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Effect of hyperglycemia on cerebral blood flow in patients with diabetes

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ABSTRACT

Aims: Diabetes interferes with cerebral blood flow (CBF) and it seems that the effect of acute hyperglycemia on CBF is different from the changes in CBF caused by chronic diabetes. The aim of the study was to check whether there are changes in CBF measured using transcranial Doppler (TCD) in patients with hyperglycemia before and after normalization of glycemia.

Methods: The study involved 29 patients with diabetes and 27 healthy subjects (control group). The TCD test evaluated mean flow velocity (Vm), systolic velocity (Vs) and Gosling's pulsatility index (PI) in both middle cerebral arteries (MCAs). It was performed twice in patients with diabetes (during hyperglycemia and after normalization of glycemia) and once in the control group.

Results: The baseline blood flow parameters were similar in both groups. After the normalization of glycemia in patients with diabetes, they showed lower values of Vm and Vs compared to the control group ($p < 0.001$). Also, the normalization of glycemia caused a decrease in Vm and Vs ($p < 0.001$) in patients with diabetes. There were no significant differences in PI.

Conclusions: In the patients with hyperglycemia, Vm and Vs in the MCA were higher than during normoglycemia, which was probably related to vasoconstriction and hypervolemia.

1. Introduction

Diabetes is an independent risk factor for cerebrovascular disease, especially stroke. Hyperglycemia causes brain damage in patients with diabetes and its presence in stroke patients on admission to hospital may worsen prognosis [1,2]. There is no doubt that diabetes interferes with the cerebral blood flow (CBF), however, our knowledge about the structural and functional changes in cerebral vessels of different caliber under the influence of hyperglycemia is insufficient. In addition, most of the previous data come from animal studies. It

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seems that the effect of acute hyperglycemia on CBF is different from changes in CBF caused by chronic diabetes [3].

Transcranial Doppler (TCD) enables non-invasive assessment of blood flow in intracranial arteries. It has been proved that changes in the diameter of cerebral vessels affect the TCD parameters, moreover CBF correlates with the flow velocity in these vessels [4].

The aim of the study was to check whether there are changes in CBF measured using the TCD in patients with hyperglycemia before and after normalization of glycemia.

2. Subjects, materials and methods

The study enrolled patients hospitalized in the Endocrinology and Diabetology Clinic due to decompensated type 1 (n = 12) and type 2 (n = 17) diabetes, who had accidental glycemia above 250 mg/dl on the first day of hospitalization. The patients were included in the study immediately after the detection of hyperglycemia using a glucometer. Afterwards, their venous blood was collected to verify plasma glucose; moreover, their blood pressure and pulse were measured. Following the blood collection, a TCD examination was performed in accordance with the standards of the Neurosonology Section of the Polish Neurological Society. During the test the patients were lying on a bed in a shaded room with constant temperature. The TCD evaluated mean flow velocity (Vm), systolic velocity (Vs) and Gosling's pulsatility index (PI) in both middle cerebral arteries (left and right MCAs). After examination, all the patients regardless of their previous way of treatment, received insulin therapy using the multiple-injection algorithm (fast-acting insulin analogue before meals and NPH insulin before sleep). The aim was to reduce fasting blood glucose to 90–110 mg/dl and postprandial glucose below 140 mg/dl while simultaneously avoiding hypoglycemia. The TCD examination, preceded by the measurement of pressure and pulse, was repeated on the 5th day of hospitalization, after confirmation of glycemia $\leq$150 mg%, on condition they did not have hypoglycemia during the day preceding the examination. Additionally, patients were examined neurologically, focusing on the presence of diabetic neuropathy diagnosed on the basis of current recommendations [5]. Routine blood tests were performed in the patients, including HbA1c, thyroid-stimulating hormone (TSH), lipid profile and creatinine. The study excluded patients with inadequate temporal acoustic windows and with diseases that could affect cerebral flow: stenosis/closure of the internal carotid artery or MCA, atrial fibrillation, water-electrolyte imbalance, metabolic acidosis, respiratory failure, heart, kidney and liver failure, hypotonia, fever, anemia and several other conditions. The control group were patients without diabetes, with normoglycemia, matched by age and burdens, who had the TCD examination performed once according to the scheme described above. This study was approved by Nicolaus Copernicus University Ethics Committee and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from each study participant.

In the present study all the measurements were performed using a Nicolet/EME Pioneer camera with a 2 MHz probe. The patients were examined in the supine position. After finding the temporal acoustic window, the central cerebral artery was identified. The probe was positioned so as to obtain the highest possible velocity from the tested vessel. Three measurements were recorded in that probe position: Vm, Vs and PI were measured at the depth of 54–56 mm in the right and left MCA. Due to the absence of statistically significant differences between the right and left MCA, the values were averaged. The TCD tests were performed by a physician with extensive experience in the field of neurosonology.

3. Results

The study involved 29 patients with diabetes and 27 people from the control group. There were no significant differences in these groups in terms of age and burdens (48.07 ± 14.63 years in the group with diabetes vs. 46.96 ± 14.74 years in the control group). Table 1 presents more information about the study group.

The blood flow parameters of the patients with diabetes during hyperglycemia were not significantly different from the corresponding values of the control group. However, after the normalization of glycemia in the patients with diabetes, they showed significantly lower values of Vm and Vs compared to the control group. There were no significant differences in PI values, although there was a tendency for higher PI values in patients with diabetes (Table 2).

The results show that the normalization of glycemia in the patients with diabetes caused a statistically significant decrease in Vm ($p < 0.001$) and Vs ($p < 0.001$). There were no significant changes in PI ($p = 0.440$) after the normalization of glycemia, although there was a tendency for this parameter to increase with a decrease of glycemia (Table 3).

Data on the absolute and relative changes in MCA blood flow parameters as a consequence of normoglycemia show that the age of the patients significantly affected the magnitude of absolute and relative changes in Vm values ($R = 0.49$; $p = 0.006$ for absolute change and $R = 0.39$; $p = 0.038$ for relative change) and absolute change in Vs ($R = 0.41$; $p = 0.027$). Thus, in older people, after the normalization of glycemia, the Vm and Vs values decreased less than in younger patients. However, there was no significant influence of age on the other blood flow parameters. It was also observed that the HbA1c value had a significant influence on the change in absolute Vm ($R = -0.35$; $p = 0.05$). On the other hand, there was no significant relation between the duration of diabetes, the BMI of the subjects, the magnitude of the absolute or relative change in the glucose level between the first and second test, and changes in blood flow after the normalization of glycemia.

The results show that there were no significant correlations between the baseline levels of cholesterol, LDL, HDL, triglycerides, creatinine, HbA1c or TSH, and the magnitude of the absolute and relative changes in the values of the parameters that were analyzed after the normalization of glycemia.

It was shown that in patients with diabetes with retinopathy the absolute and relative decrease in Vm ($p = 0.02$ and $p = 0.02$, respectively) was lower than in patients without

Table 1 – Demographic and clinical variables. Values presented as means ± SD or n (%).

Parameter	Study group	Control group
Number of patients	29	27
Age (years)	48.07 ± 14.63	46.96 ± 14.74
Sex (women/men)	12/17 (41.4/58.6)	11/16 (41.4/58.6)
Duration of diabetes (years)	9.45 ± 8.94	–
Diabetes de novo	8 (27)	–
Type of diabetes (1/2)	12/17 (41.4/58.6)	–
HbA1c (%)	10.26 ± 2.55	–
Glycemia – 1 measurement (mg%)	324.00 ± 78.84	106.84 ± 34.84
Glycemia – 2 measurement (mg%)	110.07 ± 27.23	–
Total cholesterol (mg/dl)	200.24 ± 35.85	192 ± 14.2
Hypertension	20 (69.0)	19
Smokers	8 (27.5)	9
Retinopathy	11 (37.9)	–
Polyneuropathy	13 (44.8)	–

Table 2 – Comparison of blood flow parameters in the MCA (mean ± SD) of the patients with diabetes during hyper- and normoglycemia (n = 29) and the control group (n = 27).

Parameter	Hyperglycemia (diabetes group)	Control group	p	Normoglycemia (diabetes group)	Control group	p
Vm	62.80 ± 14.14	66.70 ± 13.77	0.301	52.59 ± 14.51	66.70 ± 13.77	0.0005
Vs	97.72 ± 17.69	104.21 ± 19.66	0.199	83.50 ± 20.70	104.21 ± 19.66	0.0003
PI	0.94 ± 0.16	0.89 ± 0.14	0.282	0.95 ± 0.13	0.89 ± 0.14	0.108

Table 3 – Comparison of blood flow parameters in the MCA (mean ± SD) of patients with diabetes (n = 29) during hyperglycemia and after the normalization of glycemia.

Parameter	Hyperglycemia	Normoglycemia	p
Vm	62.80 ± 14.14	52.59 ± 14.51	<0.001
Vs	97.72 ± 17.69	83.50 ± 20.70	<0.001
PI	0.94 ± 0.16	0.95 ± 0.13	0.440

complications. In patients with diabetic polyneuropathy, the absolute and relative decrease in Vm and Vs was significantly lower. However, neither the type of diabetes mellitus nor hypertension had significant effect on the changes in blood flow parameters.

4. Discussion

Cerebral arteries and arterioles are different from other arteries because they have their own muscle tone and respond with an active contraction to the increase in transmural pressure. It is known that cerebral arteries are in a state of partial contraction, which allows them to change their diameter to regulate cerebral blood flow. Because blood flow is related to the diameter of the vessel, even a slight increase in the smooth muscle tone of the vessel will reduce its diameter and will lead to flow disturbances [6,7].

Chronic diabetes is related to endothelial dysfunction and the reduction of endothelium-dependent vascular relaxation. In patients with diabetes, the synthesis of nitric oxide (NO) is reduced, which leads to vasodilatation disturbances [8]. Furthermore, Harris et al. investigated diabetes-induced rats and found a thickening of the MCA wall and an increase in the wall-to-lumen ratio [9]. Similarly, acute hyperglycemia adversely affects the endothelium of the vessels and disturbs vasorelaxation.

The results of the present study show that in patients with diabetes the blood flow parameters measured with TCD are different from those in the healthy population. The PI index increases, which is a measure of cerebral microangiopathy, since PI reflects resistance in microcirculation. The results of studies on the blood flow velocity in cerebral vessels in patients with diabetes are contradictory. Novak et al. showed a significantly lower velocity in the group of 28 patients with type 2 diabetes compared to the control group [10]. Lee et al. did not show a significant difference in velocity between the group of patients with diabetes and the control group [11]. On the other hand, the study of Bathula et al. proves that in patients with diabetes velocity is greater than in the healthy population [12].

In our study of patients with diabetes, velocity during normoglycemia was significantly lower than in the control group, while there were no significant differences in velocity between the patients with diabetes during hyperglycemia and the control group. This explains the differences between the current studies on blood velocity in patients with diabetes – in most of these studies glycemic values were not checked while performing TCD measurements and comparing the group of patients with diabetes with the control group. Thus, patients with diabetes could have had either normoglycemia or hyperglycemia during the study, which certainly affected the different test results. As regards PI, in our study, PI values

were higher in both groups with diabetes compared to the control group, however, the results were not statistically significant, which is probably related to the small size of the study group.

To our knowledge, there are no studies about cerebral blood flow using TCD during hyperglycemia; this is the first study which compares blood flow with TCD in normo- and hyperglycemic patients.

Many authors show a decrease in cerebral blood flow during hyperglycemia [13]. The mechanism leading to a decrease in CBF appears to be multifactorial, associated with an increase in cerebral vascular resistance, increased plasma osmolarity and blood viscosity, and decreased cerebral metabolism. In our study, we showed that blood velocity in the MCA during hyperglycemia was significantly higher than during normoglycemia, with insignificant changes in PI. Assuming that the diameter of the vessels does not change, velocity correlates with CBF – therefore an increase in CBF increases blood flow velocity. Thus, an increase in velocity in patients with hyperglycemia could be associated with an increase in CBF. However, most authors have shown a decrease in CBF in patients with diabetes during hyperglycemia. It therefore follows that theoretically hyperglycemia should cause a decrease in V. Why, then, did V fall in our study? The explanation could be that there was a change in the MCA diameter in response to hyperglycemia. It is known that hyperglycemia reduces NO production, lowering vasodilatation [8]. Simultaneously, it increases the secretion of prostaglandins and eicosanoids, which shrink the vessels. The mechanisms described can lead to MCA shrinkage, which leads to an increase in the blood flow velocity in this vessel.

Dahl showed that decreased NO production was associated with a decrease in CBF by 30%, while blood flow velocity in the MCA did not change, suggesting an MCA contraction [14]. Bathula noticed that in the Asian population V and PI in the MCA were higher than in Europeans and explained this with a higher level of glycemia in this group [12]. It has been proven that under normal conditions hyperglycemia may induce vasoconstriction: *in vitro* glucose promotes vasoconstriction, *in vivo* glucose interferes with endothelium-dependent vasodilatation [3]. Paliarvi et al. noted that acute induced hyperglycemia does not significantly affect the diameter of the vessel but causes edema of the vascular endothelium, which impairs perfusion [15].

Another explanation of velocity increase in response to hyperglycemia could be increased plasma osmolarity. A sudden increase of osmolarity affects CBF, which has been confirmed in studies on mannitol. Mannitol, like glucose, is one of the sugar alcohols, therefore it should have a similar influence on CBF to that observed in hyperglycemia. It is known that a bolus of mannitol causes an increase in V and a decrease in PI [16]. The literature describes the existence of a negative correlation between increasing flow velocity in intracranial vessels and decreasing the pulsation rate. This is caused by the fact that PI reflects peripheral vascular resistance; and the lower the resistance the higher the flow velocity [17]. In our study, no significant changes in PI after glycemic control were observed, but there was a tendency for this parameter to increase with a decrease in glycemia. Thus, the flow observed during hyperglycemia was similar to that during the infusion of mannitol. Therefore, hyperglycemia could increase the flow rate also through hypervolemia.

It has been observed that in patients with complications of diabetes, such as polyneuropathy and retinopathy, and in older patients, the decrease in blood flow velocity after achieving normoglycemia was lower than in patients without these complications. This can be explained by a reduced vasoreactivity caused by the greater severity of atherosclerosis in these patients. Such an observation would confirm the theory that what is mainly responsible for the increase in blood flow velocity during hyperglycemia are vasospasms. It is puzzling that we did not observe a dependence between the magnitude of the decrease in blood flow velocity and the duration of diabetes.

The limitations of the study are the small group of patients and the unknown duration of hyperglycemia in the patients with diabetes. Besides, it should be remembered that TCD measures only the flow velocity and not the absolute CBF value. The correlation between CBF and flow velocity is variable. Cerebral blood velocity is an adequate surrogate of absolute flow only if the insonated vessel maintains constant vessel diameter across time and experimental conditions. Blood flow velocity is further influenced by several factors, including arterial blood pressure, ICP, hematocrit, PaCO2 and the status of autoregulation, thus making a direct comparison of flow velocity and CBF difficult.

It can be concluded that in the group with hyperglycemia, Vm and Vs in the MCA were higher than during normoglycemia, which is probably related to vasoconstriction and hypervolemia. Achieving normoglycemia leads to a decrease in Vm and Vs in the MCA, which was less pronounced in the group of elderly patients and patients with complications of diabetes, such as retinopathy and polyneuropathy. The magnitude of the decrease in blood flow velocity did not depend on the duration of diabetes, BMI, cholesterol and HbA1c levels or the presence of hypertension. In the group with normoglycemia and diabetes, Vm and Vs in the MCA were lower than in the control group, however in the hyperglycemic and diabetic group there were no significant differences between Vm and Vs compared to the control group and there were no significant differences in PI between the group of patients with diabetes and normoglycemia, diabetes and hyperglycemia, and the control group.

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Declaration of Competing Interest

The Authors declares that there is no conflict of interest.

Declarations of interest: none.

Contributions

Magdalena Nowaczewska – Made a substantial contribution to the concept and design, acquisition of data, analysis and interpretation of data, performed TCD, wrote the manuscript.

Anna Kamińska – Made a substantial contribution to the concept and design and acquisition of data, interpretation of data.

Beata Kukulska Pawluczuk – Made a substantial contribution to acquisition of data, performed TCD.

Roman Junik – revised article critically for important intellectual content,

Katarzyna Pawlak-Osińska – revised it critically for important intellectual content, approved the version to be published.

All authors have approved the final article.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.05.024.

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