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Neointimal proliferation within carotid stents is more pronounced in diabetic patients with initial poor glycaemic state

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Abstract

Aims/hypothesis. We studied the influence of initial hyperglycaemia on neointimal proliferation within carotid Wallstents.
Methods. A total of 112 patients were followed by duplex sonography after carotid stenting for 24 months. Patients were assigned to three groups: non-diabetic subjects (group A) and diabetic patients, who were assigned according to their baseline HbA_1c values, to group B1($HbA_1c \leq 6.5\%$) or group B2 ($HbA_1c > 6.5\%$).
Results. At baseline the groups did not differ with respect to other vascular risk factors and residual stenosis on angiograms. The maximal thickness of the layer between the stent and the perfused lumen was measured at the duplex follow-ups. At 3 months the typical ultrasonic structure of the neointima was clearly discernible. From this point on, group B2 differed significantly ($p<0.001$) compared with B1 and A with respect to the maximal thickness of neointima and the time course of its ingrowth: group A vs B1 vs B2 was 0.51±0.39 vs 0.52±0.33 vs 0.56±0.35 at 3 months, 0.91±0.27 vs 0.90±0.38 vs 1.14±0.48 at 6 months, 1.02±0.24 vs 0.97±0.34 vs 1.21±0.44 at 12 months and 1.09±0.23 vs 1.10±0.31 vs 1.23±0.37 at 24 months.
Conclusion/interpretation. Initial hyperglycaemia seems to be a predictor of more pronounced neointimal proliferation after carotid stenting independent of diabetes. As intimal hyperplasia is known to be responsible for stent restenosis, strict optimisation of the hyperglycaemic state should be aimed at before elective carotid artery stenting. [Diabetologia (2004) 47:400–406]

Keywords Carotid artery · Stent · Neointima · Hyperglycaemia · Type 2 diabetes mellitus · Duplex ultrasound

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Abbreviations: CCDS, Colour coded duplex sonography · CHD, coronary heart disease · PAOD, peripheral arterial occlusive disease · CCA, common carotid artery · ICA, internal carotid artery · IMT, intima-media thickness · UKPDS, United Kingdom Prospective Diabetes Study Group

Introduction

Over the last few years, carotid artery stenting has developed into an acceptable alternative to surgical treatment, with periprocedural complication rates comparable to those of carotid endarterectomy [1, 2, 3]. The incidence of carotid stent restenoses was reported to be low in several single-center studies [4, 5, 6]. This was also confirmed in a global questionnaire survey [7], comprising data on more than 5200 carotid stents, where a restenosis rate of 3.46% at 12 months was reported. In contrast, the incidence of carotid stent restenoses in the CAVATAS [8] is surprisingly high (22%) at the 12-month follow-up. Stent restenosis is presumed to be the result of neointimal hyperplasia.

Colour-coded duplex sonography (CCDS) of the carotid artery is an established method used to detect stenoses in native carotid arteries [9]; its diagnostic accuracy has been published in a consensus document [10].

Comparing angiograms with Doppler ultrasound haemodynamic parameters over a follow-up period of 6 months, a study [11] showed that CCDS might be an acceptable method to evaluate patency or restenosis in carotid stents too.

Recently the ultrasonic morphology of in-healing carotid Wallstents has been studied in a prospective study over 24 months [12]. The layer between the stent and the perfused lumen, the supposed neointima, increased in thickness from month 1 to 12, mirroring the in-growth of the neointima, whereas no further relevant changes of the neointima were observed during the second year. Stent restenoses were mainly observed during the first year after stenting [13]. Clinical risk factors for in-stent restenosis in the carotid artery have been poorly identified. As diabetes mellitus is an important vascular risk factor [14], a large number of patients in this prospective study were diabetic patients. The resultant hyperglycaemia and other risk factors associated with Type 2 diabetes cause premature atherosclerosis, including the cervical portion of the carotid artery and a markedly increased incidence of ischaemic stroke [15] and lead to a high risk of cardiovascular disease [16]. These subsequent vascular events are predicted by glycosylated haemoglobin (HbA_1c) [17, 18], reflecting the fasting and postprandial glucose concentrations during a 2- to 3-month window [19]. The risk varies with glucose concentrations as well as HbA_1c values. This graded relationship between plasma glucose and cardiovascular risk is observed in people with diabetes and in non-diabetic individuals with high glucose concentrations that are below the diabetes cut-offs [17].

The aim of our study was to analyse the influence of the initial glycaemic state, mirrored by HbA_1c, on the healing process of carotid Wallstents by duplex sonography, with respect to the thickness of the neointimal layer and the time course of its ingrowth.

Subject and methods

Patients. From January 1997 to November 1998, 121 carotid arteries in 112 consecutive patients (77 males) were successfully stented. The study was approved by the institutional ethics committee and written informed consent was obtained from all patients. Nine patients were stented bilaterally, six in the same session.

Carotid artery stent placement was done without a protective device in this early series, in accordance with a technical protocol described previously [6]. Self-expanding Wallstents (Boston Scientific, Natick, Mass., USA) with a rolling membrane were used throughout.

Wallstents had been sized based on a reference diameter measured from the selective angiogram. Stent deployment was followed by dilation within the stent using a 5- to 6-mm-diameter balloon catheter and a pressure of 8 to 10 atmospheres for 5 to 10 s.

Study design. The patients were prospectively followed up by CCDS to study the development of neointima within the stents for 24 months [12]. Follow-ups were scheduled at day one and at 1, 3, 6, 12, and 24 months after stent placement [12]. The study group was divided into: a non-diabetic control group (group A) and a diabetic group (group B), group B again was assigned to two subgroups (B1 and B2) according to the HbA_1c, measured at admission, prior to stenting. The development of the neointima within the three groups of patients was analysed by CCDS. A HbA_1c cut-off of 6.5% was chosen for the diabetic subgroups (group B1: $HbA_1c \leq 6.5\%$, group B2: $HbA_1c > 6.5\%$) based on the results of the Steno type 2 study [20], the UKPDS data [21] and the suggestion of the European Diabetes Policy Group.

Laboratory measurements and definitions. Analyses of lipid concentration, fasting glucose and HbA_1c (HPLC, Menarini Diagnostics [I], calibrated with EURO-TROL standards [NL]) were also obtained at the time of admission, prior to carotid stenting. All measurements were carried out directly, except for LDL, which was calculated using the Friedewald formula. Metabolic variables are reported in mmol/l in a fasting state. Dyslipidaemia was defined as follows: patients already on treatment or with serum cholesterol above 5.17 and/or HDL cholesterol below 0.90 and/or LDL cholesterol above 3.6 and/or triglycerides above 2.03 mmol/l. Hypertension was considered to be present when the patient had been previously treated with anti-hypertensive medication or had a mean blood pressure that exceeded 140 mmHg systolic and/or 90 mmHg diastolic at three consecutive measurements. Body mass index was calculated as kg/m^2. Diabetes mellitus was diagnosed according to the recommendation of the World Health Organization [22]. Current or past cigarette smokers were assigned to either subgroup. Functional non-invasive tests were used to document peripheral arterial occlusive disease (PAOD) [23]. Coronary heart disease was defined as follows: a history of myocardial infarction, coronary stenting, coronary bypass surgery and/or ECG as indices of CHD, and/or a positive treadmill test or myocardial scintigraphy.

Concomitant medical therapy. Anti-platelet therapy was started 3 days before the intervention and consisted in these early days of ticlopidine 250 mg twice a day plus acetylsalicylic acid (ASA) 100 mg per day. ASA was discontinued after 4 weeks. Ticlopidine was continued for 1 year and then converted to ASA 100 mg/day. The anti-hypertensive and lipid-lowering therapy as well as the anti-diabetic treatment for the groups are listed in Table 2.

Angiographic evaluation. Angiographic grading of primary stenoses and residual stenoses after carotid artery stenting had been done analogous to NASCET [24].

CCDS. All examinations were done with a Vingmed System 5 (VINGMED SOUND AIS, General Electric, 3191 Horton, Norway) using a 10-MHz linear array transducer (axial resolution 0.2 mm); the Doppler frequency of this duplex transducer was 5 MHz. Two experienced sonographers performed all ultrasound measurements**.** Settings for depth gain compensation, dynamic range, frame rate and persistence were held constant. Depth and magnification were adjusted according to the patient's anatomy. Gain was adjusted so that the intima-media of the native common carotid artery (CCA) proximal to the stent was clearly visualised. Colour Doppler was adjusted to avoid

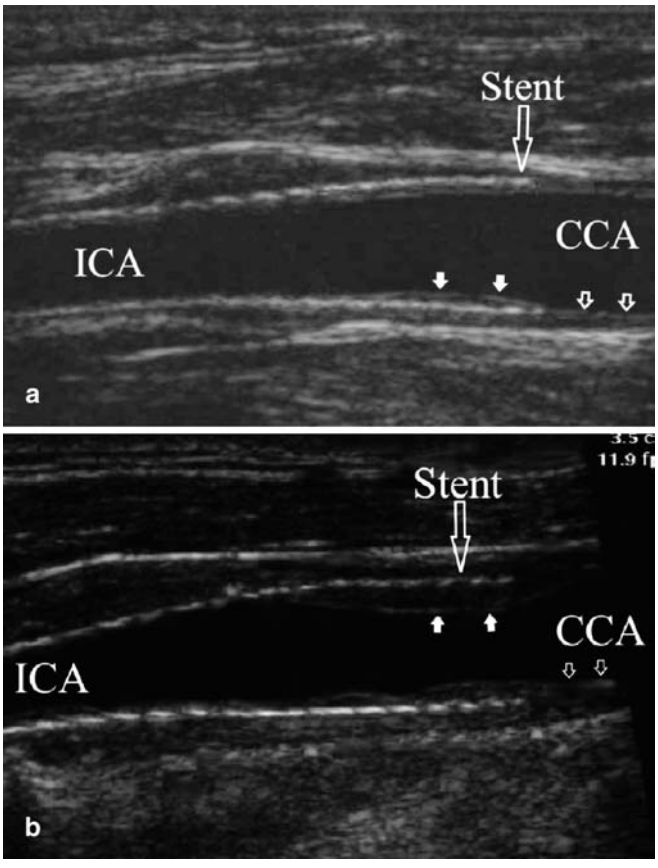

Fig. 1. a A typical subject of group A or B1 with a neointimal layer within a carotid Wallstent in B-mode ultrasound at the 12-month follow-up. **b** A similar typical example of group B2. Full white arrows indicate the ingrown neointima, framed arrows the native intima–media layer

colour overlapping into the tissue adjacent to the artery. In general, a low-velocity range was used.

The examination included the CCA proximal to the stent, the entire stent and the internal carotid artery (ICA) distal to it. All measurements were derived from three planes in the longitudinal view. The calipers for measurements were placed manually.

The following morphological parameters were measured at the follow-ups: (i) The maximal thickness of the neointima or the layer between the stent and the perfused lumen measured at any site of the stent [12], which was the basis for further calculations and (ii) the intima-media thickness (IMT) of the native CCA as described in the literature, [9] proximal to the stent. Measurements of the neointima as well as the IMT within the native carotid artery were done in the B-mode (Fig. 1). Colour Doppler images were also recorded to assist in delineating the echolucent layer between the stent and the perfused lumen at day one.

The reasonable reproducibility of the measurements of the maximal thickness of the layer between the stent and the perfused lumen (mm) has been reported earlier [12].

To grade stent-restenoses the same hemodynamic parameters as those used for the native carotid artery were applied [12, 13, 25] which were similar to those used by M. Robbin [11]. The carotid ratio was calculated by the following formula:

$$\frac{\textit{peak systolic velocity of the ICA within the stent}}{\textit{peak systolicvelocity of the CCA}}$$

A carotid ratio above 4 referred to a restenosis of above 70%, which was confirmed by angiograms in two cases within this series of patients and in a total of nine carotid stent restenoses in a larger series [13]. A carotid ratio above 2.6 was considered to be indicative of a restenosis above 50%.

Statistical method. Categorial variables are reported as counts (percentage) and continuous variables as means ± SD (standard deviation). To test for a difference between the means of non-diabetic subjects and the diabetic subgroups B1 (with $HbA_1c \leq 6.5\%$) or B2 ($HbA_1c > 6.5\%$), a univariate analysis of variance was applied for metric variables. For categorical variables either a Chi-square test or Fisher's exact test was used, depending on how the numbers of observations were distributed in the contingency table. For the analysis of neointimal thickness within the carotid stents, a mixed model analysis of variance was done. The fixed factors were time and the three groups (non-diabetic subjects and the two diabetic subgroups with a HbA_1c value ≤6.5% or >6.5%), whereas the patient group was used as a random factor. A p value of less than 0.05 was considered significant.

Results

Demographic data pertaining to the non-diabetic control group and to the two diabetic subgroups (group A vs group B1 vs group B2) are shown in Table 1. There was no significant difference between the control group and the diabetic group with excellent glycaemic state and that with poor glycaemic state with respect to age, sex, BMI, smoking status, hypertension and hyperlipidaemia. However, the vascular co-morbidity compared to PAOD did show a more pronounced generalisation of arteriosclerotic disease in group B2, whereas there was no significant difference in CHD. With the exception of diabetes-specific data (blood sugar and HbA_1c) there was no significant difference between the two groups in vascular risk factors such as hypertension or hyperlipidaemia (Table 2).

Nine of the 112 patients were lost to follow-up due to non-intervention-related deaths during the study period of 24 months: two in group A, three in group B1 and four in group B2.

Concomitant clinical events. The incidence of peri-interventional stroke was 2.8% (one major stroke) in group A versus 4.7% (two minor strokes) in group B1 versus 6.1% (two minor strokes) in group B2 ($p>0.05$). During the first year after carotid stenting, no neurological symptoms were reported in group A and B1, while two minor strokes occurred in two additional patients in group B1 and B2 each, obviously due to cardiogenic embolisation.

The rates of in-stent restenoses above 70% were 0% in group A versus 0% in group B1 versus 5.5% (2) in group B2 ($p=0.06$). Both were documented by angiograms and treated by further stent placement after the 6- and 12-month follow-up, respectively; they were lost to further follow-up. In-stent restenoses more than 50% occurred at a rate of 5.5% (2) in group

Table 1. Clinical characteristics and vascular co-morbidity

	Total	Non-diabetic subjects	Diabetic subjects with HbA_1c		*p* value
			≤6.5%	>6.5%	
		Group A	Group B1	Group B2	A vs B1 vs B2
n	112	36	43	33	
Age (SD)	68.7 (10)	67 (11)	69 (11)	70 (9)	0.42
Sex (men/women) (%)	77/35 (68.8/31.2)	23/13 (20.5/11.6)	33/10 (29.5/8.93)	21/12 (18.75/10.71)	0.35
Body mass index (SD)	26.1 (3.9)	25.2 (3.8)	26.2 (3.7)	27.2 (4.1)	0.11
Cigarette smokers (%)	63 (56.3%)	18 (50.0%)	24 (55.8%)	21 (63.6%)	0.52
Hypertension (%)	90 (80.4%)	30 (80.3%)	33 (76.7%)	27 (81.8%)	0.74
Hyperlipidaemia (%)	94 (83.9%)	31 (86.11)	35 (83.33)	28 (84.85)	0.94
Vascular co-morbidity:					
PAOD (%)	50 (44.6%)	13 (36.11%)	16 (37.2%)	21 (63.64%)	0.03 A vs B1 0.92 A vs B2 0.02 B1 vs B2 0.02
CHD (%)	63 (56.3%)	19 (52.78%)	22 (51.16)	22 (66.67%)	0.35

PAOD, Peripheral arterial occlusive disease; CHD, coronary heart disease

Table 2. Laboratory results and medical therapy at discharge

	Total	Non-diabetic subjects	Diabetic subjects with HbA_1c		*p* value
			≤6.5%	>6.5%	
		Group A	Group B1	Group B2	A vs B1 vs B2
Cholesterol mmol/l (SD)	5.66 (1.14)	5.57 (0.95)	5.62 (1.34)	5.72 (1.04)	0.83
LDL-cholesterol mmol/l (SD)	3.52 (1.09)	3.51 (0.92)	3.56 (1.30)	3.46 (0.91)	0.63
HDL-cholesterol mmol/l (SD)	1.24 (0.41)	1.21 (0.30)	1.38 (0.58)	1.16 (0.27)	0.06
Triglycerides mmol/l (SD)	2.10 (1.10)	2.11 (1.12)	1.64 (0.68)	2.31 (1.33)	0.21
HbA1c % (SD)	6.6 (1.0)	5.8 (0.2)	6.2 (0.3)	7.9 (1.0)	<0.001 A vs B1 0.03 B1 vs B2<0.001
Medication					
Statin	78/112	23/36	35/43	20/33	0.10
Fibrate	27/112	10/36	10/43	7/33	0.81
Calcium-antagonist	37/112	13/36	13/43	11/33	0.86
ACE-inhibitor	53/112	13/36	25/43	15/33	0.14
Betablocker	28/112	8/36	7/43	13/33	0.06
Oral anti-diabetic medication	34/112	0/36	20/43	14/33	<0.001 B1 vs B2 0.64
Insulin treatment	8/112	0/36	8/43	0/33	<0.001

A, 20.9% (9) in group B1 and 18.2% (6) in group B2 (p=0.13).

Peri-interventional morphological results. The pre-treatment degree of carotid stenosis on angiograms did not differ between groups A, B1 and B2:77±12, 79±10 and 77±12 percent, respectively (p=0.6). Furthermore, immediately after stenting, no difference in residual stenosis was registered between the groups: 4±11, 6±9, 5±11 percent (p=0.7).

The IMT of the CCA before the intervention differed significantly between the groups: it was 0.8±0.2 mm in group A, 0.9±0.3 mm in group B1 and 1.0±0.3 mm in group B2 (p=0.009), respectively.

Duplex ultrasound morphology at follow-up. Figure 1a shows a typical example of a normal neointimal layer adjacent to the inner surface of the stent at the 1-year follow-up, typical for a patient in group A or B1(initial HbA_1c value of 5.7%). The margin of the neointima toward the lumen is marked by a more or less continuous echogenic line. Simultaneously, a typical transition of the intima–media layer from the native CCA to the proximal stent area was seen. The

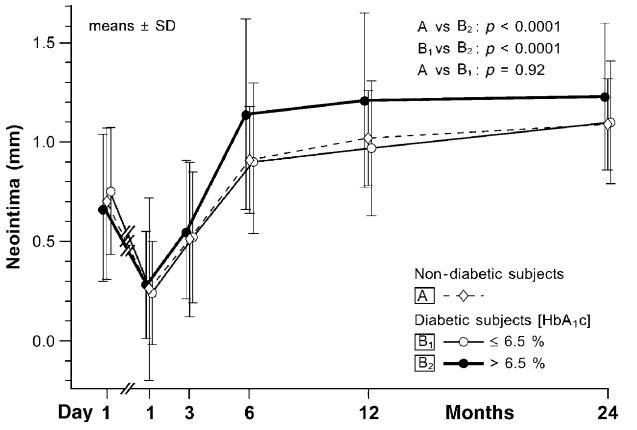

Fig. 2. Mean thickness (confidence interval) of the layer between stent and lumen in mm detailed for group A and B1 and B2

ultrasound morphology of the neointima seems to be similar to that of the intima-media of the native CCA. Figure 1b shows a typical example of rather pronounced, neointimal hyperplasia in a patient in group B2 (who had an initial HbA_1c of 8.1%). The ultrasonic structure is principally the same as that in Fig. 1a. The echogenic line at the border towards the lumen is preserved and covers a relatively thicker, less echogenic layer.

Early duplex sonographic findings. At day one after carotid artery stent placement, an echolucent gap between the stent and the perfused lumen was observed. Its thickness decreases from 0.7±0.4 mm (mean, SD) at day 1 to 0.3±0.3 mm at the 1-month follow-up in the total group [12]. There was no difference between the two groups at day 1 and at 1 month (Fig. 2).

Intermediate and long-term duplex ultrasonic findings. From the 3-month follow-up, the typical ultrasound structure of the neointima within the stent was observed in the B-mode (Fig. 1). A significant increase in the thickness of the neointima was registered in all three groups until the 24-month follow-up ($p<0.0001$). The bulk of this increase was achieved within 6 months. This increase in the thickness of the neointima over time is significantly more pronounced in group B2 (Fig. 2, $p<0.001$). The means ± SD of the neointimal thickness for the three groups at follow-up are given in Table 3, respectively.

A significant influence on neointimal thickness could be demonstrated by a mixed-model analysis of variance for the three groups (A vs B1: $p=0.92$, A vs B2: $p<0.001$, B1 vs B2: $p<0.001$), and the time of follow-up ($p<0.001$).

Development of HbA1c from baseline to the 12 month follow-up. At baseline the mean value in group A was 5.8±0.2%, whereas it was 6.2±0.3% in group B1 and 7.9±1.0% in group B2. The difference of initial HbA_1c between the three groups was statistically significant ($p<0.001$; see also Fig. 2).

Table 3. Time course of the neointima within the stents (mm)

Follow up	Non-diabetic subjects	Diabetic subjects with HbA_1c	
		≤6.5%	>6.5%
	Group A	Group B1	Group B2
Day 1	0.69±0.38	0.75±0.32	0.67±0.37
1 Month	0.26±0.46	0.24±0.26	0.28±0.27
3 Months	0.51±0.39	0.52±0.33	0.56±0.35
6 Months	0.91±0.27	0.90±0.38	1.14±0.48
12 Months	1.02±0.24	0.97±0.34	1.21±0.44
24 Months	1.09±0.23	1.10±0.31	1.23±0.37

Diabetic patients with stable HbA_1c of less than 6.5% at 12 month follow-up and those with steadily increased HbA_1c (+>5% from baseline) did not show any significant difference in the maximal thickness of the neointima within the stents at 12 months: the mean maximal thickness of the neointima within the carotid stents was 1.15 mm (±0.43) and 0.92 mm (±0.1) in the group with a stable HbA_1c of less than 6.5% and in the group with steadily increased HbA_1c at 12 months.

Discussion

Our study shows that neointimal proliferation within carotid artery Wallstents is more pronounced in diabetic patients in a poor glycaemic state than in diabetic patients with better glycaemic control or in non-diabetic subjects. As there was no difference between initial well-treated diabetic patients and the non-diabetic control group, this finding was obviously independent of the diabetes status. In addition, the IMT of the ipsilateral (with respect to the stent) native CCA was higher in group B2 than in group B1 and group A.

The echolucent gap between the stent and the perfused lumen documented at the follow-up investigation on day 1 and at 1 month obviously does not represent neointima. Although it is not of prime importance for the issues addressed in this study, it is briefly described to better elucidate Fig. 2. Principally it could be an artifact or an echolucent layer. In an earlier interpretation [12] it was presumed to represent a thrombotic layer, which was reduced from 0.7± 0.4 mm at day 1 to 0.3±0.3 at 1 month, possibly by endogenous thrombolysis.

It has been known for years that the CCA IMT is higher in diabetic than in non-diabetic patients [26, 27]. In a 3-year duplex follow-up, the increase of the native CCA IMT per year was shown to be positively correlated to the initial HbA_1c value [28]. A recent study [29] showed that the increase of CCA IMT does, indeed, depend on the value of HbA_1c, irrespec-

tive of the subject's diabetes status. Our observation of a higher CCA IMT in diabetic group B2 is in accordance with these findings. Evidently, there is an analogous dependence of HbA_1c on the maximal thickness of the neointima within the carotid stent, irrespective of the diabetes status. In addition, the ultrasonic structure (B-mode) of the CCA IMT and that of the ingrown neointima at the one-year follow-up are similar. The same mechanisms possibly play a role in the development of CCA IMT and that of neointimal thickness in carotid stents.

The IMT of the native CCA is a marker of increased cardiovascular risk and vascular manifestation. Another study showed that the risk for myocardial infarction was increased by 11% for every increase of 0.1 mm of CCA IMT [9].

Many intervention studies have tried to achieve a regression of atherosclerosis, evidenced by a decrease of CCA IMT. Regression of CCA IMT was achieved by lipid-lowering drugs or anti-platelet drugs [30, 31, 32, 33]. Long-term application of ASA and ticlopidine attenuated the progression of common carotid IMT in a series of Type 2 diabetic patients [33].

It seems reasonable to presume that antiplatelet treatment or lipid-lowering therapy might have influenced neointimal proliferation within the carotid stent in our study. However, the groups received the same antiplatelet treatment and did not differ significantly with respect to statin therapy during the follow-up period. If such an effect did occur, it would be evenly distributed between the three groups.

Intimal hyperplasia is known to be responsible for stent restenosis. We observed a higher incidence in-stent restenoses in group B2, although the increases did not achieve statistical significance; this might have been due to their rather low incidence in the whole series. Furthermore, in a larger group of 303 consecutive carotid stents (279 patients), all nine high-grade stent restenoses occurred in diabetic patients with an initial HbA_1c value above 6.2% [13].

Accordingly, there is a graded relationship between plasma glucose and cardiovascular risk observed in diabetic [18, 34] and non-diabetic individuals with high glucose concentrations that are below the diabetes cut-offs [17].

As shown in the United Kingdom Prospective Diabetes Study [34], strict glucose control is beneficial in Type 2 diabetes with regard to vascular complications. A study [34] reported the following risk reduction per 1% reduction of HbA_1c values: minus 14% for myocardial infarction and minus 21% for deaths related to diabetes. In the Steno type 2 study [20] the only symptom that showed a significant benefit with intensive treatment of diabetes was the progression of PAOD.

Our group B2 had a higher degree of generalised arteriosclerotic disease compared to group B1 or group A, which applied to PAOD, but not to CHD.

Initial hyperglycaemia or an initial HbA_1c value above 6.5% proved to be a predictor of more pronounced neointimal ingrowth, which might have been one reason for stent-restenosis. However, it is unclear whether hyperglycaemia per se or associated metabolic abnormalities promote neointimal ingrowth. Possibly AGE and the accompanying endothelial dysfunction play a major role [35]. Mechanisms or indicators of inflammation such as C-reactive protein might play an additional role to hyperglycaemia in the development of neointimal hyperplasia; patients with advanced arteriosclerosis and with both hs-CRP and HbA_1c in upper quartiles were recently shown to be a particular risk for poor cardiovascular outcome [36].

In conclusion, in patients scheduled for elective carotid artery stenting, the physician should try to achieve a strict optimisation of the hyperglycaemic state prior to the procedure, as the early phase of stent healing seems to be of importance. The purpose should be to reduce the incidence of neointimal hyperplasia and stent restenoses on the one hand, and to achieve a reduction of other vascular complications such as myocardial infarction, peripheral vascular disease and vascular death on the other.

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