

# DISORDERS OF BLOOD GLUCOSE LEVELS IN ADULT PATIENTS WITH ACUTE ISCHEMIC STROKE

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## ABSTRACT

**INTRODUCTION:** Effective and timely prevention of acute ischemic stroke (AIS) is characterized by a rising socio-medical importance as this is the most common cerebrovascular disease worldwide and in Bulgaria as well. Our purpose was to reveal the incidence rate of the disorders of glucose metabolism in AIS development among adult patients.

**MATERIAL AND METHODS:** We examined 129 male and 129 female patients with AIS at a mean age of  $70.59 \pm 7.22$  years hospitalized in the First Clinic of Neurology, St. Marina University Hospital of Varna in 2007-2013. Blood glucose concentrations at admission were examined. Statistical data processing was performed by variation (ANOVA as t-criterion was considered significant if  $p < 0.05$ ) and correlation (Pearson's coefficient) analyses.

**RESULTS:** Mean fasting blood glucose levels were most commonly elevated and total ones were higher in males than in females except for the minimal value. The males with abnormally elevated blood glucose values present with higher mean and maximal values than the females. The number and relative share of the patients with increased blood glucose values at admission considerably prevailed. The difference between the number of the males with increased values and that of those with normal values was statistically significant ( $t=3.33$ ;  $p < 0.01$ ). There was moderate correlation between the level of blood glucose and the preceding diabetes mellitus ( $r=0.431$ ) and a strong one between this level and the newly-diagnosed diabetes mellitus ( $r=0.733$ ) among our AIS patients.

**CONCLUSION:** The regular control of blood glucose by the general practitioners and the promotion of the healthy life-style in cardiovascular disease patients could successfully prevent AIS in Bulgaria.

**Keywords:** acute ischemic stroke, blood glucose, diabetes mellitus, hyperglycaemia, correlation analysis

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## INTRODUCTION

Acute ischemic stroke (AIS) is the most common cerebrovascular disease worldwide and in Bulgaria as well. The disorders of glucose metabolism are a recognized risk factor for AIS. Besides diabetes mellitus represents an unfavourable prognostic factor for AIS patients (1). Patients with diabetes mellitus have approximately twice the risk of AIS compared to those without this disease (2). Metabol-

ic pathology in diabetes mellitus causes cerebral arterial dysfunction and that is why such patients require proper management of any metabolic disorders in order to reduce atherogenesis (3). Serial blood glucose measurements might be a better predictor of clinical outcome in AIS patients treated with intravenous thrombolysis than single ones before this treatment (4). Hyperglycaemia is a strong risk factor for poor outcome after AIS, but it may be simply a marker of poor outcome rather than a cause. Glucose lowering does not relate to improved prognosis of the disease.

12 AIS patients, seven males and five females, too. Statistical data processing was performed by variation (ANOVA as *t*-criterion was considered significant if  $p < 0.05$ ) analysis and correlation (Pearson's coefficient) analysis as well. SPSS, version 13.0 software was used.

## RESULTS

Mean blood glucose concentrations vary in relatively broad limits (between 6.14 mmol/L in 2010 and 7.97 mmol/L in 2013) (Table 1). Total blood glucose values are higher in males than in females ex-

*Table 1. Annual dynamics of blood glucose levels in adult AIS patients at admission*

Years	Blood glucose (mmol/L)		
	mean values	minimal values	maximal values
2007	6.75±2.94	4.08	18.30
2008	6.61±2.14	4.08	13.70
2009	6.87±2.51	3.70	13.00
2010	6.14±2.14	3.60	14.90
2011	6.90±2.47	3.90	14.10
2012	7.57±2.98	4.40	15.20
2013	7.97±3.07	3.70	18.00
total males	7.38±2.92	3.60	18.30
total females	6.95±2.60	4.00	16.20
total	7.16±2.77	3.60	18.30

## MATERIAL AND METHODS

Our investigation covered 129 male and 129 female patients with AIS at a mean age of 70.59±7.22 years hospitalized in the First Clinic of Neurology, St. Marina University Hospital of Varna in 2007-2013. Fasting blood glucose concentrations at admission were examined and analyzed according to gender and number of accompanying cardiovascular diseases (CVDs) or pathological conditions. In 2013, glycated hemoglobin values were estimated in

*Table 2. AIS patients with mean normal and pathological blood glucose values at admission*

Patients with	Blood glucose (mmol/L)	
	males	females
normal values	5.16±0.45	5.11±0.45
increased values	8.91±2.81	8.49±2.60
decreased values	3.74±0.11	4.05±0.05

cept for the minimal value.

The analysis of the number and relative share of the patients with normal, decreased and increased blood glucose values displays the frequency of anomalies and thus illustrates the importance of regular examinations under outpatient conditions for preventive purposes (Table 2 and Table 3). The males with abnormally elevated values present with higher mean and maximal values than the females. Besides the range between the maximal concentration in the cases with pathologically increased blood glucose values and its minimal concentration in the cases with pathologically decreased blood glucose values is broader in the male than in the female patients (14.70 mmol/L versus 12.20 mmol/L). The number and relative share of the patients with elevated blood glucose values at admission considerably prevail. The difference between the number of the males with in-

**Table 3.** Number and percentage of adult AIS patients with normal and pathological blood glucose values at admission

Patients	Patients with normal values		Patients with increased values		Patients with decreased values	
	n	%	n	%	n	%
males	47	36.43	77	59.69	5	3.88
females	55	42.64	71	55.04	3	2.32
total	102	39.54	148	57.36	8	3.10

creased values and that of those with normal values is statistically significant ( $t=3.33$ ;  $p<0.01$ ).

The mean glycated hemoglobin value was 6.7% (range, 5.9% and 7.2%). The small number of these cases did not allow any reliable statistical data processing.

There is moderate positive correlation between the level of blood glucose and the preceding diabetes mellitus ( $r=0.431$ ) as well as a strong one between this level and the newly-diagnosed diabetes mellitus ( $r=0.733$ ) among our AIS patients (Table 4). This demonstrates that the disorders of glucose metabolism are associated with the occurrence of AIS, especially in males.

The blood glucose values of AIS patients presenting with at least one out of nine accompanying CVDs or pathological conditions have been analyzed. These nosologic units are the following: arterial hypertension, hypertensive heart, coronary atherosclerosis, ischemic heart disease, effort angina pectoris, myocardial infarction, atrial fibrillation, ventricular tachyarrhythmia, and heart failure. It should be noted that there is no CVD in one male patient at all while one female patient presents with eight accompanying CVDs (Table 5). The males with four and two other diseases each as well as the females with two and seven other diseases each present with the highest mean blood glucose concentrations.

**Table 4.** Correlations between admission blood glucose values, preceding and newly-diagnosed type 2 diabetes mellitus in adult AIS patients

Variables	Pearson's correlation coefficients		
	preceding diabetes mellitus	newly-diagnosed diabetes mellitus	blood glucose
preceding diabetes mellitus	1	0.733	0.431
newly-diagnosed diabetes mellitus	0.733	1	0.535
blood glucose	0.431	0.535	1

**Table 5.** Mean blood glucose values of adult AIS patients according to the number of accompanying CVDs

Number of CVDs	Blood glucose (mmol/L)	
	males	females
none	-	5.55±0.62
one	6.57±2.19	5.77±1.20
two	8.05±2.90	8.02±3.55
three	7.62±4.15	7.15±2.64
four	8.17±3.18	6.30±2.08
five	6.66±2.02	6.64±1.96
six	7.41±2.98	7.53±2.98
seven	6.59±3.03	7.54±2.17
nine	-	5.80±2.26

These findings support the relationship between diabetes mellitus and CVDs as proved risk factors for AIS in adulthood.

## DISCUSSION

Hyperglycaemia relates to poor prognosis of AIS. It is an indicator of severe AIS that can't enhance the glucose concentration in the brain. However, it further promotes cerebral ischemia. The cerebral glucose concentration controlled by the cerebral glucose transporters contributes to the energy supply to the brain, especially among AIS patients, and could become a therapeutic target for IS (5). The results from a retrospective analysis by perfusion CT

of 26 patients suggests that chronic hyperglycaemia might be linked with cerebral microvascular remodeling in man (6). A randomized, blinded efficacy trial outlines the potential benefits and risks of standard versus intensive hyperglycaemia management in AIS patients (7). The detrimental effects of hyperglycaemia on the morbidity and mortality of AIS patients during the initial 48 hours of the disease were emphasized (8). A study of 2 639 IS patients in China shows that impaired glucose regulation as assessed by the glucose tolerance test is an independent risk factor for their one-year mortality ( $p=0.006$ ) and should be highlighted and intervened actively in such patients (9).

Hyperglycaemia is commonly encountered in patients with or without diabetes mellitus in AIS. The evidence links it with neurotoxicity coupled with the failure of intensive glucose control regimens to improve functional outcomes in AIS and suggests that novel approaches should be devised. Glycaemic variability was a proven predictor of prognosis in critically ill AIS patients (10).

Admission hyperglycaemia was very common in AIS patients and was related to worse prognosis in non-lacunar brain infarction. The association between hyperglycaemia and clinical outcome in 689 consecutive lacunar AIS patients in a hospitalized Chinese population was investigated (11). Of them, 159 (23%) presented with diabetes mellitus. In non-lacunar AIS, admission hyperglycaemia was independently associated with increased risk of poor outcome ( $p=0.0005$ ) while in lacunar AIS, it was not related to functional outcome at one year ( $p=0.086$ ) irrespective of the diabetic status. Chronic hyperglycemia aggravated haemorrhagic transformation after stroke through mitochondrial dysfunction and morphological alteration (12).

The prevalence of prediabetes mellitus, an intermediate metabolic state between normal glucose metabolism and diabetes mellitus, in previously non-diabetic patients with a recent AIS ranges from 23 to 53% and represents undiagnosed abnormal glucose metabolism. This pathology seems to be a modest predictor for AIS, but doubles the risk for recurrent disease. It could become one of the most important modifiable therapeutic targets in both primary and secondary prevention (13).

The retrospective analysis of a prospective series of first-ever AIS patients revealed that the patients with prediabetes mellitus presented more commonly with arterial hypertension ( $p=0.006$ ) and higher waist circumference ( $p<0.0001$ ) than those without diabetes mellitus, and diabetes mellitus patients had more hypercholesterolemia ( $p<0.0001$ ), coronary artery disease ( $p=0.005$ ) and higher body mass index ( $p=0.017$ ) than those with prediabetes (14).

The investigation of 1 316 AIS patients without previous diabetes mellitus in China demonstrated that the combination of glycated hemoglobin and fasting plasma glucose increased the diagnostic rate of diabetes mellitus when compared with oral glucose tolerance test as well as with glycated hemoglobin or fasting plasma glucose alone. The glycated hemoglobin could significantly detect more cases of prediabetes than the oral glucose tolerance test ( $p<0.001$ ) (15). The glycated hemoglobin  $\geq 7.2\%$  ( $>55$  mmol/mol) was an independent risk predictor for one-year all-cause mortality after first-ever AIS (16).

Among 1052 AIS patients without diabetes mellitus, hazard ratio for AIS was 1.04 (95% CI 0.83-1.30) for the lowest glycated hemoglobin quartile ( $<6.35\%$ ) and 1.63 (95% CI 1.33-2.00) for the highest quartile ( $>7.70\%$ ) (for trend,  $p<0.001$ ) while in 11 176 AIS patients with diabetes mellitus, it was 1.17 (95% CI 1.09-1.26) for every 1% increment in glycated hemoglobin level (17).

In 140 out of 242 consecutive AIS patients without previously diagnosed diabetes mellitus, the disease was proved by means of glucose tolerance test at admission (18). In multivariate analysis, the risk of early neurological deterioration was significantly higher in these patients than in those with normal glucose tolerance ( $p=0.019$ ) while the risk of poor outcome was more significantly higher ( $p<0.001$ ), even after adjusting for confounding factors ( $p=0.008$ ).

In a population-based study in Greater Cincinnati/Northern Kentucky region, a rising incidence of the history of diabetes mellitus among first IS patients - from 28% in 1993/1994 to 29% in 1999 and 33% in 2005 was reported (19). Risk ratios for rates of IS among the patients with versus without diabetes mellitus for blacks reduced significantly from 5.6 in 1993/1994 to 3.2 in 2005. They varied

with age, with an overall 5- to 14-fold increased risk among the patients aged 20 to 65 years. Diabetes mellitus or impaired fasting glucose in young AIS survivors was frequent and was associated with recurrent vascular events. Regular screening yielded potential for secondary AIS prevention (20). Type 2 diabetes mellitus was present in 32.2% of 482 AIS patients at a mean age of  $78.8 \pm 6.7$  years (21). AIS patients with diabetes mellitus should not be excluded from intravenous thrombolysis as it was independently associated with a lower risk of poor outcome in such patients ( $p=0.002$ ) (22).

## CONCLUSION

The results from the present study and the recent literature data available illustrate the effect of the common disorders of glucose metabolism such as hyperglycaemia, prediabetes and diabetes mellitus on the development of AIS in adult patients. We could draw the conclusion that the regular control of blood glucose by the general practitioners and the promotion of the healthy life-style in CVD patients could successfully contribute to the prevention of AIS in Bulgaria.

## REFERENCES

- Palacio S, McClure LA, Benavente OR, Bazan C 3<sup>rd</sup>, Pergola P, Hart RG. Lacunar strokes in patients with diabetes mellitus: risk factors, infarct location, and prognosis: the secondary prevention of small subcortical strokes study. *Stroke*. 2014;45(9):2689-94.
- Hill MD. Stroke and diabetes mellitus. *Handb Clin Neurol*. 2014;126:167-74.
- Shindo A, Tomimoto H. Diabetes and ischemic stroke. *Brain Nerve*. 2014;66(2):107-19. Japanese.
- Yoo DS, Chang J, Kim JT, Choi MJ, Choi J, Choi KH, et al. Various blood glucose parameters that indicate hyperglycemia after intravenous thrombolysis in acute ischemic stroke could predict worse outcome. *PLoS One*. 2014;9(4):e94364. doi: 10.1371/journal.pone.0094364.
- Zhang S, Zuo W, Guo XF, He WB, Chen NH. Cerebral glucose transporter: the possible therapeutic target for ischemic stroke. *Neurochem Int*. 2014;70:22-9.
- Hou Q, Zuo Z, Michel P, Zhang Y, Eskandari A, Man F, et al. Influence of chronic hyperglycemia on cerebral microvascular remodeling: an in vivo study using perfusion computed tomography in acute ischemic stroke patients. *Stroke*. 2013;44(12):3557-60.
- Bruno A, Durkalski VL, Hall CE, Juneja R, Barsan WG, Janis S, et al.; SHINE investigators. The Stroke Hyperglycemia Insulin Network Effort (SHINE) trial protocol: a randomized, blinded, efficacy trial of standard vs. intensive hyperglycemia management in acute stroke. *Int J Stroke*. 2014;9(2):246-51.
- Clark ME, Payton JE, Pittiglio LI. Acute ischemic stroke and hyperglycemia. *Crit Care Nurs Q*. 2014;37(2):182-7.
- Jia Q, Liu G, Zheng H, Zhao X, Wang C, Wang Y, et al.; Investigators for the Survey on Abnormal Glucose Regulation in Patients With Acute Stroke Across China. Impaired glucose regulation predicted 1-year mortality of Chinese patients with ischemic stroke: data from abnormal glucose regulation in patients with acute stroke across China. *Stroke*. 2014;45(5):1498-500.
- González-Moreno EI, Cámara-Lemarroy CR, González-González JG, Góngora-Rivera F. Glycemic variability and acute ischemic stroke: the missing link? *Transl Stroke Res*. 2014;5(6):638-46.
- Fang Y, Zhang S, Wu B, Liu M. Hyperglycaemia in acute lacunar stroke: a Chinese hospital-based study. *Diab Vasc Dis Res*. 2013;10(3):216-21.
- Mishiro K, Imai T, Sugitani S, Kitashoji A, Suzuki Y, Takagi T, et al. Diabetes mellitus aggravates hemorrhagic transformation after ischemic stroke via mitochondrial defects leading to endothelial apoptosis. *PLoS One*. 2014;9(8):e103818. doi: 10.1371/journal.pone.0103818.
- Fonville S, Zandbergen AA, Koudstaal PJ, den Hertog HM. Prediabetes in patients with stroke or transient ischemic attack: prevalence, risk and clinical management. *Cerebrovasc Dis*. 2014;37(6):393-400.
- Roquer J, Rodríguez-Campello A, Cuadrado-Godia E, Giralt-Steinhauer E, Jiménez-Conde J, Dégano IR, et al. Ischemic stroke in prediabetic patients. *J Neurol*. 2014;261(10):1866-70.
- Wu S, Shi Y, Pan Y, Li J, Jia Q, Zhang N, et al. Glycated hemoglobin independently or in combination with fasting plasma glucose versus oral glucose tolerance test to detect abnormal glycometabolism in acute ischemic stroke: a

- Chinese cross-sectional study. *BMC Neurol.* 2014;14:177. doi: 10.1186/s12883-014-0177-0.
16. Wu S, Wang C, Jia Q, Liu G, Hoff K, Wang X, et al. HbA1c is associated with increased all-cause mortality in the first year after acute ischemic stroke. *Neurol Res.* 2014a;36(5):444-52.
  17. Khoury JC, Kleindorfer D, Alwell K, Moomaw CJ, Woo D, Adeoye O, et al. Diabetes mellitus: a risk factor for ischemic stroke in a large biracial population. *Stroke.* 2013;44(6):1500-4.
  18. Saliba W, Barnett-Griness O, Elias M, Rennert G. Glycated hemoglobin and risk of first episode stroke in diabetic patients with atrial fibrillation: A cohort study. *Heart Rhythm.* 2015;12(5):886-92.
  19. Tanaka R, Ueno Y, Miyamoto N, Yamashiro K, Tanaka Y, Shimura H, et al. Impact of diabetes and prediabetes on the short-term prognosis in patients with acute ischemic stroke. *J Neurol Sci.* 2013;332(1-2):45-50.
  20. Khoury JC, Kleindorfer D, Alwell K, Moomaw CJ, Woo D, Adeoye O, Flaherty ML, et al. Diabetes mellitus: a risk factor for ischemic stroke in a large biracial population. *Stroke.* 2013;44(6):1500-4.
  21. Rutten-Jacobs LC, Keurlings PA, Arntz RM, Maaijwee NA, Schoonderwaldt HC, Dorresteijn LD, et al. High incidence of diabetes after stroke in young adults and risk of recurrent vascular events: the FUTURE study. *PLoS One.* 2014;9(1):e87171. doi: 10.1371/journal.pone.0087171.
  22. Tziomalos K, Spanou M, Bouziana SD, Papadopoulou M, Giampatzis V, Kostaki S, et al. Type 2 diabetes is associated with a worse functional outcome of ischemic stroke. *World J Diabetes.* 2014;5(6):939-44.
  23. Fuentes B, Masjuan J, Alonso de Leciñana M, Simal P, Egido J, Díaz-Otero F, et al.; Madrid Stroke Network. Benefits of intravenous thrombolysis in acute ischemic stroke related to extracranial internal carotid dissection. Dream or reality? *Int J Stroke.* 2012;7(1):7-13.