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Insulin Resistance and Hyperglycaemia are Associated With Recurrent Stenosis in Diabetic Patients After Percutaneous Coronary Intervention

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Background: The objective of the present study was to investigate the influence of insulin resistance and hyperglycaemia on restenosis after percutaneous coronary intervention in diabetic patients with coronary artery disease and coronary lesions eligible for balloon angioplasty.

Methods: Percutaneous coronary intervention was carried out in 218 diabetic patients. Prior to percutaneous coronary intervention we analysed the association of diabetes-associated metabolic factors reflecting on: (1) glycaemic control (haemoglobin A1c, fasting glucose), and (2) insulinaemia (C peptide) and restenosis after percutaneous coronary intervention. Primary combined endpoint was angiographic target lesion revascularization (TLR) at 6-month follow-up and major adverse cardiac events (MACE).

Results: In 85.8 % of cases, a follow-up coronary angiogram was obtained. MACE was 8.5 %, without significant difference between diabetic patients with or without advantageous glycaemic control. Advantageous glycaemic control was associated with significantly lower TLR in insulin-treated diabetic patients (independent of insulin resistance) and in non-insulin-treated diabetic patients without insulin resistance.

Conclusion: Insulin-treated and insulin resistant non-insulin treated diabetic patients have less restenosis if glycaemic control is advantageous. Optimization of measures against insulin resistance and glycaemic control before angioplasty can likely reduce restenosis after percutaneous coronary intervention. *J Clin Basic Cardiol 2002; 5: 241–6.*

Key words: diabetes mellitus, coronary artery disease, percutaneous coronary intervention, restenosis, hyperglycaemia, insulin resistance

We have learned from experience to date that restenosis after percutaneous coronary intervention is more common among diabetic patients, and that adverse long-term clinical outcome is associated with recurrent coronary stenosis [1]. Although various studies have revealed no differences in periprocedural angioplasty results, long-term outcome after balloon angioplasty is inferior in diabetic compared to non-diabetic patients, with divergence of the angioplasty-outcome curves within the period of highest risk for restenosis after percutaneous coronary intervention (first 6 months) [2].

Analogous to experience with non-diabetic patients, the restenotic process in diabetic patients originates from morphological, angioplasty-procedural, and other heretofore unknown constituents. We have by now learned that each constituent of the angioplasty related restenotic process can feasibly be influenced by the diabetes-specific metabolic state: 1) The initiatory platelet aggregation at the injured site: In diabetic patients, platelets are more frequently activated and exhibit greater adhesion, synthesis of thromboxane A_2, aggregability, and mitogenic activity. The levels of circulating fibrinogen and factor VII are furthermore elevated, while plasma-fibrinolytic and antithrombin-III activities are diminished [3]. 2) Diabetes-associated endothelial dysfunction promotes restenosis through thrombosis, vasoconstriction, and exposure of medial cells to circulating mitogens [4]. 3) Increased smooth-muscle-cell proliferation and extracellular matrix formation on the basis of increased diabetes-associated expression, activity, and responsiveness to various circulating growth factors [4].

For investigation of diabetes-associated metabolic influence on the different constituents of the angioplasty-related restenotic process, as well as additional effects from insulin resistance in diabetic patients, it is necessary to determine in clinical practice the interdependence among diabetes-associated metabolic state, insulin resistance, and restenosis after percutaneous coronary intervention. In the clinical study described below we investigated the association among the following diabetes-associated metabolic factors: glycaemic control, insulinaemia (reflecting insulin resistance), and the incidence of recurrent stenosis in diabetic patients after percutaneous coronary intervention.

Methods

Between January 1999 and December 2000, all diabetic patients on drug- or insulin-therapy admitted to the Department of Cardiology for percutaneous coronary intervention for stable or unstable angina and more than 10 days after an acute myocardial infarction without previous revascularization, were enrolled into the study. The study design included: 1) Informed consent, 2) investigation of all enrolled patients accordingly their diabetes-associated variables with focus on their glycaemic status, and status of insulinaemia, broken down into groups with favourable or unfavourable status of their metabolic factors on the basis of the arbitrary cut points shown in Table 1. The arbitrary cut points were determined before the beginning of the study according to the definition of normal and abnormal values of the measured parameters of the laboratory (Institut fuer Klinische Chemie, EMA-University, Greifswald) used for analysis of the blood samples. 3) Analysis of the continuous measurements of the diabetes-associated metabolic variables, as an indication of glycaemic control (haemoglobin A1c and fasting glucose) and of insulinaemia (C-peptide) including implementation into a multivariate model.

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Definitions

We analysed the primary combined endpoint of the study-population – ie, target lesion revascularization (TLR) and major adverse cardiac events (MACE) – in groups with respect to their glycaemic status (fasting-glucose; HbA1c) and status of insulinaemia (C-Peptide) as shown in Table 1 and in addition separately according whether they were insulin-treated (insulin-treatment) or not (no-insulin treatment).

Individuals with an elevated C-peptide have more than normal beta cell secretory function, which was rationalized as characteristic for evidence of insulin resistance.

For all analysed groups we performed comparison with baseline characteristics. Patients were classified as having diabetes on the basis of their medical history and of diabetes medication taken (insulin or oral therapy). Patients only on diet treatment of diabetes were excluded. The left ventricular ejection fraction (LV-EF) was measured by echocardiography using Simpson's method (apical four-chamber view). Arterial hypertension was defined according to the pertinent WHO criteria [5].

Angioplasty Procedure

We performed all angioplasty procedures (balloon angioplasty and stent implantation) by standard techniques. Other devices and techniques were excluded. We determined the reference coronary segment diameter (target vessel) by quantitative angiographic analysis (Cardiovascular Angiography Analysis System II [CAAS II QCA], Pie Medical Imaging BV, Netherlands), as described elsewhere, and with previously stipulated and validated edge-detection algorithms using a catheter for calibration [6, 7]. Angioplasty was carried out by blinded high-volume interventional cardiologists who had no information on the patients, on any of their laboratory results, or on their diabetes therapy. Stent implantation in diabetic patients was considered in the same manner as for non-diabetic patients (dissections > Type C, strong recoil with > 50 % luminal loss), on the basis of decisions reached by the interventionists. Procedural success was defined as < 50 % residual stenosis after PTCA, without major catheterization laboratory complications (death, emergency bypass surgery, or sustained coronary occlusion), and with non-impaired antegrade flow assessed on the basis of the thrombolysis-in-myocardial-infarction scale (TIMI). Clinical success was defined as obtaining residual stenosis < 50 %, survival of the hospital period without myocardial infarction (MI; Q wave or non-Q wave) including elevation of creatine kinase (CK) levels greater than twice the normal laboratory values, abnormal MB fractions, development of new pathologic Q waves on the ECG, or the need for repeat angioplasty or bypass surgery. Because GPIIb/IIIa-antagonists were administered during the study period only under exceptional conditions, none of the study-patients received these antagonists.

Data Collection

Baseline characteristics as well as demographic, clinical, angiographic, and procedural data were recorded prospectively on standardized forms and entered into a computerized data base.

Table 1. Definition of the arbitrary cut points (favourable; unfavourable) of the investigated diabetes-associated metabolic factors (HbA1c; fasting-glucose; C-Peptide)

	Favourable	Unfavourable
HbA1c	≤ 6.7	> 6.7
Fasting-glucose (mmol/l)	≤ 6.0	> 6.0
C-Peptide (nmol/l)	≤ 1.32	> 1.32

To detect possible bias by factors influencing restenosis, we collected data on the following: gender, age, history of diabetes and arterial hypertension, body mass index, cholesterol values for high and low-density lipoproteins (HDL/LDL), left ventricular ejection fraction, severity and extent of lesion distribution resulting from coronary artery disease, stenosis morphology, previous myocardial infarction, condition of infarct-related arteries, unstable angina pectoris, creatine kinase values, as well as reference coronary diameters of treated coronary vessels. Stenosis morphology was classified as type A, B1, B2, or C stenosis according to AHA/ACC guidelines [8].

Follow-Up

After 6 months we obtained follow-up information by performing coronary angiography. Coronary angiograms were obtained in a routine manner by experienced cardiologists, who had no information about patients including laboratory results or diabetes-treatment. Angiograms were evaluated by digital calipers or visual assessment. At follow-up we once again analysed haemoglobin A1c, fasting-glucose, and C-peptide.

Primary combined study endpoints were target-lesion revascularization (TLR) and major adverse cardiac events (MACE). Target lesion revascularisation was defined as significant restenosis of the previously dilated segment (target lesion), with need for revascularization either by re-angioplasty or coronary artery bypass graft. Major adverse cardiac events (MACE) were defined as cardiovascular death, unstable angina pectoris, or myocardial infarction (Q and non-Q wave), including elevation of creatine kinase (CK) levels greater than twice the normal laboratory values with any abnormal MB fraction and the development of new pathologic Q waves on the electrocardiogram. A non-Q wave MI was defined as the development of similar CK elevations without Q waves. Unstable angina was defined as new-onset, crescendo, rest, or postinfarction angina.

Statistical Analysis

Baseline characteristics were analysed for all analysed groups. Results are expressed as proportions or mean value ± standard deviation (SD). Differences in categorical variables were analysed by chi-square analysis or Fisher's exact test, and differences in continuous variables by Student's t-test. Target lesion revascularization rate (TLR) and major adverse cardiac events (MACE) were determined for the total population, as well as for each subgroup. Significant statistical differences were assumed when $p = 0.05$. Continuous variables were included in a multivariate model.

Results

93 of the 218 enrolled patients were insulin-treated diabetic patients (42.7 %) and 125 non-insulin-treated diabetic patients (57.3 %). In 85 patients (39.0 %) a stent had been implanted. Invasive 6-month follow-up data were available for 187 patients (85.8 %). Their demographic baseline data are shown in Table 2. Thirty-one patients had no angiographic follow-up: 26 of the 31 patients did not show up at follow-up due to personal reasons, 5 of the 31 patients died during the follow-up period: 1 patient (0.5 %) due to cardiac causes, 1 patient (0.5 %) due to neurologic causes and 3 patients (1.3 %) due to other causes. In 25 of the 187 patients with angiographic follow-up, follow-up coronary angiograms had been performed prematurely as a result of symptoms such as angina (14 patients with unstable angina) and ischaemia. At follow-up, 11 of 187 patients (5.8 %) experienced a change in

at least one analysed metabolic factor from unfavourable to favourable (4.2 %), or from favourable to unfavourable (1.6 %). Study endpoints were analysed for all 187 patients with angiographic follow-up.

Baseline Comparisons: The baseline characteristics of the separately analysed groups are shown in Table 2. In the C-peptide groups, diabetic patients with no remaining insulin production (type-1 diabetic patients) were excluded. Procedural success rates did not differ among the analysed groups (Tab. 2).

Glycaemic control (Haemoglobin A1c): Those demonstrating an unfavourable HbA1c level were similar in this respect to those with favourable HbA1c levels (Tab. 2). Among the many comparisons, however, C-peptide values differed significantly between the unfavourable and favourable-HbA1c groups (Tab. 2).

Glycaemic control (fasting glucose): Those demonstrating an unfavourable fasting-glucose level were similar in this respect to those with favourable fasting glucose levels (Tab. 2).

Endogenous Insulin-values (C-peptide): Those who exhibited an unfavourable C-peptide level were similar in results to those with a favourable C-peptide-level, but significantly more insulin-treated diabetic patients (type-1 diabetic patients excluded) and fewer non-insulin-treated diabetic patients were in the favourable C-peptide group (Tab. 2).

Angiographic Follow-Up

Invasive 6-month follow-up data were obtained by angiography for 187 patients (85.8 %).

Target-lesion revascularization: Angiographic target-lesion revascularization rates (TLR) for the different groups are shown in Figure 1.

Sub-analysis (centered on insulin treatment) revealed significantly higher target lesion revascularization rate for insulin-treated diabetic patients in the unfavourable HbA1c and fasting-glucose groups (Fig. 2). Non-insulin-treated diabetic patients in the favourable-HbA1c and fasting-glucose groups revealed significantly higher target lesion revascularization rate (Fig. 2).

Analysis considering endogenous insulin-values showed significant differences in target lesion revascularization rate in patients with or without favourable C-peptide values (Fig. 1). The more detailed subanalysis performed for insulin treatment in this group showed a significantly higher target lesion revascularization rate for insulin-treated diabetic patients (type-1 diabetic patients excluded) and non-insulin-treated diabetic patients for the patient group with insulin resistance (Fig. 2).

Although continuous C-peptide values did not differ significantly between diabetic patients with a favourable or unfavourable HbA1c or fasting-glucose in diabetic patients without relevant restenosis (no-TLR) (Tab. 3A), C-peptide values were significantly higher in non-insulin-treated diabetic patients and relevant restenosis (TLR), who had favourable HbA1c and fasting-glucose, while no differences in continuous C-peptide values were detected in insulin-treated diabetic patients (Tab. 3B).

Multivariate analysis revealed that, in contrast to non-insulin-treated diabetic patients with insulin resistance, the predictability of target lesion revascularization rate is lower for those non-insulin-treated diabetic patients without insulin resistance if glycaemic control is favourable (Tab. 4A).

In insulin-treated diabetic patients, the difference in target lesion revascularization rate slightly increased between those

Table 2. Patients' characteristics of the 187 follow-up patients at baseline

	HbA1c (%)			Fasting-glucose (mmol/l)			C-Peptide* (nmol/l)		
	≤ 6.7	> 6.7	p-value	≤ 6.0	> 6.0	p-value	≤ 1.32	> 1.32	p-value
N =	86	101		76	111		99	68	
Age (years)	66.4 ± 10.6	65.9 ± 10.8	n.s.	61.9 ± 11.0	68.1 ± 12.2	n.s.	65.1 ± 10.0	67.0 ± 11.1	n.s.
Male (%)	77.9	78.2	n.s.	77.6	76.6	n.s.	77.8	77.9	n.s.
Stent implantation (%)	43.0	48.5	n.s.	44.7	45.9	n.s.	44.4	44.1	n.s.
No insulin treatment (%)	53.5	54.5	n.s.	51.3	55.9	n.s.	54.5	67.7	< 0.1
Insulin treatment (%)	46.5	45.5	n.s.	48.7	44.1	n.s.	45.5	32.3	< 0.05
Diabetes history (years)	10.5 ± 6.2	11.8 ± 6.8	n.s.	11.1 ± 7.8	12.0 ± 7.9	n.s.	12.8 ± 8.0	9.9 ± 6.5	< 0.1
Hypertension (%)	34.9	36.6	n.s.	35.5	36.0	n.s.	32.3	36.8	n.s.
LV-EF	48.3 ± 19.0	47.9 ± 20.0	n.s.	47.0 ± 18.5	50.1 ± 21.1	n.s.	49.9 ± 18.9	48.5 ± 17.9	n.s.
HDL (mmol/l)	1.2 ± 0.4	1.4 ± 0.5	n.s.	1.1 ± 0.4	1.1 ± 0.5	n.s.	1.2 ± 0.4	1.0 ± 0.4	n.s.
LDL (mmol/l)	3.6 ± 1.4	3.8 ± 1.3	n.s.	3.5 ± 1.2	3.6 ± 1.2	n.s.	3.4 ± 1.3	3.5 ± 1.2	n.s.
C-peptide* (pmol/l)	934 ± 121	770 ± 111	n.s.	890 ± 135	830 ± 117	n.s.			
CAD 1-vessel (%)	37.2	34.6	n.s.	38.1	38.7	n.s.	34.3	33.8	n.s.
2-vessel (%)	32.6	33.7	n.s.	31.5	32.4	n.s.	31.3	30.9	n.s.
3-vessel (%)	30.2	31.7	n.s.	30.3	28.8	n.s.	34.3	35.3	n.s.
Stenosis morphology									
A (%)	18.6	19.8	n.s.	21.0	19.8	n.s.	21.2	20.6	n.s.
B_1 (%)	57.0	54.4	n.s.	55.3	57.7	n.s.	55.6	57.3	n.s.
B_2 (%)	16.3	13.9	n.s.	15.8	16.2	n.s.	14.1	16.2	n.s.
C (%)	8.1	11.9	< 0.1	7.9	6.3	n.s.	9.0	5.9	< 0.1
RCSD (mm)	2.5 ± 0.4	2.6 ± 0.4	n.s.	2.5 ± 0.3	2.5 ± 0.4	n.s.	2.5 ± 0.4	2.5 ± 0.3	n.s.
Infarct related artery (%)	7.0	7.9	n.s.	5.2	6.3	n.s.	6.1	5.9	n.s.
Unstable angina (%)	19.8	18.8	n.s.	23.6	20.7	n.s.	20.2	17.6	n.s.
Procedural success (%)	99.2	98.9	n.s.	100.0	99.2	n.s.	98.6	98.3	n.s.

* = type 1 diabetics excluded; LVEF = left ventricular ejection fraction; HDL = high density lipoproteins; LDL = low density lipoproteins; CAD = coronary artery disease; RCSD = reference coronary segment diameter

Table 3A. Diabetics without relevant restenosis at follow-up (no-TLR): Endogeneous insulin-values (mean C-Peptide ± SD in nmol/l) in relation to glycaemic control (HbA1c, fasting-glucose) and insulin-treatment

C-peptide	HbA1c (%)			Fasting-glucose (mmol/l)		
(nmol/l)	≤ 6.7	> 6.7	p	≤ 6.0	> 6.0	p
IT	801 ± 305	615 ± 258	0.18	582 ± 291	712 ± 244	0.20
No-IT	1171 ± 479	990 ± 298	0.21	941 ± 408	1141 ± 450	0.19

(IT = insulin-treatment; No-IT = no insulin-treatment); p = p-value

Table 3B. Diabetics with relevant restenosis at follow-up (TLR): Endogeneous insulin-values (mean C-Peptide ± SD in nmol/l) in relation to glycaemic control (HbA1c, fasting-glucose) and insulin-treatment

C-Peptide	HbA1c (%)			Fasting-glucose (mmol/l)		
(nmol/l)	≤ 6.7	> 6.7	p	≤ 6.0	> 6.0	p
IT	642 ± 281	661 ± 308	0.39	531 ± 300	634 ± 255	0.27
No-IT	1201 ± 452	748 ± 301	0.009	1382 ± 460	996 ± 328	0.01

(IT = insulin-treatment; No-IT = no insulin-treatment; p = p-value)

with favourable glycaemic control and those with unfavourable glycaemic control after including insulin resistance as an additional variable (Tab. 4B).

Major adverse cardiac events: The rate of major adverse cardiac events (MACE) was 8.5 % (6.4 %–13.0 %), without significant difference between the favourable and unfavourable groups) (p-values between 0.31 and 0.11) (Figs. 1, 2).

Discussion

Laboratory findings and relatively small clinical studies have disclosed that hyperglycaemia can influence the different constituents of the angioplasty-related restenotic process [9, 10]. These findings include the fact that hyperglycaemia disrupts the inhibition of smooth muscle migration and proliferation and promotes the formation of extracellular matrix proteoglycans: which provides cellular migration leading to stenosis and restenosis [11, 12]. Hyperglycaemia can induce restenosis on the basis of hyperglycaemia-induced persistent platelet activation [3]. Hyperglycaemia furthermore directly inactivates endothelial relaxation factors and leads to the increased production of advanced glycolization end products (AGE). This occurs via non-enzymatic glycolization in capillaries and vessels. Hyperglycaemia leads to enhanced produc-

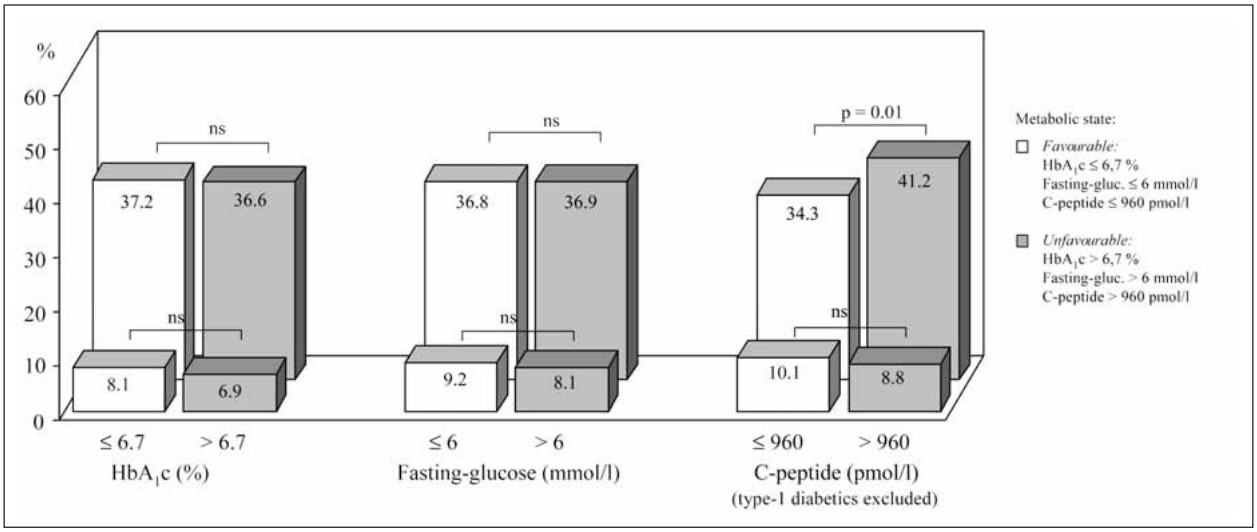

Figure 1. Percent target lesion revascularisation (TLR) in the different subgroups associated with glycaemic control (HbA_1c; fasting-glucose) and insulinaemia (C-peptide)

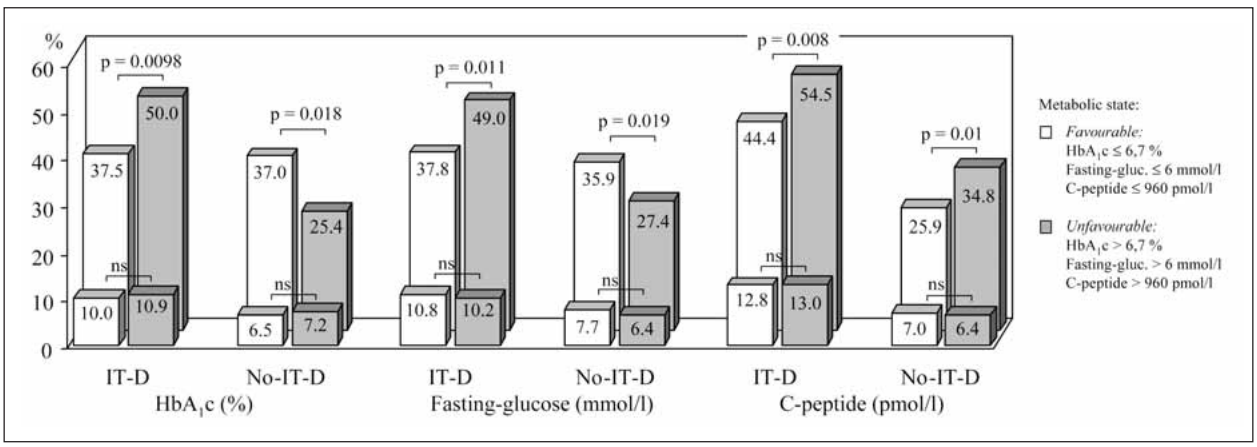

Figure 2. Percent target lesion revascularisation (TLR) associated with glycaemic control (HbA_1c, fasting-glucose) and insulinaemia (C-peptide) in relation to insulin-treatment (IT = insulin treatment; No-IT = no insulin treatment)

tion of endothelin-1, which supports restenosis [13]. Recently published data furthermore suggest a higher restenotic and atherosclerotic risk for diabetic patients with hyperinsulinaemia than for those with elevated serum glucose values [14]. In addition, diabetic patients with remaining or elevated endogenous insulin secretion demonstrated higher frequency of atherosclerotic coronary artery disease than diabetic patients without endogenous insulin production [15].

Until now, the only verified clinical effects of hyperglycaemia and insulinaemia on coronary artery disease in patients with diabetes mellitus have been limited to effects on cardiovascular morbidity and mortality. These results have shown that diabetic patients with higher fasting-plasma glucose or haemoglobin-A1c levels exhibited greater cardiovascular morbidity and mortality [16, 17]. Analogous to smaller, partly non-prospective studies on angioplasty-induced restenosis in diabetic patients [18–20], our study, if focused on the whole group of diabetic patients (no matter whether insulin-treated or not), showed no significant influence of glycaemic control on restenosis after percutaneous coronary intervention. But in contrast to the so far attainable data, we discovered significant differences in restenosis if glycaemic control was favourable or not after analyzing the data separately for insulin-treated and non-insulin treated diabetic patients, conceding a positive correlation between the diabetes-specific metabolic state and the angioplasty-induced restenotic process in diabetic patients.

Analogous to Ronnemaa, who has described heightened CAD risk among hyperinsulinaemic diabetic patients [15], our study disclosed likewise, that hyperinsulinaemia appeared to be a convincing predictor of angioplasty-related restenosis in insulin-treated and non-insulin treated diabetic patients (Fig. 2).

Glycaemic control furthermore proved to be a potent predictor of restenosis among insulin-treated diabetic patients and diabetic patients without insulin resistance. However, analysis in greater detail (and without consideration of insulin resistance) revealed that the negative influence of hyperglycaemia on angioplasty outcome was limited to insulin-treated patients. Among non-insulin-treated patients we detected comparatively inferior results in cases in which glycaemic control was satisfactory during percutaneous coronary intervention (Fig. 2). Surprisingly, it was precisely in these patients that subanalysis of endogenous insulin levels revealed significantly higher C-peptide values: rendering possible an influence of insulin resistance on angioplasty outcome (Tab. 4A, B). In non-insulin-treated diabetic patients the probability of favourable angioplasty results was significantly greater only among those non-insulin-treated diabetic patients who had no insulin resistance.

The analysis of the entire population revealed significantly higher probability of an unfavourable angioplasty outcome in insulin-treated diabetic patients (type-1 diabetic patients excluded) and non-insulin treated diabetic patients if C-peptide was unfavourable. This supports the hypothesis that insulin resistance may directly promote the restenotic process in diabetic patients. But insulin resistance and glycaemic control apparently affect each other: our study revealed that the positive influence of favourable glycaemic control on angioplasty outcome was limited to certain insulinaemia conditions: 1) In diabetic patients (whether or not insulin-treated) the probability of favourable angioplasty outcome was significantly higher in patients without insulin resistance if glycaemic control was favourable (Tab. 4A, B). 2) In insulin-treated diabetic patients, favourable glycaemic control improved angioplasty outcome significantly in patients with insulin resistance (Tab. 4B). 3) In insulin-resistant non-insulin treated diabetic patients, glycaemic control obviously showed no influence on angioplasty outcome (Tab. 4A). One possible explanation is that hyperinsulinaemia in these patients apparently dominated the influence of glycaemic control on angioplasty outcome.

The results of this study might have been biased by the different angioplasty outcome influencing factors like stenosis morphology, diabetes history or concomitant diseases like hypertension or impaired left ventricular function, but the characteristics of these parameters at baseline did not differ between those who had a favourable glycaemic and insulinaemic control and those who had not (Tab. 1).

In conclusion, the findings of this study of the influence of diabetes-specific metabolic status on restenosis after percutaneous coronary intervention have supplied evidence that hyperglycaemia and hyperinsulinaemia influence the restenotic process in diabetic patients. In analogy to the findings of the DIGAMI study on patients after myocardial infarction, our findings signify that all diabetic patients – and particularly patients at high risk for angioplasty-related restenosis (insulin-resistant insulin-treated diabetic patients) – can be recognised early, and that therapies potentially improving angioplasty outcome can be initiated before percutaneous coronary intervention (ie, optimization of glycaemic control and insulin resistance). Future studies are required to disclose whether op-

Table 4A. Multivariate analysis for prediction of TLR at 6-months follow-up for non-insulin-treated diabetic patients (A), and after offering insulin resistance (C-peptide > 1.32 nmol/l) as an additional variable (B)

	Variable	OR (95 % CI)	p-value
A	Age	0.9 (0.7–1.2)	0.4
	Male gender	1.2 (0.8–1.6)	0.4
	Diabetes history > 10 years	0.9 (0.4–1.3)	0.09
	LV-function < 50 %	0.9 (0.5–1.2)	0.1
	Reference coronary segment diameter	0.8 (0.3–1.4)	0.1
	HbA1c	1.9 (0.9–2.7)	0.01
	Fasting-glucose	2.1 (1.1–3.0)	0.009
B	HbA1c > 6.7 %	0.5 (0.3–0.9)	0.03
	Fasting-glucose > 6.0 mmol/l	0.6 (0.2–1.0)	0.04

(CI = confidence interval; OR = odds ratio; LV = left ventricular)

Table 4B. Multivariate analysis for prediction of TLR at 6-months follow-up for insulin-treated diabetic patients (A), and after offering insulin resistance (C-peptide > 1.32 nmol/l) as an additional variable (B)

	Variable	OR (95 % CI)	p-value
A	Age	1.1 (0.7–1.4)	0.4
	Male gender	1.2 (0.8–1.6)	0.4
	Diabetes history > 10 years	1.3 (0.8–1.8)	0.2
	LV-function < 50 %	1.2 (0.7–1.6)	0.1
	Reference coronary segment diameter	1.1 (0.8–1.5)	0.2
	HbA1c	1.6 (0.9–2.2)	0.04
	Fasting-glucose	1.7 (0.8–2.3)	0.03
B	HbA1c > 6.7 %	1.9 (1.0–3.4)	0.009
	Fasting-glucose > 6.0 mmol/l	2.1 (1.1–4.0)	0.007

(CI = confidence interval; OR = odds ratio; LV = left ventricular)

timization of glycaemia and insulin resistance prior to and during percutaneous coronary intervention can improve angioplasty-related restenosis.

Study Limitations

Although the restenotic process is a continuous process over the course of at least 6 months, our study was solely focussed on endogenous insulin and glycaemic variables during percutaneous coronary intervention. This restriction took consideration of the fact that only a few patients would profoundly change their metabolic control during the restenotic process (less than 5 % in our study).

Even though hyperglycaemia can induce glycolization in many human structures, our investigation was limited to glycolisated haemoglobin and did not cover other glycolisated structures: which, if included, could strengthen the power of study.

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