measurements of glucose with small portable meters and the continuous intravenous insulin infusion in rather high, but continuously adjusted, doses are simple but effective means for the successful completion of the intervention. A balanced diet is also essential for the uneventful postoperative metabolic status. At the same time, the other risk factors of atheromatosis should always be controlled aggressively.

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