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Stenotic Occlusive Lesions of Internal Carotid Artery in Diabetic Patients

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A B S T R A C T

Diabetes deteriorates atherosclerotic changes in the arteries. The aim of the study was to assess the prevalence and localization of stenotic atherosclerotic lesions of the internal carotid artery (ICA) in patients with diabetes. A prospective analysis of angiography findings was carried out in 150 diabetic and 150 non-diabetic patients with symptoms of cerebral ischemia using double-blind angiogram readings by two independent investigators. The degree of stenosis was determined using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria. Stenoses of the proximal arterial segment accounted for the majority of extracranial ICA stenoses, being more frequent in diabetic (left ICA 50.7%, right ICA 58.0%) than in the non-diabetic patients (left ICA 29.3%, right ICA 32.7%). Diabetic patients revealed a more significant rate of unilateral tandem ICA stenoses (14.0–21.3%), as well as a statistically significantly higher prevalence of intracranial ICA stenoses (left ICA 24.0% and right ICA 17.3%) than did non-diabetic patients (left and right ICA 3.3% each). Our results confirm that there is a morphological basis in ICA for increased incidence of ICA lesions in patients with diabetes as compared to those without it. Data on the incidence of stenotic ICA lesions in diabetes suggest the importance of assessing overall ICA status using digital subtraction angiography. Such an assessment is a precondition for an optimal therapeutic approach, especially in diabetic patients who are at an increased risk of cerebrovascular disease.

Key words: *internal carotid artery, diabetes mellitus, atherosclerotic lesions, digital subtraction angiography*

Introduction

Atherosclerosis is a diffuse disease with higher involvement of particular blood vessels. In diabetic patients atherosclerotic changes of the arterial wall are more extensive, diffuse and more unevenly distributed as compared with non-diabetic subjects[1]. Many prospective studies have demonstrated a higher grade of atherosclerotic arterial lesions in diabetic patients, with a mortality rate twofold that from cerebrovascular and coronary diseases. In non-diabetic patients, stenotic changes of lower extremity arteries are more frequently found on large conductive arteries (aortoiliac and femoropopliteal arteries), whereas in diabetic patients they more commonly involve peroneal and tibial (terminal) arteries[2–8]. Atherosclerotic lesions of intracranial or extracranial vessels may lead to cerebrovascular disease. Clinical deficit in thromboembolic cerebral ischemia is less pronounced in the absence of distal vascular insufficiency. Stenosis of the common carotid artery (CCA) and internal carotid artery (ICA) is a common cause of cerebrovascular ischemia. The existence of stenosis is supported by the esti-

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mated perioperative incidence of cerebral ischemia of 2.9 and 6.7% in asymptomatic patients; and of 18 and 26% in symptomatic patients with unilateral and bilateral stenosis, respectively. The perioperative risk of stroke associated with coronary bypass surgery is considerably lower in the absence of atherosclerotic lesions of the aortic arch and origin of large supra-aortic arteries[9,10]. A 4.2% rate of significant stenoses of the intracranial segment of ICA has been reported in the literature[11–13]. Hence, it is of utmost importance to know the features of atherosclerotic lesions of carotid arteries. In symptomatic patients, these lesions may even interfere with therapeutic effect[12–14].

As atherosclerotic processes on the arteries are histopathologically identical, and are additionally worsened by diabetes mellitus, the aim of the study was to identify possible differences in the prevalence of stenotic lesions of the extracranial and intracranial ICA segments between diabetic and non-diabetic patients.

Patients and Methods

The study included patients treated for cerebrovascular ischemia in the form of transient ischemic attack (TIA), reversible ischemic neurologic deficit (RIND) or stroke from June 1999 till June 2003. Patients were referred for digital subtraction angiography (DSA) by a vascular surgeon or neurologist because of inadequate findings previously obtained by non-invasive diagnostic procedures performed according to cerebrovascular ischemia algorithm. The patients were divided into two groups of 150 patients each according to the presence or absence of glucose metabolism impairment (diabetes mellitus, DM). There was no significant between-group difference in the prevalence of particular forms of cerebrovascular ischemia or clinical lateralization.

In the group of 150 diabetic patients, nine had insulin dependent diabetes (IDDM) and 141 had non-insulin dependent diabetes (NIDDM). Among them, 49 were women aged 43–69 years (mean 62), and 101 men aged 40–79 years (mean 68). There were 97 patients with hypertension (on continuous antihypertensive therapy for at least two years), 66 smokers (more than 10 cigarettes daily for the last 5 years), and 100 patients with elevated blood lipids (cholesterol >5.2 mmol/L and triglycerides >1.7 mmol/L).

In the group of 150 non-diabetic patients, there were 52 women aged 46–72 (mean 64) years, and 98 men aged 44–72 (mean 69) years. Hypertension was present in 88 patients, cigarette smoking in 90, and elevated blood lipids in 71 patients. As for risk factors, the rate of cigarette smoking was statistically significantly higher in the non-diabetic than in the diabetic patient group, whereas hyperlipidemia was significantly more frequent in the latter ($p<0.001$ both). There was no statistically significant between-group difference in the rate of other risk factors.

Selective DSA procedures of carotid arteries were performed on a Siemens Angiostar device (Erlangen, Germany), with an informed consent obtained from all patients. Images of studied arteries were obtained in two (vertical and lateral) projections and analyzed in approximately real size. Projections with most clearly visible stenosis were magnified for more precise measurement of its degree. Each of the studied arteries was longitudinally divided into equal thirds (proximal, medial, and distal), and intracranial segment including the branch in the temporal bone canal into preclinoid and postclinoid segments to obtain more precise stenosis localization. Standard values for aortography of the arch are 80–100 mL of nonionic contrast medium (Omnipaque-iohexol, Amersham Health, Oslo, Norway) at a concentration of 350 mg/mL, while for selective arteriography of the internal carotid artery the use of nonionic contrast medium at a concentration of 300 mg/mL is mandatory. The 5 F catheters for selective angiography were used. Patients received premedication with intramuscular injection of Apaurin (diazepam, Krka, Novo Mesto, Slovenia) at a concentration of 10 mg/2 mL. Vital functions were monitored during the procedure, and an anaesthesiologist was consulted when required by a patient's clinical status.

Carotid arteries were comparatively analyzed in diabetic and non-diabetic patients. Angiograms were analyzed by double-blind image interpretation. Two independent examiners were blinded for the presence of diabetes in a particular patient until final analysis. A coded computer file was created for each individual patient. The analysis included each artery separately and all arteries in total. The degree of stenosis was determined using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria[15]. Results were expressed in appropriate tables of contingency and analyzed by using χ^2-test. The highly conservative level of significance of 0.001 was used in result interpretation.

Results

Isolated stenoses of the left ICA were found in 50.7% of diabetic patients and 29.3% of non-diabetic patients, whereas multiple stenoses of the left ICA were recorded in 21.3% of diabetic and 2.0% of non-diabetic patients. Isolated stenoses of the right ICA were detected in 58.0% of diabetic and 32.7% of non-diabetic patients, and multiple stenoses of the right ICA in 14.0% of diabetic and 2.0% of non-diabetic patients. The prevalence of isolated and multiple stenoses in both left and right ICA was statistically significantly higher in diabetic than in non-diabetic patients ($p<0.001$, Table 1). Isolated stenoses of the intracranial segment of left ICA were found in 24.0% of diabetic and 3.3% of non-diabetic patients. The respective figures for the intracranial segment of the right ICA were 17.3 and 3.3%. Comparison of the two patient groups showed a statistically significantly higher ($p<0.001$) prevalence of isolated stenoses of the intracranial segments of both ICA in patients with diabetes than in non-diabetic patients (Table 2). In diabetic patients, the rate of isolated stenoses of the extracranial segment of

TABLE 1
NUMBER OF STENOSES OF THE EXTRACRANIAL SEGMENT OF INTERNAL CAROTID ARTERY (ICA)

Left ICA	No stenosis		One stenosis		Two stenoses		Three stenoses		Total	
	n	%	n	%	n	%	n	%	Total	%
Non-DM	103	68.7	44	29.3	3	2.0	0	0	150	100
DM	42	28.0	76	50.7	31	20.7	1	0.7	150	100
Total	145	48.3	120	40.0	34	11.3	1	0.3	300	100
p<0.001				S		S				
Right ICA	No stenosis		One stenosis		Two stenoses		Three stenoses		Total	
	n	%	n	%	n	%	n	%	Total	%
Non-DM	98	65.3	49	32.7	3	2.0	0	0	150	100
DM	42	28.0	87	58.0	19	12.7	2	1.3	150	100
Total	140	46.7	136	45.3	22	7.3	2	0.7	300	100
p<0.001				S		S				

ICA – internal carotid artery, Non-DM – non-diabetic patient group, DM – diabetic patient group, S – significant (p<0.001)

TABLE 2
NUMBER OF STENOSES OF THE INTRACRANIAL SEGMENT (IC) OF INTERNAL CAROTID ARTERY (ICA)

ICA ic	Left				Right				Total	
	No stenosis		One stenosis		No stenosis		One stenosis			
	n	%	n	%	n	%	n	%	n	%
Non-DM	145	96.7	5	3.3	145	96.7	5	3.3	150	100
DM	114	76.0	36	24.0	124	82.7	26	17.3	150	100
Total	259	86.3	41	13.7	269	89.7	31	10.3	300	100
p<0.001				S				S		

ICA – internal carotid artery, ic – intracranial segment, Non-DM – non-diabetic patient group, DM – diabetic patient group, S – significant (p<0.001)

ICA was almost twofold that in patients who did not have diabetes. Diabetic patients had a 2–3 times higher overall rate of extracranial than intracranial stenoses. However, the rate of stenoses found in the intracranial segment of ICA in diabetic patients was 6- to 7-fold that recorded in non-diabetic patients, suggesting diabetes to be a significant factor for the occurrence of intracranial ICA stenoses (Table 1 and 2).

There was no statistically significant difference in the prevalence of stenoses according to localization in either left or right ICA between the diabetic and non-diabetic groups. The prevalence of tandem stenoses was statistically significantly higher in the diabetic than in non-diabetic patients (21.3 *vs.* 2.0%; p<0.001, Table 3). Stenosis of the preclinoid and postclinoid parts of the intracranial segment of the left ICA was found in 15.3 and 8.7% of diabetic patients and 2.0 and 1.3% of non-diabetic patients, respectively. Isolated stenoses of the preclinoid and postclinoid parts of the intracranial segment of the right ICA were detected in 8.7% of diabetic patients each. In the non-diabetic group, isolated stenoses of the preclinoid part of the intracranial segment of the right ICA were found in 3.3% of patients, whereas none of these patients showed stenosis of the postclinoid part of the intracranial segment of the right ICA. A comparison of the prevalence of stenoses of the infra- and supraclinoid parts of the intracranial segments of both internal carotid arteries between the diabetic (where they are known to be more common) and non-diabetic group according to localization (preclinoid or postclinoid) revealed no statistically significant difference (p>0.001, Table 4).

Atherosclerotic ICA lesions were most frequently observed in the 60–69 age group. No statistically significant between-group difference in age was found for the prevalence of these lesions.

Discussion

Diabetic patients had a statistically significantly higher prevalence of ICA stenoses than non-diabetic patients. This observation is of great importance in view of the studies which have shown the causes of cerebral ischemia to most commonly be associated with lesions of ICA, and of its origin in particular. The increased rate of

TABLE 3
LOCALIZATION OF STENOSES OF THE EXTRACRANIAL SEGMENT OF INTERNAL CAROTID ARTERY (ICA)

Left ICA	No stenosis		Proximal		Medial		Distal		Tandem		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
Non-DM	103	68.7	41	27.3	0	0	3	2.0	3	2.0	150	100
DM	42	28.0	62	41.3	5	3.3	9	6.0	32	21.3	150	100
Total	145	48.3	103	34.3	5	1.7	12	4.0	35	11.3	150	100
p<0.001				NS				NS		S		
Right ICA	No stenosis		Proximal		Medial		Distal		Tandem		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
Non-DM	98	65.3	48	32.0	0	0	1	0.7	3	2.0	150	100
DM	42	28.0	74	49.3	3	2.0	10	6.7	21	14.0	150	100
Total	140	46.7	122	40.7	3	1.0	11	3.7	24	16.0	150	100
p<0.001				NS				NS		NS		

ICA – internal carotid artery, Non-DM – non-diabetic patient group, DM – diabetic patient group, S – significant (p<0.001), NS – nonsignificant

TABLE 4
LOCALIZATION OF STENOSES OF THE INTRACRANIAL SEGMENT (IC) OF INTERNAL CAROTID ARTERY (ICA)

ICA ic	Left						Right						Total	
	No stenosis		Preclinoid		Postclinoid		No stenosis		Preclinoid		Postclinoid			
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Non-DM	145	96.7	3	2.0	2	1.3	145	96.7	5	3.3	0	0	150	100
DM	114	76.0	23	15.3	13	8.7	124	82.7	13	8.7	13	8.7	150	100
Total	259	86.3	26	8.7	15	5.0	269	89.7	18	6.0	13	4.3	300	100
p<0.001				NS		NS				NS				

ICA – internal carotid artery, ic – intracranial segment, DM – diabetic patient group, Non-DM – non-diabetic patient group, NS – nonsignificant

stenoses in diabetic patients explains the higher prevalence of cerebral ischemia in these patients as compared to non-diabetic ones[16–19]. Stenoses of the proximal arterial segment accounted for the majority of extracranial ICA stenoses in both diabetic (left ICA 50.7%, right ICA 58.0%) and non-diabetic (left ICA 29.3%, right ICA 32.7%) patients. These localizations are the most common sites of operative treatment. Besides other characteristics assessed on US B-mode image (plaque, ulceration, etc.), the carotid intima media thickness is an important factor in the analysis of atherosclerotic plaque features. Enlargement of intima media thickness has been found in diabetic patients with or without hypertension, hyperlipidemia, and cigarette smoking[20]. Thus, Schumacher *et al.* have found plaque embolism to be responsible for most cases of stroke, whereas hypoperfusion had a minor role due to marked carotid stenoses. They have reported on a 13% and 1–2% risk of stroke in symptomatic and asymptomatic ICA stenosis, respectively. Unstable plaque rupture is considered to be primarily responsible for embolism and cerebral ischemia[21–23]. On the other hand, Van Everdinge *et al.* have failed to demonstrate any association between the degree of ICA stenosis (on the symptomatic and asymptomatic side) and the severity of cerebral ischemia[24]. Accordingly, thorough knowledge of the characteristics of atherosclerotic lesions of carotid arteries is of paramount importance[12–14].

The present study revealed the prevalence of stenosis sites other than the proximal extracranial segments of ICA to be rather negligible. In diabetic patients, the rate of tandem stenoses of the extracranial segment of ICA was 7- to 10-fold that in the non-diabetic patients. Comparison with the published data on the prevalence of bilateral and ipsilateral common carotid artery and internal carotid artery stenoses showed a significant rate of unilateral tandem stenoses of the internal carotid artery in diabetic patients (14.0–21.3%)[9,10]. Data on the high prevalence of tandem stenoses in diabetic patients point to the need of complete ICA assessment for therapy planning (operative, percutaneous).

Analysis of the prevalence of intracranial ICA stenoses revealed a similar pattern as for the extracranial ICA segment. Diabetic patients had a statistically significantly higher prevalence of intracranial ICA stenoses

(left ICA 24.0% and right ICA 17.3%) in comparison with non-diabetic patients (left and right ICA 3.3% each). This finding additionally points to the role of evaluation of the intracranial ICA segment in addition to assessment of proximal and tandem stenoses of extracranial ICA.

Comparison of the prevalence of stenotic lesions in the extracranial and intracranial segments of ICA showed the lesions of proximal ICA to prevail. Diabetic patients had an increased prevalence of stenosis in the proximal parts of the arteries, with the proximal »conductive« ICA segment involvement prevailing over the intracranial terminal one. Such a distribution of ICA stenoses is inconsistent with the known effect of diabetes mellitus on lower extremity arteries, where stenotic lesions of terminal arteries (leg and foot arteries) prevail[2].

Data on the risk of stenotic ICA lesions in diabetes, obtained by appropriate assessment of complete arterial status, suggest the necessity of other non-invasive diagnostic methods such as CT angiography and MRA besides US doppler[25,26]. Despite its shortcomings, DSA as a diagnostic method has proved valuable in assessing the extent of stenotic lesions of the arteries, and is employed as the »gold standard« of comparison in assessing the sensitivity and specificity of non-invasive diagnostic methods[27,28].

Therefore, ICA status should be precisely evaluated in diabetic patients to reach an optimal therapeutic decision. An overestimated degree of carotid artery stenosis entails unnecessary classical surgical or invasive percutaneous procedures, whereas an underestimated degree may erroneously indicate conservative therapy, and thus lead to an increased risk of cerebral ischemia.

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STENOTIČNO OKLUZIVNE PROMJENE UNUTARNJE KAROTIDNE ARTERIJE U DIJABETIČKIH BOLESNIKA

SAŽETAK

Šećerna bolest doprinosi razvoju aterosklerotskih promjena na arterijama. Cilj istraživanja bio je odrediti učestalost i lokalizaciju stenotičnih aterosklerotskih promjena unutarnje karotidne arterije (ACI) u dijabetičkih bolesnika. Metodom dvostrukog slijepog očitavanja angiograma od strane dva nezavisna ispitivača prospektivno su analizirani angio-

grami 150 dijabetičkih i 150 nedijabetičkih bolesnika sa simptomima ishemijske bolesti mozga. Stupanj stenoze ACI određivan je sukladno kriterijima North American Symptomatic Carotid Endarterectomy Trial (NASCET). Većinu stenoza ekstrakranijalnog dijela ACI čine one na proksimalnom dijelu arterije, a brojnije su u dijabetičkih bolesnika (lijeva ACI – 50,7%, desna ACI – 58,0%) nego u bolesnika bez dijabetesa (lijeva ACI – 29,3%, desna ACI – 32,7%). Kod dijabetičkih bolesnika nađena je značajnija unilateralna zastupljenost tandem stenoza ACI (14,0–21,3%), kao i statistički značajno veća učestalost stenoza intrakranijalnog (i.c.) dijela ACI (lijeva ACI i.c. – 24,0%; desna ACI i.c. – 17,3%) u usporedbi s bolesnicima bez šećerne bolesti (lijeva ACI i.c. – 3,3%; desna ACI i.c. – 3,3%). Rezultati potvrđuju kako u dijabetičkih bolesnika postoji morfološka osnova povećane incidencije promjena na ACI u odnosu na bolesnike bez dijabetesa. Spoznaja o učestalosti razvoja stenotičnih promjena ACI kod dijabetičkih bolesnika naglašava važnost procjene cjelokupnog statusa ACI digitalnom suptrakcijskom angiografijom. Takva je procjena preduvjet optimalnog pristupa liječenju, osobito bolesnika sa šećernom bolešću koji su izloženiji povećanom riziku razvoja cerebrovaskularne bolesti.