Increased Burden of Cerebral Small Vessel Disease in Patients With Type 2 Diabetes and Retinopathy

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OBJECTIVE: We sought to examine the presence and severity of brain small vessel disease in a group of patients with type 2 diabetes (T2D) and diabetic retinopathy (DR) compared with a group of patients with T2D without DR.

METHODS: A total of 312 patients with T2D (men, 51%; mean age, 57 yrs; age range 40–75 yrs) were included in the study; 153 (49%) of the patients had DR. A brain magnetic resonance was perfomed to evaluate the presence and severity (ARWMC scale) of white matter lesions and microbleeds. A transcranial Doppler ultrasonound was performed to measure the Gosling's pulsatility index of the middle cerebral artery (MCA-PI).

RESULTS: No differences were observed in the prevalence of LA between patients with or without DR (39.72% *vs* 30.76%, p=0.0638). The severity of LA was significantly higher in patients with DR compared to those without DR (p=0.0429). In the regression analysis age (p<0.001) and systolic blood pressure (p=0.0244) were associated with LA. No differences were observed in the presence of microbleeds between patients with or without DR (2.5% *vs* 3.5%, p=0.45). Patients with DR showed a higher MCA-PI compared to those without DR (p<0.0001). Variables associated with an increased MCA-PI in the regression analysis were age (p<0.0001),systolic and dyastolic blood pressure (p=0.0001) and retinopathy (p=0.037). A positive correlation was found between severity of LA and MCA-PI values (p=0.0058).

CONCLUSIONS: Patients with T2D and DR have a more severe grade of LA and higher MCA-PI values compared to those without DR. Moreover, in these patients MCA-PI and LA severity are positively associated. Our findings support

the hypothesis that the brain is a target organ for microangiopathy similar to other classic target organs such the retina.

Introduction

Patients with type 2 diabetes mellitus (T2D) have an increased risk for cardiovascular morbidity and mortality. The chronic deleterious effects of hyperglycaemia are classically separated into microvascular and macrovascular complications. The main clinical entities of diabetic microvascular disease include retinopathy, neuropathy, and nephropathy, while stroke, acute coronary syndromes and peripheral vascular disease are classified as macrovascular complications of T2D (1). Despite intensified blood glucose control, patients with T2D remain at greatly increased risk for macrovascular events such as ischemic stroke (2). In these patients a high prevalence atherotrombotic disease has been described in large extracranial vessels such as internal carotid artery (3). Furthermore, besides classical target organs of microangiopathy such as the retina or the kidneys, the brain has also been described more recently as a target organ for diabetic microvascular complications (4). Cerebral small vessel disease (SVD) is the term commonly used to describe a syndrome of clinical, cognitive, neuroimaging, and neuropathological findings thought to arise from disease affecting the perforating cerebral arterioles, capillaries, and venules, and the resulting brain damage in the cerebral white and deep grey matter (5). At MRI examination SVD, as outlined in the Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) position paper, can show distinct forms: most typically, symptomatic small subcortical infarcts, subclinical lacunes, white matter hyperintensities, and cerebral microbleeds (6). Leukoaraiosis (LA) or white matter disease is a descriptive term to denominate cerebral white matter lesions (WMLs) frequently seen on brain imaging which is considered to be a

radiological sign of tissue damage produced by chronic ischemia caused by SVD (7). Different terms such as white matter (WM) hyperintensities, WM changes, WM disease and WM lesions are used as synonyms of LA (8). It is associated with cognitive decline and a higher risk of stroke and death. Moreover, its severity and progression indicates an increased risk of cerebrovascular events (9,10). Studies of the relationship between diabetes and WM disease have shown conflicting results. Several studies have reported an association between diabetes and LA, while others have not confirmed this association (11,12).

Microbleeds are small (generally 2–5 mm in diameter, but sometimes up to 10 mm) areas of signal void with associated blooming seen on T2*-weighted MRI or other sequences that are sensitive to susceptibility effects (13). Histo- pathological studies indicate that these lesions reflect haemosiderin-laden macrophages in perivascular tissue consistent with vascular leakage of blood cells at capillary, small artery and arteriolar levels (14).

Finally, another method used for the evaluation of cerebral SVD is the measurement of vascular resistance by using a pulsatility index (PI) by Transcranial Doppler ultrasonography(TCD) which has long been proposed to reflect vascular resistance of the small vessels. Several studies have demonstrated increased PI in patients with WM disease (15,16), including populations of hypertensive patients (17) and patients with diabetes mellitus (18).

The microvascular bed of the retina mirrors the cerebral small vessels in embryological origin, anatomic features, and physiologic properties (19). Cross-

sectional studies performed in general population show that people with retinopathy are more likely to have concomitant cerebral infarct, WMLs and microbleeds on MRI than those without retinopathy (20,21). Moreover, prospective studies also perfomed in general population show evidence that the presence of microvascular retinal abnormalities are associated with incident stroke and subclinical infarcts (22,23). More recently, presence of any retinopathy has also been reported to be associated with a greater progression of LA (24).

In patients with diabetes it has been reported that the presence and severity of retinopathy are associated with future CV events including ischemic stroke (25-27).

In the present study we sought to examine whether there was any difference in the presence and severity of several markers of cerebral SVS (LA, microbleeds and PI index) in a group of patients with T2D and retinopathy compared with a group of patients with T2D without retinopathy, both of them without previous CV events.

Research Design and Methods

Subjects

The study design and assessments of the cohort participants have been previously described by our group in a previous study in the presence and extension of carotid plaques was analyzed in patients with T2D with and without DR (28). Briefly, 312 subjects with T2D without previous cardiovascular events and with a normal renal function were recruited from the outpatient clinic at our

centre. One-hundred fifty-three patients with DR and 159 without DR were included in the study. An experienced ophthalmologist assessed and classified retinopathy according to an international consensus on clinical diabetic retinopathy (29) as follows: a) mild nonproliferative DR - microaneurysms only; b) moderate nonproliferative DR - more than just microaneurysms but less than severe nonproliferative DR; c) severe nonproliferative DR by any of the following - more than 20 intraretinal haemorrhages in each of 4 quadrants, definite venous beading in 2+ quadrants, prominent intraretinal microvascular abnormalities in 1+ quadrant, and no signs of proliferative retinopathy; and d) proliferative DR, by neovascularization and/or vitreous/preretinal haemorrhage. The sex distribution did not differ between groups. However, as expected, age, cardiovascular risk factors, disease duration, and microalbuminuria were different between groups due to the selection criteria or the metabolic condition or disease stage of the participants. Diabetic patients with retinopathy, compared with those without retinopathy, had higher prevalence of hypertension, systolic blood pressure, waist circumference, HbA1c concentration and urinary albumin excretion, and were more frequently treated with insulin (alone or in combination with oral agents) and aspirin.

Methods

In the present study, a brain MR was performed in 289 patients because of contraindication for MRI study in 15 patients (claustrophobia in 13) and lack of complicance with the appointed visit in 8 cases. We calculated mean MCA PI by averaging bilateral MCA PI. Mean MCA PI of good quality was obtained in 218 patients (115 patients with retinopathy and 103 patients without retinopathy).

The local Ethics Committee approved the protocol, and all patients signed the written informed consent form.

MRI study protocol. Brain MR images were acquired on a Philips Intera 1.5 T, The Netherlands, with a standardised protocol. The protocol comprised an axial T2-weighted turbo spin-echo (4800/120/3; TR/TE/excitations), T1-weighted spin-echo (540/15/2), turbo fluid-attenuated inversion recovery (8000/2200/120/2; TR/TI/TE), and echo-planar diffusion images (3900/95).

White matter lesions (WMLs) were scored according to age-related white matter changes (ARWMC) scale (30). It is a simple and well-validated scale applicable to both CT and MRI with a good interrater reliability. The degree of white matter changes is rated on a 4-point scale from 0 to 3 in five different regions (frontal, parieto-occipital, temporal, basal ganglia, infratentorial) in the right and left sides of the brain separately, on T2 and FLAIR images. The rating scores were: 0: No lesions (including symmetrical, well-defined caps or bands), 1: Focal lesions, 2: Beginning confluence of lesions, 3: Diffuse involvement of the entire region, with or without involvement of U fibers. To analyze the correlation between LA severity and retinopathy patients were categorized into two groups taking into account the results obtained in the ARWC score (group A: absence of or mild LA, and group B moderate and severe LA).

We used the microbleed anatomical rating scale (MARS) to measure the number and distribution of microbleeds in the brain (31). This reliable scale classifies microbleeds into definite and possible categories. The initial study protocol included defined patients with microbleeds as those with definite lesions. The number of microbleeds is rated in different infratentorial, deep and

individual lobar regions in the right and left sides, similar to ARWMC scale. This allows to study the distribution of microbleeds and to correlate it with the distribution of white matter changes.

WMLs and microbleeds were scored by a single trained neuroradiologyst (JD) who was blinded to the patient's clinical data.

Transcranial Doppler ultrasonography.

All TCD studies were performed with a hanheld 2-3 MHz transcranial probe (Aplio MX, Toshiba Medical Systems Corp., Japan) at the temporal bone window on both sides. The middle cerebral artery (MCA) main stem was first evaluated with colour Doppler and then it was insonated at the depth giving the optimal waveform to assure a good quality Doppler spectrum. Gosling pulsatility index (PI) of each MCA was calculated automatically as (systolic velocity-diastolic velocity)/mean velocity. We only considered measurements if Doppler spectrum waveform envelope was of very good quality and if at least 4 consecutive good-quality waveforms were reliable for each measurement, to assure accurate PI values. Therefore, not all patients had IP values for the study . If available, the mean value of both sides was calculated for analysis.

Sample size calculation – falta i ho escriuré jo mateix si cal (ho tinc inclòs al projecte FIS).

We calculated the sample size of each group based on the hypothesis that we would find frequencies of white matter lesions of 25% in the group of patients with retinopathy and 10% in the group without retinopathy, with and expected drop-out rate of 10%. This calculation yielded a sample size of 144 subjects in

each study group that would allow an 90% power to detect differences between groups with a significance level of < 0.05.

Statistical analysis

Cal que parlem amb Emilio Ortega. Es pot fer un esborrany basant-nos en altres articles

Results

Leucoaraiosis (LA)

MRI was performed in 289 patients (n=146 with retinopathy and n=143 without retinopathy). Fifty-eight patients with retinopathy (39.72%) and 44 patients without retinopathy (30.76%) had WMLs (p=0.063).

Concerning the frequency of LA, no differences were observed in the percentage of patients with LA when patients with T2D without RD were compared to those with mild retinopathy (30,1% *vs* 30,4%). In contrast, the percentage of patients with T2D and LA was higher in those with a more severe grade of retinopathy compared to those with mild retinopathy (47.1% *vs* 30.4%, p=0.002).

In relation to the severity of LA assessed by ARWC score, most of the patients (n=187) had no lesions of LA, 70 patients had mild LA, 29 patients had moderate LA and in 3 patients LA was severe. A positive correlation was observed between the severity of LA and either the presence (although non-significant, p=0.052) or the grade of DR (p=0.0409).

In the univariate analysis, the presence of LA was associated with age (p<0.001), systolic blood pressure (p=0.005), a previous diagnosis of hypertension (p=0.024), and the presence of carotid plaques. However, only

age (p<0.001) and systolic blood pressure (p=0.024) were associated with LA in the regression analysis.

Microbleeds

Microbleeds were only identified in 3 patients with retinopathy (2.05%) and 5 patients without retinopathy (3.5%) (not significantly different, p=0.45).

Pulsatility index (PI)

Transcranial Doppler ultrasonography results showed that differences were observed in the mean MCA-PI in relation to either the presence or grade of DR. Thus, mean MCA-PI was statistically higher in patients with DR compared to those without DR (0.92 (0.80-1.02 *vs* 1.06 (0.93-1.20) p<0.0001) and, mean MCA-PI was statistically higher in those with severe grades of DR compared to those with mild DR (1.11 (1.01-1.26) *vs* 0.94 (0.85-1.11), p=0.0004). No differences were observed when patients with mild DR were compared to those without DR (0.94 (0.85-1.11) *vs* 0.92 (0.80-1.02).

In the univariate analysis, age (p<0.001), systolic blood pressure (p<0.0001), diastolic blood pressure (p=0.0008), presence of hypertension (p=0.002), presence of retinopathy (p=0.03), HbA1c (p=0.03) and aspirin treatment (p=0.0008) were associated with mean MCA-PI.

However, in the multivariate analysis only age (p<0.0001), systolic blood pressure (p=0.0001), diastolic blood pressure (p=0.0001) and presence of retinopathy (p=0.0327) were associated with mean MCA-PI.

Finally, a positive correlation was found between severity of LA and mean MCA-PI. Thus those patients with more severe grades of LA (group B) had

significantly higher values of MCA-PI than those without LA or mild LA (group A) (1.19 (1.098-1.32) *vs* 0.96 (0.86-1.11), p=0.0058).

Conclusions

The main finding of the present study is that patients with T2D and DR, without previous CV disease, show manifestations of cerebral SVD compared to those without DR. More specifically, those patients with more severe grades of DR show a more severe grade of LA and higher MCA-PI values.

It is accepted that T2D is associated with and increased risk of stroke and cognitive decline. In relation to cerebral SVD, an increased prevalence of lacunar infarcts has been described in people with T2DM compared to subjects without DM (32). The association between T2D and WM hyperintensities such as LA is less clear (33). In relation to cross-sectional studies performed in patients with T2D that have used the same methods as ours, i.e visual rating scales, to evaluate the presence and severity of WMLs conflicting results have been described. Some (12) have described a higher frequency and severity (12, 34, 35) of WMLs compared to people without DM, specially those located in the deep cerebral area, while others have found no differences (11). However, with the use of more sensitive brain magnetic resonance techniques, recent studies seem to show, more firmly than previously reported, a relationship between DM and both the presence and severity of LA (36). In the present study, the severity of LA was higher in patients with T2D and DR compared to those without DR. However, we found no differences in the percentage of patients with LA when both groups (patients with or without DR) were compared. The low prevalence of LA found in our study could be influenced by the selection of our population

study, as patients included in the present study were younger than those in previous studies. As in previous studies, our results show a higher frequency of LA in patients with a previous diagnosis of hypertension or elevated systolic blood pressure. As far as we know there are no data in the literature about the prevalence and severity of WMLs in patients with T2D in relation to the presence and grade of DR.

In relation to microbleeds, an additional cerebral microvascular lesion analyzed in the present study, no differences were observed when T2D patients with DR were compared to those without DR. In general population brain microbleeds have been described to be associated with diabetes mellitus, hypertension (35, 37) and retinal microvascular abnormalities (35). However, a recent study specifically performed in a group of 350 patients with T2D found no differences in microbleeds occurrence compared with a control group (4% and 6%, respectively) (38). This result is similar to that recently reported by Brundel M et al (39) that used an ultra-high field MRI for the evaluation of microbleeds. These results are similar to those obtained in the present study. To the best of our knowledge the presence of brain microbleeds and its relationship with DR has not previously been addressed in a population of patients with T2D. In patients with T1D, the presence of proliferative DR has recently been described by Woerdeman J *et al* to be associated with a higher prevalence of brain microbleeds whereas not with the presence of ischemic SVD as assessed by WM hyperintesities on MRI without finding any difference between T1D patients without proliferative retinopathy and controls (4). The authors of this study suggest that this might be explained by its different etiology, i.e vessel wall leakage in cerebral microbleeds and ischaemic tissue damage in WM lesions.

One of the possible explanations for the lack of difference in microbleeds prevalence between patients with or without DR in the present study might be due to the fact that the number of patients with T2D and proliferative DR was low. Another possible explanation for the differences in the prevalence of microbleeds between patients with T1D and T2D is that usually T2D typically develops in the context of a cluster of vascular and metabolic risk factors, like hypertension, dyslipidemia and obesity, which each could lead to brain damage itself.

The pulsatility index, as derived from Transcranial Doppler ultrasound has been interpreted as a consequence of SVD due to changes in vascular resistance (40). In patients with T2D, Lippera *et al* described in a group of 86 T2D patients an increased PI in those with proliferative DR compared to those without DR or background DR (41). These results are consistent with those reported by Lee *et al* that described a significantly higher PI of the MCA in a group of 33 patients with a microvascular complication with either retinopathy, nephropathy or neuropathy (18).

In general elderly population, MCA-PI has been described to correlate with WML severity (7, 42). In patients with recent transient ischemic attack or stroke, Webb *et al* have recently described that MCA-PI is associated with the presence and severity of LA as well as with both pulsatility and arterial stiffness in both the aorta and the MCA (43). Thus, the authors of this latest study suggest a causative pathophysiological relationship between LA and large artery stiffening. Arterial stiffness has been shown to be an independent risk factor for adverse cardiovascular events and all-cause mortality in the general population (44). In patients with T2D an increased pulse wave velocity (PWv) in

the large arteries, a mesure used for the evaluation of arterial stiffness, has been described (45). In these patients arterial stiffness has also been reported to be independently associated with the severity of cerebral WMLs (46). On the other hand, in patients with T2D, DR has been independently associated with PWv, the severity of DR being associated with a greater peripheral vascular stiffness (47). The stiffening of large arteries like the aorta may promote more penetration of the pulsatile enery into the microvasculature of the brain with resulting smaller lumen and reduced vasodilatory reserve. Several potential mechanisms have been proposed for the arterial wall stiffening observed in patients with T2D. Our group has recently described that one of these mechanisms may be the existence of a diabetic microangiopathic complication affecting the wall of the large arteries, specially in those patients with a microvascular complication such as retinopathy (48). To our knowledge, there are no data in the literature about the relationship between LA, presence and severity of retinopathy and MCA-PI in a group of patients with T2D.

The present study has several limitations. A direct relationship between retinopathy and cerebral microangiopathy cannot be demonstrated due to the the cross-sectional design of the study. The lack of an age-matched control group without diabetes prevents the extrapolation of these results to the general diabetic population. The frequency of cerebral MRI findings is lower than expected initially to calculate the sample size. Recent studies have related cerebral PI to Aortic and proximal large artery stiffness (43). We cannot rule out this hypothesis because the study was not designed for this purpose.

The strengths of the present study are its specific design aimed to test the hypothesis that the brain is a target organ to diabetic microangiopathy related to

retinopathy. Thus, a large number of patients with retinopathy were included. All PI measurements were made by the same neurologyst with an standardised method, and only good quality individually revised Doppler spectrum waveform PI were used to evaluate measurements.

In conclusion, in the present study we found that patients with T2D patients and DR have a more severe grade of LA and a higher MCA-PI compared with those without DR. These data are at the expense of those patients with more severe grades of DR. Moreover, a positive association has been found between LA severity and MCA-PI values. Future studies are needed to evaluate the usefulness of measuring the MCA-PI as well as the presence and severity of DR as possible markers of cerebral microvascular lesions in patients with T2D. Results of the present suggest that in T2D, DR is associated with a microangiopathic affection of cerebral vessels supporting the hypothesis that the brain is a target organ for microvascular complications of diabetes similar to other organs such the retina. Thus, patients with T2D and DR could be a target population for screening of cerebral microangiopathy.

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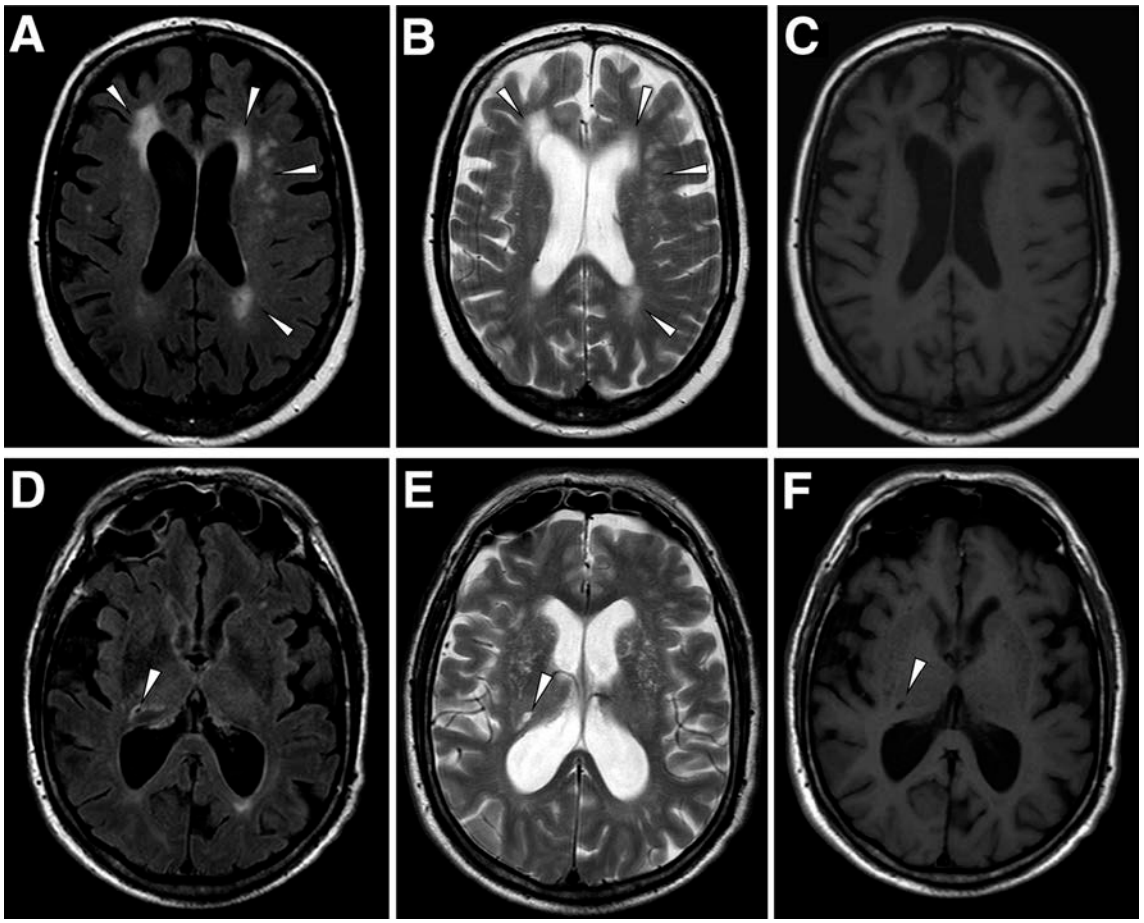

FIg 1

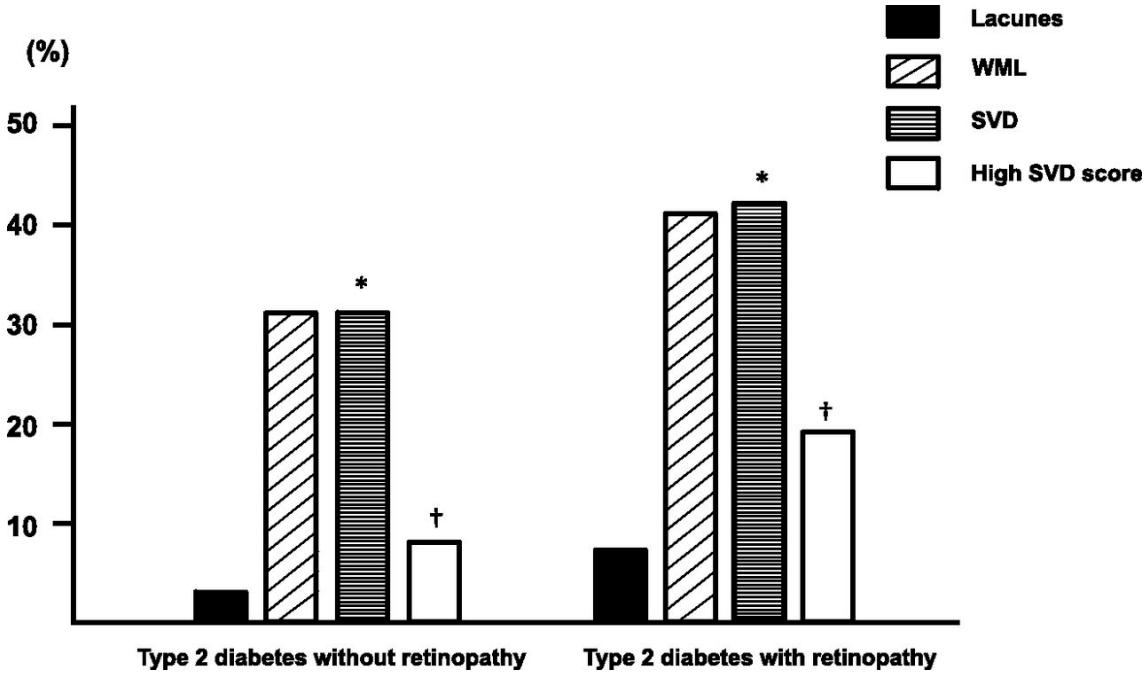
(%)
50
40
30
20
10
Lacunes
WML
SVD
High SVD score
*
*
†
†
Type 2 diabetes without retinopathy
Type 2 diabetes with retinopathy

Fig 2

	Diabetes without DR(*n* = 159)	**Diabetes with DR(*n* = 153)**	***P* value**
Sex (male/female)	82/77	76/77	0.74
Age (years)	59 (48–66)	61 (54–68)	0.01
Disease duration (years)	6 (2–10)	11 (6–20)	<0.01
Insulin treatment (*n*)	20 (12.6%)	84 (54.9%)	<0.01
Smoking (yes/past/never)	71/54/32	78/44/30	0.51
Antiplatelet agents (yes/no)	112/47 (29.6%)	82/71 (46.4%)	<0.01
Dyslipidemia (yes/no)	88/71 (44.7%)	79/74 (48.4%)	0.51
Hypertension (yes/no)	83/76 (47.8%)	48/105 (68.3%)	<0.01
Systolic BP (mmHg)	134 (123–145)	143 (133–159)	<0.01
Diastolic BP (mmHg)	76 (70–83)	77.5 (68.5–85.5)	0.75
HR (bpm)	75 (68–82)	77 (70–86)	0.08
BMI (kg/m^2)	30.3 (27.4–34.0)	31.1 (28.3–35)	0.25
Waist circumference (cm)	103 (96–111)	107.5 (163–114)	<0.01
Hemoglobin A_{1c} (mmol/mol)	53 (48–63)	65 (55–76)	<0.01
Hemoglobin A_{1c} (%)	7.1 (6.5–7.9)	8.1 (7.2–9.1)	<0.01
Total cholesterol (mmol/L)	184 (163–207)	181 (162–204.5)	0.99
HDL cholesterol (mmol/L)	47 (40–57)	50.5 (42–60.5)	0.03
LDL cholesterol (mmol/L)	108 (90.2–130.2)	105.4 (86.5–127.8)	0.27
Triglycerides (mmol/L)	118 (89–171)	116 (83–168)	0.62
Serum creatinine (μmol/L)	0.79 (0.69–0.92)	0.79 (0.68–0.93)	0.80
Urinary albumin/creatinine ratio (mg/g)	5.8 (3.2–11)	12.4 (6–32.7)	<0.01
Carotid plaques, *n* (%)	83 (52.2%)	104 (68%)	<0.01

Table 1

Table 2. White matter lesions by MRI of the study group

	No DR	**Mild DR**	**More than mild DR**	***p*-value**
WMLs presence (%)	30	30	47	0.022
High WMLs score (%)	7.5	7.14	17.19	0.016
MCA-PI	0.92 (0.80-1.02)	0.94 (0.85-1.11)	1.11 (1.01-1.26)	<0.001

WMLs: whitte matter lesions
MCA-PI: pulsatility index of the middle cerebral artery
High WMLs score: ARWC score 2-3