Original Article

Cerebral Microangiopathy in Patients with Non-insulin-dependent Diabetes Mellitus

Ligia Petrica,[1] MD, PhD, Maxim Petrica,[2] MD, PhD, Mircea Munteanu,[3] MD, PhD, Adrian Vlad,[3] MD, PhD, Flaviu Bob,[1] MD, PhD, Cristina Gluhovschi,[1] MD, PhD, Gheorghe Gluhovschi,[1] MD, PhD, Catalin Jianu,[2] MD, PhD, Adalbert Schiller,[1] MD, PhD, Silvia Velciov,[1] MD, PhD, Virginia Trandafirescu,[1] MD, PhD, Gheorghe Bozdog,[1] MD, PhD

Abstract

Introduction: The aim of the study was to evaluate cerebral microangiopathy in type 2 non-insulin-dependent diabetes mellitus (NIDDM) patients and to establish potentially conducive factors. **Materials and Methods:** A group of 34 patients with NIDDM and 31 gender- and age-matched normal controls (NC) were assessed by extracranial Doppler ultrasound, in order to evaluate the pulsatility index (PI) and the resistance index (RI) in the internal carotid arteries (ICAs); transcranial Doppler was utilised to assess the same parameters in the middle cerebral arteries (MCAs). All patients underwent screening for favouring factors for cerebral vascular remodelling. **Results:** Of the 34 NIDDM patients, 21 patients (61.76%) (subgroup A) presented with microangiopathic complications [of these, 19 patients (90.46%) had diabetic nephropathy (DN)] versus 13 NIDDM patients (38.24%) (subgroup B) without complications. In subgroup A, 16 patients (76.19%) had PI >1 and RI >0.7 in the ICAs and MCAs (changes consistent with cerebral microangiopathy) versus 5 patients (35.46%) in subgroup B, and no modifications in NC. Of the 19 patients with DN, 14 patients (73.68 %) had impaired haemodynamic indices. Univariate regression analysis showed the following risk factors for the cerebral haemodynamics changes: fibrinogen (F) (OR = 3.11), C-reactive protein (CRP) (OR = 2.40), duration of DM (OR = 2.40), proteinuria (OR = 1.80), serum creatinine (OR = 1.66). Multivariate regression analysis showed as predictors for impaired haemodynamic indices: duration of DM (HR = 1.70), proteinuria (HR = 1.70). The haemodynamic indices in the ICAs correlated with duration of DM (r = 0.87, P <0.0001), F (r = 0.86; P <0.0001), CRP (r = 0.80; P <0.0001); in the MCAs with the duration of DM (r = 0.66, P <0.0001), F (r = 0.38; P <0.0001), CRP (r = 0.88; P <0.0001). **Conclusion:** Cerebral microangiopathy has a high prevalence in NIDDM patients. These cerebral vascular changes correlate with the duration of DM, parameters of inflammation, and proteinuria.

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Key words: Cerebral microangiopathy, Diabetic nephropathy, Doppler ultrasound, Non-insulin-dependent diabetes mellitus, Risk factors

Introduction

Cardiovascular complications account for the highest rate of morbidity and mortality in patients with diabetes mellitus (DM), type 1 and type 2, respectively. The Copenhagen City Heart Study, carried out in 13,105 subjects followed up prospectively for 20 years, reported that in patients with type 2 DM, the risk of having an incident myocardial infarction or stroke is increased two- to three-fold and the risk of death is increased two-fold, independent of other known risk factors for cardiovascular disease.[1]

DM represents a strong independent risk factor of stroke.[2] The incidence of cerebrovascular disease in diabetic men has been reported to be twice that of non-diabetic subjects and almost 3 times greater in diabetic women in the Framingham Study.[3]

Classic cardiovascular risk factors (hypertension, smoking, dyslipidaemia) and diabetes-related risk factors (glycaemic control, diabetes duration, diabetic complications, insulin resistance/hyperinsulinaemia) have proved instrumental in the occurrence of cardiovascular

[1] Department of Nephrology
[2] Department of Neurology
[3] Department of Diabetology
County Emergency Hospital, University of Medicine and Pharmacy, Timisoara, Romania
Address for Correspondence: Dr Ligia Petrica, Str. Telegrafului, B1 C11, Et 3, Ap 7, Timisoara 300125, Romania.
Email: ligiapetrica@rdslink.ro

complications in the course of DM, including major cerebrovascular events.[2]

Relevant data have been provided by the World Health Organization Multinational Study of Vascular Disease in Diabetes (WHO MSVDD), in which a cohort of 4743 diabetic patients were followed up for 12 years to investigate the incidence of fatal and non-fatal cardiovascular disease outcomes. This large cohort study showed the major importance of diabetes-associated risk factors, such as glycaemic control, proteinuria and retinopathy, along with classic risk factors, such as blood pressure, smoking and dyslipidaemia.[4]

Vascular remodelling involving cerebral vessels consists of 2 main processes: atherosclerosis or large-artery disease (which implies carotid and middle cerebral arteries) and arteriosclerosis or small-vessel disease (which implies small cerebral vessels).[5] The latter, known as cerebral microangiopathy, is associated with similar morphological abnormalities in other microvascular territories, such as the kidney, the retina and the peripheral nervous system.

Extracranial and intracranial vessels are frequently responsible for ischaemic stroke in diabetic patients. Of the cerebral vessels, small-sized vessels and their implication in cerebrovascular complications have raised interest in the clinical practice. Several attempts have been made to detect minor modifications in their structure and function by utilising various imaging techniques. Of these, transcranial Doppler (TCD) ultrasonography seems to be the most simple, non-invasive and accurate method. Other methods, such as single-photon emission computed tomography, positron emission tomography and Xe-computed tomography failed to support microangiopathic changes in the cerebral vessels.[6]

Previous studies conducted on diabetic patients demonstrated by means of TCD increased pulsatility indices and reduced cerebrovascular reactivity of the middle cerebral artery (MCA), changes consistent with microangiopathic remodelling of the cerebral vessels.[7] However, hypertension, which is a major cerebrovascular risk factor, was present in the studied patients, modifying the interpretation of the data. In order to exclude the interference of hypertension, other studies were performed in normotensive patients with longstanding type 1 DM[8] and type 2 DM, respectively.[6,9] These studies cast light upon the fact that impaired haemodynamic indices may be found even in normotensive patients with DM in association with other microvascular complications of DM. The modifications were attributed to cerebral microangiopathy, which proved to be closely related to the duration of DM.[6,8,9]

The aim of our study was to evaluate the prevalence of cerebral microangiopathy in normotensive type 2 DM patients by utilising Doppler ultrasound in the exploration of extra- and intracranial vessels. In addition, potentially conducive factors shared by cerebral microangiopathy and other microangiopathic complications were also assessed. A particular focus was directed towards diabetes-specific cerebrovascular risk factors, such as glycaemic control, inflammation and the relationship with proteinuria, namely diabetic nephropathy.

Materials and Methods

The study was carried out in a group of 34 normotensive non-insulin-dependent diabetes mellitus (NIDDM) patients and a group of 31 gender- and age-matched normal controls. The group of NIDDM patients was divided into a subgroup of 21 patients with complications [who presented with microangiopathic complications – diabetic nephropathy (overt diabetic nephropathy defined as proteinuria >0.3 g/24 h), diabetic retinopathy and diabetic peripheral nerve disease; 12 males, 9 females; mean age, 58.77 ± 8.91 years], and a subgroup of 13 patients without complications (8 males, 5 females; mean age, 56.34 ± 9.83 years). The normal controls group consisted of 17 males, 14 females, mean age, 58.43 ± 6.31. Exclusion criteria were hypertension and past or present symptomatic cerebrovascular disease.

Doppler Ultrasonography

All patients and normal controls were evaluated by Doppler ultrasound using the Gosling's pulsatility index (PI) – (PI = systolic velocity-diastolic velocity/ mean velocity; normal value PI <1) and the Pourcellot's resistance index (RI) – (RI = systolic velocity-diastolic velocity/ systolic velocity; normal value RI <0.7)[10] in the internal carotid arteries (ICAs) and the middle cerebral arteries (MCAs), bilaterally. For the assessment of ICAs, extracranial Doppler (ECD) was performed by means of a Doppler velocimeter with fast-Fourier transformation spectral analysis (Explorer CVC-DMS, Montpellier, France), with a 4 MHz CW probe. MCAs were assessed by utilising TCD, with a 2 MHz PW probe, through the transtemporal window, at a depth of 50 mm.

Clinical and Biological Data

In both groups, screening for favouring factors for cerebral vascular remodelling was performed with regard to: systolic blood pressure (SBP), diastolic blood pressure (DBP), (hypertension defined as SBP >130 mm Hg; DBP >80 mm Hg), serum cholesterol, triglycerides, fibrinogen, C-reactive protein, haematocrit, proteinuria, serum creatinine, glycosylated haemoglobin, fasting glycaemia, median glycaemia and smoking (pack-years).

Statistical Analysis

Data were expressed as means ± SD. Statistical analysis was performed with a computerised programme (Epi Info

v.3.2.2 and SPSS v.10 software). An unpaired Student's *t*-test was utilised to compare 2 subject groups, and one-way analysis of variance (ANOVA) was used to assess the significance of difference among 3 subject groups. Associations between risk factors and impaired cerebral haemodynamic indices were assessed using univariate logistic regression. Odds ratios (ORs) and their 95% confidence intervals (CI) were calculated. The independent variables that were statistically significant were entered into multivariate logistic regression models (Cox proportional hazard models). Using backward elimination procedures, the most parsimonious multivariate logistic model was produced for predicting impaired cerebral haemodynamic indices. Hazard ratios (HRs) and their confidence intervals (CI) were calculated. Crude HRs were then adjusted for age and sex as potential confounders. Pearson's correlation analysis was used to assess the significance of the relationship between the PI and RI, and classic and diabetes-related cerebrovascular risk factors, respectively. All *P* values were calculated based on two-sided statistical tests. Significance was considered as *P* <0.05.

Results

Characteristics of the Subject Groups

The group of 34 normotensive patients with NIDDM was divided according to the associated complications in a subgroup A of 21 patients (61.76%) with microangiopathic complications [2 patients (9.54%) only with diabetic retinopathy; 9 patients (42.85%) with diabetic retinopathy and nephropathy; 10 patients (47.61%) with diabetic retinopathy, nephropathy and polyneuropathy]; subgroup B (13 patients or 38.24%) presented with no such complications.

Clinical and Biological Characteristics

The clinical and biological characteristics of patients with NIDDM and normal controls (group C) are presented in Table 1.

The duration of DM was 16.77 ± 11.23 years in the complicated group versus 7.12 ± 1.08 years in the non-complicated group (*P* <0.0043).

No major differences were found between subgroups A, B and C concerning clinical and biological parameters, except for fibrinogen (*P* <0.0001), C-reactive protein (*P* <0.0001), glycosylated haemoglobin (*P* <0.0001), fasting glycaemia (*P* <0.0001), proteinuria (*P* <0.0001), and serum creatinine (*P* <0.0001).

Assessment of Cerebral Haemodynamic Indices

Doppler ultrasound evaluations showed impaired haemodynamic indices (PI >1; RI >0.7) in 16 patients from the group with complications (76.19%) versus 5 patients (35.46%) from the group without complications in the ICAs and MCAs (Table 1). In the group with complications, 19 patients (90.46%) presented with diabetic nephropathy and out of these, 14 patients (73.68%) had modified haemodynamic indices in the ICAs and MCAs, which are indicative of cerebral vessels remodelling consistent with cerebral microangiopathy.

Relationship Cerebral Microangiopathy – Risk Factors

In the complicated group, the following risk factors proved to be of predictive value for the occurrence of cerebral microangiopathy: duration of DM (OR = 2.40, *P* <0.001), C-reactive protein (OR = 2.40, *P* <0.0001), fibrinogen (OR = 3.11, *P* <0.001), proteinuria (OR = 1.80, *P* <0.05), and serum creatinine (OR = 1.66, *P* <0.04) (Table 2). The multivariate logistic model showed as predictors for cerebral microangiopathy duration of DM (HR = 1.70, *P* = 0.016) and proteinuria (HR = 1.70, *P* = 0.036) (Table 3).

Correlation analysis showed a significant direct correlation between the modified haemodynamic indices in the ICAs and the duration of DM (r = 0.87; *P* <0.0001), C-reactive protein levels (r = 0.80; *P* <0.0001), and fibrinogen levels (r = 0.86: *P* <0.0001) (Figs. 1 to 3). The same correlation was found between the PI and RI in the MCAs and the duration of DM (r = 0.66; *P* <0.0001), C-reactive protein levels (r = 0.88; *P* <0.0001), and fibrinogen levels (r = 0.38; *P* <0.0001) (Figs. 4 to 6).

Discussion

Amongst vascular complications in the course of DM, atherosclerosis and arteriosclerosis are well defined. Both imply impaired cerebral haemodynamics, which result in increased prevalence of stroke in type 1 and type 2 DM patients.[2] Also, the involvement of downstream cerebral small vessels, which is consistent with underlying microangiopathic modifications, is of major import for the occurrence of stroke. This particular vascular remodelling, as demonstrated by Doppler ultrasound, has a high prevalence in diabetic patients. In our study, the prevalence of cerebral microangiopathy (which was assessed through specific haemodynamic indices) was significantly increased (76.19%) in type 2 DM patients with complications. The increased PI and RI in the IACs and MCAs reflected increased resistance in the examined vessels. It has been postulated that carotid haemodynamic parameters may be instrumental in the risk for cerebral infarction in type 2 diabetic patients. Ultrasound examinations which evaluated the PI and the RI in the common carotid artery showed that these indices were increased in diabetic patients with previous cerebral infarction compared with patients without

Table 1. Comparison between Diabetic Patients with Complications, Diabetic Patients without Complications and Normal Controls Concerning Clinical and Biological Data, Extracranial and Transcranial Doppler

Parameter	A DM patients with complications	B DM patients without complications	C Normal controls	AB	AC	BC	ABC
No. of subjects	21	13	31	t-test	t-test	t-test	ANOVA
Age (y)	58.77 ± 8.91	56.34 ± 9.83	58.43 ± 6.31	P = 0.4628	P = 0.8725	P = 0.4030	P = 0.6608
Gender (Male/Female)	12/9	8/5	17/14				
Duration of DM (y)	16.77 ± 11.23	7.12 ± 1.08		P = 0.0043			
Body mass index	24.3 ± 2.20	23.6 ± 3.23	24.8 ± 1.70	P = 0.4569	P = 0.3602	P = 0.1134	P = 0.2656
SBP (mm Hg)	130.15 ± 8.44	127.15 ± 8.46	123.16 ± 6.09	P = 0.3218	P = 0.0011	P = 0.0853	P = 0.0053
DBP (mm Hg)	78.16 ± 3.17	76.19 ± 2.17	73.40 ± 6.23	P = 0.0289	P = 0.0022	P = 0.1248	P = 0.0031
Serum cholesterol (mg%)	189.40 ± 13.10	186.23 ± 10.54	179.10 ± 6.12	P = 0.4670	P = 0.0004	P = 0.0073	P = 0.0012
Triglycerides (mg%)	186.33 ± 10.09	181.40 ± 7.20	176.23 ± 7.08	P = 0.1352	P <0.0001	P = 0.0334	P = 0.0002
Fibrinogen (mg%)	598.27 ± 12.80	430.16 ± 8.42	321.16 ± 11.20	P <0.0001	P <0.0001	P <0.0001	P <0.0001
C-reactive protein (mg%)	5.66 ± 2.02	2.66 ± 0.89	1.02 ± 0.08	P <0.0001	P <0.0001	P <0.0001	P <0.0001
Haematocrit (%)	41.30 ± 2.80	39.86 ± 2.66	40.07 ± 1.56	P = 0.1474	P = 0.0477	P = 0.7447	P = 0.1012
Proteinuria (g/24h)	2.45 ± 1.12	0.202 ± 0.07	0.120 ± 0.016	P <0.0001	P <0.0001	P <0.0001	P <0.0001
Serum creatinine (mg%)	1.46 ± 0.20	0.96 ± 0.10	0.81 ± 0.05	P <0.0001	P <0.0001	P <0.0001	P <0.0001
HbAc (%)	12.06 ± 1.20	7.21 ± 0.89		P <0.0001			
Glycaemia - fasting	126.83 ± 11.76	110.76 ± 9.12	96.23 ± 8.12	P = 0.0002	P <0.0001	P <0.0001	P <0.0001
Glycaemia - median	108.40 ± 23.18	106.50 ± 12.70		P = 0.7886			
Smoking (% of subjects)	52.38	53.84	58.06				
Pack-years (in smokers)	36 ± 9	32 ± 10	29 ± 6	P = 0.2361	P = 0.2015	P = 0.2247	P = 0.2108
PI - ICA	1.16 ± 0.21	0.82 ± 0.20	0.70 ± 0.13	P <0.0001	P <0.0001	P = 0.0225	P <0.0001
RI - ICA	0.86 ± 0.11	0.73 ± 0.16	0.60 ± 0.13	P = 0.0083	P <0.0001	P = 0.0072	P <0.0001
PI - MCA	1.18 ± 0.16	0.84 ± 0.21	0.72 ± 0.22	P <0.0001	P <0.0001	P = 0.1019	P <0.0001
RI - MCA	0.89 ± 0.08	0.76 ± 0.17	0.61 ± 0.11	P = 0.0049	P <0.0001	P = 0.0011	P <0.0001

DBP: diastolic blood pressure; DM: diabetes mellitus; ICA: internal carotid artery; MCA: middle cerebral artery; PI: pulsatility index; RI: resistance index; SBP: systolic blood pressure

Comparison between groups AB, BC, AC Student's t-test; ABC – one-way ANOVA, statistical significance P <0.05

Table 2. Univariate Logistic Regression Results (comparison between diabetic patients with complications and diabetic patients without complications)

| Variable	OR	95% CI for OR Lower	95% CI for OR Upper	P
Proteinuria	1.80	1.10	2.85	0.05
Serum creatinine	1.66	1.01	2.77	0.04
Fibrinogen	3.11	0.22	91.70	<0.0001
CRP	2.40	0.16	71.29	<0.0001
Duration of DM	2.40	0.16	71.29	<0.0001

95% CI: 95% confidence interval; CRP: C-reactive protein; DM: diabetes mellitus; OR: odds ratio

Associations between risk factors and impaired cerebral haemodynamic indices were assessed using univariate logistic regression.
All P values were calculated based on 2-sided statistical tests.

cerebral infarction. The subjects who displayed impaired haemodynamic indices had a higher risk of developing stroke than the subjects who presented with no significant modifications of these parameters.[11] Most relevant to the diagnosis of microangiopathic modifications in the small cerebral vessels are the values of PI and RI in the MCAs. These data are in agreement with the results of Lee et al,[6] who found high PIs in the MCAs in 54% of complicated normotensive NIDDM patients. Of interest, in our diabetic patients who presented with diabetic nephropathy, the prevalence of cerebral microangiopathy was also increased, which suggests a possible link between the 2 vascular territories with regard to common mechanisms.

From the practical standpoint, TCD is the most accurate method in the evaluation of cerebral haemodynamic changes in diabetic microangiopathy. In the study performed by
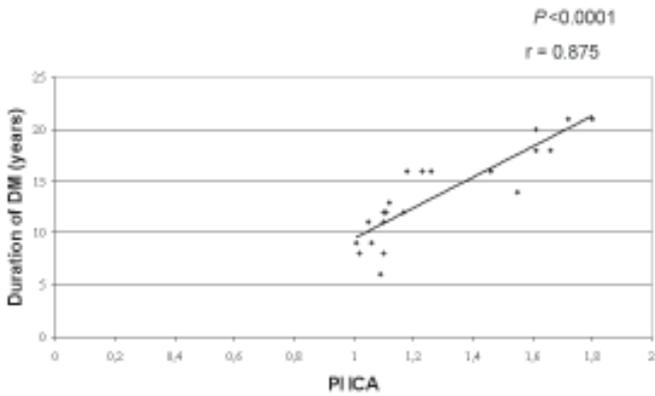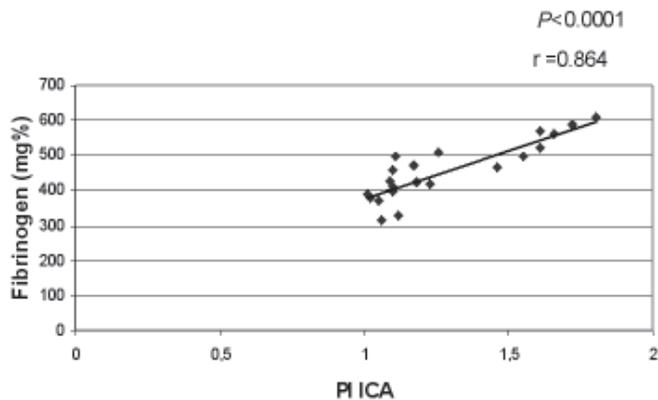
DM: diabetes mellitus; ICA: internal carotid artery; PI: pulsatility index

Fig. 1. Correlation between PI in ICA and duration of DM.
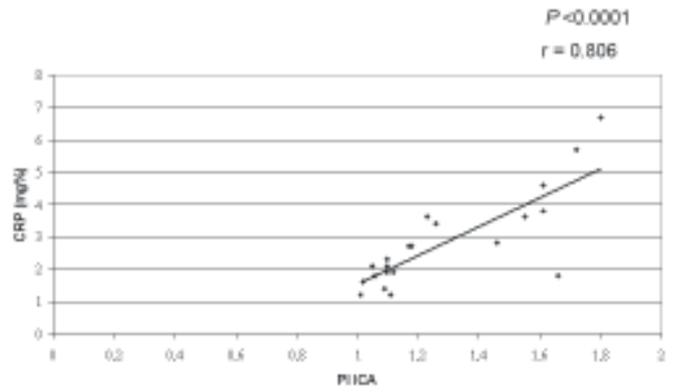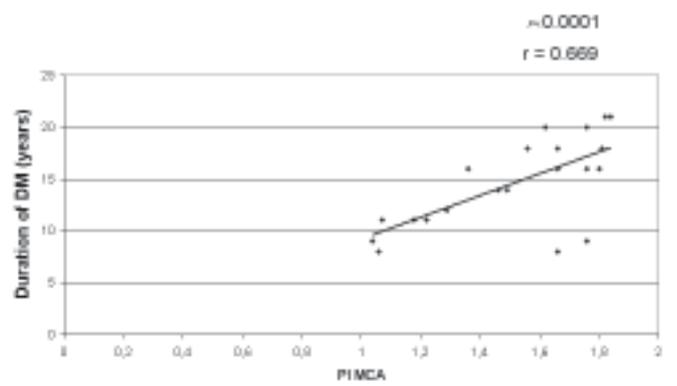

CRP: C-reactive protein; ICA: internal carotid artery; PI: pulsatility index

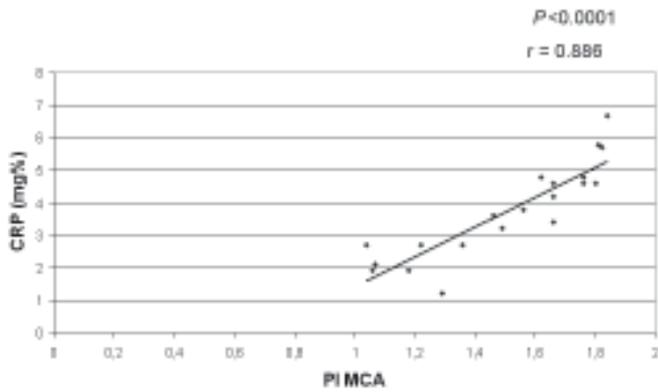Fig. 2. Correlation between PI in ICA and CRP.

ICA: internal carotid artery; PI: pulsatility index

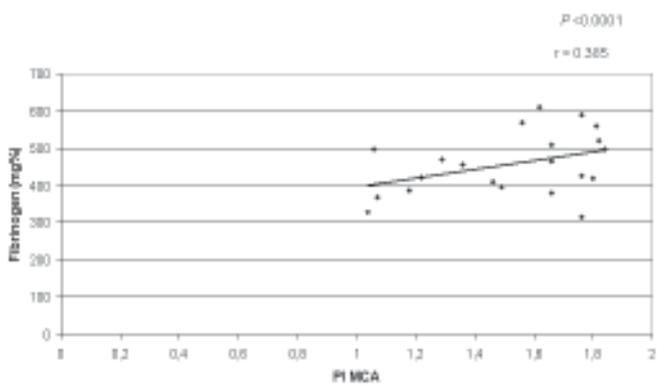Fig. 3. Correlation between PI in ICA and fibrinogen.

DM: diabetes mellitus; MCA: middle cerebral artery; PI: pulsatility index

Fig. 4. Correlation between PI in MCA and duration of DM.

CRP: C-reactive protein; MCA: middle cerebral artery; PI: pulsatility index

Fig. 5. Correlation between PI in MCA and CRP.

MCA: middle cerebral artery; PI: pulsatility index

Fig. 6. Correlation between PI in MCA and fibrinogen.

Shen et al[12] in asymptomatic type 2 DM patients, the PIs of MCAs were significantly higher in diabetic patients than those in healthy controls. Also, the PIs in the MCAs were significantly increased in patients with complications than those in patients without complications. The authors conclude that the marked increase in the PIs of MCAs may reflect the microangiopathic changes of cerebral vessels in diabetic patients.[12]

Similar changes have been described by other studies performed on type 2 DM patients in whom TCD revealed increased PI in the MCAs and was considered a valuable tool for detecting arterial lesions and abnormalities of cerebral haemodynamics related to DM.[13,14] Furthermore, TCD proved a reliable screening method for the examination of brain haemodynamic impairment in NIDDM patients with retinal microangiopathy and asymptomatic for

Table 3. Multivariate Logistic Regression Results
(comparison between diabetic patients with complications and diabetic patients without complications)

Variables	Crude HR	95% CI for HR		P	Adjusted HR*	95% CI for HR		P
		Lower	Upper			Lower	Upper	
Duration of DM	1.80	1.21	3.00	0.006	1.70	1.12	2.90	0.016
Proteinuria	1.72	1.05	2.89	0.031	1.70	1.04	2.85	0.036

95% CI: 95% confidence interval; DM: diabetes mellitus; HR: hazard ratios
* adjusted for age and sex

The independent variables that were statistically significant were entered into multivariate logistic regression models(Cox proportional hazard models).
Using backward elimination procedures, the most parsimonious multivariate logistic model was produced for predicting impaired cerebral haemodynamic indices.
HRs and their 95% CIs were calculated. Crude HRs were then adjusted for age and sex as potential confounders.
All P values were calculated based on 2-sided statistical tests.

cerebrovascular disease, who presented with increased PI in the MCAs.[7]

In another study conducted on patients with a previous stroke or transient ischaemic attack, TCD investigations showed that type 2 diabetic patients have significantly higher PIs than non-diabetic patients in all examined intracranial arteries. The PI reflects the vascular resistance of intracranial arteries and could therefore be used as an estimate of the severity of vascular damage. The study demonstrates that type 2 diabetic patients have increased intracranial arterial resistance, which may be ascribed to severe damage to cerebral blood flow in DM.[15]

It is worth mentioning that the presence of cerebral microangiopathy may be of positive predictive value for the diagnosis of microangiopathic lesions in other vascular territories, such as the kidney and the retina. Lee et al[6] found the most significantly impaired haemodynamic parameters in complicated NIDDM patients, including patients with diabetic nephropathy. Moreover, Lippera et al[7] described significantly higher PIs in the MCAs, anterior cerebral arteries and ophthalmic arteries in NIDDM patients with proliferative diabetic retinopathy, far more significant than in patients with background retinopathy and patients with no retinopathy. The authors hypothesise that diabetic patients may present with a silent cerebral microangiopathy, with concomitant signs of micro-angiopathic damage in other districts.[7]

To date, the role of endothelial dysfunction in the pathogenesis of diabetic microangiopathy is well established. Two types of modifications have been described as reversible alterations in microcirculation, which are detected at an early stage in the course of DM and consist of increased capillary pressure, blood flow and endothelial permeability, and irreversible structural modifications of the vessel wall, which are found in the later stages of DM and comprise the thickening of the basement membranes

due to extracellular accumulation of proteins[16] and proliferation of the endothelium.[17]

Endothelial dysfunction may precede the onset of microangiopathic vascular remodelling in DM. Several factors are central in the development of these vascular lesions: hyperglycaemia, abnormalities of lipoprotein metabolism, accumulation of advanced glycation end-products, increased oxidative stress, and hyperinsulinism with associated insulin resistance.[16-19]

This particular pathogenic mechanism related to hyperinsulinism requires special attention. First of all, it is worth pointing out that increased insulin responses and elevated glucose levels after oral glucose stimulation or increased fasting insulin levels have been found in patients with cerebrovascular disease. In addition, the cerebral microvascular endothelium is highly susceptible to the mitogenic and metabolic effects of insulin as compared with the endothelium from other vascular territories, and elevated insulin and C-peptide levels are associated with cerebral small-vessel disease.[17]

Attention has focused on the implication of several classic and diabetes-related risk factors in the occurrence of diabetic cerebral microangiopathy.

Hypertension, serum cholesterol and proteinuria are considered predictors for cardiovascular disease mortality, fatal and non-fatal myocardial infarction and stroke in type 1 and type 2 DM. Serum triglycerides, fasting plasma glucose and the presence of retinopathy are also independently related to stroke in type 2 DM, as demonstrated by the WHO MSVDD.[4]

In our study, relevant risk factors for cerebral microangiopathy proved to be the duration of DM, fibrinogen, C-reactive protein levels, proteinuria, and serum creatinine. The haemodynamic indices correlated significantly with the duration of DM and the parameters of inflammation. The PIs and RIs in the ICAs and MCAs

paralleled the duration of DM and increased abruptly after 10 to 12 years of the onset of DM. Chronic hyperglycaemia (assessed by glycosylated haemoglobin levels) is related to the development of microvascular disease.[20] The levels of HbA1c were significantly increased in patients with complications as compared to those without complications.

Interestingly, the vast majority of our patients with modified cerebral haemodynamics had associated microangiopathic complications, and of these, diabetic nephropathy was a prominent feature.

These results are in keeping with those of Lee at al,[6] who demonstrated a significant correlation between the PIs in the MCAs and the duration of DM in NIDDM. The same aspects were discussed by Lippera et al,[7] who found increased PIs of the MCAs in type 1 DM patients with diabetic retinopathy. The latter study, however, deals with hypertensive patients and, therefore, the authors could not exclude the interfering effect of hypertension in the TCD modifications. This was not the case with the patients in the studies by Lee et al[6] and Nagata et al[9] and our study, where the evaluation of cerebral microangiopathy was performed on normotensive patients.

As far as the stroke risk factor profile for cerebral small vessels remodelling (such as age, dyslipidaemia and smoking) showed similar values in our normotensive NIDDM patients, whether they had complications or not, we may conclude that the only reason for modified cerebral haemodynamic indices is the intervention of diabetes-related risk factors.

The presence of cerebral microangiopathy is of predictive value for the concomitant development of diabetic nephropathy. The reverse is also valid. Proteinuria is an independent risk factor for ischaemic stroke in NIDDM.[21] In our patients with NIDDM and cerebral haemodynamic changes, proteinuria was demonstrated as an important independent risk factor for the development of cerebral microangiopathy. Moreover, albuminuria is considered a marker of intracranial cerebrovascular disease and may be accepted as an independent predictor of increasing levels of vascular risk factors, and microvascular and macrovascular disease in type 2 diabetic patients.[22] Also, microalbuminuria may identify cerebrovascular diabetic involvement, as it predicts both macroangiopathic carotid alterations and microvascular brain impairment.[23,24]

Compelling evidence has shown the significant and independent role of inflammation in atherosclerotic and arteriosclerotic remodelling of cerebral vessels in diabetic patients.[25] Markers of inflammation are prominently modified in patients with cerebral large-vessel disease. Less has been discussed about their involvement in small-vessel disease.

In our study group, patients with significantly increased cerebral vascular resistance presented with modified parameters of inflammation, namely, increased levels of fibrinogen and C-reactive protein. It is worth mentioning that these parameters correlated significantly with the haemodynamic indices in the ICAs as well as the MCAs, suggesting their involvement in the microvascular remodelling of cerebral vessels, including downstream cerebral small vessels.

In a study performed by Grau et al,[26] subjects with a history of cerebrovascular disease, especially type 2 diabetic patients, had higher leucocyte counts, fibrinogen and C-reactive protein than subjects without vascular risk factors. These results support the hypothesis that inflammation is associated with increased vascular risk and that inflammatory mechanisms may enhance the risk of major cerebrovascular events.[26] Furthermore, inflammation (indicated by high-sensitivity C-reactive protein), and hyperglycaemia (indicated by HbA1c), jointly contribute to the cardiovascular risk of patients with advanced atherosclerosis, and also with microvascular lesions in the brain and major cerebrovascular events.[27]

The prospective study conducted by Schulze et al[28] showed that high plasma levels of C-reactive protein were associated with an increased risk of incident stroke among diabetic men, independent of classic cardiovascular risk factors. It is noteworthy that low-grade inflammation (high-sensitivity C-reactive protein) and insulin resistance are independently related to all causes of death and cardiovascular disease, including stroke, in type 2 diabetic patients. The coexistence of low-grade inflammation and insulin resistance may amplify the risk for cerebrovascular disease in type 2 DM.[29]

The vast majority of studies discuss TCD findings in hypertensive DM patients. Nonetheless, even normotensive diabetic patients show impaired cerebral haemodynamic indices, have an increased risk for stroke and, most interestingly, display decreased cerebrovascular reactivity. Thus, late recovery after a major cerebrovascular event is a direct consequence of an impaired microvascular supply and an inadequate cerebrovascular reserve.[6,8,14]

In conclusion, cerebrovascular microangiopathy is highly prevalent in normotensive NIDDM patients. These cerebral vascular changes correlate with the duration of DM, parameters of inflammation and proteinuria. Doppler ultrasound is a sensitive and reliable tool in the detection of cerebral microangiopathy in diabetic patients. TCD may be of positive predictive value for the strong association between diabetic nephropathy and cerebral microangiopathy. It also provides prognostic data on the potential evolution of a major cerebrovascular event. Therefore, TCD should be considered as a non-invasive and simple routine examination in diabetic patients.

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