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

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Abstract

Adults with type 2 diabetes are at higher risk for developing certain brain diseases, including stroke, dementia, and depression. Although these diseases 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 individuals with diabetes that also affects the brain. Cerebral microvascular dysfunction is also observed among 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. In this review, we discuss the pathophysiology and drivers of diabetes-related cerebral microvascular dysfunction, and summarize recent evidence on the association of diabetes-related microvascular dysfunction to stroke, cognitive dysfunction, and depression. We also highlight potential therapeutic targets and interventions.

Introduction

Brain diseases, including stroke, dementia, and depression, are increasingly recognized as clinically important complications of type 2 diabetes (T2D). T2D is associated with a 2·5 times higher risk of ischaemic stroke, an 1·5 times higher risk of haemorrhagic stroke,[1] and a 1·5 times higher risk of dementia.[2] In addition, individuals with T2D are 1·5-to-2·0 times more likely to suffer from major depression as compared with individuals free from T2D.[3]

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Contribution

All authors contributed to the search and assessment of the literature. Van Sloten prepared the first draft. Sedaghat prepared the sections on stroke and type 2 diabetes-associated cognitive decrements, mild cognitive impairment and dementia, and created the figures. All authors edited the manuscript and provided crucial comment. All authors approved the final version for submission.

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Stroke and dementia are also more common among adults with prediabetes,[4,5] suggesting that brain disease processes start before the onset of diabetes.

The pathogenesis of T2D-related stroke, dementia and depression is complex, multifactorial and incompletely understood. In view of ageing populations and growing prevalence of T2D, there is an urgent need to identify the mechanisms linking T2D with brain diseases. Stroke, cognitive dysfunction and depression frequently co-occur in T2D,[6–8] and they may share various underlying mechanisms. One of these mechanisms may be microvascular dysfunction. In T2D, microvascular disease has been shown to affect many, if not all, organs, including the brain.

In this review, we shall discuss how the cerebral microvasculature affects brain function in T2D. We shall review emerging evidence that cerebral microvascular dysfunction and damage are: 1) common in T2D; 2) present in individuals with prediabetic levels of hyperglycaemia; and, 3) a potentially modifiable central mechanism underlying T2D-related stroke, cognitive dysfunction, and depression. We shall also highlight potential therapeutic targets and interventions.

Cerebral microvascular dysfunction in type 2 diabetes

Optimal brain function depends on a healthy microvasculature. Panel 1 describes the functions of the cerebral microvasculature and the definition and measures of microvascular dysfunction. Panel 2 and Figure 1 describe the adverse effects of cerebral microvascular dysfunction.

Most direct evidence of cerebral microvascular dysfunction in diabetes derives from in vitro and animal models (reviewed in [22,23]). Data in humans are relatively limited. Table 1 summarizes studies on cerebral microvascular structure and function in adults with T2D (references to the individual studies are given in the online appendix). Morphologically, changes of the cerebral microcirculation include basement membrane thickening and increased angiogenesis. Functionally, studies suggest increased blood-brain permeability and altered blood flow regulation.

Blood-brain barrier permeability

Blood-brain barrier permeability can be assessed using neuroimaging or with biochemical methods. Several small studies using magnetic resonance imaging (MRI) or computed tomography (CT) found postcontrast enhancement of brain parenchyma in T2D (Table 1), which is presumed to indicate 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 levels, known as the albumin quotient, can be used as an indirect measure of blood-brain barrier permeability. A recent study[24] found that the albumin quotient was higher in individuals with T2D and in individuals with dementia, and a higher albumin quotient in this study was associated with cerebrospinal fluid markers of microvascular endothelial dysfunction (vascular endotseehelial growth factor, intracellular

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adhesion molecule 1, and vascular cell adhesion molecule 1) and angiogenesis (vascular endothelial growth factor).

Cerebrovascular reactivity, cerebral autoregulation and resting cerebral blood flow

Cerebrovascular reactivity is defined as the change in flow in response to increased neuronal activity (i.e. 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 done with use of Doppler ultrasound. Vasoreactivity measured in a large artery may reflect not only the function of arterioles and capillaries, but also of larger cerebral arteries themselves.[27] Nevertheless, most studies have found reduced vasoreactivity in T2D (either at the tissue level or at the level of larger cerebral arteries) (Table 1) consistent with the presence of cerebral microvascular dysfunction. In addition, a recent task-based functional MRI study has shown that T2D is associated with impaired neurovascular coupling, and this impairment was related to an altered microvascular haemodynamic response.[28]

Microvascular dysfunction may also contribute to altered cerebral autoregulation. Data on cerebral autoregulation in T2D are, however, scarce. Several small studies showed altered cerebral autoregulation, although not consistently (Table 1), and these studies are difficult to compare due to methodological differences.

Altered *resting* cerebral blood flow may be another manifestation of cerebral microvascular dysfunction, but whether T2D influences resting blood flow remains incompletely understood. Results of studies in T2D have been inconsistent and are difficult to compare due to patient and methodological differences. Furthermore, the interpretation of resting cerebral blood flow is complex. Reduced resting blood flow may reflect loss of viable tissue, may be a cause of tissue damage, or both. In addition, resting cerebral blood flow may increase or decrease depending on the disease stage. Cerebral microvascular blood flow may be increased in early T2D to compensate for reduced oxygen extraction efficacy related to subtle, or early, microvascular dysfunction, whereas in more advanced stages of the disease, blood flow may be reduced.[15] This may be compared how the pancreas tries to adapt to increased homeostatic load due to insulin resistance: at first insulin production increases; later beta-cell failure and insulin insufficiency occur. In accordance, we recently found that blood flow at the level of the microvasculature in the hippocampus was increased in individuals with relatively well-controlled T2D.[29] In addition, studies have found that markers of more advanced disease (e.g. presence of retinopathy,[30] higher HbA1c levels,[30,31] and higher insulin resistance[31]) or presence of hypertension[32] were associated with reduced cerebral blood flow. Increased microvascular blood flow related to arteriolar widening may be a generalized phenomenon in early diabetes, as it has been associated with early diabetes (especially type 1 diabetes, but also T2D) in many other organs in addition to the brain.[9] An increased microvascular blood flow may at first be protective, but may, if not accompanied by venular widening, increase capillary pressure and eventually contribute to

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organ damage.[9] However, the biochemical basis, mediators responsible, and development over time of changes in resting cerebral blood flow in T2D remain to be further clarified.

Features of cerebral small vessel disease

Features of cerebral small vessel disease (CSVD), as measured by MRI, may 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 '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] In addition, 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 development of new white matter hyperintensities over time.[10] T2D is associated with a higher occurrence of CSVD features (Table 1). This includes a modest increase in white matter hyperintensity volume, greater number of lacunes, and slight decrease in total brain parenchyma volume. In addition, some studies found an association with cerebral microbleeds, whereas data are scarce on perivascular spaces and microinfarcts.

Retinal microvascular changes

The retina offers a unique 'window' to study microvascular changes in the brain because it allows direct visualization of the microvasculature, which is impossible with current neuroimaging.[34] Furthermore, the vessels of the retina share embryological, morphological, and functional similarities with the cerebral microvasculature.[34] Clearly, T2D is associated with retinal microvascular dysfunction. This 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 presence and progression of features of CSVD in T2D.[35,36]

Cerebral microvascular dysfunction and prediabetes: ticking clock hypothesis

—Recently, we[37] and others[38] have found that features of CSVD progress linearly from normal glucose metabolism to prediabetes and T2D, and are associated with level of glycaemia, even in the prediabetes range. In addition, 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. This suggests that in T2D a 'ticking clock' may exist with regard to microvascular disease, that is, microvascular disease processes may start long before the onset of T2D, and contribute to brain diseases not only in individuals with T2D, but also in individuals with prediabetes or normal glucose metabolism.[9]

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

Cerebral microvascular endothelial cells, pericytes, and astrocytes are thought to be major targets of hyperglycaemic damage because these cells cannot downregulate glucose transport rate when glucose concentration is elevated, resulting in high intracellular glucose levels.[9,41] This is thought to induce dysfunction of these cells (e.g. increased permeability of microvascular endothelial cells, leukocyte 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 extra- 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 higher RAGE expression have various detrimental effects on these cells, including increased oxidative stress and upregulation of inflammatory cytokines.[22,42] Increased oxidative stress and inflammation are closely linked, and are both thought to contribute to microvascular endothelial dysfunction via reducing the availability of nitric oxide. In addition, they may directly disrupt the blood-brain barrier and damage neuronal tissue.[20]

Obesity, notably visceral obesity, which is common in T2D, is associated with microvascular dysfunction in many organs.[43] In the brain, this 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 thought to be multifactorial.[44] A consequence of obesity is that it 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, and this can contribute to impaired neuronal function.[45,46] Insulin resistance in the brain is also thought to have other detrimental effects, including increased oxidative stress, mitochondrial dysfunction, and decreased neuronal viability.[21]

Hypertension and T2D commonly coexist.[47] Hypertension, T2D 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 characterized by high flow and low impedance, allowing the pulsatile load to penetrate deeply into its microvascular bed.[47] In contrast, the microvasculature of other organs may be able to protect itself through autoregulation and/or vascular remodeling. This 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] This may explain why, in T2D, the brain is more frequently affected by microvascular disease than are organs with high microvascular impedance.[9]

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Contribution of cerebral microvascular dysfunction to type 2 diabetes-related brain diseases: observational studies

There is a body of research describing the association between cerebral microvascular dysfunction and T2D-related brain diseases.

Stroke

Microvascular dysfunction has been reported to contribute to higher risk of lacunar ischaemic stroke and deep haemorrhagic stroke.[10] Also, T2D is an established risk factor for lacunar stroke,[50] and it may increase the risk of haemorrhagic stroke. However, data on specific subtypes of haemorrhagic stroke in T2D are limited. A recent Mendelian randomization study showed that a genetic predisposition to T2D was related to lacunar stroke.[51] An effect of T2D on deep haemorhagic stroke was also found that was quantitatively similar to that seen for lacunar stroke; although this effect was not statistically significant, this study had limited power due to the small number of haemorrhagic strokes. Adults with T2D who experience a lacunar stroke compared to those without T2D have a higher mortality, poorer functional recovery, and higher stroke recurrence risk.[52,53] T2D also increases the risk of non-lacunar ischaemic strokes (i.e., large artery and cardio-embolic stroke).[50]

Features of CSVD have been consistently associated with a higher risk of ischaemic and haemorrhagic stroke,[54] and results are similar in adults with and without T2D (Table 2) (references to the individual studies are given in the online appendix, Table S2). Most, but not all, studies report that diabetic retinopathy and subtle retinal microvascular abnormalities increase the risk of stroke (Table 2). One study on diabetic retinopathy evaluated subtypes of stroke, and found that diabetic retinopathy is a predictor of lacunar ischaemic stroke, but not of large artery or non-lacunar ischaemic stroke,[55] consistent with a role of cerebral microvascular dysfunction.

In at least one study of adults with T2D, cerebral microvascular dysfunction was associated with worse outcomes after stroke. In this neuroimaging study of acute stroke patients, blood-brain barrier permeability was higher in individuals with T2D and was associated with worse stroke outcome.[56]

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

Cognitive dysfunction in individuals with T2D and prediabetes likely has multiple underlying mechanisms, and increasing data suggest that microvascular dysfunction may be one such mechanism.

T2D and prediabetes are related to different stages of cognitive dysfunction, including subtle cognitive changes (also termed T2D-associated cognitive decrements), mild cognitive impairment (MCI), and dementia.[57] Subtle cognitive changes occur in all age groups of individuals with T2D and progresses slowly over time, whereas MCI and dementia are more severe stages of cognitive dysfunction, with progressive deficits, that predominantly affect older individuals. These different stages may have other underlying mechanisms.[57]

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However, most studies on cerebral microvascular dysfunction in T2D have evaluated cognitive function using neuropsychological tests that reflect non-clinical levels of cognitive dysfunction. Relatively fewer studies have specifically focused on the severe stages of cognitive dysfunction, i.e. MCI or dementia.

Neuropathology studies have shown that lacunes of presumed vascular origin are related to lower cognitive function in individuals with T2D (Table 2). For example, a large study including 2,365 autopsied persons with cognitive function tested before death showed that individuals with T2D had a higher prevalence of brain infarcts, notably lacunes, and presence of T2D and infarcts was associated with lower cognitive scores than T2D and infarcts alone.[58] Functional studies have shown that, in T2D, reduced cerebral vasoreactivity and altered resting cerebral blood flow are associated with worse scores on cognitive tests (Table 2). In addition, most neuroimaging studies, but not all, have shown that, among individuals with T2D, features of CSVD are associated with worse cognitive function and accelerated cognitive decline (Table 2). For example, the AGES-Reykjavik study found that individuals with T2D had poorer performance on cognitive tests of processing speed and executive function as compared to individuals without T2D. This association was mediated in part by features of CSVD.[59] Furthermore, most studies have reported associations between diabetic retinopathy and T2D-related subtle retinal microvascular changes and worse cognitive function and accelerated cognitive decline (Table 2).

In contrast, data on the association between cerebral microvascular dysfunction and dementia in T2D are scarce and inconsistent (Table 2). To date, only one small study on features of CSVD in T2D evaluated severe stages of cognitive dysfunction, i.e. MCI and dementia, and did not find an association between white matter hyperintensities, lacunes, or microbleeds, and cognitive dysfunction.[60] In contrast, most larger retinal imaging studies,[61,62] but not all,[63] did find an association between diabetic retinopathy and a higher incidence of dementia.

Altered neuronal connectivity may be a crucial step in the putative pathway of microvascular dysfunction leading to cognitive decline.[64] In T2D, studies show widespread changes in structural white matter connectivity (using diffusion tension imaging), and functional connectivity (using 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 T2D have found that features of CSVD are associated with altered structural and functional connectivity,[64] but no study has evaluated these associations in T2D.

Depression

T2D, depression and cognitive dysfunction commonly occur together; individuals with T2D have a doubled risk for depression as compared with individuals without T2D, and individuals with depression have a 1·5 times higher risk of T2D.[67] Furthermore, individuals with T2D and co-morbid depression also have a greater risk of dementia, in particular dementia of the vascular type, and the combined effect of both disorders appeared more than additive.[68]

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The mechanisms underlying the relationships among T2D, depression and cognitive dysfunction are complex and multifactorial. These may include shared risk factors (e.g. obesity, physical inactivity or psychosocial stress related to any chronic disorder) and shared underlying mechanisms (e.g. 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, may lead to depression in older individuals.[70] In accordance, studies have shown that increased blood-brain barrier permeability,[71] reduced cerebrovascular reactivity,[72] and features of CSVD[54,73] are associated with depression. In addition, arterial stiffening has been associated with a higher risk of development of depressive symptoms in older individuals,[74] and this association may be mediated by CSVD as assessed by MRI.[75]

However, current evidence for a link between microvascular dysfunction, T2D, depression and cognitive dysfunction is relatively weak. Only a few studies have investigated microvascular function, T2D, depression and cognitive dysfunction together, and clearly this issue requires further study. One cross-sectional study[76] reported that adults with T2D and depression had wider retinal arterioles than individuals with T2D but without depression, suggesting that depression is associated with early microvascular changes in T2D. A recent meta-analysis[77] found that presence of any diabetic microvascular complication (retinopathy, nephropathy or neuropathy) increases the risk of depression. However, it is unclear to what extent this association is explained by the burden related to those complications. A meta-analysis reported a consistent association between T2D and hippocampal atrophy.[78] Hippocampal atrophy, which may be partly due to microvascular alterations in T2D,[29] may be a common neuropathological aetiology for the comorbidity of T2DM with depression and dementia, and this requires further study.

Interventions to improve cerebral microvascular dysfunction

Established lifestyle and pharmacological interventions for T2D may improve cerebral microvascular dysfunction. Table 3 summarizes evidence of the effect of these interventions on CSVD, retinopathy, stroke, cognitive dysfunction, and depression (references to the individual studies are given in the online appendix, Table S3). In addition, specific treatments to improve cerebral microvascular dysfunction are under investigation.

Lifestyle factors

Microvascular dysfunction may be at least partially reversible through weight loss and exercise.[9] Most evidence for the beneficial effects of a healthy lifestyle in T2D comes from the Look AHEAD (Action for Health in Diabetes) trial. This was a multisite randomized clinical trial conducted in the United States that included 5,145 individuals aged 45–76 years who were overweight or obese and had T2D.[79] In this study, an intensive lifestyle intervention through weight loss and exercise compared to regular diabetes support and education had beneficial effects on white matter hyperintensities,[80] ventricle volume (a measure of total brain atrophy),[80] and depression.[81] However, no effects were found on stroke[79] or cognitive function.[82] Most other lifestyle intervention studies in T2D on stroke,

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cognitive function, or depression had similar results (Table 3). To what extent these results are mediated by improvement of microvascular function remains to be studied.

Established pharmacological interventions

Only one randomized clinical trial, i.e. ACCORD-MIND (Action to Control Cardiovascular Risk in Diabetes-Memory In Diabetes), has evaluated the effects on CSVD of intensified versus standard therapeutic strategies to lower blood glucose levels.[83] This was a substudy (n=2,977, aged 55–80 years) of ACCORD. ACCORD was two-by-two factorial parallel treatment trial and tested the effect on cardiovascular events of therapeutic strategies to control blood glucose, blood pressure, and lipid levels, and included 10,251 individuals with T2D, high glycated haemoglobin (HbA1c) concentrations (>7·5%; >58 mmol/mol), and a high risk of cardiovascular events. Participants were randomly assigned to receive intensive glycaemic control targeting HbA1c to less than 6·0% (42 mmol/mol) or a standard strategy targeting HbA1c 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 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 may have attenuated treatment effects in this trial are the relatively young mean age (62 years) of participants and the relatively small difference in HbA1c (approximately 1%) between the intensive and standard group. Most other trials on intensified glucose-lowering treatment had similar results on retinopathy, stroke, or cognitive function (Table 3). Some glucose-lowering agents, such as incretin-based therapies (the glucagon-like-peptide-1 agonists and dipeptidyl peptidase-4-inhibitors) may improve cerebral microvascular function and demonstrate neuroprotective effects through non-glucose pathways.[87,88] However, in the recent CARMELINA (CArdiovascular and Renal Microvascular outcomE study with LINAgliptin)-COG substudy, linagliptin, a dipeptidyl peptidase-4-inhibitor, did not modulate cognitive decline over 2.5 years.[89] Meta-analyses of other trials with incretin-based therapies or sodium-glucose co-transporter 2 inhibitors also found no beneficial effect on retinopathy, all stroke, or cognitive function, although a beneficial effect was found for glucagon-like-peptide-1 agonists on nonfatal stroke (Table 3). Other trials that evaluate the effect of incretin-based treatments on brain function in humans are ongoing (e.g. NCT01243424, NCT04034524, NCT01843075, NCT03881995, NCT03948347, and as reviewed elsewhere[88]).

Blood pressure lowering may also improve cerebral microvascular dysfunction, either directly at the level of the microvasculature, or indirectly via lowering arterial stiffness.[47] Trials have shown that, in T2D, blood pressure-lowering treatment is associated with a lower risk of retinopathy and stroke, but not cognitive dysfunction or depression (Table 3). A post-hoc analysis of ACCORD-MIND also noted reduced progression in white matter hyperintensity volume over time with intensified versus standard blood pressure-lowering treatment.[90] However, total brain volume decreased in the intensified versus standard blood treatment group, although the between-group difference was small.[83] It should be noted that a decline of total brain volume may be due not only to long-term changes (e.g. neurodegeneration), but also to short-term changes (e.g. removal of excess interstitial fluid

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that may 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. Experimental studies suggest that inhibitors of the renin angiotensin system may have beneficial effects on the cerebral microvasculature beyond their blood pressure-lowering effect, including prevention of diabetes-related blood-brain barrier disruption[92] and enhanced nitric oxide-mediated vasodilatation.[93] However, it is currently unclear whether these effects can be translated to humans.

The effect of lipid-modifying therapy on cerebral microvascular function is unclear. Statin therapy prevents ischaemic stroke, and fenofibrate may slow progression of retinopathy (Table 3). The effect of fenofibrate on retinopathy may be beyond the effects of this drug on lipid concentrations. However, in ACCORD-MIND, combination therapy with a statin plus a fibrate compared to statin alone had no beneficial effects on total brain atrophy or cognitive function (Table 3). In addition, in a subgroup analysis of PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), statin monotherapy had no beneficial effects on cognitive function in T2D (Table 3).

Novel pharmacological interventions

An important question is whether cerebral outcomes in T2D 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 may be one pathway through which hyperglycaemia exerts its deleterious effects. Higher levels of methylglyoxal are associated with a higher risk of cardiovascular disease[95] and worse cognitive performance.[96] In addition, interventions that reduce methylglyoxal levels 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 in part mediated through interactions with their receptor (RAGE).[94] An ongoing trial evaluates the effect of inhibiting RAGE in individuals with mild Alzheimer's disease and impaired glucose tolerance (NCT03980730).

Augmenting cerebral insulin signaling may be another strategy to improve cerebral microvascular function. A proof-of-concept study used intranasal insulin administration to normalize brain insulin concentrations in the brain in individuals with and without T2D.[99] Intranasal administration of insulin allows direct transport into the central nervous system, bypassing the blood-brain barrier. This therapy was associated with acute improvements in cognitive function, potentially through improved cerebrovascular reactivity. A larger trial that tests this intervention in T2D is ongoing (NCT02415556).

Other potentially interesting interventions are drugs approved for other indications with relevant modes of action. These include drugs that enhance signaling of nitric oxide or prostacyclin I_2 (or related prostaglandins), such as nitric oxide donors (e.g. isosorbide mononitrate), phosphodiesterase (PDE) 3 inhibitors (e.g. cilostazol), and PDE 5 inhibitors (e.g. dipyridamole). Experimental studies have shown that these drugs that can improve blood-brain barrier integrity and vasoreactivity.[100] Trials testing these drugs for recurrent

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stroke and cognitive decline in in patients with stroke (with or without diabetes) are ongoing (e.g. ISRCTN99503308, EudraCT2015–001953-33, EudraCT 2016–002277-35, NCT02122718 ad EudraCT 2015–001235-20 and as reviewed elsewhere[10]).

Conclusions

Microvascular dysfunction in T2D affects the brain. A growing body of evidence from human studies suggests that microvascular dysfunction is a common pathophysiological pathway in T2D-associated brain diseases. Subtle microvascular dysfunction may already be present in individuals with prediabetes, and this can explain the observation that these diseases occur with greater frequency in prediabetes. Using pharmacological interventions to improve cerebral microvascular dysfunction is an active area of investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Declaration of interests

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Panel 1.

Functions and measures of the cerebral microvasculature

Core functions of the cerebral microcirculation, defined as cerebral vessels <150 μm (arterioles, capillaries and venules), are 1) to optimize the delivery of nutrients and removal of waste products in response to variations in neuronal activity; 2) to maintain the cerebral interstitial milieu for proper cell function; and 3) 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 end-feet. It protects neurons from factors present in the systemic circulation and maintains the highly controlled central nervous system 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 compared 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 multiple cells. 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 leads to homogenization of capillary flow patterns, which facilitates efficient oxygen extraction.[15]

Renewal of neurons and non-neuronal cells

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 central nervous system (e.g. oligodendrocytes), amongst others via release of soluble growth factors.[16,17]

Measures of cerebral microvascular function

Cerebral microvascular function can be evaluated in humans with 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. In addition, retinal microvascular changes may be used as a proxy for microvascular changes in the brain.

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Panel 2.

Detrimental effects of cerebral microvascular dysfunction

Cerebral microvascular dysfunction leads to increased blood-brain barrier permeability, perfusion defects, hypoxia and increased angiogenesis. The effect on accumulation of Alzheimer's diseaserelated pathologies is unclear, as described below.

Increased blood-brain barrier permeability and inflammatory and immune responses

Increased blood-brain permeability leads to leakage of proteins and other plasma constituents into the perivascular space. This may directly damage neurons, is related to inflammatory and immune responses, and may 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 may also contribute to impaired neurovascular coupling.[18] This 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 lack pericyte support.[19]

Unclear role in accumulation of Alzheimer's diseases-related pathologies

Experimental studies suggest that type 2 diabetes-associated cerebral microvascular dysfunction may also contribute to accumulation of neurofibrillary tangles and amyloid-beta plaques, the hallmark neuropathologic features of Alzheimer's disease, amongst others via enhanced endothelial expression of RAGE and insulin resistance.[20] RAGE and central insulin resistance may stimulate the production of amyloid-beta and reduce its clearance via various mechanisms.[21] However, the importance of these effects in humans is unclear. Studies on in vivo biomarkers of Alzheimer disease pathology and brain autopsy studies have shown that neurofibrillary tangles and amyloid plaques are not more common in type 2 diabetes.[21]

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Search strategy and selection criteria

We searched PubMed, Google Scholar and ClinicalTrials.gov from inception to August 20, 2019 by use of the terms (and synonyms and related terms): “diabetes” or “prediabetes” in combination with “ cerebral microvasculature”, “blood-brain barrier”, “neurovascular coupling”, “vasoreactivity”, “autoregulation”, “cerebral blood flow”, “cerebral small vessel disease” (and related terms: “white matter hyperintensities”, “lacunes”, “cerebral microbleeds”, “perivascular spaces”, “total cerebral atrophy” and “microinfarcts”), and “retinal microvasculature”. These terms were also combined for with terms “stroke”, “dementia”, “Alzheimer’s disease”, “cognitive impairment”, “depression”, “treatment”, “lifestyle”, “pharmacological interventions”, and “trials” for the corresponding sections. We checked the reference list of relevant articles. The search was limited to papers published in English, German and French. Because of space constraints, we could not cite every paper of potential relevance in the main text. Of interventional studies, meta-analyses of randomized trials were prioritized where possible. Of observational studies, meta-analyses and prospective studies received priority where possible. References to individual studies are given in the online appendix.

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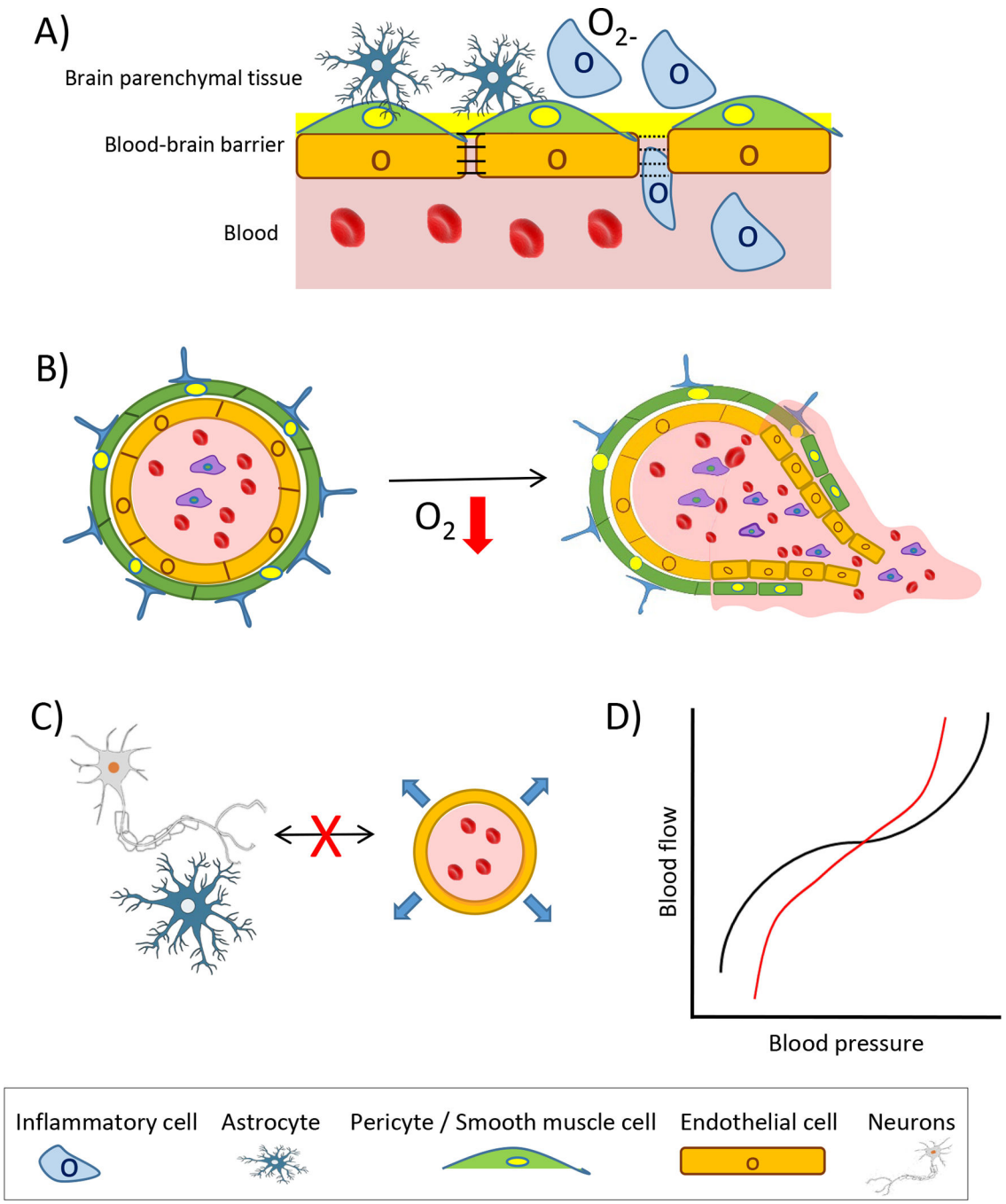

Figure 1. Detrimental effects of cerebral microvascular dysfunction

Type 2 diabetes-related microvascular dysfunction has various detrimental effects on the brain. It is related to inflammatory and immune responses, and may lead to increased blood-brain barrier permeability (A); perfusion defects, hypoxia and increased angiogenesis (B); and may impair neurovascular coupling (C) and cerebral autoregulation (D).

A) Type 2 diabetes-related microvascular dysfunction is related to increased oxidative stress and inflammatory and immune responses, and increased blood-brain barrier permeability, resulting in leakage of proteins and other plasma constituents into the perivascular space

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B) Microvascular dysfunction may lead to perfusion defects, hypoxia and increased angiogenesis. Angiogenesis is associated with formation of capillaries that are leaky and poorly perfused, and that lack pericyte support
C) Microvascular dysfunction may 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 may 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 expresses the relation-ship between cerebral blood flow and mean blood pressure (black curve) may become more linear and steeper, and perfusion becomes pressure--dependent (red curve)

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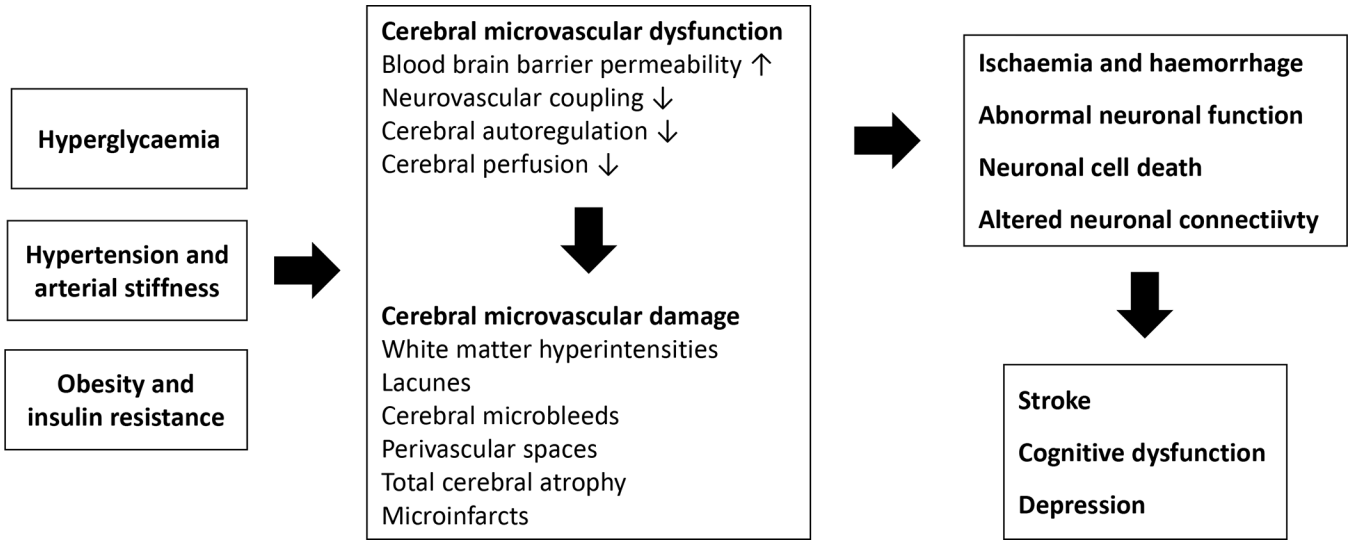

Figure 2. Presumed pathway by which type 2 diabetes-related cerebral microvascular dysfunction contributes to multiple brain diseases

In type 2 diabetes and prediabetes, drivers of cerebral microvascular dysfunction include hyperglycaemia, obesity and insulin resistance, as well as hypertension and arterial stiffening. Cerebral microvascular dysfunction and damage may lead to ischaemia, haemorrhage, abnormal neuronal function, neuronal cell death, and altered neuronal connectivity. Thereby, microvascular dysfunction may contribute to stroke, cognitive dysfunction, and depression.

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Table 1.

Altered cerebral microvascular function and structure in individuals with type 2 diabetes as compared to individuals without type 2 diabetes: summary of findings in humans

Manifestation of altered cerebral microvascular function and structure	**Technique(s)**	**Findings in individuals with type 2 diabetes as compared to individuals without 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	Most studies, but not all, found reduced cerebral vasoreactivity as determined at the tissue level, or at the level of a large cerebral artery
Impaired cerebral autoregulation	TCD	Some studies, but not all, found impaired cerebral autoregulation
Altered resting cerebral blood flow	TCD; PC-MRA; ASL; SPECT; IVIM	Inconsistent findings. Some studies found altered regional or global cerebral perfusion independently of cerebral atrophy, but others did not
Cerebral small vessel disease features	Neuropathology MRI: T1W, T2W, T2*W, FLAIR	Neuropathology studies found an increased burden of cerebrovascular lesions, especially lacunes. MRI studies found increased occurrence of lacunes, a modest increase in the volume of white matter hyperintensities and a decrease in total brain parenchyma volume. Some studies found increased occurrence of cerebral microbleeds. Data are scarce on perivascular spaces and microinfarcts

References to the individual studies are given in the online appendix

Qalb = cerebrospinal fluid/plasma albumin ratio; DCE-MRI = dynamic contrast-enhanced MRI; PCT = dynamic perfusion CT; TCD = transcranial doppler; PC-MRA = phase-contrast magnetic resonance angiography; ASL = arterial spin labeling; , BOLD = blood oxygenation level dependent; SPECT = single-photon emission computed tomography; IVIM = intravoxel incoherent imaging; T1W = T1-weighted MRI images; T2W = T2-weighted MRI images; T2*W = T2-star weighted MRI images, FLAIR = fluid-attenuated inversion recovery MRI

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Table 2.

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

Microvascular dysfunction or connectivity measure	Stroke	Cognitive dysfunction‡	Depression
Increased blood-brain barrier permeability	One cross-sectional study# found an association. Blood-brain barrier permeability assessed by contrast-enhanced MRI	No studies	No studies
Reduced cerebral vasoreactivity	No studies	Some studies (two prospective1x*,1x#), but not all (one prospective‖), found an association. Vasoreactivity assessed by arterial spin labeling MRI and transcranial doppler	No studies
Impaired cerebral autoregulation	No studies	No studies	No studies
Altered resting cerebral blood flow	No studies	Most studies (three cross-sectional1x*,1x#,1x‖ and four prospective3x*,1x#), but not all (two cross-sectional2x* and one prospective‖), found an association. Cerebral blood flow assessed by various MRI techniques	No studies
Cerebral small vessel disease features	Two prospective MRI studies2x‖ found an association. Features studied: silent infarcts, including lacunes, and white matter hyperintensities	Five neuropathology studies5x‖ found an association between increased burden of cerebrovascular lesions and cognitive dysfunction. Most MRI studies (eleven cross-sectional2x#, 9x‖ and five prospective2x#, 3x‖) found an association, whereas only few (three cross-sectional2x*,1x#) and one prospective#) did not. Features studied: white matter hyperintensities, lacunes, cerebral microbleeds, total brain atrophy, and microinfarcts	No studies
Diabetic retinopathy	Most studies (one cross-sectional‖ and eight prospective8x‖) found an association, whereas few did not (three prospective3x‖)	Most studies (three cross-sectional3x‖ and four prospective4x‖), but not all (three cross- sectional3x‖ and one prospective‖), found an association	Meta-analysis and systematic review found an association between any microvascular complication (neuropathy, nephropathy, retinopathy) and incident depression
Subtle retinal microvascular changes†	Two prospective studies2x‖ found an association	Most studies (three cross-sectional3x‖ and one prospective study‖), but not all (one cross-sectional‖), found an association	One cross-sectional study‖ found an association

References to the individual studies are given in the online appendix

‡Most studies in type 2 diabetes evaluated cognitive function with use of various neuropsychological tests that mostly reflect subtle cognitive changes, and only few studies specifically focused on more severe stages of cognitive dysfunction, i.e. mild cognitive impairment or dementia

†Subtle retinal microvascular changes studied include arteriolar narrowing and widening, venular widening, arteriovenous nicking and venular tortuosity

*Study with sample size n<50

#Study with sample size between n=50 and n=100

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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[‡]

Intervention	Cerebral small vessel disease	Retinopathy	Stroke	Cognitive dysfunction[†]	Depression
Lifestyle interventions (diet and/or exercise)	Look AHEAD found beneficial effects on WMHV and TBV	Systematic review found insufficient evidence for beneficial effect	Systematic review found insufficient evidence for beneficial effect	Systematic review found insufficient evidence for beneficial effect	Meta-analysis of 15 trials found beneficial effect
Intensified vs. standard glucose-lowering treatment	ACCORD MIND found beneficial effect on TBV, but not on WMHV	Meta-analysis with individual participant data of four trials found beneficial effect. Another meta-analysis including 9 trials also found a beneficial effect	Meta-analysis of 13 trials found no beneficial effect	Meta-analysis of 4 trials found no beneficial effect	ACCORD found no beneficial effect
Novel glucose-lowering drugs: DPP4 inhibitors, GLP-1 agonists and SGLT2 inhibitors	No data available	Meta-analysis of 37 trials found no beneficial effect for DDP4i, GLP-1a and SGLT2i	Meta-analysis of 97 trials found no beneficial effect on all strokes for DDP4i, GLP-1a and SGLT2i. However, GLP1a, but not DDP4i and SGLT2i, were associated with reduction in nonfatal strokes	Systematic review on DPP4i and GLP-1a found insufficient evidence for beneficial effect. Recent trial on DDP4i found no beneficial effect. No data on SLGT2 inhibitors	No data available
Antihypertensive drugs	ACCORD- MIND found beneficial effect on WMHV, but not on TBV	Meta-analysis of 7 trials found beneficial effect	Two meta-analyses including 19 trials and 49 trials, respectively, found beneficial effect	ACCORD-MIND and ADVANCE found no beneficial effect	ACCORD found no beneficial effect
Lipid-modifying drugs	ACCORD-MIND found no beneficial effect of fenofibrate on TBV	Meta-analysis of 8 trials, mostly on fenofibrate, showed protective effect on retinopathy progression	A meta-analysis of the Cholesterol Treatment Trialists' Collaboration of 14 statin trials and another meta-analysis of 12 trials, mostly on statins, found beneficial effect	ACCORD on fenofibrate and substudy of the PROSPER trial on statins found no beneficial effect	No data available

References to the individual studies are given in the online appendix

[‡]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

Look AHEAD = Action for Health in Diabetes; ACCORD-MIND = Action to Control Cardiovascular Risk in Diabetes-Memory In Diabetes; DPP4i = dipeptidyl peptidase-4-inhibitors; GLP-1a = glucagon-like-peptide-1 agonists; SGLT2i = sodium-glucose co-transporter 2 inhibitors; WMHV = white matter hyperintensity volume; TBV = total brain volume; PROSPER = Pravastatin in elderly individuals at risk of vascular disease