Interactions between Hyperglycemia and Prior Ischemic Events in Patients Undergoing Percutaneous Coronary Revascularization: Contrasting Evidence from Bench and Bedside?

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Abstract

Objectives and Background: Many clinical studies have established an increased risk of death and myocardial infarction in patients with diabetes mellitus (DM) undergoing percutaneous coronary intervention (PCI), experimental evidence is increasingly suggesting a greater resistance of diabetic animals to ischemic injury. Whether this holds true also in humans is debated.

Methods: Consecutive patients undergoing PCI in our centre between July 2002 and June 2004 were divided into 4 groups: patients with DM and a history of myocardial ischemia (i.e. prior myocardial infarction [MI] or prior coronary revascularization) were included in the diabetes and ischemia (DI) group, those with DM but without prior ischemia in the diabetes only (DO) group, those with previous ischemia but non diabetic in ischemic only group (IO) and non-diabetics without ischemia in the ND group. The primary outcomes were 30-day and at least three years rates of death, myocardial infarction, or repeat revascularization.

Results: A total of 152 patients were included in the DI group, 173 in the DO group, 449 in the IO group and 836 in the ND group. Overall, patients belonging to DI groups had higher rates of risk factors, but did not report higher incidence of adverse outcomes, both at short and at long term follow-up.

Conclusions: Clinical evidence suggests a neutral interaction between diabetes and previous ischemic injury, thus paving the way to establish if the presence of previous cardiovascular events influences the cogency of different glycemia target level protocols.

Keywords: Coronary artery disease; Diabetes mellitus; Myocardial ischemia; Percutaneous transluminal coronary angioplasty

Introduction

Diabetes mellitus (DM) is considered not only a risk factor for coronary artery disease but a coronary artery disease equivalent [1]. Actually patients with diabetes mellitus tend to have worse outcomes after percutaneous coronary intervention (PCI) than non diabetic patients [2-7], thus proving negative clinical relation between exposition to high level of glucose and cardiac ischemia [8-13]. Nonetheless, there is contrasting evidence about target level of glucose to pursue for patients undergoing PCI, without a clear benefit related to an aggressive glucose lowering strategy [14-18,38]. Counterintuitive experimental research proved that diabetes seems to be protective for ischemic heart in animal models, through increased expression of cell survival proteins and decreased infarct size [19], greater plasticity and cellular resistance to injury [20] and the enhanced myocardial activity against oxidative damage during both ischemia and reperfusion [21].

To our knowledge no observational studies performed on patients have investigated value and degree of interaction between diabetes mellitus and cardiac ischemia. In order to address this issue, we retrospectively analyzed an unselected population undergoing PCI in our center.

Methods

The present retrospective study included all consecutive patients undergoing PTCA in our centre between July 2002 and December 2004.These patients were first divided into 2 cohorts: in the first diabetic patients, both insulin and non insulin dependent, and in the second non diabetic patients. Moreover they were divided into 4 groups: patients with DM and a history of myocardial ischemia, that is a prior myocardial infarction (MI) or a prior percutaneous or surgical revascularization, were included in the diabetes and ischemia (DI) group, those with a diagnosis of DM without ischemia in the diabetes only (DO) group, those with previous ischemia but non diabetic in ischemic only group (IO) and non-diabetics without an history of ischemia in the ND group. All patients provided written informed consent for the procedure, and ethical approval was waived given the retrospective observational design.

All patients were pre-treated with aspirin, 100 mg once daily, and clopidogrel 75 mg once daily or ticlopidine 250 mg twice daily at least three days before the procedure. A loading dose of 300-600 mg of clopidogrel and 250-500 mg of aspirin were given to patients not pre-treated. At the start of the procedure, unfractionated heparin was administered at a dose of 70-100 UI/KG to achieve an activated clotting time ≥ 250 seconds. The use of glycoprotein IIb/IIIa was left to the discretion of the operators. Coronary vasodilators (nitroglycerin) have been routinely used both pre and post-procedure. Coronary angioplasty and stent implantation were performed according to the current practice and technical guidelines.

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The diagnosis of diabetes mellitus was made according to the WHO Consultation [20]. The primary outcomes were rates of death, MI (defined as Q-wave or non Q-wave with elevation of total CK-MB 2 times above the upper limit of normal), or repeat revascularization. In order to assess all procedural and in-hospital outcomes, we consulted our institutional electronic database and individual patient charts. We recorded short term outcomes with at least 3 years of follow up, performed with phone calling, ambulatorial visits or or formal query of primary care physicians

Continuous variables were expressed as mean±standard deviation and were compared with ANOVA, with a provision to perform additional Gosset t tests with Bonferroni adjustment in case of overall $p<0.05$. Categorical variables were presented as counts and percentage and were compared with the chi-squared test, with a provision to perform additional chi-squared tests with Bonferroni adjustment in case of overall $p<0.05$. Statistical significance was set at the two-tailed 0.05 level. Computations were performed with SPSS 11.0 (SPSS, Chicago, IL, USA).

Results

A total of 1610 patients were identified: 403 had diabetes, and 1207 were non-diabetic. Thus 152 patients were assigned to the DI group, 173 to the DO, 449 patients to the DI group and 836 to the ND group. Clinical, angiographic and procedural characteristics were summarized, respectively, in Table 1 and Table 2.

While non diabetic patients were more likely to be male, diabetic patients more frequently reported in their history a diagnosis of hypertension, renal failure or heart failure in addition to higher rates of previous surgical revascularization. During coronary angiography small vessel disease was more frequently found in diabetic people (35.2% vs 22.9%, $p<0.001$): moreover the number of diseased vessels and number and length of stent length were higher in people with diabetes mellitus.

Short term outcomes are reported in Table 3 and Table 4. Both

at short and long term follow up patients belonging to DI groups did not show higher rates of death and AMI and percutaneous revascularization among the four groups, also when stratified for admission diagnosis. The only significant difference was the lower incidence of short term incidence of AMI in patients presenting with unstable angina or NSTEMI between non-diabetic patients (1.8% vs 0.5% vs 5.4% and vs 3.8%; $p=0.049$), and of long term incidence of target vessel revascularization of patients with diabetes mellitus, or a previous ischemia or both (29.5% vs 25.3% vs 25.3% vs 17.5%; $p<0.001$)

Discussion

Diabetes mellitus is an important risk factor burdened by higher rates of cardiovascular events but in our article its negative impact was attenuated after dividing patients according to the presence or not of previous cardiovascular ischemia.

Actually the negative effect of diabetes mellitus has been widely supported [2-11], as outlined in our registry. Death and myocardial infarction were more likely to be reported in patients with diabetes, probably both because of its proved negative effects on cell survival [23] and because of higher rates of important co morbidities like renal failure [25], previous coronary artery bypass graft [26], peripheral artery disease [27] and small vessels [28].

On the contrary a clinical endorsement to experimental positive interaction between exposure to both previous ischemia and high glucose levels could be elicited from our results. Actually while experimental data arise from biological background [19-21], their main limit is that they are performed in a non-human clinical setting. Moreover many studies performed in clinical setting have demonstrated a negative predictive value both for previous ischemia [25-28] and for diabetes mellitus in the setting of coronary revascularization [2-12]. Our article on the contrary demonstrated that the combination of both these risk factors did not play a negative role for our patients. This could be related to the protective effect of antischemical drugs [29-32], but also to the previous reported biological correlation [33].

Variable	DI (diabetes and ischemia) N=152	DO (diabetes only) N=173	IO (ischemic only group) N=449	ND (nor diabetic nor ischemia) N=836	P
Age, years	70±8	71±10	69±8	72±7	0.119
Male gender	76.2%	70.3%	82.6%	76.2%	0.006
Hyperlipidemia	65.5%	60.6%	71.8%	61.3%	0.003
Hypertension	86.4%	76.8%	79.3%	75.6%	0.031
Smoke Current smoker Former smoker Ever a smoker	52.1% 37.5% 10.3%	65.0% 22.5% 12.5%	53.1% 34.0% 12.9%	51.4% 26.6% 22-0%	<0.001
Renal failure	17.7%	18.5%	6.9%	8.7%	<0.001
Left ventricular ejection fraction ≤35%	15.9%	9.9%	11.4%	9.0%	0.124
Congestive heart failure	10.4%	5.4%	5.3%	5.8%	0.167
Peripheral artery disease	19.3%	13.9%	13.5%	9.4%	0.05
Indication Silent ischemia/stable coronary artery disease	21.3% 38.5%	23.3% 35.4%			0.058 0.081
Unstable coronary artery disease Non-ST-elevation myocardial infarction	14.5%	13.7%			0.387
ST-elevation myocardial infarction Other	21% 4.7%	20.3% 7.3%			0.479 0.109
Primary percutaneous coronary intervention	7.5%	18.1%	5.0%	22.8%	0.235

Table 1: Baseline features comparing patients with vs those without diabetes mellitus (DM).

Variable	DI (diabetes and ischemia) N=152	DO (diabetes only) N=173	IO (ischemic only group) N=449	ND (nor diabetic nor ischemia) N=836	P
Chronic total occlusion	43.4%	22.0%	37.0%	21.6%	<0.001
In stent-restenosis	12.6%	4.1%	16.7%	3.5%	<0.001
Coronary perforation	0.7%	0.6%	0.5%	0.5%	0.987
Unprotected left main coronary artery	8.1%	6.4%	12.0%	8.5%	0.097
Bifurcation	23.4%	18.9%	17.5%	16.4%	0.215
Saphenous vein graft PCI	13.5%	0%	4.7%	0.7%	<0.001
Thrombosis	3.6%	11.3%	4.8%%	14.2%	<0.001
Vessels <2.75 mm	38.0%	29.1%	25.8%	23.7%	0.003
American College of Cardiology/American Heart Association type C lesion	26.4%	21.5%	25.5%	14.6%	<0.001
Total number of diseased vessels	2.36±0.73	2.07±0.78	2.24±0.770	1.94±0,813	0.029
Total number of treated vessels	1.68±0.83	1.69±0.75	1.73±0.737	1.63±0.727	0.318
Total number of target lesions	2.54±1.48	2.42±1.44	2.39±1.27	2.26±1.32	0.006
Total number of stent	2.73±1.71	2.54±1.62	2.31±1,34	2.30±1,49	<0.0001
Total length of stent (mm)	42.70±29.18	35.95±24.8	33.90±22.41	32.61±21.70	<0.0001
Total BMS number	1.77±2.33	1.78±1.44	1.59±1.39	1.64±2.082	0.018
Total BMS length (mm)	36.10±24.75	29.38±17.98	29.03±20.75	29.29±21.44	0.082
Total DES number	0.66±1.92	0.76±1.23	0.72±1.12	0.66±1.78	0.035
Total DES length (mm)	35.89±29.2	30.46±21.18	29.46±19.44	30.26±20.34	0.730
Intra-aortic balloon pump	1.3%	1.8%	2.1%	1.2%	0.714
Intravenous glycoprotein IIb/IIIa inhibitors	18.2%	34.1%	13.5%	25.3%	<0.001

BMS=bare-metal stent; DES=drug-eluting stent

Table 2: Angiographic features comparing patients with vs those without diabetes mellitus (DM).

Variable	DI (diabetes and ischemia) N=152	DO (diabetes only) N=173	IO (ischemic only group) N=449	ND (nor diabetic nor ischemia) N=836	P
Death	2.3	1.4%	1.1%	2.7%	0.389
AMI	5.3%	2.7%	1.3%	2.5%	0.077
Percutaneous revascularization	8,7%	3,4%	13.3%	24.8%	0.035 P<0.05 between ND and DO
Silent ischemia/stable angina					
Death	0.0%	0.0%	0.0%	1.1%	0.630
AMI	3.0%	3.6%	0.0%	1.8%	0.277
Percutaneous revascularization	25.0%	8.0%	15%	18.8%	0.346
Unstable Angina/Non ST Segment Elevation Myocardial Infarction					
Death	1,3%	1,4%	1,6%	1,5%	0.989
AMI	5,4%	3,8%	0,5%	1,8%	0.049 P<0.005 between ND and DI; DO and IO
Percutaneous revascularization	14,3%	4,5%	15,6%	18,2%	0.499
ST Segment Elevation Myocardial Infarction					
Death	0%	2,6%	0%	5%	0.542
AMI	0%	0%	3,6%	0%	0.410
Percutaneous revascularization	50%	45%	40%	37,9%	0.585

Table 3: Thirty-day outcomes.

One of the main clinical applications of all the previously cited work is to perceive the target level of glucose to be achieved in diabetic patients undergoing PCI [37]. Actually no evenness of results has been achieved, in different clinical settings. For example in the DIGAMI trial, who was the only experimental work to report a mortality reduction for patients with a tight glucose control [17], about 35% of patients had a history of previous cardiac ischemia, while in the DIGAMI 2, in which this benefit disappeared, more than 50% of patients reported previous cardiovascular events or interventions [18]. Many explanations have been reported [14-18,38], and a possible reason of this variability is that clinical history of the patients could have influenced these outcomes:

these data and their interpretation should be evaluated in the ongoing trials [34-36].

This study has several founding limitations, including the retrospective nonrandomized design and the descriptive aim. Moreover information about drug taken from our patients and their glucose blood level are lacking, thus this article should be viewed as hypothesis-generating only.

Conclusions

Diabetes mellitus and previous cardiac ischemic injury interplay an

Variable	DI (diabetes and ischemia) N=152	DO (diabetes only) N=173	IO (ischemic only group) N=449	ND (nor diabetic nor ischemia) N=836	P
Death	20.6%	16.6%	14.2%	16.6%	0.361
AMI	13.7%	8.7%	9.5%	8.8%	0.359
rePTCA TVR	29.5%	25.3%	25.3%	17.5%	<0.001
rePTCA non TVR	22.5%	16.4%	16.5%	15.3%	0.257
CABG	4.6%	2.7%	2.3%	2.3%	0.507
Stroke	1.5%	2.7%	3.1%	3.1%	0.788
Stent thrombosis	3.1%	1.4%	3.1%	1.9%	0.489

Table 4: Long term outcomes.

indifferent interaction in our study, thus fostering further researches in order to establish if patients' cardiovascular history could influence the effectiveness of different glycemia target level protocols.

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