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Grzegorz M. Kozera[1], Bogumił Wolnik[2], Jolanta Neubauer-Geryk[3], Sebastian Szczyrba[4],
Katarzyna B. Kunicka[3], Joanna Wojczal[5], Ulf Schminke[6], Walenty M. Nyka[4], Leszek Bieniaszewski[3]

[1]Department of Neurology, Collegium Medicum Nicolaus Copernicus, Bydgoszcz, Poland
[2]Department of Hypertension and Diabetology, Medical University of Gdańsk, Poland
[3]Department of Clinical Physiology, Medical University of Gdańsk, Poland
[4]Department of Neurology, Medical University of Gdańsk, Poland
[5]Department of Neurology, Medical University in Lublin, Poland
[6]Department of Neurology, Ernst Moritz Arndt University, Greifswald, Germany

Cigarette smoking and cerebral microvasculature in patients with type 1 diabetes: a pilot study

Corresponding author:

Grzegorz M. Kozera
Department of Neurology, Collegium
Medicum Nicolaus Copernicus
9 Skłodowskiej Curie Street,
85–094 Bydgoszcz, Poland
Tel./fax: 52 585 40 32
E-mail: gkozera@cm.umk.pl

ABSTRACT

Introduction. A decrease in vasomotor reactivity reserve (VMRr) or an increase in pulsatility index (PI) are the early signs of cerebral microangiopathy in type 1 diabetes. Cigarette smoking is a risk factor for microvascular complications of type 1 diabetes, but cigarette smokers are routinely excluded from studies on VMRr or PI in type 1 diabetes (T1DM) and there is no evidence of any significant impact of smoking on these variables in T1DM. Therefore, we aimed to assess the impact of cigarette smoking on VMRr and PI in these patients.

Methods. VMRr and PI of the middle cerebral artery were measured with Transcranial Doppler in 79 patients with T1DM (median age 33.0 years, range 20–51, 44% males) without a history of cerebrovascular events, coronary heart disease or carotid stenosis. The relationship between cigarette smoking (n = 20, mean pack-years 9.4 ± 6.1) and VMRr, PI, concomitant risk factors, medications and the presence of systemic microvascular complications were analysed.

Results. Smokers and non-smokers did not differ in terms of their clinical characteristics, with an exception of higher circadian insulin demand in smokers (60 ± 12.9 v. 49.2 ± 14.2 units; p = 0.004). A correlation between pack-years and PI (r = 0.6, p = 0.004), but not with VMRr, was found in smokers. However, no significant differences between smokers and non-smokers were found regarding either VMRr (mean $85.9 \pm 20\%$ v. $84.1 \pm 20.1\%$; p = 0.74) or PI (median 0.85, range 0.61–1.09 v. 0.88, range 0.48–1.52; p = 0.2).

Conclusions. We did not prove any significant impact of smoking on VMRr in T1DM patients, but the association between pack-years and PI may indicate the negative impact of intensive cigarette smoking on the cerebral microvasculature in type 1 diabetes.

Key words: cigarette smoking, cerebral microangiopathy, type 1 diabetes, Transcranial Doppler

Introduction

Cigarette smoking is considered a risk factor for the development of microvascular complications of type 1 diabetes mellitus, both diabetic nephro- and retinopathy [1–4]. It has also been reported that cigarette smoking increases the risk of diabetic neuropathy in patients with type 1 diabetes [5].

Cerebral microangiopathy can be reflected by a decrease in vasomotor reactivity reserve (VMRr) or an increase in pulsatility index (PI) [6–10]. However, smokers have not been included in the previous studies that showed VMR impairment in patients with type 1 diabetes [6–9]. The rationale for excluding smokers from the studies on VMRr in patients with type 1 diabetes is probably based on the short-term effect of cigarette smoking on CO_2-induced vasomotor reactivity in healthy subjects [11–12]. However, it remains unclear whether long-time effects of smoking on VMRr exist in humans who are independent of the presence of vascular risk factors.

Thus, in the present study, we aimed to assess the long-time effect of cigarette smoking on cerebral vessel

reactivity or pulsatility in patients with type 1 diabetes without advanced diabetic complications or prior cerebrovascular events.

Methods

The study was performed as a continuation of a previously published one and was based on a similar research protocol and methods [9].

Patients and controls

The study population consisted of 79 patients with type 1 diabetes (44 women and 35 men, median age 33.0 years, range limits 20–51 years). Study group combined a sample of 59 non-smokers who have already been reported for the presence of VMRr impairment and a new sample of 20 smokers recruited from the Regional Diabetological Centre of Medical University of Gdańsk [9]. We included patients with minimal diabetes duration of two years, free of focal neurological deficits, respiratory tract disease (at present and in the history) and renal insufficiency. We excluded patients with past cerebrovascular events or head trauma, pregnant women, heavy drinkers, subjects with incidents of severe hypoglycaemia within 30 days prior to the initiation of the study and users of any hormonal therapy within 30 days prior to the initiation of the study.

All examinations were performed under standardised conditions at the same time of the day (between 10:00 a.m. and 2:00 p.m.). All participants were asked not to drink coffee for 12 h before the examination, to avoid sleep deprivation, and to eat normal meals the day before the examination. Smokers were asked not to smoke for 2 h before the examination.

The study protocol included history taking, neurological examination, extracranial and transcranial ultrasound, fundoscopy and laboratory testing. The study protocol was approved by the Medical Ethics Committee of the Medical University of Gdańsk (NKEBN/3/2005 and NKEBN/335/2008). Upon entry, each participant gave her/his informed consent.

Subject characteristics

Patient history was obtained including information on past and current disorders, cigarette smoking habits (active or past, number of pack-years) as well as co-morbid conditions and treatment. Weight and height were recorded and expressed as the body mass index (BMI). Focal neurological deficits were excluded by neurological examination performed by a neurologists certified by the Polish Neurological Society. Diabetic neuropathy was diagnosed using the criteria of the Neurological Symptom Score (NSS) based on patient's complaints and neuropathic deficits found upon neurological examination [13]. Hypertension was diagnosed if two consecutive measurements of systolic or diastolic blood pressure exceeded 140 mm Hg and 90 mm Hg, respectively, or if anti-hypertensive medication was used [14].

Laboratory examinations in patients with type 1 diabetes included measurements of 24 h urinary protein or microalbuminuria, total serum cholesterol and glycated haemoglobin (HbA_{1c}). The biochemical examinations were performed at least 1 month ($\pm$7 days) prior to Transcranial Doppler (TCD). Hyperlipidaemia was diagnosed if total cholesterol and/or triglycerides exceeded 175 mg/dL and 150 mg/dL, respectively, or if cholesterol/triglyceride-lowering medications were used [15]. Nephropathy was diagnosed if the excretion of albumin in 24 h exceeded 30 mg in two of three urine collections repeated at intervals of up to 6 months, with both readings in the presence of microalbuminuria and overt nephropathy [16]. Quantitative measurements of urine protein excretion in a sample obtained from 24 h urine collection were used to assess the severity of proteinuria. The albumin and protein concentrations in urine were measured by the turbidimetric method.

Fundoscopy

Retinopathy was recognised on fundoscopy performed by an ophthalmologist certified by the Polish Ophthalmological Society. Grading was assessed through the use of the Stages of Diabetic Retinopathy scale of the American Academy of Ophthalmology (AAO). Previous therapy with photocoagulation was also recognised as a marker of diabetic retinopathy [17].

Carotid Doppler examination

Standard examinations of both carotid arteries were performed by well-trained investigators (KBK with 12 years of experience and GK with 11 years of experience) using Aloka 5000 ultrasound device (Aloka Co., Ltd, Japan) equipped with a linear probe with a central working frequency of 7.5 MHz and range limits of 5–10 MHz or Vivid I device (GE Healthcare, USA) equipped with a linear probe with a central working frequency of 6.3 MHz and range limits of 3.96–8.4 MHz.

Transcranial Doppler examination

Middle cerebral artery (MCA) flow parameters were measured by TCD through the temporal bone window using MultiDop T2 DWL device (DWL Elektronische Systeme, Singen, Germany) equipped with a 2 MHz pulse

wave probe. Velocity measurements were performed simultaneously in both MCA by one well-trained ultrasonographer (GK) using a two-channel monitoring kit: two probes at 2 MHz PW, a fixation band and a monitoring programme (MF version 8.27 L, DWL). The physiological technique of provoking cerebrovascular reactivity by changes in pCO_2 was applied according to the published standards [18–19]. During the CO_2 reactivity test, the CO_2 content in expired air (end-tidal CO_2 concentration) was monitored continuously (capnograph Datex Normocap, Helsinki, Finland). Before and after the tests, the systemic blood pressure was measured. The vasomotor reactivity reserve expressed as a percent change from baseline was calculated according to a standard protocol published previously [18–19]. The median values of the arithmetic means of the velocity measurements at rest (rest Vmean), VMRr and the Pulsatility Index (PI) of both MCAs were used for further analyses.

Statistics

All the statistical analyses were performed with STATISTICA, version 9.1 (StatSoft Inc, Tulsa, OK). Shapiro-Wilk tests were performed to analyse the distribution of continuous variables. Differences between groups were analysed with Student's t-test in the case of normally distributed variables (circadian insulin demand, VMRr) or with the Mann-Whitney U test in the case of non-normally distributed variables (age, type 1 diabetes duration, BMI, diastolic and systolic blood pressure, rest Vmean, PI, end tidal CO_2 concentration). The Chi-square test was used to compare the proportion of females to males, the prevalence of systemic microvascular complications and concomitant risk factors in groups. Correlation was assessed by the Spearman's rank correlation test. The level of $p < 0.05$ was regarded as statistically significant.

Results

Twenty patients (25.3%) reported active smoking (range from 0.75 to 18 pack-years, mean 9.28 ± 6.08). There were no past smokers in the study group considering both, period of 5 years prior to the study as well as the entire previous history.

Based on medical history, physical examination, biochemical analysis, carotid and transcranial ultrasound, none of the study subjects had an established diagnosis of coronary heart disease, diabetic foot, orthostatic hypotension, chronic renal insufficiency or significant stenosis (> 50%) of the extra- and intracranial arteries. In spite of the higher mean circadian insulin demand in smoking than in non-smoking patients (60 ± 12.9 v.

49.2 ± 14.2 units; p = 0.004), both groups did not differ in terms of age, gender, diabetes duration, BMI, systolic and diastolic blood pressure or prevalence of systemic microvascular complications and co-morbidities (Tab. 1).

We found a significant correlation between PI and pack-years in the subgroup of smoking patients with type 1 diabetes (r = 0.61, p = 0.004) (Fig. 1). No significant correlation between VMRr and pack-years was observed (r = 0.18, p = 0.42). We found no significant differences between smoking and non-smoking patients regarding mean VMRr (85.9 ± 20 v. 84.1 ± 20.1%; p = 0.74) or median PI (0.85, range 0.61–1.09 v. 0.88, range 0.48–1.52; p = 0.2). No differences between the groups existed regarding MCA mean flow velocities at rest, or in the median end-tidal CO_2 concentrations after hyperventilation or after breath-holding (Tab.1).

Discussion

This pilot study indicates that long-term effects of cigarette smoking do not influence cerebral vasomotor reactivity in patients with type 1 diabetes. Nevertheless, our study reveals a correlation between pack-years and PI, which may indicate the negative influence of intensive cigarette smoking on the cerebral microvasculature in type 1 diabetes.

To the best of our knowledge, no published data exist on the correlation between smoking and VMRr in patients with type 1 diabetes. To date, only the short-term negative effects of smoking on VMRr have been reported in groups of healthy subjects [11–12]. Thus, we cannot contrast our results with the findings of other authors due to the lack of similar reports. Similarly, reports on PI in diabetes are sparse, and no correlation between cerebral pulsatility and smoking load has yet been shown [20]. Therefore, regardless of the negative results, we believe that our findings broaden the knowledge about the risk factors for the development of cerebral microangiopathy in diabetes.

Our findings are in line with some reports that show no contribution of smoking to the development of diabetic nephropathy and retinopathy in type 1 diabetes [21, 22]. Similarly, we have not found any significant differences between the subgroups of smoking and non-smoking patients regarding the prevalence of nephropathy and retinopathy. The only difference between the studied groups was a higher circadian insulin demand in smoking patients. This is in agreement with a previous report which investigated increased insulin requirements in smokers with type 1 diabetes [23].

However, despite the lack of an association between smoking and VMRr, we cannot deny a negative impact of smoking on the cerebral microvasculature in type 1

Table 1. Characteristics of smoking and non–smoking patients with type 1 diabetes

	Non–smokers n = 59	Smokers n = 20	p
Age (years)	32 (21–51)	35.5 (20–49)	0.08
F:M ratio	34:25	10:10	0.55; χ^2 0.35
BMI [kg/m^2]	24.1 (20.1–31.6)	25.5 (20.8–33.5)	0.18
Systolic blood pressure [mm Hg]	122 (98–145)	124 (98–175)	0.68
Diastolic blood pressure [mm Hg]	80 (45–98)	80 (49–95)	0.11
Hyperlipidaemia (%)	67.8	70.0	0.85; $\chi^2 = 0.03$
Arterial Hypertension (%)	15.0	20.3	0.84; $\chi^2 = 0.04$
Neuropathy (%)	25.4	20,0	0.85; $\chi^2 = 0.03$
Retinopathy(%)	42.4	50.0	0.55; $\chi^2 = 0.35$
Nephropathy(%)	15.2	15.0	0.11; $\chi^2 = 0.73$
Type 1 diabetes duration (years)	15.0 (3–33)	14.0 (5–35)	0.70
HbA$_{1C}$ (%)	7.8 (5.9–12.0)	7.9 (6.4–11.9)	0.65
Daily insulin demand [U]	49.2 ± 14.2	60.0 ± 13.0	<0.01
ACEI or ARB treatment (%)	16.9	10.0	0.70; $\chi^2 = 0.15$
Statin treatment (%)	10.2	15.0	0.86; $\chi^2 = 0.03$
Rest V$_{mean}$ [cm/s]	60.2 (35.8–106.5)	62.9 (32.1–110.0)	0.43
Pulsatility index	0.88 (0.48–1.52)	0.85 (0.61–1.09)	0.20
VMRr (%)	84.1 ± 20.1	85.9 ± 20.0	0.74
Delta etCO$_2$ HV(%)	1.7 (1.0–2.5)	1.8 (1.1–2.5)	0.31
Delta etCO$_2$ BH(%)	1.1 (0.5–2.0)	1.2 (0.7–1.7)	0.26

F:M ratio — female to male ratio; BMI — body mass index; HbA$_{1c}$ — glycated haemoglobin; ACEI — angiotensin–converting enzyme inhibitor; ABR — angiotensin receptor blocker, Rest V$_{mean}$ — mean flow velocity measured at rest; VMRr — vasomotor reactivity reserve; Delta etCO$_2$HV — delta end–tidal CO_2 during hyperventilation; Delta etCO$_2$ BH — delta end–tidal CO_2 during breath holding
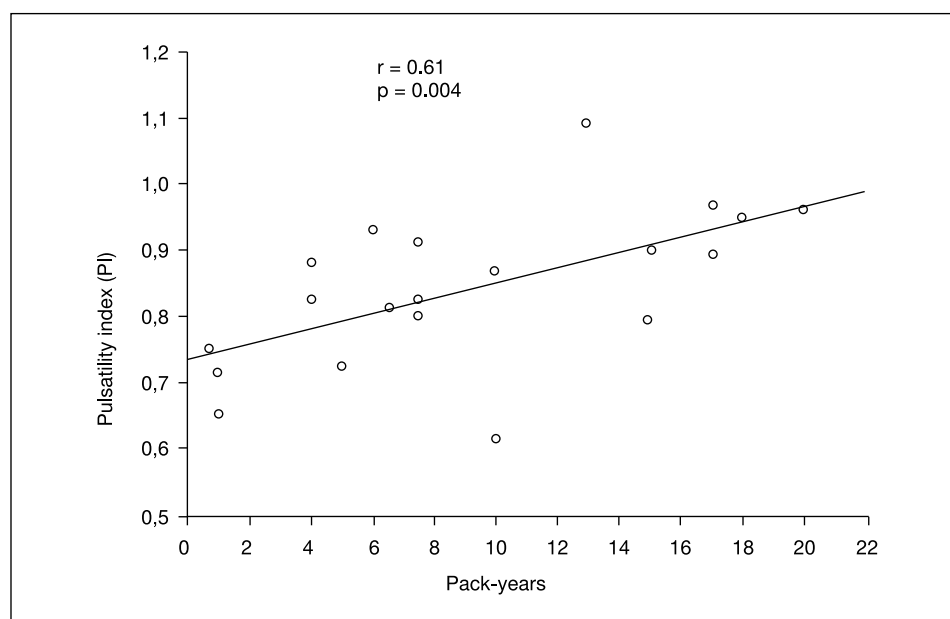

Figure 1. Correlation between PI and pack-years in a subgroup of smoking patients with type 1 diabetes

diabetes. The correlation between cerebral pulsatility and smoking load indicates an association between the intensive tobacco use and the development of cerebral microangiopathy in type 1 diabetes. We also believe that our data indicate a different impact of smoking on systemic and cerebral microcirculatory dysfunction. Thus we find the rationale for further studies on VMRr in larger, population-based cohorts of patients with type 1 diabetes.

Conclusions

The intensive tobacco use may play a role in the development of cerebral microangiopathy in type 1 diabetes, which is reflected by the increase of cerebral pulsatility measured with transcranial Doppler.

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