Pathogenesis and neuroimaging of cerebral large and small vessel disease in type 2 diabetes: A possible link between cerebral and retinal microvascular abnormalities

Toshitaka Umemura1*, Takahiko Kawamura2,3, Nigishi Hotta2

Departments of 1Neurology, 2Diabetes and Endocrine Internal Medicine, and 3Preventive Medical Center, Chubu Rosai Hospital, Nagoya, Japan

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*Correspondence
Toshitaka Umemura
Tel.: +81-052-652-5511
Fax: +81-052-653-3533
E-mail address: tumemura@bg7.so-net.ne.jp

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ABSTRACT
Diabetes patients have more than double the risk of ischemic stroke compared with non-diabetic individuals, and its neuroimaging characteristics have important clinical implications. To understand the pathophysiology of ischemic stroke in diabetes, it is important to focus not only on the stroke subtype, but also on the size and location of the occlusive vessels. Specifically, ischemic stroke in diabetes patients might be attributed to both large and small vessels, and intracranial internal carotid artery disease and small infarcts of the posterior circulation often occur. An additional feature is that asymptomatic lacunar infarctions are often seen in the basal ganglia and brain stem on brain magnetic resonance imaging. In particular, cerebral small vessel disease (SVD), including lacunar infarctions, white matter lesions and cerebral microbleeds, has been shown to be associated not only with stroke incidence, but also with the development and progression of dementia and diabetic microangiopathy. However, the pathogenesis of cerebral SVD is not fully understood. In addition, data on the association between neuroimaging findings of the cerebral SVD and diabetes are limited. Recently, the clinical importance of the link between cerebral SVD and retinal microvascular abnormalities has been a topic of considerable interest. Several clinical studies have shown that retinal microvascular abnormalities are closely related to cerebral SVD, suggesting that retinal microvascular abnormalities might be pathophysiologically linked to ischemic cerebral SVD. We review the literature relating to the pathophysiology and neuroimaging of cerebrovascular disease in diabetes, and discuss the problems based on the concept of cerebral large and small vessel disease.

INTRODUCTION
The continually increasing number of diabetes patients is a social problem worldwide, and thus prevention of the incidence and recurrence of macrovascular complications, stroke and ischemic heart disease in particular, is extremely important. Compared with non-diabetics, ischemic stroke is two- to three-fold more prevalent in diabetes patients1–4, and a recent meta-analysis has reported that hemorrhagic stroke is approximately 1.5-fold more prevalent in diabetes patients than in individuals without diabetes5. However, as there are ethnic differences in hemorrhagic stroke prevalence6, diabetes is not recognized as a risk factor for hemorrhagic stroke.

Regarding the characteristics of cerebral infarctions, according to past autopsy studies7,8, small infarctions (lacunar infarctions) in the thalamus, pons and other parts of the vertebrobasilar artery system, and intracranial internal carotid artery disease are more frequent in diabetes patients. In the acute phase, there is often early neurological deterioration and recurrence, and the prognosis is frequently poor. Generally, in diabetes, endothelial nitric oxide synthase activity and nitric oxide production decrease, leading to progression of endothelial dysfunction and impaired vasodilatation. As intracranial vessels are particularly susceptible to the effects of oxidative stress9, there is a possibility that blood–brain barrier (BBB) disruption in the intracranial carotid artery would precede the formation of atherosclerotic lesions.
The pathogenesis of cerebral small vessel disease (SVD) is not fully understood. Endothelial activation, increased BBB permeability and inflammatory processes have been implicated. In addition, a previous study has shown that hyperglycemia-induced polyol pathway hyperactivity might play an important part in the development of diabetes atherosclerosis. Recently, the clinical importance of the link between cerebral SVD and retinal microvascular abnormalities has been a topic of considerable interest. Hyperglycemia-induced polyol pathway hyperactivity is considered to be one possible mechanism underlying the development of diabetic retinopathy. As retinal microvascular abnormalities are associated with magnetic resonance imaging (MRI) markers of cerebral SVD, polyol pathway hyperactivity might play a possible pathogenic role in the development and progression of cerebral SVD in diabetes patients. In the present review, we discuss the possible mechanism underlying the development and progression of diabetes atherosclerosis, and relevant neurovascular imaging studies.

**EPIDEMIOLOGY OF STROKE IN DIABETES PATIENTS**

The number of diabetes patients has been increasing worldwide, and it has become a major public health problem, with the recent International Diabetes Federation report stating that it had surpassed 400 million. When diabetes is accompanied by stroke, in many cases a caregiver is required to assist the patient in daily life because of physical disability and cognitive impairment. Compared with non-diabetic individuals, the incidence of cerebral infarction in diabetes patients is two- to threefold higher because of the combined effect of multiple risk factors for atherosclerosis. A recent meta-analysis showed that diabetes raised the risk not only of cerebral infarction, but also of brain hemorrhage. The Trial of Org 10172 in Acute Stroke Treatment classification is often used in stroke-related clinical research has cerebral large vessel disease and SVD as subtypes. When thinking about the pathophysiology of cerebral infarction in diabetes, it is important to focus on the size of the cerebral vessel that has been impaired. Diabetes is a significant risk factor for both large vessel disease and SVD, and it is present in approximately 30% of cerebral infarction cases. An autopsy study that examined cerebral infarctions by vascular territory supply found that compared with non-diabetics, infarctions more often occurred in the vertebrobasilar artery system of diabetes patients, in the pontine basal portion in particular.

Although few studies have examined an association between the duration of diabetes and stroke incidence in detail, it has been reported that for a disease duration of 10 years or more, the risk of developing ischemic stroke was twofold greater as compared with up to 5 years. Compared with the recurrence rate within 2 years of the initial stroke in non-diabetic individuals of 11.4%, the recurrence rate in diabetes patients was significantly higher at 15.2%, and for recurrence from 5 years onwards, diabetes was the strongest predictive factor. In contrast, glycated hemoglobin level was not associated with the risk of stroke recurrence.

**PATHOGENESIS OF ISCHEMIC CEREBROVASCULAR DISORDERS IN DIABETES**

The hyperglycemic state causes cell damage by promoting advanced glycation end-products, activating protein kinase C and through polyol pathway activation. In particular, activation of the polyol pathway consumes nicotinamide adenine dinucleotide phosphate, which reduces endothelial nitric oxide synthase activity and decreases nitric oxide production, causing endothelial dysfunction. By increasing adhesion molecule expression in the endothelium, and reducing anti-inflammatory and vasodilatation actions, this is thought to promote atherosclerosis, leading to thrombus formation, and further to incidence and progression of cerebral infarction.

The risk factors for the development of atherosclerosis in patients with diabetes are chronic hyperglycemia, dyslipidemia, hypertension and hyperinsulinemia. These risk factors and their related abnormalities, such as decreased bioavailability of vascular nitric oxide, are well known for patients with a long duration of diabetes and older age. The involvement in atherosclerosis development of increased levels of molecular mediators, such as circulating vascular cell adhesion molecule-1 and plasminogen activator inhibitor-1 and tissue factor, as well as increased platelet activation, are also well known for such patients. All of this contributes to vascular dysfunction with ischemia/hypoxia. In addition, a possible pathogenesis of diabetic complications, including microvascular disease and atherosclerosis, has been proposed on the basis of findings for hyperglycemia-induced metabolic abnormalities, such as oxidative stress, changes in protein kinase C, glycation and the polyol pathway. Increasing evidence suggests that oxidative stress, glycation, protein kinase C activity and myoinositol metabolism have cross-links with the polyol pathway (Figure 1).

Previous studies by our group and others have suggested that hyperglycemia-induced polyol pathway hyperactivity might, in part, play an important role in the development of diabetes atherosclerosis. Recently, and others have observed that the combination of hyperglycemia during collagen activation leads to a positive feedback cycle of release of platelet thrombomodulin and enhanced platelet aggregation through polyol pathway hyperactivity. This was ameliorated by an aldose reductase (AR) inhibitor. Furthermore, a study using diabetic apo E4 human AR mice aortas by Vedantham et al. surmised that glucose flux through the polyol pathway in hyperglycemia mediates atherosclerosis in part by influencing nicotinamide phosphoribosyl transferase-mediated nicotinamide adenine dinucleotide biosynthesis, resulting in increased expression of vascular cell adhesion molecule-1 and tissue factor. All of their observations were improved by an AR inhibitor. The aforementioned previous studies and the novel findings of...
Tang et al. and Vedantham et al. strongly suggest that diabetes atherosclerosis has similarities with diabetic microangiopathy, and might partly develop from the metabolic cascade activated through hyperglycemia-induced polyol pathway hyperactivity, as seen in Figure 1.

Insulin resistance is also thought to be a risk factor for cerebral infarction, and it has been reported that insulin resistance was observed in approximately half of non-diabetic individuals who had experienced transient ischemic attack or ischemic stroke. Insulin resistance is not only related to impaired glucose tolerance, it is also considered to promote atherosclerosis by causing hypertension, dyslipidemia, reduced fibrinolytic activity and increased platelet agglutination, and promoting endothelial dysfunction. Furthermore, insulin resistance has also been reported to be a risk factor for atherothrombotic infarction in non-diabetic individuals.

**DIABETES AND CEREBRAL LARGE VESSEL DISEASE**

**Carotid artery disease**

In extracranial large arteries causing cerebral infarctions, atherosclerosis frequently occurs in the bifurcation of the carotid artery and origin of the vertebral artery. As an imaging modality for evaluating atherosclerotic lesions in diabetes patients, carotid artery ultrasonography is convenient, yields much information and has high diagnostic value. The intima-media thickness of the carotid artery is an indicator of atherosclerosis that is superior in terms of quantitativeness and reproducibility, and large-scale observational studies have shown that it is a predictor of cardiovascular events, as well as a factor for poor outcomes. There is a strong tendency for intima-media thickness to be greater in diabetes patients, and it is important for evaluating stenotic lesions caused by plaque. In a study that analyzed carotid artery plaque characteristics in diabetes patients and non-diabetic individuals by high-resolution ultrasonography, it was reported that there was significantly more echolucent plaque in the diabetes patients. Because echolucent plaque is associated with cerebrovascular events, in recent years, evaluation of plaque characteristics using MR plaque images and computed tomography angiography has been playing an important role in this field (Figure 2a–c). Hyperintense plaque on MR T1-weighted images is treated as unstable plaque having a lipid-rich necrotic core or intraplaque hemorrhage. A recently published study showed that calcified plaque in type 2 diabetes patients predicted future cardiovascular events, so it will be necessary to explore further studies on an association of plaque characteristics and vascular events.
In the treatment of carotid artery disease, it has been shown that some statins have a stabilizing action on carotid artery plaque, excepting patients with symptomatic severe carotid artery stenosis and those at high risk, so optimal medical treatment combining antiplatelet agents and statin would tend to be superior to surgical treatment (carotid endarterectomy and carotid artery stenting).

Intracranial artery disease

It has been noted that ischemic stroke as a result of intracranial large artery steno-occlusive lesions is more common in Asian populations than in Caucasian populations. Also, in a recent Chinese study, intracranial large artery stenosis (>50% stenosis) was observed in 46.6% of acute ischemic stroke. Regarding risk factors for intracranial large artery disease, besides age and hypertension, which are the main related factors, it has been suggested that there are also associations with diabetes, insulin resistance and dyslipidemia. In this regard, a strong association between diabetes and intracranial internal carotid artery stenosis has been shown (Figure 3). In autopsy study findings, there was an association between diabetes and both intracranial stenosis and intracranial plaque.

Compared with extracranial vessels, the adventitia is thinner in internal vessels and the BBB is present. It is therefore considered that, for intracranial large arteries, BBB disruption might precede the formation of atherosclerotic lesions. It has been reported that anti-oxidant enzymes are significantly more abundant in intracranial vessels than in extracranial vessels, and the effect of oxidative stress is particularly remarkable in cranial vessels. Also, the decrease in endothelium-dependent vasodilation reactions with age is significantly greater in intracranial arteries as compared with extracranial arteries, and vasodilation capacity is particularly susceptible to decline in diabetes patients. This is possibly a reason for the large number of intracranial internal carotid artery lesions in patients with diabetes.

Figure 2 | Extracranial carotid artery disease. A 75-year-old man with symptomatic carotid artery stenosis. (a,b) Reconstructed computed tomography angiography and 3-D computed tomography angiography show severe stenosis of the left internal carotid artery (arrows). (c) Unstable plaque is visualized as a hyperintense signal on axial fat-suppressed black-blood T1-weighted image (arrow).

Figure 3 | Intracranial carotid artery disease. A 66-year-old woman with an ipsilateral transient ischemic attack. Magnetic resonance imaging angiography volume rendering image shows severe stenosis in the right intracranial internal carotid artery.
DIABETES AND CEREBRAL SVD

Branch atheromatous disease and lacunar infarction

Lacunar infarctions (LIs) are attributed to disease of penetrating branches of large cerebral arteries, and the pathological mechanism is considered to mainly involve arteriosclerosis as a result of lipohyalinosis caused by hypertension. Multiple LIs are more frequent in diabetes patients. In a 5-year observation of type 2 diabetes patients, macroalbuminuria was the only contributing factor to the increased lacuna. As multiple LIs are associated not only with stroke recurrence, but also cognitive decline, they have an important clinical implication. Also, it has been reported that diabetes patients with lacunar infarctions are associated with the high recurrence rate of ischemic stroke and worse clinical outcomes. Past research based on autopsy subjects and diagnostic imaging has also noted that posterior circulation stroke is more frequent in diabetes patients. Furthermore, with recent advances in MRI technology, it has become possible to diagnose small brainstem infarcts at the early phase of onset. The paramedian pontine artery is more directly branched at the orifice of the basilar artery, and when it becomes occluded, infarcts extending to the basal surface of the pons occur, in many cases with a poor functional prognosis.

Caplan et al. proposed the term ‘branch atheromatous disease’, having as its cause microatheroma at the orifice of the penetrating artery. It has been noted that in diabetes, there are relatively many infarcts of this type that occur in the paramedian pontine artery area, and neurological deterioration is likely to progress in the acute phase. In contrast, for penetrating artery infarcts including branch atheromatous disease in the region of the lenticulostriate artery, which branches from the middle cerebral artery (Figure 4d,e), it was reported that there was no significant association between diabetes and early neurological deterioration, whereas albuminuria was an independently related factor. In this regard, using diffusion-tensor imaging (Figure 4f), a study aiming to predict neurological deterioration by evaluating the location of the corticospinal tract has been carried out. In recent years, the ability to visualize plaque lesions by high-resolution MRI in penetrating branches of the basilar and middle cerebral arteries has been receiving attention. Regarding treatment of branch atheromatous disease, in the acute phase, many patients have resistance to drugs, and although small-scale research suggests that administration of cilostazol, a drug with endothelial protective and vasodilatory actions, in addition to anticoagulants (argatroban), free radical scavengers (edaravon) and statins is efficacious, there is no established optimal medical therapy at present. However, in Asian populations, as the risk of intracranial hemorrhage increases with the use of antithrombotic drugs, it is important to consider hemorrhagic risk when choosing agents for medical therapy.

Silent brain infarctions, white matter lesions and cerebral microbleeds

In elderly diabetes patients without a history of stroke, silent brain infarctions (SBIs), white matter lesions (WMLs) and cerebral microbleeds (CMBs) are often observed on brain MRI...
These lesions are MRI expressions of SVD, and have an important clinical significance because of the association of their progression with stroke incidence. A recent systematic review and meta-analysis showed that SBI is associated with a twofold increased risk of future stroke. Apart from age, hypertension is the most widely accepted risk factor for SBI; however, whether diabetes is also a risk factor for SBI remains unclear. Indeed, the results of large-scale observational studies have been inconsistent with the relationship between diabetes and the incidence of SBI. Also, neuroimaging findings for diabetes patients have found associations of diabetes with LI and brain atrophy, but there is no unified view regarding an association with SBIs and WMLs.

The pathogenesis of cerebral SVD is not fully understood. Cerebral SVD is considered to be caused by an increased permeability of the BBB, leading to development of SBIs, WMLs and CMBs. A previous small study showed that type 2 diabetes patients showed increased BBB permeability associated with neuroimaging features using MRI with intravenous gadolinium-diethylene triamine pentaacetic acid. However, it is not clear whether BBB permeability readily increases in diabetes. Regarding the possible mechanism for the development of WMLs, recent pathological research suggests that there is first a decline in vessel integrity and then an increase in BBB permeability as a result of endothelial dysfunction. Inflammatory processes are also involved in the pathogenesis of cerebral SVD. Endothelial dysfunction is a possible causal factor, and circulating markers of endothelial activation and inflammation are elevated in patients with SVD. Circulating levels of endothelial and inflammatory markers are elevated in people with type 2 diabetes compared with non-diabetic population.

Figure 5 | Magnetic resonance imaging expressions of cerebral small vessel disease. (a) New lacunes (arrows) in the basal ganglia and lateral ventricular anterior horn have appeared on 8-year follow-up fluid-attenuated inversion recovery images. (b) Periventricular white matter lesions (open circle) extend into deep white matter over 6-year follow up. (c) Gradient-recalled echo T2*-weighted magnetic resonance imaging of patients who had developed new microbleeds without cardiovascular events over 3-year follow up. Arrows indicate new microbleeds on the follow-up scan.
| Author, reference (year of publication) | Study design | Mean follow-up period (years) | Participants | Mean age (years) | Mean diabetes duration (years) | Outcome measures results | P-value | Adjustment variables |
|--------------------------------------|--------------|-------------------------------|--------------|-----------------|-----------------------------|-------------------------|---------|---------------------|
| Manschot et al. (2006)               | Cross-sectional – | T2DM n = 113 Control n = 51 | 66.1 | 8.8 | PWML (Scheltens scale 0–12) | 0.13 | NA |
|                                      |              | T2DM with HT n = 44 Control n = 44 | 73.5 | 1.9 | DWML (Scheltens scale 0–36) | 0.02 | |
|                                      |              | T2DM without HT n = 44 Control n = 44 | 73.1 | 1.6 | Silent brain infarction (SBF) | 0.06 | |
|                                      |              |                             |              |                 | Cerebral atrophy            |                | |
| van Harten et al. (2007)             | Cross-sectional – | T2DM with HT n = 44 Control n = 44 | 73.5 | 11.9 | PVH (Scheltens score 0–6) | NS | NA |
|                                      |              | T2DM without HT n = 44 Control n = 44 | 73.4 | 16.5 | DWML (Scheltens score 0–24) | P < 0.05 | |
|                                      |              |                             |              |                 | Lacunar infarction          | NS | |
|                                      |              |                             |              |                 | Global atrophy              | NS | |
| Jongen et al. (2007)                 | Cross-sectional – | T2DM n = 99 Control n = 46 | 65.9 | 8.7 | Total brain volume* | P < 0.01 | Age, sex, intracranial volume and education level |
|                                      |              |                             |              |                 | –21.8 (–34.2 to –4)         | P < 0.05 | |
|                                      |              |                             |              |                 | WMH volume*†                 |                | |
|                                      |              |                             |              |                 | 0.45 (0.04–0.86)            |                | |
| Umemura et al. (2008)                | Cross-sectional – | T2DM n = 130 Control n = 130 | 59.6 | 11.9 | SBI | NS | NA |
|                                      |              |                             |              |                 | OR (95%CI) =1.22 (0.70–2.14) |                | |
| De Bresser et al. (2010)             | Longitudinal 4 | T2DM n = 55 Control n = 28 | 65.9 | 9.5 | Total brain volume** | NS | Age and sex |
|                                      |              |                             |              |                 | –0.18 (–0.49 to 0.13)       |                | |
|                                      |              |                             |              |                 | WMH volume**                 | NS | |
| Van Elderen et al. (2010)            | Longitudinal 3 | DM n = 89 Control n = 438 | 74.7 | NA | Total brain atrophy (%)*** | P < 0.01 | Age and sex |
|                                      |              |                             |              |                 | 1.57 (0.29) vs 0.96 (0.10)  |                | |
|                                      |              |                             |              |                 | Total WMH volume (cc)***     | NS | |
|                                      |              |                             |              |                 | 1.78 (0.29) vs 2.21(0.17)    |                | |
|                                      |              |                             |              |                 | Infarction*** 0.40 (1.23) vs 0.19 (0.68) | P = 0.07 | |
| Espeland et al. (2013)               | Cross-sectional – | T2DM n = 58 Control n = 640 | 77.8 | NA | Total brain atrophy | P = 0.11 | Age, clinic site, WHI treatment, time from WHI enrollment, time between scans and baseline volume |
|                                      |              |                             |              |                 | –3.02 cc (diff)              |                | |
|                                      |              |                             |              |                 | Gray matter volume           | P = 0.22 | |
|                                      |              |                             |              |                 | –3.02 cc (diff)              |                | |
|                                      |              |                             |              |                 | WML volume 2.41 cc (diff)    | P = 0.66 | |

* = Median (Q1–Q3) ** = p-value corrected for multiple comparisons by Bonferroni correction *** = not significant.
previously reported associations between levels of soluble intercellular adhesion molecule-1, a marker of vascular endothelial dysfunction, and progression of SBI and WMLs in type 2 diabetes patients. Furthermore, previous studies showed that higher levels of soluble intercellular adhesion molecule-1 and high-sensitivity C-reactive protein were associated with the risk of future stroke in type 2 diabetes patients. Vascular endothelial dysfunction easily progresses in diabetes patients, and at the level of small and microvessels in the brain, associations with incidence and progression of SVD are also possible, as a result of microcirculation and vasodilatation disorders.

CMBs are also a manifestation of cerebral SVD on brain MRI, and have attracted considerable attention. CMBs are visualized as small, round, well-defined foci of low signal intensity on T2*-weighted MRI. It has been suggested that CMBs are a useful imaging marker for pathological damage to small vessels from hypertension or cerebral amyloid angiopathy. Histologically, CMBs represent hemosiderin, likely from leakage through cerebral small vessels, contained within surrounding macrophages in the brain parenchyma. Age and hypertension have been strictly associated with CMBs. However, the relationship between diabetes and the development of CMBs is still unclear.

**IMPACT OF CEREBRAL SVD AND BRAIN ATROPHY ON COGNITIVE IMPAIRMENT IN DIABETES**

It has been known for some time that diabetes is associated not only with the risk of vascular dementia, but also with Alzheimer’s disease (AD). Regarding associations of diabetes and AD, it has been reported that there was significant atrophy in the medial temporal lobe, including the hippocampus and amygdala, in diabetes patients as compared with non-diabetic individuals, and an association between medial temporal lobe atrophy and insulin resistance was also shown. Recently, computer-assisted voxel-based morphometry has been applied to detect early brain atrophic changes. Matsuda et al. developed a computer-assisted analysis using voxel-based morphometry for diagnosing AD at an early phase. Atrophy in the medial temporal lobe might be semiquantitatively assessed using free software for this procedure, called voxel-based specific regional analysis system for analysis system for Alzheimer’s disease (VSRAD) (Eisai Co., Ltd, Tokyo, Japan), and it is used as a diagnostic tool for the early diagnosis of AD. It has been reported that, as evaluated by VSRAD, internal hippocampal atrophy was stronger in degree in diabetes patients than in non-diabetic individuals, and that there was an association of such atrophy and cognitive dysfunction.

It has also been shown that elderly people with diabetes develop extensive vascular pathology, which alone or together with AD-type pathology, particularly in apo E4 carriers, results in an increased risk of clinical dementia. Although significant associations of severity and progression of brain atrophy with cognitive decline have been reported in diabetes patients, as there might also be an influence from WMLs, the ability to evaluate brain microstructure and damage...
to vessel integrity from MRI is important to understanding the pathophysiology of the disease in the early phase.

SVD is associated with dementia, and it has been noted that progression of SBIs and WMLs is associated with cognitive decline, in particular frontal lobe dysfunction. A previous longitudinal follow-up study showed that the rate of brain atrophy in patients with SVD is approximately twice compared with age-matched control subjects. Although the mechanism of brain atrophy in SVD is not fully understood, endothelial and inflammatory biomarkers would be associated with neuroimaging markers of brain atrophy. Regarding associations between biomarkers and brain atrophy, an association of high levels of sICAM-1 and vasodilatation impairment in the brain has been reported in type 2 diabetes patients, and it has been suggested that changes in vasoregulation might be related to brain atrophy. In community-based cross-sectional analysis, circulating inflammatory markers (interleukin-6, osteoprotegerin and tumor necrosis factor-α) were significantly associated with total brain volume. Also, higher interleukin-6 levels were associated with MRI markers of brain atrophy including white matter hyperintensities volume, lower gray matter and hippocampal volumes in community-dwelling participants. Furthermore, a previous study suggested that albuminuria, a maker of chronic kidney disease, was associated with increased white matter hyperintensity volume. A recent study has shown that albuminuria is associated with the severity and progression of hippocampal atrophy in elderly type 2 diabetes patients.

In the future, irrespective of the presence or absence of diabetes, it will be necessary to elucidate mechanisms for associations between biomarkers of chronic kidney disease and cardiac failure with brain atrophy, as well as with atrophy of the hippocampus and amygdala. Regarding prevention, as it remains unclear whether the administration of drugs with vascular endothelial protective effects, such as statins and antihypertensives (angiotensin receptor blockers, etc.), and agents with neuroprotective effects (dipeptidyl peptidase-4 inhibitors, etc.) will reduce the incidence and progression of SVD or the progression of brain atrophy, it will be necessary to explore their associations in prospective research.

INTERACTION BETWEEN CEREBRAL AND RETINAL MICROVASCULAR ABNORMALITIES IN DIABETES

Association of hyperglycemia and polyol pathway hyperactivity with diabetes atherosclerosis

Cerebral and retinal small vessels have similar vascular structure (end small arteries that have no anastomoses), and the BBB is structurally and functionally similar to the blood–retinal barrier. The retinal vascular bed can be visualized directly and non-invasively using retinal photography, and retinal microvascular abnormalities (arteriovenous nicking, focal arteriolar narrowing, microaneurysms and microhemorrhages) can be serially evaluated. Several clinical studies have shown that retinal microvascular abnormalities are closely related to cerebral SVD, including SBIs, WMLs and CMBs, suggesting that retinal microvascular abnormalities are an imaging marker for cerebral small-vessel disease.

Figure 6 | Cerebro–retinal interaction in diabetes. A 76-year-old woman with simple diabetic retinopathy. (a) Magnetic resonance imaging expressions of cerebral small vessel disease including silent brain infarction (red arrow), white matter lesion (white arrow) and microbleed (arrow head). (b) Retinal photograph of diabetic retinopathy signs showing microaneurysm and retinal hemorrhages (arrow), and hard exudates (arrow head).

Cerebro-retinal interaction in diabetes

Cerebral small-vessel disease

Retinal microvascular abnormalities
cerebral microvascular disease. In addition, previous population-based studies suggest that retinal microvascular abnormalities are also associated with decline in cognitive performance, such as executive function and processing speed. These studies further reinforce the idea that retinal microvascular abnormalities might be pathophysiologically linked to ischemic cerebral SVD.

In fact, there are several studies suggesting an association between diabetic retinopathy and lacunar stroke or cognitive impairment in patients with diabetes. As a potential mechanism of lacunar stroke in patients with diabetes, they hypothesize that similar changes, as well as those in the blood–retina barrier, might induce breakdown of the BBB with subsequent damage to the walls of the small vessels and perivascular edema. In addition, other findings strongly support an association between retinal microvascular signs and lacunar stroke. Furthermore, as some cognitive dysfunction in patients with diabetes is associated with vascular impairment, breakdown of the BBB might play an important role in the development of cognitive dysfunction.

The retinal tissue is protected from the bloodstream by a tight barrier. It consists of an anterior blood–retina barrier component towards the retinal circulation and a posterior blood–retina barrier component towards the choroidal circulation. The anatomical bases of the posterior and anterior blood–retina barriers are tight junctions between the pigment epithelial cells, and between the retinal vascular endothelial cells, respectively. Müller cells are also involved in the maintenance of the blood–retina barrier. Clinically, breakdown of the blood–retina barrier in patients with diabetes can be observed as leakage of intravenously administered fluorescein. Furthermore, it is well known that the loss of pericytes located outside of the endothelial cells of the microvascular wall in the retinal tissue initiates the abnormality of morphological detection in the early stage of diabetic retinopathy. The interaction between pericytes and the endothelial cells plays a crucial role in maintaining the structural and functional integrity of the retinal vascular walls. The failure of this integrity induced by hyperglycemia might contribute to breakdown of the blood–retina barrier, and the subsequent development of diabetic retinopathy. Although an exact mechanism for the disruption of the blood–retina barrier in patients with diabetes has not been established, one of the possibilities is that hyperglycemia-induced polyol pathway hyperactivity might partially play an important role. Indeed, studies on human retinal tissues, as well as those on animal retinal tissues, have shown the presence of AR, a key enzyme of the polyol pathway, in blood vessels, pigment epithelial cells and Müller cells. Based on all of this evidence, besides the proposed mechanism for blood–retina barrier disruption mentioned above, acceleration of the polyol pathway hyperactivity-induced metabolic cascade (Figure 1) might be partly involved in lacunar stroke or cognitive impairment in patients with diabetes. As retinal microvascular abnormalities are associated with neuroimaging markers of cerebral SVD (Figure 6), polyol pathway hyperactivity might be a possible mechanism for the development and progression of cerebral SVD in diabetes patients.

**CONCLUSION AND FUTURE PERSPECTIVE**

Diabetes promotes atherosclerosis and raises the risk of stroke, in particular that of ischemic stroke. As vasodilatation impairment as a result of endothelial dysfunction is an important factor in diabetes, it will be necessary to develop endothelium-targeted therapeutic strategies in the future. In particular, as prevention of SVD progression not only leads to preventing stroke incidence, but also dementia, comprehensive treatment is desirable from the early stage of diabetes. Collaboration between diabetologists and neurologists would help achieve such therapeutic strategies.

**DISCLOSURE**

The authors declare no conflict of interest.

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