

## HYPERGLYCEMIA IN ISCHEMIC STROKE PATIENTS

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**SUMMARY** – The aim of the study was to determine the possible association between the duration of diabetes mellitus and prevalence of ischemic stroke. Also, the effect of hyperglycemia in the acute phase of ischemic stroke on short-term outcome of stroke was studied. Study group consisted of 429 patients hospitalized at our department for ischemic stroke during 12 consecutive months. The diagnosis and type of diabetes were established on the basis of pre-stroke history data and confirmed by consultant diabetologist (glucose monitoring by repeated blood tests). The diagnosis and outcome of brain infarction were assessed on the basis of clinical and neuroimaging criteria. Hyperglycemia was recorded in 95 patients with ischemic stroke (22.1% of all cases); 72 of them had the diagnosis of diabetes mellitus established prior to stroke (type 1 in nine, and type 2 in 63 patients). There were 63 females and 42 males, mean age  $68.6 \pm 7.8$  years. Hypertension was an additional risk factor for stroke in 87.4%, while elevated blood cholesterol was found in only 31.1% of patients. Brain imaging showed territorial infarction in 46 cases of ischemic stroke, followed by 21 cases of lacunar infarction, and hemodynamic stroke in two cases. Diabetes of  $\geq 6$  years of duration was associated with a higher rate of ischemic stroke than the shorter diabetes duration of up to 5 years (50 vs 22 patients). Further analysis revealed a significant difference in stroke prevalence between the patients with type 2 diabetes duration of 6-10 and  $\geq 11$  years ( $p < 0.01$ ); in the group of patients with longest diabetes duration, the presence of this disease facilitated the occurrence of stroke. The functional outcome of stroke as assessed by the Modified Rankin Scale showed a more severe functional deficit in the group of patients with hyperglycemia (Rankin 0 and 1 in 7.4%, Rankin 2 and 3 in 28.7%, and Rankin 4 and 5 in 35.2% of all cases) than in the group of ischemic stroke patients without hyperglycemia (Rankin 0 and 1 in 24.2%, Rankin 2 and 3 in 27.4%, and Rankin 4 and 5 in 26.2% of all cases). The case fatality rate was higher in the former than in the latter group of patients (28.7% vs 22.2% of all cases). Diabetes was found to be an important risk factor for ischemic stroke. Prolonged duration of diabetes had greater impact on the occurrence of stroke than shorter duration of the disease. The presence of hyperglycemia in the acute phase of stroke aggravates the final outcome of ischemic stroke. Thus, early detection and management of hyperglycemia should be considered important measures for the prevention of stroke.

**Key words:** *Brain ischemia, complications; Hyperglycemia; Diabetes mellitus, complications; Diabetes mellitus, epidemiology*

### Introduction

Large population-based epidemiological studies have demonstrated that diabetes mellitus is a major risk factor for ischemic stroke<sup>1-4</sup>. The risk of thromboembolic stroke

may be increased through multiple and synergistic mechanisms such as acceleration of large artery sclerosis, adverse effects on high density lipoprotein (HDL) cholesterol levels, increased level of thrombohexane, and hyperinsulinemia<sup>5</sup>. However, tight control of blood glucose levels does not reduce significantly the risk of macrovascular complications in diabetics, as it does in case of microvascular complications of diabetes mellitus<sup>6</sup>. Furthermore, there is a dispute whether hyperglycemia in the acute

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phase of stroke is associated with poor stroke prognosis<sup>7</sup>. It has been suggested that the duration of hyperglycemia preceding cerebral ischemia may also be a contributory factor for the occurrence of stroke, although the mechanism of this effect remains uncertain<sup>8</sup>.

In this study, an attempt was made to determine the possible association between the duration of diabetes mellitus and prevalence of ischemic stroke. Also, the effect of hyperglycemia on the short-term outcome of the acute phase of ischemic stroke was assessed.

## Patients and Methods

Data were collected from ischemic stroke patients admitted to the Department of Neurology, Osijek University Hospital, Osijek, Croatia, during 12 consecutive months. Basic patient characteristics are shown in Table 1. The diagnosis and type of diabetes mellitus (insulin dependent (IDDM) or non-insulin dependent (NIDDM) diabetes mellitus) were established on the basis of pre-stroke history data and confirmed by a consultant diabetologist. Glucose levels were monitored by repeated blood tests. Blood samples for serum glucose determination were obtained immediately upon admission, and then daily throughout their hospital stay. Non-diabetic patients were considered to have hyperglycemia if their fasting glucose levels exceeded 6.4 mmol/L on admission and spontaneously normalized during the first week of hospitalization.

The diagnosis of brain infarction was made on the basis of clinical and neuroimaging criteria. Computed tomography (CT) images were used to define stroke subtype: lacunar infarction, territorial infarction, hemodynamic infarction, or undefined infarction. The outcome of stroke was assessed 30 days upon admission using the Modified Rankin Scale.

## Results

In the present study, 95 (22.1%) patients had elevated fasting blood glucose level in the acute phase of ischemic stroke. Seventy-two (16.8% of all ischemic stroke patients) patients had a history of diabetes (nine IDDM and 63 NIDDM) prior to stroke. Patients with glucose intolerance were on an average older than those with ischemic stroke. The former group was characterized by female predominance, while an equal sex distribution was observed in the latter (Table 1). Hypertension was found to

be an additional risk factor for ischemic stroke in 87.4% of patients with hyperglycemia, while elevated blood cholesterol was recorded in only 31.1% of them.

Table 1. Basic patient characteristics

Characteristic	Ischemic stroke patients	
	With glucose intolerance	Total
No. of patients	95	429
Mean age (yrs)	68.6±7.8	63.6±12.3
Sex (M/F)	42/53	220/209

Brain imaging analysis showed territorial infarction in 46 cases of ischemic stroke and hyperglycemia, followed by 21 cases of lacunar infarction, while two stroke cases were found to have a hemodynamic pathophysiology. In 26 cases, the localization or pathophysiology of stroke could not be determined by CT brain scan. There was no clinical or CT evidence of hemorrhage in the infarction area.

Diabetic patients were classified into three groups according to their history data: diabetes duration of ≤5, 6-10 or ≥11 years. The prevalence of ischemic stroke and its association with the duration of either IDDM or NIDDM are presented in Fig. 1. Diabetes duration of ≥6 years was associated with more ischemic stroke cases than shorter diabetes duration of ≤5 years. Further analysis yielded a significant difference in stroke prevalence between patients with NIDDM duration of 6-10 years and ≥11 years ( $p < 0.01$ ). In the group of patients with the longest dura-

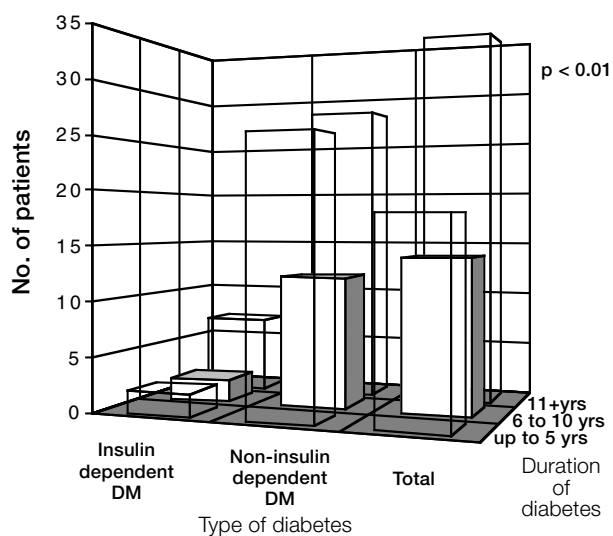


Fig. 1. Duration of diabetes and prevalence of ischemic stroke

tion of diabetes mellitus, most of stroke cases were found to have been facilitated by the presence of diabetes.

The functional outcome of stroke as assessed by the Modified Rankin Scale showed a more severe functional deficit in the group of patients with hyperglycemia in comparison to the group of ischemic stroke patients without hyperglycemia. The case fatality rate was higher in the former than in the latter group (28.7% *vs* 22.2% of all cases) (Fig. 2).

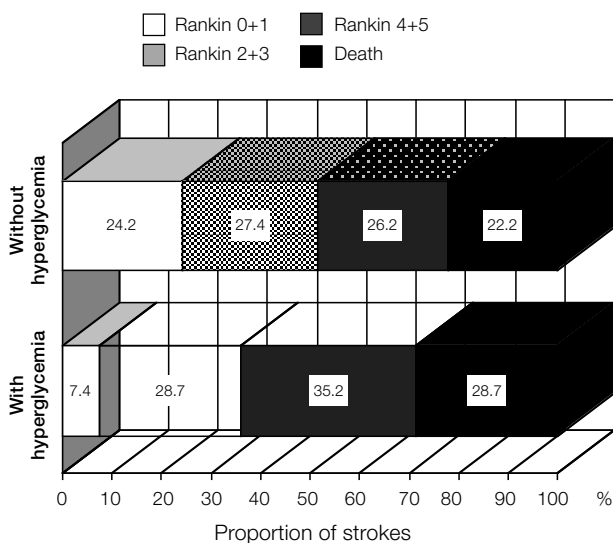


Fig. 2. Ischemic stroke outcome 30 days after onset (Modified Rankin Scale)

## Discussion

Results of our study conducted in the population of the Osijek area confirmed diabetes mellitus as a major risk factor for ischemic stroke, accounting for 17% of all ischemic stroke patients, i.e. a proportion similar to those reported from large population-based studies in developed countries<sup>2,4,9</sup>. In our diabetic patients, ischemic stroke was found to be associated with age, female gender, hypertension, and to a lesser extent with blood cholesterol. Our findings are consistent with the results of a multivariate regression analysis study of risk factors for atherothrombotic brain infarction, showing that glucose intolerance is an independent contributor to stroke only in women aged over 65, and of another study on stroke in type 2 diabetes patients showing that hypertension has to be regarded as the best predictor of stroke outcome<sup>10,11</sup>.

NIDDM was the most common cause of hyperglycemia in our stroke patients, followed by IDDM and stress

hyperglycemia. One can only speculate that some of the patients who had hyperglycemia and no history of diabetes may have had a previously unrecognized (latent) form of diabetes.

Using CT images, we demonstrated that most of the infarctions associated with hyperglycemia occurred in the territory of large cerebral vessels, and they were likely caused by a thrombotic and/or embolic event following atherosclerotic plaque transformation. Some evidence indicate that hyperglycemia intensifies brain injury secondary to cerebral ischemia in animals. On the other hand, large strokes may lead to stress hyperglycemia and to poorer prognosis<sup>12</sup>. No hemorrhagic transformation of the infarction with acute hyperglycemia was detected on CT scans, as it has previously been reported<sup>13</sup>.

We found that longer duration of diabetes significantly contributed to the occurrence of ischemic stroke. This association seems not to be as linear as suggested by two previously published multivariate analyses of the main risk factors for stroke in middle-aged and elderly population of Finland<sup>8,14</sup>. There was a fall in the risk of ischemic stroke for patients with NIDDM duration of 6-10 years, so it may seem that in this period diabetes is not as critical for brain ischemia. However, history data for NIDDM are not reliable enough to determine the onset of NIDDM, because there is strong evidence that its onset may actually occur many years before the clinical diagnosis<sup>15</sup>.

Acute hyperglycemia influenced the outcome of ischemic stroke at 30 days from its onset. The neurologic deficit in our patients with hyperglycemia was more severe than in those without hyperglycemia. Consequently, the case fatality rate was higher in the former group. Our data are comparable with the results of Toni et al.<sup>7</sup>, although they speculate that moderate hyperglycemia in some of their non-diabetic patients (those with supposedly slight reduction of blood flow in the brain infarction area) may have even had some beneficial effect. On the other hand, van Knooten et al.<sup>16</sup> report that 'stress' hyperglycemia in acute stroke had no impact on stroke severity at early onset, but significantly correlated with stroke outcome. In fact, many of these patients may have a latent form of diabetes mellitus<sup>17</sup>.

In conclusion, diabetes mellitus is an important risk factor for ischemic stroke. Prolonged diabetes duration has a greater contributory effect on the occurrence of stroke than shorter duration of the disease. The presence of hyperglycemia in the acute phase of stroke aggravates the final outcome of ischemic stroke. Thus, early detection and

management of hyperglycemia should be considered important measures in the prevention of stroke.

## References

1. BILLER J, LOVE BB. Diabetes and stroke. *Med Clin North Am* 1993;77:95-100.
2. SPRAFKA JM, VIRNIG BA, SHAHAR E, McGOVERN PG. Trends in diabetes prevalence among stroke patients and the effect of diabetes on stroke survival: the Minnesota Heart Survey. *Diabet Med* 1994;11:95-110.
3. ABBOTT RD, DONAHUE RP, MacMAHON SW, REED DM, YANO K. Diabetes and the risk factor of stroke. The Honolulu Heart Program. *JAMA* 1987;257:949-52.
4. STEGMAYER B, ASPLUND K. Diabetes as a risk factor for stroke. A population perspective. *Diabetologia* 1995;38:1061-8.
5. De SYO D, PODOBNIK-ŠARKANJI S, DESPOT I, FERENČIĆ Ž. Patologija okluzivne cerebrovaskularne bolesti. In: DEMARIN V et al. *Moždani krvotok – klinički pristup*. Zagreb: Naprijed, 1994:26-50.
6. The Diabetes Control and Complication Trial (DCCT) Research Group. Effect of intensive diabetes management on macrovascular events and risk factors in the Diabetes Control and Complications Trial. *Am J Cardiol* 1995;75:894-903.
7. TONI D, SACCHETTI ML, ARGENTINO C, GENTILE M, CAVALLETTI C, FRONTONI M, FIESCHI C. Does hyperglycemia play a role on the outcome of acute ischaemic stroke patients? *J Neurol* 1992;239:382-6.
8. TUOMILEHTO J, RASTENYTE D, JOUSILAHTI P, SARTI C, VARTAINEN E. Diabetes mellitus as a risk factor for death from stroke. Prospective study on the middle-aged Finnish population. *Stroke* 1996;27:210-5.
9. JORGENSEN HB, NAKAYAMA H, RAASCHOU HO, OLSEN TB. Stroke in patients with diabetes. The Copenhagen Stroke Study. *Stroke* 1994;25:1977-84.
10. WOLF PA, BELANGER AJ, D'AGOSTINO LD. Management of risk factors. *Neurol Clin* 1992;10:177-91.
11. DAVIS TME, MILLINS H, STRATTON IM, HOLMAN RR, TURNER RC. Risk factors for stroke in type 2 diabetes mellitus. *Arch Intern Med* 1999;159:1097-103.
12. KIERS L, DAVIS SM, LARKINS R, HOPPER J, TRESS B, ROSSITER SC, CARLIN J, RATNAIKE S. Stroke topography and outcome in relation to hyperglycemia and diabetes. *J Neurol Neurosurg Psychiatry* 1992;55:263-70.
13. BRODERICK JP, HAGEN T, BROTT T, TOMSICK T. Hyperglycemia and hemorrhagic transformation of cerebral infarcts. *Stroke* 1995;26:484-7.
14. KUUSISTO J, MYKKÄNEN L, PYÖRÄLÄ K, LAAKSO M. Non-insulin dependent diabetes and its metabolic control are important predictors of stroke in elderly subjects. *Stroke* 1994;25: 1157-64.
15. HARRIS MI, KLEIN R, WELBORN TA, KNUIMAN MW. Onset of NIDDM occurs at least 4-7 years before clinical diagnosis. *Diabetes Care* 1992;15:815-9.
16. Van KNOOTEN F, HOOGERBRUGGE N, NAARDING P, KOUDSTAAL PJ. Hyperglycemia in the acute phase of stroke is not caused by stress. *Stroke* 1993;24:1129-32.
17. OPPENHEIMER SM, HOFFBRAND BI, OSWALD GA, YUDKIN JS. Diabetes mellitus and early mortality from stroke. *BMJ* 1985;291:1014-5.

## Sažetak

### HIPERGLIKEMIJA U BOLESNIKA S ISHEMIJSKIM MOŽDANIM UDAROM

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Cilj ovoga istraživanja bio je utvrditi moguću povezanost duljine trajanja dijabetesa i pojave ishemijskog moždanog udara (IMU). Usto, ispitan je i učinak hiperglikemije u akutnoj fazi IMU na ishod nakon 30 dana liječenja. U ispitivanju je bilo obuhvaćeno 429 hospitaliziranih bolesnika koji su liječeni tijekom 12 uzastopnih mjeseci zbog IMU na našoj klinici. Dijagnoza dijabetesa i njegove podvrste postavljena je na osnovi povijesti, a potvrđena konzilijarnim pregledom dijabetologa. Glikemija je praćena ponovljenim serumskim pretragama. Dijagnoza i ishod IMU procijenjeni su prema kliničkim i neuroradiološkim kriterijima. Hiperglikemija je ustanovljena u 95 bolesnika s IMU (u 22,1% svih slučajeva IMU); od toga je 72 bolesnika imalo dijagnozu dijabetesa prije moždanog udara (devetoro tipa 1, a 63 tipa 2). Prosječna dob bila je 68,6±7,8 godina, 53 žene i 42 muškarca. Hipertenzija je bila dodatni čimbenik rizika u 87,4%, dok je povišeni kolesterol nađen u samo 31,1% bolesnika. Neuroradiološki je teritorijalni infarkt dokazan u 46, a lakunarni infarkt u 21 bolesnika s IMU, dok je samo dvoje bolesnika imalo hemodinamski infarkt. Trajanje dijabetesa od više od 6 godina bilo je značajno povezano s većim brojem IMU nego kraće trajanje dijabetesa do 5 godina (50 prema 22 bolesnika). Daljnja analiza pokazala je statistički značajnu razliku u broju IMU između skupine s trajanjem dijabetesa tipa 2 od 6-10 godina i one s 11 i više godina ( $p<0,01$ ), gdje je veći broj bolesnika s IMU zabilježen u skupini s najdužim trajanjem dijabetesa. Funkcionalni ishod IMU procijenjen je modificiranom Rankinovom ljestvicom. U skupini bolesnika s hiperglikemijom neurološki deficit bio je težega stupnja (Rankin 0 i 1 u 7,4%, Rankin 2 i 3 u 28,7% te Rankin 4 i 5 u 35,2% bolesnika) u usporedbi s bolesnicima bez hiperglikemije (Rankin 0 i 1 u 24,2%, Rankin 2 i 3 u 27,4% te Rankin 4 i 5 u 26,2% bolesnika). Stopa smrtnosti nakon 30 dana bila je viša u prvoj nego u potonjoj skupini bolesnika (28,7% prema 22,2%). Dijabetes je važan čimbenik rizika za IMU u promatranoj populaciji. Duže trajanje dijabetesa značajno više doprinosi pojavi IMU nego kraće trajanje bolesti. Prisutnost hiperglikemije u akutnoj fazi moždanog udara pogoršava kratkoročni ishod IMU. Zato je rano otkrivanje i liječenje hiperglikemije važan čimbenik u prevenciji moždanog udara.

*Ključne riječi: Moždani ishemija, komplikacije; Hiperglikemija; Diabetes mellitus, komplikacije; Diabetes mellitus, epidemiologija*