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Cerebral microvascular complications of type 2 diabetes: stroke, cognitive dysfunction, and depression

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Adults with type 2 diabetes are at an increased risk of developing certain brain or mental disorders, including stroke, dementia, and depression. Although these disorders are not usually considered classic microvascular complications of diabetes, evidence is growing that microvascular dysfunction is one of the key underlying mechanisms. Microvascular dysfunction is a widespread phenomenon in people with diabetes, including effects on the brain. Cerebral microvascular dysfunction is also apparent in adults with prediabetes, suggesting that cerebral microvascular disease processes start before the onset of diabetes. The microvasculature is involved in the regulation of many cerebral processes that when impaired predispose to lacunar and haemorrhagic stroke, cognitive dysfunction, and depression. Main drivers of diabetes-related cerebral microvascular dysfunction are hyperglycaemia, obesity and insulin resistance, and hypertension. Increasing amounts of data from observational studies suggest that diabetes-related microvascular dysfunction is associated with a higher risk of stroke, cognitive dysfunction, and depression. Cerebral outcomes in diabetes might be improved following treatments targeting the pathways through which diabetes damages the microcirculation. These treatments might include drugs that reduce dicarbonyl compounds, augment cerebral insulin signalling, or improve blood–brain barrier permeability and cerebral vasoreactivity.

Introduction

Stroke, dementia, and depression are increasingly recognised as clinically important complications of type 2 diabetes. Type 2 diabetes is associated with a 2·5-times increased risk of ischaemic stroke, a 1·5-times increased risk of haemorrhagic stroke,[1] and a 1·5-times increased risk of dementia.[2] Additionally, people with type 2 diabetes are 1·5–2·0 times more likely than those without diabetes to have major depression.[3] Stroke and dementia are also more common among adults with prediabetes than among people with normoglycaemia,[4,5] suggesting that brain disease processes start before the onset of diabetes.

The pathogenesis of type 2 diabetes-related stroke, dementia, and depression is complex, multifactorial, and incompletely understood. In view of ageing populations and the growing prevalence of type 2 diabetes, there is an urgent need to identify the mechanisms linking type 2 diabetes with brain and mental disorders. Stroke, cognitive dysfunction, and depression frequently co-occur in type 2 diabetes,[6–8] and might share various underlying mechanisms. One mechanism might be microvascular dysfunction. In type 2 diabetes, microvascular disease has been shown to affect many, if not all, organs including the brain.

In this Review, we discuss how the cerebral microvasculature affects brain function in type 2 diabetes. We review emerging evidence that cerebral microvascular dysfunction and damage are common in type 2 diabetes, present in individuals with prediabetic levels of hyperglycaemia, and a potentially modifiable central mechanism underlying type 2 diabetes-related stroke, cognitive dysfunction, and depression. We also highlight potential therapeutic targets and interventions.

Cerebral microvascular dysfunction in type 2 diabetes

Optimal brain function depends on a healthy microvasculature (panels 1 and 2, figure 1, figure 2). Most direct evidence of cerebral microvascular dysfunction in diabetes derives from in vitro and animal models.[22,23], whereas data from human beings are relatively scarce. A summary of studies on cerebral microvascular structure and function in adults with type 2 diabetes is shown in table 1 and in the appendix (p 2). Morphologically, changes of the cerebral microcirculation in diabetes include basement membrane thickening and increased angiogenesis. Functionally, study findings suggest increased blood–brain permeability and altered blood flow regulation.

Blood–brain barrier permeability

Blood–brain barrier permeability can be assessed via neuroimaging or biochemical methods. Several small studies that have used MRI or CT showed postcontrast enhancement of brain parenchyma in type 2 diabetes (table 1), which is presumed to suggest increased blood–brain barrier permeability. Biochemical identification is also possible because albumin originates solely from the systemic circulation and cannot cross an intact blood–brain barrier. Thus, an increase in the ratio of cerebrospinal fluid albumin to serum albumin concentrations, known as the albumin quotient, can be used as an indirect measure of blood–brain barrier permeability. In one study,[24] the albumin quotient was higher in individuals with type 2 diabetes and in individuals with dementia, and a higher albumin quotient was associated with cerebrospinal fluid markers of microvascular endothelial dysfunction (vascular endothelial growth factor [VEGF], intracellular adhesion molecule 1, and vascular cell adhesion molecule 1) and angiogenesis (VEGF).

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See **Online** for appendix

Core functions of the cerebral microcirculation, defined as cerebral vessels smaller than 150 μm (arterioles, capillaries, and venules), are to optimise the delivery of nutrients and removal of waste products in response to variations in neuronal activity; to maintain the cerebral interstitial milieu for proper cell function; and to decrease and stabilise pulsatile hydrostatic pressure at the level of capillaries.[9,10] Cerebral microvascular dysfunction can be defined as an impairment in any of these functions.

Blood–brain barrier integrity
The cerebral microvasculature is a key site of the blood–brain barrier. This barrier is formed by a tightly linked layer of endothelial cells, together with a basement membrane, mural cells (pericytes in capillaries and vascular smooth muscle cells in arterioles), and astrocyte endfeet. The blood–brain barrier protects neurons from factors present in the systemic circulation and maintains the highly controlled CNS internal milieu.[10,11]

Cerebral autoregulation
The high metabolic demand of the brain necessitates a relatively constant level of blood flow.[12] Cerebral autoregulation is a process that regulates and maintains global brain perfusion across a range of blood pressures.[13,14] Arterioles together with larger cerebral arteries regulate this process by varying peripheral resistance through myogenic responses.[13]

Neurovascular coupling
The brain can rapidly increase local blood flow and oxygen delivery to its activated regions, a mechanism known as neurovascular coupling. Although changes in global blood flow due to local activity are relatively small relative to the constant level of blood flow (5% or less),[12] neurovascular coupling is crucial for neuronal functioning. Neurovascular coupling involves a complex interaction between various cell types. Signals from neuronal cells, astrocytes, and endothelial cells engage smooth muscle cells and, possibly, pericytes to induce vasodilatation and increase local blood flow.[13] This process leads to homogenisation of capillary flow patterns, which facilitates efficient oxygen extraction.[15]

Renewal of neurons and non-neuronal cells
Data from experimental studies suggest that cerebral microvascular endothelial cells, pericytes, and astrocytes are involved in the renewal or generation of neurons and non-neuronal cells in the CNS (eg, oligodendrocytes), amongst others, via release of soluble growth factors.[16,17]

Measures of cerebral microvascular function
Cerebral microvascular function can be assessed in human beings with the use of various indirect and direct measures, including assessment of cerebral microvascular morphology (neuropathology), blood–brain permeability (neuropathology, neuroimaging, or biochemical measures), cerebral resting blood flow and vasoreactivity (neuroimaging), cerebral autoregulation (transcranial doppler), and MRI features of cerebral small vessel disease. Additionally, retinal microvascular changes can be used as a proxy for microvascular changes in the brain.

Cerebrovascular reactivity, cerebral autoregulation, and resting cerebral blood flow

Cerebrovascular reactivity is defined as the change in flow in response to increased neuronal activity (ie, neurovascular coupling) or a metabolic or vasodilatory stimulus, such as an increase in partial pressure of carbon dioxide.[25] This response reflects the ability of the cerebrovasculature, notably arterioles and capillaries, to dilate in response to increased neuronal metabolic demand, and is endothelium dependent.[13,26] Cerebrovascular reactivity can be assessed at the tissue level, with use of MRI, or at the level of a large artery, most commonly with use of Doppler ultrasound. Vasoreactivity measured in a large artery might reflect not only the function of arterioles and capillaries, but also of larger cerebral arteries themselves.[27] Nevertheless, most studies have shown reduced vasoreactivity in type 2 diabetes (either at the tissue level or at the level of larger cerebral arteries; table 1), consistent with the presence of cerebral microvascular dysfunction. Additionally, in a task-based functional MRI study, type 2 diabetes was shown to be associated with impaired neurovascular coupling, and this impairment was related to an altered microvascular haemodynamic response.[28]

Microvascular dysfunction might also contribute to altered cerebral autoregulation. However, data on cerebral autoregulation in type 2 diabetes are scarce. Altered cerebral autoregulation was identified in several small studies, although this finding was not consistent (table 1), and these studies are difficult to compare because of methodological differences.

Altered resting cerebral blood flow might be another manifestation of cerebral microvascular dysfunction, but the extent to which type 2 diabetes affects resting blood flow remains incompletely understood. Results of studies in type 2 diabetes have been inconsistent and are difficult to compare because of differences in the patient populations assessed and methodological differences. Furthermore, the interpretation of resting cerebral blood flow is complex. Reduced resting blood flow might reflect loss of viable tissue, might be a cause of tissue damage, or both. Additionally, resting cerebral blood flow might increase or decrease depending on the disease stage. For instance, cerebral microvascular blood flow might be increased in early type 2 diabetes to compensate for reduced oxygen extraction efficacy related to subtle, or early, microvascular dysfunction, whereas in more advanced stages of the disease, blood flow might be reduced.[15] This scenario can be compared with how the

Panel 2: Detrimental effects of cerebral microvascular dysfunction

Cerebral microvascular dysfunction leads to increased blood–brain barrier permeability, perfusion defects, hypoxia, and increased angiogenesis (figure 2). The effect on accumulation of Alzheimer's disease-related pathologies is unclear.

Increased blood–brain barrier permeability and inflammatory and immune responses

Increased blood–brain barrier permeability leads to leakage of proteins and other plasma constituents into the perivascular space. This effect might directly damage neurons, is related to inflammatory and immune responses, and might also lead to enlargement of perivascular spaces, oedema, and thickening and stiffening of arteriolar walls.[10]

Perfusion defects, hypoxia, and increased angiogenesis

Cerebral microvascular dysfunction leads to impaired blood-flow regulation with impaired autoregulation and neurovascular coupling, and disturbed capillary flow patterns. Type 2 diabetes-related neurodegeneration might also contribute to impaired neurovascular coupling.[18] This impaired neurovascular coupling can result in perfusion deficits, reduced oxygen extraction, and hypoxia.[15] Hypoxia leads to activation of hypoxia-inducible transcription factors, which in turn trigger inflammation and expression of matrix metalloproteinases and pro-angiogenic factors.[11] Matrix metalloproteinases damage endothelial tight junctions, leading to increased blood–brain barrier permeability. Pro-angiogenetic factors, including vascular endothelial growth factor, increase the permeability of the blood–brain barrier and stimulate angiogenesis. Angiogenesis is associated with formation of capillaries that are leaky and poorly perfused, and that have reduced pericyte support.[19]

Unclear role in Alzheimer's diseases-related pathologies

Findings from experimental studies suggest that type 2 diabetes-associated cerebral microvascular dysfunction might also contribute to accumulation of neurofibrillary tangles and amyloid-β plaques, the hallmark neuropathologic features of Alzheimer's disease, via enhanced endothelial expression of the receptor for advanced glycation end products (RAGE) and insulin resistance.[20] RAGE and central insulin resistance might stimulate the production of amyloid β and reduce its clearance via various mechanisms.[21] However, the importance of these effects in human beings is unclear. Studies of in-vivo biomarkers of Alzheimer's disease pathology and brain autopsy studies have shown that neurofibrillary tangles and amyloid plaques are not more common in type 2 diabetes.[21]

pancreas tries to adapt to increased homeostatic load due to insulin resistance: at first insulin production increases and then β-cell failure and insulin insufficiency occur. Notably, blood flow at the level of the microvasculature in the hippocampus has been shown to be increased in individuals with relatively well controlled type 2 diabetes.[29] Additionally, markers of more advanced diabetes (eg, presence of retinopathy,[30] higher HbA_{1c} levels,[30,31] and higher insulin resistance[31]) and the presence of hypertension[32] have been shown to be associated with reduced cerebral blood flow. Increased microvascular blood flow related to arteriolar widening might be a generalised phenomenon in early diabetes, as it has been associated with early diabetes (especially type 1 diabetes, but also type 2 diabetes) in many other organs in addition to the brain.[9] An increased microvascular blood flow might at first be protective, but might, if not accompanied by venular widening, increase capillary pressure and eventually contribute to organ damage.[9] However, the biochemical basis, mediators responsible, and development over time of changes in resting cerebral blood flow in type 2 diabetes remain to be clarified.

Features of cerebral small vessel disease

Features of cerebral small vessel disease (CSVD), as measured by MRI, might be a manifestation of cerebral microvascular dysfunction. MRI features of CSVD include white matter hyperintensities and lacunes of presumed vascular origin, cerebral microbleeds, perivascular spaces, total cerebral atrophy, and microinfarcts.[33] These features are indirect or so-called end-stage markers of small vessel abnormalities because they reflect brain parenchymal damage potentially related to various functional and structural small vessel changes.[33] Evidence suggests that microvascular dysfunction underlies these features. For example, CSVD features are associated with increased blood–brain barrier permeability and reduced cerebrovascular reactivity.[10] Additionally, blood–brain barrier permeability is increased in normal-appearing white matter of patients with other features of CSVD, worsens with proximity to the white matter hyperintensity, and is linked to the development of new white matter hyperintensities over time.[10] Type 2 diabetes is associated with an increased occurrence of CSVD features, including a modest increase in white matter hyperintensity volume, a greater number of lacunes, and a slight decrease in total brain parenchyma volume (table 1). Furthermore, in some studies an association with cerebral microbleeds was identified, whereas data are scarce on perivascular spaces and microinfarcts.

Retinal microvascular changes

The retina offers a unique opportunity to study microvascular changes in the brain because it allows direct visualisation of the microvasculature, which is impossible with current neuroimaging techniques.[34] Furthermore, the vessels of the retina share embryological, morphological, and functional similarities with the
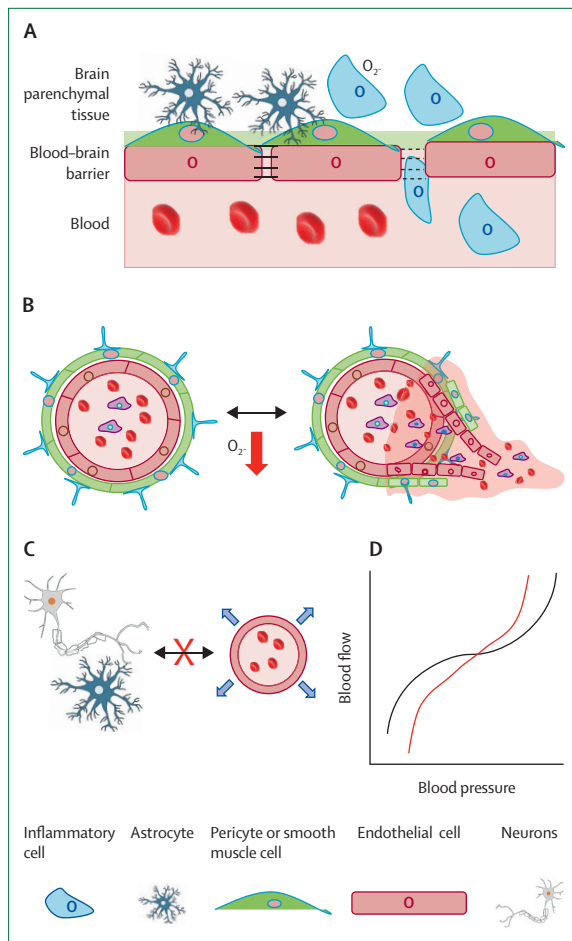
Figure 1: Detrimental effects of cerebral microvascular dysfunction
(A) Type 2 diabetes-related microvascular dysfunction is related to increased oxidative stress, inflammatory and immune responses, and increased blood–brain barrier permeability, resulting in leakage of proteins and other plasma constituents into the perivascular space. (B) Microvascular dysfunction might lead to perfusion defects, hypoxia, and increased angiogenesis. Angiogenesis is associated with formation of capillaries that are leaky, poorly perfused, and have reduced pericyte support. (C) Microvascular dysfunction might contribute to impaired neurovascular coupling, leading to compromised neuronal function. Neurovascular coupling is the mechanism that links transient local neural activity to the subsequent increase in blood flow. (D) Microvascular dysfunction might impair cerebral autoregulation, leading to greater vulnerability of brain tissue to the harmful effects of blood pressure changes. With impaired autoregulation, the normal autoregulation curve that shows the relation between cerebral blood flow and mean blood pressure (black curve) might become more linear and steeper, with perfusion becoming pressure dependent (red curve).

cerebral microvasculature.[34] Type 2 diabetes is clearly associated with retinal microvascular dysfunction. This association includes not only diabetic retinopathy, but also subtle abnormalities of retinal microvascular structure (retinal arteriolar widening, greater fractal dimension, and greater arteriolar tortuosity) and function (reduced retinal arteriolar and venular dilation after flicker-light stimulation), which precede common clinical features of diabetic retinopathy.[9] Consistent with the hypothesis that the microvasculatures of the retina and brain are closely linked, retinopathy and subtle retinal microvascular abnormalities are associated with the presence and progression of features of CSVD in type 2 diabetes.[35,36]

Cerebral microvascular dysfunction and prediabetes: ticking clock hypothesis

Features of CSVD have been shown to progress linearly from normal glucose metabolism to prediabetes and type 2 diabetes, and are associated with the level of glycaemia, even in the prediabetes range.[37,38] Additionally, subtle retinal microvascular abnormalities, including arteriolar widening[39] and reduced arteriolar vasodilatation after flicker-light stimulation,[40] are seen more frequently in individuals with prediabetes than in individuals with normal glucose metabolism. These findings suggest that in type 2 diabetes a ticking clock might exist with regard to microvascular disease—ie, microvascular disease processes might start long before the onset of type 2 diabetes, and contribute to brain and mental disorders not only in people with type 2 diabetes, but also in those with prediabetes or normal glucose metabolism.[9]

Drivers of microvascular dysfunction in type 2 diabetes: hyperglycaemia, obesity and insulin resistance, and hypertension

Cerebral microvascular endothelial cells, pericytes, and astrocytes are believed to be major targets of hyperglycaemic damage because these cells cannot downregulate glucose transport rate when glucose concentration is raised, resulting in high intracellular glucose concentrations.[9,41] This high intracellular glucose concentration is believed to induce dysfunction of these cells (eg, increased permeability of microvascular endothelial, leucocyte adhesion, higher procoagulant activity, and reduced availability of nitric oxide) through various biochemical pathways initiated by mitochondrial overproduction of reactive oxygen species.[20] Chronic hyperglycaemia also leads to increased extracellular and intracellular formation of advanced glycation end products (AGEs), which upregulate expression of receptor for AGE (RAGE) in many cells in the brain, including microvascular endothelial cells, pericytes, and astrocytes.[42] AGEs and increased RAGE expression have various detrimental effects on these cells, including increased oxidative stress and production of inflammatory cytokines.[22,42] Increased oxidative stress and inflammation are closely linked, and are both believed to contribute to microvascular endothelial dysfunction via reducing the availability of nitric oxide. Additionally, they might directly disrupt the blood–brain barrier and damage neuronal tissue.[20]

Obesity, notably visceral obesity, which is common in people with type 2 diabetes, is associated with microvascular dysfunction in many organs.[43] In the brain, this dysfunction includes blood–brain barrier disruption[44] and altered cerebral blood flow regulation.[43] The mechanisms underlying the association between

obesity and cerebral microvascular dysfunction are believed to be multifactorial.[44] Obesity contributes to impairment of insulin-mediated vasodilation. Experimental studies have shown that insulin normally increases cerebral perfusion, but that this response is impaired in the presence of insulin resistance, which can contribute to impaired neuronal function.[45,46] Insulin resistance in the brain is also believed to have other detrimental effects, including increased oxidative stress, mitochondrial dysfunction, and decreased neuronal viability.[21]

Hypertension and type 2 diabetes commonly coexist.[47] Hypertension, type 2 diabetes, and, to a lesser extent, obesity and insulin resistance, cause stiffening of large arteries, which impairs their cushioning function and increases pressure and flow pulsatility.[47] An increased pulsatile load transmits distally and can damage the microcirculation. The microvasculature of the brain is particularly vulnerable as it is characterised by high flow and low impedance, allowing the pulsatile load to penetrate deeply into its microvascular bed.[47] By contrast, the microvasculature of other organs might be able to protect itself through autoregulation or vascular remodelling, or both. This protective effect would dissipate most of the increased pulsatile energy by arteries and large arterioles proximal to capillary beds and hence limit penetration of the increased load. Indeed, arterial stiffening is associated with microvascular dysfunction in the brain,[48] but not, for example, in skin.[49] The low microvascular impedance of the brain might explain why, in type 2 diabetes, the brain is more frequently affected by microvascular disease than are organs with high microvascular impedance.[9]

Contribution of cerebral microvascular dysfunction to type 2 diabetes-related brain diseases: observational studies
Stroke
Microvascular dysfunction has been reported to be associated with an increased risk of lacunar ischaemic stroke and deep haemorrhagic stroke.[10] Also, type 2 diabetes is an established risk factor for lacunar stroke,[50] and might increase the risk of haemorrhagic stroke. However, data on specific subtypes of haemorrhagic stroke in type 2 diabetes are scarce. Findings from a mendelian randomisation study showed that a genetic predisposition to type 2 diabetes was related to lacunar stroke.[51] An effect of type 2 diabetes on deep haemorrhagic stroke was also identified, which was quantitatively similar to that seen for lacunar stroke; although this effect was not statistically significant, the study power was limited by the small number of haemorrhagic strokes. Compared with those without type 2 diabetes, adults with type 2 diabetes who have a lacunar stroke have a higher mortality, poorer functional recovery, and higher risk of stroke recurrence.[52,53] Type 2 diabetes is also associated with an increased risk of non-lacunar
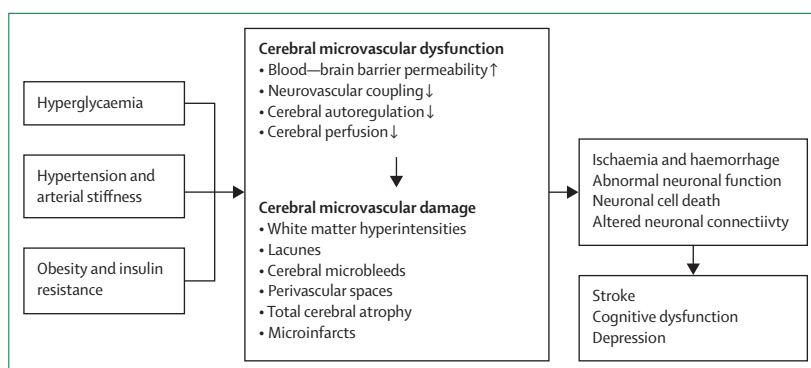

Figure 2: **Presumed pathway by which type 2 diabetes-related cerebral microvascular dysfunction contributes to stroke, cognitive dysfunction, and depression**
In type 2 diabetes and prediabetes, drivers of cerebral microvascular dysfunction include hyperglycaemia, obesity, insulin resistance, hypertension, and arterial stiffening. Cerebral microvascular dysfunction and damage might lead to ischaemia, haemorrhage, abnormal neuronal function, neuronal cell death, and altered neuronal connectivity. Thereby, microvascular dysfunction might contribute to stroke, cognitive dysfunction, and depression.

	Techniques	Findings in people with type 2 diabetes
Altered cerebral microvascular morphology	Neuropathology	Thickened capillary basement membrane and increased angiogenesis
Increased blood–brain barrier permeability	Qalb; DCE-MRI; PCT; neuropathology	Increased blood–brain barrier permeability in most, but not all, studies
Reduced cerebral vasoreactivity	TCD; PC-MRA; ASL; BOLD imaging	Reduced cerebral vasoreactivity, as determined at the tissue level or at the level of a large cerebral artery, in most, but not all, studies
Impaired cerebral autoregulation	TCD	Impaired cerebral autoregulation in some, but not all, studies
Altered resting cerebral blood flow	TCD; PC-MRA; ASL; SPECT; IVIM	Inconsistent findings; some studies showed altered regional or global cerebral perfusion independent of cerebral atrophy, but others did not
Cerebral small vessel disease features	Neuropathology; MRI (T1W, T2W, T2*W, and FLAIR)	Neuropathology studies showed an increased burden of cerebrovascular lesions, especially lacunes; MRI studies showed increased occurrence of lacunes, a modest increase in the volume of white matter hyperintensities, and a decrease in total brain parenchyma volume; some studies showed increased occurrence of cerebral microbleeds; data on perivascular spaces and microinfarcts are scarce

References to the individual studies are provided in the appendix (p 2). Qalb=albumin quotient (ratio of cerebrospinal fluid albumin to plasma albumin concentration). DCE-MRI=dynamic contrast-enhanced MRI. PCT=dynamic perfusion CT. TCD=transcranial doppler. PC-MRA=phase-contrast magnetic resonance angiography. ASL=arterial spin labelling. BOLD=blood-oxygenation-level-dependent. SPECT=single-photon emission CT. IVIM=intravoxel incoherent imaging. T1W=T1-weighted MRI. T2W=T2-weighted MRI. T2*W=T2-star weighted MRI. FLAIR=fluid-attenuated inversion recovery MRI.

Table 1: **Altered cerebral microvascular function and structure in people with type 2 diabetes**

	Stroke	Cognitive dysfunction*	Depression
Increased blood–brain barrier permeability	One cross-sectional study (moderate)† showed an association; blood–brain barrier permeability assessed by contrast-enhanced MRI	No studies	No studies
Reduced cerebral vasoreactivity	No studies	Some studies (one prospective [moderate]† and one prospective [small]‡), but not all (one prospective [large]§), showed an association; vasoreactivity assessed by arterial spin labelling MRI and transcranial doppler	No studies
Impaired cerebral autoregulation	No studies	No studies	No studies
Altered resting cerebral blood flow	No studies	Most studies (one cross-sectional [moderate]†, one cross-sectional [small]‡, one cross-sectional [large]§, three prospective [small]‡, and one prospective [moderate]†), but not all (two cross-sectional [small]‡ and one prospective [large]§), showed an association; cerebral blood flow assessed by various MRI techniques	No studies
Cerebral small vessel disease features	Two large prospective MRI studies§ showed an association; features studied were silent infarcts (including lacunes) and white matter hyperintensities	Five neuropathology studies§ showed an association between increased burden of cerebrovascular lesions and cognitive dysfunction; most MRI studies (two cross-sectional [moderate]†, nine cross-sectional, two prospective [moderate]†, and three prospective [large]§) showed an association, but a few (two cross-sectional [small]‡, one cross-sectional [moderate]†, and one prospective [moderate]†) did not; features studied were white matter hyperintensities, lacunes, cerebral microbleeds, total brain atrophy, and microinfarcts	No studies
Diabetic retinopathy	Most studies (one cross-sectional [large]§ and eight prospective [large]§) showed an association, but a few did not (three prospective [large]§)	Most studies (three cross-sectional [large]§ and four prospective [large]§), but not all (three cross-sectional [large]§ and one prospective [large]§), showed an association	Systematic review and meta-analysis showed an association between any microvascular complication (neuropathy, nephropathy, retinopathy) and incident depression
Subtle retinal microvascular changes¶	Two prospective studies (large)§ showed an association	Most studies (three cross-sectional [large]§ and one prospective [large]§), but not all (one cross-sectional [large]§), showed an association	One cross-sectional study (large)§ showed an association

References to the individual studies are provided in the appendix (p 3). *Most studies in type 2 diabetes assessed cognitive function with the use of various neuropsychological tests that mostly reflect subtle cognitive changes, and only few studies specifically focused on more severe stages of cognitive dysfunction—ie, mild cognitive impairment or dementia. †Study with sample size between n=50 and n=100. ‡Study with sample size n<50. §Study with sample size n>100. ¶Subtle retinal microvascular changes studied include arteriolar narrowing and widening, venular widening, arteriovenous nicking, and venular tortuosity.

Table 2: Summary of studies on the association between cerebral microvascular dysfunction and stroke, cognitive dysfunction, and depression in people with type 2 diabetes

ischaemic strokes (ie, large artery and cardioembolic stroke).[50]

Features of CSVD have been consistently associated with an increased risk of ischaemic and haemorrhagic stroke,[54] and results are similar in adults with and without type 2 diabetes (table 2, appendix p 3). Most, but not all, studies have shown that diabetic retinopathy and subtle retinal microvascular abnormalities are associated with an increased risk of stroke (table 2). In one study, diabetic retinopathy was shown to be a predictor of lacunar ischaemic stroke, but not of large artery or non-lacunar ischaemic stroke,[55] consistent with a role for cerebral microvascular dysfunction.

In at least one study of adults with type 2 diabetes, cerebral microvascular dysfunction was associated with worse outcomes after stroke. In this neuroimaging study of patients with acute stroke, blood–brain barrier permeability was higher in individuals with type 2 diabetes and was associated with worse stroke outcome.[56]

Type 2 diabetes-associated cognitive decrements, mild cognitive impairment, and dementia

Cognitive dysfunction in individuals with type 2 diabetes and prediabetes probably has multiple underlying mechanisms, and increasing data suggest that microvascular dysfunction might be one such mechanism.

Type 2 diabetes and prediabetes are related to different stages of cognitive dysfunction, including subtle cognitive changes (also termed type 2 diabetes-associated cognitive decrements), mild cognitive impairment, and dementia.[57] Subtle cognitive changes occur in all age groups of individuals with type 2 diabetes and progress slowly over time, whereas mild cognitive impairment and dementia are more severe stages of cognitive dysfunction, with progressive deficits, that predominantly affect older individuals. These different stages might have other underlying mechanisms.[57] However, most studies on cerebral microvascular dysfunction in type 2 diabetes have assessed cognitive function with neuropsychological tests that reflect non-clinical levels of

cognitive dysfunction, with fewer studies specifically focusing on the severe stages of cognitive dysfunction—ie, mild cognitive impairment and dementia.

Neuropathology studies have shown that lacunes of presumed vascular origin are related to lower cognitive function in individuals with type 2 diabetes (table 2). For example, a large study including 2365 autopsied people with cognitive function tested before death showed that individuals with type 2 diabetes had a higher prevalence of brain infarcts, notably lacunes, and the presence of type 2 diabetes and infarcts was associated with lower cognitive scores than were type 2 diabetes or infarcts alone.[58] Functional studies have shown that, in type 2 diabetes, reduced cerebral vasoreactivity and altered resting cerebral blood flow are associated with worse scores on cognitive tests (table 2). Additionally, most neuroimaging studies, but not all, have shown that, among individuals with type 2 diabetes, features of CSVD are associated with worse cognitive function and accelerated cognitive decline (table 2). For example, in the AGES–Reykjavik study,[59] individuals with type 2 diabetes had poorer performance on cognitive tests of processing speed and executive function than individuals without type 2 diabetes. This association was partly mediated by features of CSVD. Furthermore, most studies have shown associations between diabetic retinopathy and type 2 diabetes-related subtle retinal microvascular changes and worse cognitive function and accelerated cognitive decline (table 2).

By contrast, data on the association between cerebral microvascular dysfunction and dementia in type 2 diabetes are scarce and inconsistent (table 2). To date, only one small study on features of CSVD in type 2 diabetes has assessed severe stages of cognitive dysfunction–ie, mild cognitive impairment and dementia–and did not find an association between white matter hyperintensities, lacunes, or microbleeds, and cognitive dysfunction.[60] By contrast, most larger retinal imaging studies,[61,62] but not all,[63] did find an association between diabetic retinopathy and an increased incidence of dementia.

Altered neuronal connectivity might be a crucial step in the putative pathway of microvascular dysfunction leading to cognitive decline.[64] In type 2 diabetes, studies show widespread changes in structural white matter connectivity (assessed with diffusion tension imaging), and functional connectivity (functional MRI) involving the default mode network, a region involved in global cognitive processing, and these changes are related to worse cognitive function.[65,66] Studies in individuals without type 2 diabetes have shown that features of CSVD are associated with altered structural and functional connectivity,[64] but no study has been done to investigate these associations in type 2 diabetes.

Depression
Type 2 diabetes, depression, and cognitive dysfunction commonly occur together; individuals with type 2 diabetes have a doubled risk for depression compared with individuals without type 2 diabetes, and individuals with depression have a 1·5 times increased risk of type 2 diabetes.[67] Furthermore, the presence of type 2 diabetes and comorbid depression is associated with a greater risk of dementia, particularly vascular dementia, and the combined effect of both disorders might be more than additive.[68]

The mechanisms underlying the relations between type 2 diabetes, depression, and cognitive dysfunction are complex and multifactorial. The links between these conditions might include shared risk factors (eg, obesity, physical inactivity, or psychosocial stress related to any chronic disorder) and shared underlying mechanisms (eg, inflammation, alterations in hypothalamic–pituitary–adrenal axis and the sympathetic nervous system, and vascular pathology).[67,69]

The vascular depression hypothesis proposes that vascular damage in frontal and subcortical brain regions, which are involved in mood regulation, might lead to depression in older individuals.[70] Accordingly, studies have shown that increased blood–brain barrier permeability,[71] reduced cerebrovascular reactivity,[72] and features of CSVD[54,73] are associated with depression. Additionally, arterial stiffening has been associated with an increased risk of development of depressive symptoms in older individuals,[74] and this association might be mediated by CSVD as assessed by MRI.[75]

However, current evidence for a link between microvascular dysfunction, type 2 diabetes, depression, and cognitive dysfunction is relatively weak. Only a few studies have investigated microvascular function, type 2 diabetes, depression, and cognitive dysfunction together, and clearly this issue requires further study. In one cross-sectional study,[76] adults with type 2 diabetes and depression had wider retinal arterioles than individuals with type 2 diabetes but without depression, suggesting that depression is associated with early microvascular changes in type 2 diabetes. In a recent meta-analysis,[77] the presence of any diabetic microvascular complication (retinopathy, nephropathy, or neuropathy) was associated with an increased risk of depression. However, to what extent this association is explained by the psychological burden related to those complications is unclear. In another meta-analysis, a consistent association between type 2 diabetes and hippocampal atrophy was reported.[78] Hippocampal atrophy, which might be partly due to microvascular alterations in type 2 diabetes,[29] could be a common neuropathological cause for the comorbidity of type 2 diabetes with depression and dementia; this possibility requires further study.

Interventions to improve cerebral microvascular dysfunction
Established lifestyle and pharmacological interventions for type 2 diabetes might improve cerebral microvascular dysfunction. A summary of the evidence of the effect of these interventions on CSVD, retinopathy, stroke,

	Cerebral small vessel disease	Retinopathy	Stroke	Cognitive dysfunction†	Depression
Lifestyle interventions (diet or exercise, or both)	Look AHEAD study showed beneficial effects on WMHV and TBV	Systematic review showed insufficient evidence for a beneficial effect	Systematic review showed insufficient evidence for a beneficial effect	Systematic review showed insufficient evidence for a beneficial effect	Meta-analysis of 15 trials showed a beneficial effect
Intensified vs standard glucose-lowering treatment	ACCORD MIND study showed a beneficial effect on TBV, but not on WMHV	Meta-analysis of individual participant data from four trials showed a beneficial effect; another meta-analysis including nine trials also showed a beneficial effect	Meta-analysis of 13 trials showed no beneficial effect	Meta-analysis of four trials showed no beneficial effect	ACCORD study showed no beneficial effect
Novel glucose-lowering drugs (DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors)	No data available	Meta-analysis of 37 trials showed no beneficial effect for DDP-4 inhibitors, GLP-1 receptor agonists, or SGLT2 inhibitors	Meta-analysis of 97 trials showed no beneficial effect on total stroke for DDP-4 inhibitors, GLP-1 receptor agonists, or SGLT2 inhibitors; however, use of GLP-1 receptor agonists was associated with a reduction in non-fatal strokes	Systematic review on DPP-4 inhibitors and GLP-1 receptor agonists showed insufficient evidence for a beneficial effect; a DPP-4 inhibitor trial showed no beneficial effect; no data available for SLGT2 inhibitors	No data available
Antihypertensive drugs	ACCORD MIND study showed a beneficial effect on WMHV, but not on TBV	Meta-analysis of seven trials showed a beneficial effect	Two meta-analyses, including 19 and 49 trials, respectively, showed a beneficial effect	ACCORD MIND and ADVANCE studies showed no beneficial effect	ACCORD study showed no beneficial effect
Lipid-modifying drugs	ACCORD MIND study showed no beneficial effect of fenofibrate on TBV	Meta-analysis of eight trials, mostly with fenofibrate, showed protective effect on retinopathy progression	Meta-analysis of 14 statin trials and another meta-analysis of 12 trials (mostly with statins) showed a beneficial effect	ACCORD study (fenofibrate) and substudy of the PROSPER trial (statin) showed no beneficial effect	No data available

References to the individual studies are provided in the appendix (p 4). WMHV=white matter hyperintensity volume. TBV=total brain volume. *Evidence based on trials that had MRI features of cerebral small vessel disease, retinopathy, stroke, cognitive dysfunction, or depression as a primary or secondary outcome or in which type 2 diabetes status was used in a subgroup analysis; no data available on other measures of cerebral microvascular function or structure. †Cognitive dysfunction includes cognitive decline, incident mild cognitive impairment, and incident dementia.

Table 3: Summary of evidence from intervention studies of established lifestyle and pharmacological interventions for type 2 diabetes on cerebral small vessel disease, retinopathy, stroke, cognitive dysfunction, and depression*

cognitive dysfunction, and depression is shown in table 3 and in the appendix (p 4). Furthermore, specific treatments to improve cerebral microvascular dysfunction are under investigation.

Lifestyle factors

Microvascular dysfunction might be at least partly reversible through weight loss and exercise.[9] Most evidence for the beneficial effects of a healthy lifestyle in type 2 diabetes comes from the Look AHEAD trial. Look AHEAD was a multisite randomised clinical trial done in the USA that included 5145 individuals aged 45–76 years who were overweight or obese and had type 2 diabetes.[79] Compared with control (regular diabetes support and education) the intensive lifestyle intervention of weight loss and exercise had beneficial effects on white matter hyperintensities,[80] ventricle volume (a measure of total brain atrophy),[80] and depression.[81] However, no effects were identified on stroke[79] or cognitive function.[82] Most other lifestyle intervention studies in type 2 diabetes had no effects on stroke and cognitive function, but beneficial effects on depression (table 3). To what extent any effects of these interventions are mediated by improvement of microvascular function remains to be elucidated.

Established pharmacological interventions

Only one randomised clinical trial, ACCORD MIND, has been done to investigate the effects on CSVD of intensified versus standard therapeutic strategies to lower blood glucose concentrations.[83] ACCORD MIND was a substudy (n=2977, aged 55–80 years) of the ACCORD trial, a two-by-two factorial parallel-treatment trial done to test the effect on cardiovascular events of therapeutic strategies to control blood glucose, blood pressure, and lipid concentrations, which included 10251 individuals with type 2 diabetes, high HbA$_{1c}$ (>7·5% [58 mmol/mol]), and a high risk of cardiovascular events. Participants were randomly assigned to receive intensive glycaemic control targeting HbA$_{1c}$ to less than 6·0% (42 mmol/mol) or a standard strategy targeting HbA$_{1c}$ to 7·0–7·9% (53–63 mmol/mol) for 40 months.[83] In ACCORD-MIND, intensified treatment was associated with a reduced decline in total brain volume, but a greater increase in white matter hyperintensity volume. The anatomical basis and functional significance of the differential effects on these brain volumes is unclear. In ACCORD, intensified treatment had a beneficial effect on retinopathy,[84] but not on stroke,[85] cognitive function,[83] or depression.[86] Factors that might have attenuated treatment effects in the trial are the fairly young mean

age (62 years) of participants and the fairly small difference in HbA$_{1c}$ (about 1%) between the intensive and standard groups. Most other trials of intensified glucose-lowering treatment had similar findings with respect to retinopathy, stroke, and cognitive function (table 3). Some glucose-lowering drugs, such as incretin-based therapies (GLP-1 receptor agonists and DPP-4 inhibitors) might improve cerebral microvascular function and have neuroprotective effects through non-glucose pathways.[87,88] However, in the recent CARMELINA-COG substudy, the DPP-4 inhibitor linagliptin did not affect cognitive decline over 2·5 years.[89] Meta-analyses of other trials with incretin-based therapies or SGLT2 inhibitors also identified no beneficial effect on retinopathy, total stroke, or cognitive function, although a beneficial effect was shown for GLP-1 receptor agonists on non-fatal stroke (table 3). Other trials are ongoing to assess the effect of incretin-based treatments on brain function (eg, NCT01243424, NCT04034524, NCT01843075, NCT03881995, NCT03948347).[88]

Blood pressure lowering might also improve cerebral microvascular dysfunction, either directly at the level of the microvasculature, or indirectly via reducing arterial stiffness.[47] Trials have shown that, in type 2 diabetes, blood pressure-lowering treatment is associated with a reduced risk of retinopathy and stroke, but not cognitive dysfunction or depression (table 3). In a post-hoc analysis of ACCORD MIND, progression in white matter hyperintensity volume over time was reduced with intensified versus standard blood pressure-lowering treatment.[90] However, total brain volume decreased in the intensified versus standard treatment group, although the between-group difference was small.[83] A decline of total brain volume might be due not only to long-term changes (eg, neurodegeneration), but also to short-term changes (eg, removal of excess interstitial fluid that might be related to improved vascular risk control), or both, complicating interpretation of such changes. In ACCORD MIND, blood pressure-lowering treatment was not associated with beneficial effects on cognitive function[83] or depression,[91] and this issue requires further study. Findings from experimental studies suggest that inhibitors of the renin–angiotensin system might have beneficial effects on the cerebral microvasculature beyond their blood pressure-lowering effects, including prevention of diabetes-related blood–brain barrier disruption[92] and enhanced nitric oxide-mediated vasodilatation.[93] However, whether these effects can be translated to human beings is unclear.

The effect of lipid-modifying therapy on cerebral microvascular function is unclear. Statin therapy prevents ischaemic stroke, and fenofibrate might slow progression of retinopathy (table 3). The effect of fenofibrate on retinopathy might not be solely due to its effect on lipid concentrations. However, in ACCORD MIND, combination therapy with a statin plus a fibrate compared with statin alone had no beneficial effects on total brain atrophy or cognitive function (table 3). Furthermore, in a subgroup analysis of the PROSPER study of pravastatin, statin monotherapy had no beneficial effects on cognitive function in type 2 diabetes (table 3).

Novel pharmacological interventions

An important question is whether cerebral outcomes in type 2 diabetes improve following specific treatments targeting the pathways through which hyperglycaemia damages the cerebral microvasculature. For example, dicarbonyl compounds, such as methylglyoxal, are reactive glucose metabolites that interact with protein residues to form AGEs.[94] This might be one pathway through which hyperglycaemia exerts its deleterious effects. Higher concentrations of methylglyoxal are associated with an increased risk of cardiovascular disease[95] and worse cognitive performance.[96] Additionally, interventions that reduce methylglyoxal concentrations are associated with improved vascular function,[97] and, in animal studies, improved cognitive function.[98] The detrimental effects of AGEs on the cerebral microvasculature are partly mediated through interactions with their receptor (RAGE).[94] A trial (NCT03980730) is being done to assess the effect of inhibiting RAGE in individuals with mild Alzheimer's disease and impaired glucose tolerance.

Augmenting cerebral insulin signalling might be another strategy to improve cerebral microvascular function. In a proof-of-concept study, intranasal insulin administration was used to normalise brain insulin concentrations in individuals with and without type 2 diabetes.[99] Intranasal administration of insulin allows direct transport into the CNS, bypassing the blood–brain barrier. This therapy was associated with acute improvements in cognitive function, potentially through improved cerebrovascular reactivity. A larger trial (NCT02415556) that tests this intervention in type 2 diabetes is ongoing.

Other potentially interesting interventions are drugs approved for other indications with relevant modes of action, including drugs that enhance signalling of nitric oxide or prostacyclin (also known as prostaglandin I$_2$; or related prostaglandins), such as nitric oxide donors (eg, isosorbide mononitrate), phosphodiesterase 3 inhibitors (eg, cilostazol), and phosphodiesterase 5 inhibitors (eg, dipyridamole). Experimental studies have shown that these drugs can improve blood–brain barrier integrity and vasoreactivity.[100] Trials testing these drugs for recurrent stroke and cognitive decline in patients with stroke (with or without diabetes) are ongoing (eg, ISRCTN99503308, EudraCT2015-001953-33, EudraCT 2016-002277-35, NCT02122718, and EudraCT 2015-001235-20).[10]

Conclusions

Microvascular dysfunction in type 2 diabetes affects the brain. Growing evidence from human studies suggests that microvascular dysfunction is a common

pathophysiological pathway in type 2 diabetes-associated brain and mental disorders. Subtle microvascular dysfunction might already be present in individuals with prediabetes, accounting for the observation that these diseases occur with greater frequency in people with prediabetes than in people with normoglycaemia. Use of pharmacological interventions to improve cerebral microvascular dysfunction is an active area of investigation.

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