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MEDIUM-TERM GLYCEMIC CONTROL IN DIABETICS BEFORE CORONARY BYPASS SURGERY

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Abstract The aim of this study was to determine the association between preoperative medium-term (60-90 days) glycemic control, as reflected by glycosylated hemoglobin levels (HbA1c), and the incidence of major complications (mediastinitis, perioperative infarction, heart failure, stroke and kidney failure dialysis) and mortality in diabetic patients undergoing elective coronary artery by-pass graft surgery (CABG). This study suggests that aggressive glycemic control three months before surgery, achieving HbA1c $\leq$ 7% improvement results with less postoperative morbidity and mortality.

Key words: coronary artery by-pass graft surgery, diabetes, glycosylated hemoglobin

Resumen ***Control de la glucemia a mediano plazo en diabéticos antes de la cirugía coronaria*****.** El propósito de este estudio fue determinar la asociación entre el control glucémico a mediano plazo, 2-3 meses previos a la cirugía cardiaca, evaluado mediante el dosaje de hemoglobina glicosilada (HbA1c), y la incidencia de muerte y complicaciones mayores (mediastinitis, infarto perioperatorio, insuficiencia cardíaca, accidente cerebrovascular e insuficiencia renal dialítica) en pacientes diabéticos tipo 2. Este estudio sugiere que el control glucémico 3 meses antes de la cirugía en pacientes con diabetes mellitus tipo 2, logrando HbA1c $\leq$ 7%, mejora los resultados en el posoperatorio observándose menor morbilidad y mortalidad.

Palabras clave: cirugía coronaria, diabetes, hemoglobina glicosilada

It is well known that poor glycemic control is the major risk factor for diabetic complications which results in high cost medical care for diabetic patients, and that HbA1c, as a measure of medium-term glycemic control, correlates with diabetic morbidity and mortality.

Current statistics estimate that out of 1.5 million revascularization procedures performed worldwide each year, 25% correspond to diabetic patients. These figures stress the enormous health care challenge represented by diabetic patients with coronary artery disease (CAD), therefore diabetes is a major risk factor for the development and progression of CAD[1-5].

Considering that post-coronary artery bypass graft (CABG) surgery morbidity and mortality are higher in diabetic patients than in non-diabetic patients, agressive glycemic control in the short term preoperative period significantly reduces major complications in diabetic patients undergoing open-heart surgical procedures[7-9]. However, the impact of the preoperative medium-term (60-90 days) glycemic control in diabetic patients undergoing cardiovascular surgery, in the context of an adequate control in the immediate postoperative period, is unknown.

The purpose of this study is to determine the association between preoperative medium-term glycemic control, as reflected by glycosylated hemoglobin levels (HbA1c), and the incidence of major complications and mortality in diabetic patients undergoing elective CABG surgery.

Materials and Methods

This study was approved by the *Comité de Ética y el Departamento de Investigación del Hospital Universitario Fundación Favaloro*.

For a period of two years, consecutive type II diabetic patients, defined as patients treated with insulin or oral hypoglycemic medications, undergoing planned CABG surgery were identified and screened to participate in this study. Adults 18 to 80 years of age were eligible for inclusion. Diet-controlled or type I diabetic patients, combined surgery and patients requiring urgent procedures due to unstable coronary syndromes were excluded. A total of 96 eligible diabetic patients were prospectively enrolled during this period.

Seventy-four non-diabetic patients who underwent elective CABG surgery during the same period were randomly selected as the control group.

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Before surgery, baseline standard laboratory studies and HbA1c measured using a validated immunoturbidimetric method (Roche-Diagnostics), were done.

In accordance with the American Diabetes Association guidelines[9] diabetic patients were stratified into two groups based on preoperatory medium-term glycemic control. "Optimal medium-term glycemic control" was defined as HbA1c ≤ 7%, and "suboptimal medium-term glycemic control" was defined as HbA1c > 7%.

Coronary surgery was performed, using standard techniques. The use of extracorporeal circulation was decided by the surgeon, according to the analysis of the coronary anatomy.

All patients were treated with aspirin before the surgery, which was followed by standard treatment with beta-blockers, inhibitors of angiotensin converting enzyme, aspirin and statins after the procedure. Other adjunctive pharmacotherapy was administered according to the clinical cardiologist criterion.

With the purpose of assuring glycemic values of less than 120 mg/dl in intensive areas and less than 150 mg/dl in non intensive areas, the Portland protocol[10] was used.

The composite primary endpoint of the study was hospital death and major complications. We consider hospital death the patient who died subsequent to CABG surgery during the same admission. We consider how major complications: perioperative myocardial infarction, defined as the presence of new Q waves on the follow-up electrocardiogram or elevation of creatine kinase over five times normal; mediastinitis, defined as an infection of the deeper tissues of the operative wound, which can also involve the mediastinal space; sepsis, defined as presence of two or more systemic inflammatory response syndrome (SIRS) criteria plus a presumed or confirmed source of infection; cardiac failure, defined as a cardiac index less than 2.0 or inotropic support 6 hours after the operation; acute renal failure, defined as an increase in serum creatinine, for at least 2 days, of (A) 0.5 mg/dl for patients with baseline serum creatinine level of less than 2.0 mg/dl, (B) 1.0 mg/dl with baseline 2.0 to 5.0 mg/dl, and (C) 1.5 mg/dl with baseline 5.0 mg/dl or higher; stroke defined as an acute neurologic deficit of presumed vascular origin lasting ≥ 24 hours, or the presence of brain infarction on neuroimaging.

The secondary endpoint was to analyze the postoperative length of stay (LOS) according to the preoperative medium term glycemic control. LOS was defined as number of days from the index operation to the date of discharge or death.

Statistical analysis was performed using the SPSS version 10 (SPSSInc, Chicago, IL)). Continuous variables are expressed as the mean $\pm$ SD and were analyzed for significant differences using one-way analysis of variance, when being compared among all three groups, or the two-tailed Student t test, when comparing between diabetic and non-diabetic patients and between diabetic patients with HbA1c ≤ 7% and those with HbA1c > 7%. Categorical variables were analyzed for significant differences, using Pearson's chi-square test or two-tailed Fischer exact test, as appropriate. In the diabetic cohort, all baseline characteristics, laboratory data, and angiographic parameters were analyzed to determine the independent predictors of major postoperative complications. All variables with a p value ≤ 0.2 were entered into a forward stepwise multiple logistic regression analysis to determine the most parsimonious subset of variables that best explained the occurrence of post-CABG surgery morbidity and mortality among diabetic patients. A p value ≤ 0.05 was considered statistically significant.

Results

A total of 170 patients who underwent CABG surgery were included (96 with diabetes and 74 without diabetes). Diabetic patients were stratified into two groups based on preoperatory medium-term glycemic control: Thirty eight patients with optimal glycemic control (HbA1c ≤ 7%), and 58 patients with suboptimal control (HbA1c > 7%). Patients without diabetes represented the control group.

The mean age was 63 ± 9 year, 85 % were male. Table 1 contains baseline characteristics of the whole group. Diabetic patients versus non-diabetic patients (control group): Non-diabetic patients were less likely to have peripheral vascular disease (p = 0.02), severe left ventricular function (p = 0.004) and congestive heart failure (p = 0.04). The mean age, gender, risk factors, and incidence of multivessel disease were similar between patients with and without diabetes. Both groups had low preoperative risk as measured by the Parsonnet score.

Diabetic patients with optimal versus suboptimal glycemic control: Diabetic patients with suboptimal glycemic control (HbA1c > 7%) were more often treated with insulin (31% vs. 10%). Both diabetic patients with HbA1c > 7% as well as those with HbA1c < 7% had similar risk factors, historical profile and preoperative according to the Parsonnet score. Angiographic analysis revealed no significant differences in the incidence of multivessel disease (Table 1). The mean A1c in the suboptimal glycemic group was 8.3 ± 1% whereas in the optimal glycemic group was 6.2 ± 0.4% (p = 0.0001). Hospital glycemic control in the short term postoperative period was similar in both groups (150.9 vs. 140.7 mg/dl, p = 0.2).

Analysis of the primary combined endpoint revealed no significant differences in the rate of major events between patients with optimal glycemic control (HbA1c < 7%) and patients without diabetes (control group) (5% vs. 8%, p = 0.6). However, the analysis in the diabetic group revealed significant differences in the rate of major complications between patients with suboptimal glycemic control (HbA1c > 7%) and patients with optimal glycemic control (A1c < 7%) (24% vs. 5%, p = 0.02). Hospital major complications rates are expressed in Table 2.

Multivariate analysis disclosed that HbA1c > 7% was a significant independent predictor of major complications (p = 0.02), Odds ratio 2.4; (95% confidence interval 1.1 to 2.5).

The analysis of the secondary endpoint revealed that HbA1c was significantly associated with postoperative LOS. Patients with suboptimal medium-term glycemic control (HbA1c > 7%) had more LOS than patients with optimal medium-term glycemic control (HbA1c < 7%) (mean postoperative LOS 6 days vs. 7.5 days; postoperative LOS mean rank: 32 days vs 46 days; p = 0.008).

Discussion

Our findings demonstrated that diabetic patients with HbA1c ≤ 7% at the time of CABG surgery had a

TABLE 1.– *Clinical characteristics in diabetic and nondiabetic patients*

	A1c > 7 (%) n 58	A1c < 7 (%) n 38	Non DM (%) n 74	% All groups n 170	Across groups	DM vs. Non DM	DM A1c>7 vs.< 7
Age (years)	64 ± 9	63 ± 8	62 ± 9	63 ± 9	0.4	0.2	0.6
Males	46 (79)	33 (87)	65 (88)	85	0.3	0.3	0.1
Hypertension	51 (88)	35 (92)	62 (84)	87	0.4	0.3	0.1
Current smoker	10 (17)	5 (13)	13 (18)	15	0.8	0.5	0.7
Hyperlipidemia	46 (79)	31 (82)	53 (71)	77	0.4	0.2	0.4
PVD	10 (17)	5 (13)	3 (4)	11	0.04	0.02	0.7
Stroke	4 (7)	1 (2)	2 (2)	4	0.4	0.7	0.6
MI	20 (35)	14 (37)	24 (32)	37	0.1	0.1	0.8
Renal failure	3 (5)	4 (10)	4 (5)	6	0.5	0.7	0.4
CHF	7 (12)	3 (8)	2 (2)	7	0.1	0.04	0.7
PTCA	10 (17)	9 (23)	15 (20)	20	0.7	0.9	0.4
LMCAD	15 (26)	9 (23)	19 (26)	25	0.8	0.5	1
Multivessel disease	52 (90)	31 (81)	57 (77)	82	0.1	0.4	0.7
Severe left ventricular function	12 (20)	6 (16)	3 (4)	12	0.01	0.004	0.7
Insulin treatment	18 (31)	4 (10)		13			0.02
Use of internal mammary artery	56 (96)	35 (92)	74 (100)		0.06	0.06	1
CE	4 (7)	1 (2)	6 (8)	6	0.5	0.5	0.6
EC	43 (74)	24 (63)	54 (73)	71	0.4	0.7	0.4
Body mass index (kg/m^2)	29 ± 0.5	28 ± 0.4	27 ± 3	28 ± 4	0.05	0.2	0.03
HbA1c (%)	8.3 ± 1	6.2 ± 0.4	5.7 ± 0.3	6.8	0.001	0.001	0.001
Parsonnet median	4	3.5	3		0.001	0.001	0.3

A1c: hemoglobin A1c; DM: diabetics; non DM: non diabetics; CHF: congestive heart failure; PVD: peripheral vascular disease; MI:myocardial infarction; PTCA: percutaneous transluminal coronary angioplasty; LMCA: left main coronary artery disease; CE: coronary endarterectomy; EC: extracorporeal circulation

TABLE 2.– *Hospital major complications rates. Differences*

	A1c >7 n 58 (%)	A1c < 7 n 38 (%)	Non DM n 74 (%)	Across groups	DM vs. non DM	DM A1c > 6 vs. < 7
All patientes with combined end point	14 (24)	2 (5)	6 (8)	0.007	0.1	0.02
Death	4 (7)	1 (2.5)	1 (1.3)	0.2	0.2	0.6
Mediastinitis	3 (5)	0 (0)	0 (0)	0.06	0.2	0.2
Sepsis	5 (8)	0 (0)	2 (2.6)	0.08	0.7	0.1
CHF	3 (5)	0 (0)	2 (2.6)	0.3	0.5	0.2
MI	4 (7)	1 (2.5)	1 (1.3)	0.2	0.2	0.6
Renal failure	6 (10)	0 (0)	3 (4)	0.07	0.7	0.07
Stroke	0 (0)	0 (0)	0 (0)			

A1c:hemoglobin A1c; DM: diabetics; non DM: non diabetics; CHF: congestive heart failure; MI: myocardial infarction

significantly lower rate of post-CABG surgery major complications and mortality than those with HbA1c > 7%. For each increase unit in the percentage of HbA1c the risk of major complications and death increases 2.4 times in post-CABG surgery patients. Furthermore, optimally controlled diabetic patients and non-diabetic patients have similar rates of post-CABG surgery major complications and mortality. These observations show the importance of medium term (60-90 days) preoperative glycemic control in the reduction of morbi-mortality after CABG intervention. Hyperglycemia after cardiac surgery is a common finding associated with the worse outcomes affecting both diabetic and non diabetic patients. Despite the large number of publications available, there is no universally accepted approach to this problem[11].

The relationship between suboptimal glycemic control 2-3 months before surgery and poor outcomes is yet to be understood. The mechanism of hyperglycemic harm on various cells and organ systems has been studied in multiple researches, but has not been studied in patients with suboptimal preoperative medium-term glycemic control. This study was not intended to definitively answer this question, however, on the basis of previously published literature; we have hypothesized that the possible harm mechanism derived from suboptimal glycemic control could be similar or equal to that in hyperglycemia. Hyperglycemia produces alterations in multiple systems such as: immune function with dysfunction[12], encouraging development of infections; ischemic preconditioning in the cardiovascular system[13] inducing cardiac myocyte death through apoptosis[14,15] blood pressure changes produced by catecholamine elevations; platelet hyperactivity[16,17] induced by elevated plasma fibrinogen concentrations and von Willebrand factor activity; induced inflammation with production of increased levels of IL-6, tumor necrosis factor (TNF)[18,19] and IL-18 levels[20]; and increased oxidative stress, and ROS generation, which causes cell and tissue injury[21].

In our patients, intraoperative and hospital glycemic control was similar in both groups, but it is possible that patients with suboptimal glycemic control could have an associated easier trigger mechanism of the harms mentioned above.

When analyzing the baseline characteristics, there were not statistically significant differences in the incidence of macrovascular complications between patients with HbA1C > 7 and < 7, probably because of the low number of samples.

Regarding the incidence of major complications, patients with previous poor metabolic control, tend to have higher diabetes-related complications that may influence adverse outcomes.

The most common complication in the postoperative period was acute renal failure. Compared with diabetic patients with HbA1c $\leq$ 7%, those with HbA1c > 7% had more incidence of renal failure, but which was not statistically significant (10 % vs. 0%; p 0.07).

While some of these adverse outcomes may be due to the baseline characteristics already mentioned, after analyzing all the variables with a $p \leq 0.2$ value into a forward stepwise multiple logistic regression, HbA1c persisted as a worse outcome independent risk factor.

In a secondary analysis, in the diabetic patients group, the HbA1c levels correlate with postoperative LOS. The patients with suboptimal glycemic control had longer LOS than the patients with optimal glycemic control. These data lead us to speculate that efforts to improve glycemic control before CABG surgery may reduce LOS and consequently both direct and indirect costs of CABG surgery for diabetic patients. Monisha Medh et al.[22] found similar LOS results in 143 patients who underwent coronary surgery.

Interestingly, we also found, in our study, that 60% of the patients who arrived to surgery had suboptimal medium-term glycemic control. There is an inadequate blood glucose control in this high risk patient group, despite the strict medical control that they should have before surgery.

The coronary anatomy analyzed by coronary angiography and ventricular function were similar among the 3 groups. It is also important to mention that the Parsonnet score of preoperative risk showed no differences between groups. All of the above help to confirm that the populations analyzed in our study were very similar, and that there is a real increase in complications in the group with suboptimal glycemic control.

As mentioned above, several studies noted the effectiveness of blood glucose control in the immediate postoperative period through the use of specific protocols, even in people without a prior history of diabetes such as those patients in the Van den Bergh[9] study.

The control of hyperglycemia in postoperative period reduces mortality, deep infections, dialysis requirement, time of mechanical ventilation and hospital stay.

In our study, intraoperative and hospital glycemic control was similar in both groups. In order to achieve this, as we have already mentioned, the Portland protocol was used.

In analyzing this study the fact that patients with poorer glycemic profile were in a more advanced stage of coronary atherosclerosis cannot be excluded. Moreover, diabetic patients often have multiple co-existing cardiovascular risk factors, so that the therapeutic efficacy of treatments aimed at reducing the overall cardiovascular risk (for example, lipid-lowering and antiplatelet therapy) should be considered. A limitation of the study is the small sample size. However, the results, support the realization of a prospective study to confirm these findings.

In conclusion, in this study we found a significantly higher rate of major complications and mortality in diabetic patients with preoperative suboptimal medium-term glycemic control. Furthermore, well-controlled diabetic patients had rates of adverse outcome comparable to those of non-diabetic patients.

These data suggest that aggressive treatment of diabetes to achieve HbA1c levels $\leq$ 7% may be beneficial to reduce the risk of major complications and death, and may improve the clinical outcome following CABG surgery.

Additional studies with a higher number of patients are needed to confirm our findings.

Conflict of interest: None to declare

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Es inútil repetir que las causas primeras escaparán siempre a nuestra investigación. El quid del universo no es más obscuro que el del alma; cualquier existencia es un enigma sin clave humana. Nuestra ciencia es ilimitada, en el sentido que aumentará sin tregua, mientras persistan las condiciones habitables en nuestro planeta. Es una serie infinita, un eterno caminar por una senda que no tiene término. Se habla siempre del pozo de la ciencia: adoptemos la metáfora. Hace millares de años que la humanidad se afana por desaguar el pozo y ver su fondo: mide por siglos la profundidad del agua restante y el nivel resulta siempre igual. Sin embargo, no puede negarse que aumente el caudal extraído, pero el que queda se alimenta con las filtraciones invisibles de la tierra. La ciencia adelanta, pero hay que perder la esperanza de agotar jamás nuestra ignorancia. No tocaremos con el dedo lo absoluto.

Paul Groussac (1849-1929)

Enfermedades de la voluntad. El viaje intelectual. Primera serie (1904). Buenos Aires: Simurg, 2005, p 345-6