**Abstract**

Type 2 diabetes mellitus is increasingly common, and previously unrecognized complications are emerging; namely, cognitive impairment and dementia. The mechanisms that link these factors together are still unknown, but likely result from the interplay of several variables, including vascular change, poor glycemic control, inflammation, and hypothalamic pituitary adrenal overactivity. At present, it is still too early to propose best practices related to the management of diabetes-induced cognitive change. All things considered, however, patients should be aware that proper management of metabolic and vascular complications may minimize the adverse effects of type 2 diabetes on cognitive function and quality of life.

**Keywords:** type 2 diabetes, cognition, dementia, vascular, metabolic

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Type 2 diabetes mellitus is becoming increasingly common; over the next two decades, the number of adults diagnosed with diabetes in developed countries is expected to rise by 20% overall, and by 38% for those over 60 years of age. This rise in prevalence has been attributed to a sedentary lifestyle, obesity, and critically, to better health care, which has improved longevity for aging adults.

As a result of people living longer with diabetes, previously unrecognized complications...
Atherosclerotic vascular disease is one of the unequivocal risk factors associated with type 2 diabetes. The mechanisms that link type 2 diabetes to cognitive impairment and dementia are still unknown, however they are most likely multifactorial and result from the interplay of a range of variables, including macro- and microvascular changes, poor glycemic control, inflammatory mediators, rheological factors, and heightened hypothalamic pituitary adrenal (HPA) axis activity. This represents an expanded understanding of the impact of type 2 diabetes on brain health. The adverse effects of vascular dysfunction remain a concern; however, it is now acknowledged that other metabolic disturbances in type 2 diabetes are equally harmful.

Macrovascular and microvascular complications of type 2 diabetes

Atherosclerotic vascular disease is one of the unequivocal risk factors associated with type 2 diabetes. Critically, most of these individuals have additional co-occurring vascular risk factors that comprise the metabolic syndrome, such as hypertension, hypercholesterolemia, dyslipidemia, and obesity. Vascular damage resulting from diabetes can affect multiple organs in the body, leading to retinopathy, nephropathy, and/or coronary or peripheral vascular disease. In the brain, these macro- and microvascular changes result in inadequate regulation of cerebral blood flow (CBF), which impacts the delivery of nutrients and oxygen to meet metabolic demands. The presence of cerebrovascular disease in diabetic individuals is associated with a 2-5 fold increase in stroke occurrence; moreover, for reasons that are not fully understood, individuals with diabetes are at a high risk for recurrence within 30 days of the initial stroke event.

In the early stages of diabetes, prolonged hyperglycemia causes a decrease in the concentration of nitric oxide (NO), a vasodilator, and an increase in the concentration of endothelin-1, a vasoconstrictor. This results in decreased ability of blood vessels to dilate to accommodate increased blood flow demand (Figure 1). In later stages of the disease,
chronic exposure to high concentrations of endothelin-1 and decreased concentrations of NO contribute to diminished vessel elasticity, and structural changes in the vessel wall that result in atherosclerotic plaque formation. Indeed, adults with diabetes show global decreases in cerebral blood flow (CBF), particularly in frontal regions, and decreased blood vessel dilation in response to vasodilatory stimuli (i.e., CO2 inhalation; Figure 2).

These vascular changes may help explain the association between type 2 diabetes, cognitive dysfunction, and progression to dementia. For example, deficits in executive functioning in this population are presumably mediated at least partially by reduced cerebrovascular reactivity, particularly in frontal regions. Studies have also shown that individuals with type 2 diabetes and a history of vascular events (e.g., myocardial infarcts, stroke, or operative treatment for coronary, carotid, or peripheral artery disease) perform more poorly on neuropsychological tests of processing speed,

Figure 1: Hyperglycemic-induced reductions in the vasodilator nitric oxide (NO) and increases in the vasoconstrictor endothelin-1 impair dilation of blood vessels. Over time, this results in structural changes in the vessel wall that result in atherosclerotic plaque formation.

Key Point
Global decreases in cerebral blood flow and reduced response to vasodilatory stimuli impact the delivery of nutrients and oxygen to meet metabolic demand.

Taken in part from:
http://www.strokecenter.org/patients/about-stroke/what-is-a-stroke/
http://www.control-your-blood-pressure.com/how-breathing-and-music-reduce-blood-pressure.html
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Figure 2: Type 2 diabetes is associated with reduced cerebral blood flow (CBF) in resting and activated conditions (baseline versus CO$_2$ rebreathing, respectively). These changes in cerebrovascular reactivity are implicated in the cognitive decline and dementia risk in those with type 2 diabetes.

Key Point
Disrupted brain insulin levels and dysfunctional insulin signalling may contribute to beta-amyloid (Aβ) plaque deposition and the formation of neurofibrillary tangles; processes that are inextricably linked to Alzheimer’s disease.

Metabolic complications of type 2 diabetes

For older adults with or without type 2 diabetes, vascular disease is a significant risk factor for cognitive decline and dementia. Some studies, however, point to an independent effect of type 2 diabetes on brain structure and function; cortical and subcortical changes that cannot be explained solely on the basis of CBF dysregulation and/or vascular lesions. This makes it apparent that the hormonal and

memory, and abstract reasoning.$^{12}$ Critically, all of these effects appear to be exaggerated with increased disease duration. Microvascular changes have also been linked to cognitive impairment; severity of diabetic retinopathy—closely correlated with cerebral microvascular change—was associated with impaired performance across a variety of cognitive tasks.$^{13}$ White matter hyperintensities, another manifestation of small vessel disease, were also associated with cognitive decline.$^{14}$
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**Figure 3:** Impact of type 2 diabetes on brain function, and its contribution to Alzheimer’s disease pathology.

Both the metabolic and vascular disturbances of type 2 diabetes contribute directly to brain dysfunction (heavier arrows). Importantly, the metabolic and vascular components also interact with one another (lighter arrows), primarily through oxidative stress and inflammation. Additionally, there is growing evidence that Aβ itself can contribute to Tau pathology and microglial activation (stippled lines). Collectively, these disturbances create the potential for increased rates of neuropathologic damage and accelerated cognitive dysfunction.

(AGEs = advanced glycation end-products; ROS = reactive oxygen species; NO = nitric oxide; HPA = hypothalamic pituitary adrenal axis; GSK3 = glycogen-synthase kinase-3; IDE = insulin degrading enzyme; Aβ = beta-amyloid).

metabolic disturbances characteristic of type 2 diabetes can themselves lead to neuronal damage and/or accelerate other neuropathologic changes.

**Insulin dysregulation**

Insulin receptors are abundant in crucial cognitive brain regions (i.e., hippocampus, entorhinal cortex, amygdala, hypothalamus), and activation of insulin signalling pathways is essential for cognitive functioning. Thus, decreased brain insulin levels and disrupted brain insulin signalling in individuals with type 2 diabetes presumably contribute to cognitive decline. Even in otherwise-healthy middle-aged and older adults, including adults with insulin resistance or pre-diabetes, decreased brain insu-
lin signalling was associated with impairments in declarative memory (the type of long term memory involved in recalling facts), working memory, and executive function (cognitive control).17

Disrupted brain insulin levels and insulin signalling may also contribute to beta-amyloid (Aβ) plaque deposition and the formation of neurofibrillary tangles; processes that are inextricably linked to Alzheimer disease pathogenesis. More specifically, uptake of insulin across the blood brain barrier is reduced in the face of peripheral hyperinsulinemia. This produces a brain hypoinsulinemic state, which results in the down-regulation of insulin degrading enzyme (IDE).18 Because IDE degrades Aβ as well as insulin,19 Aβ degradation is also effectively reduced. As a result, Aβ accumulates in the brain, contributing to Aβ aggregation and plaque formation. Decreased brain insulin signalling also suppresses the enzymes involved in tau phosphorylation, which ultimately contributes to the formation of neurofibrillary tangles.20 It remains unclear whether type 2 diabetes is the causal pathway for Alzheimer’s disease, or if it simply produces an environment where Alzheimer’s disease progression is exacerbated or accelerated once other factors contribute to its initiation. Regardless, it is evident that disruptions to brain insulin levels and insulin signalling contribute to cognitive declines and Alzheimer’s pathology.

Hyperglycemia and advanced glycation end-products

Normal metabolism and aging naturally produce advanced glycation end-products (AGEs) on proteins with slower rates of turnover (e.g., hemoglobin A1c). When bound to their receptors, which are found in many cells of the body (e.g., endothelial, liver, lung, kidney, and peripheral blood), AGEs activate inflammatory pathways that induce the secretion of cytokines and ultimately enhance oxidative stress.16 Prolonged hyperglycemia—the hallmark of type 2 diabetes—further increases oxidative stress, and thus exacerbates the production of AGEs beyond ‘normal’ levels.

AGEs impact cognitive functioning in several ways, particularly for individuals with type 2 diabetes. For example, under hyperglycemic conditions, the Aβ protein itself can become glycolysated, which allows it to act as an AGE and bind to AGE receptors, thereby enhancing activation of inflammatory pathways.21 Glycosylated Aβ also enhances its own aggregation,18 resulting in amyloid plaque formation—pathology characteristic of Alzheimer’s disease.

AGEs can also reduce insulin signalling, and thus can have a more direct negative impact
on cognitive function. Together, these processes enhance neuronal damage and ultimately affect cognitive processing.

**Inflammation**

A common, although non-unique pathology to type 2 diabetes and dementia is inflammation. Inflammation occurs in the context of normal aging, but pathological increases are thought to underlie chronic degenerative diseases such as arthritis, Alzheimer’s disease and other dementias, fibromyalgia, atherosclerosis, and stroke. Systemic low-grade inflammation results from the release of pro-inflammatory cytokines (i.e. TNF-α, Interleukin-6) from activated immune cells. Adipose tissue—central abdominal fat, in particular—is also involved in the inflammatory response, and becomes even more active releasing pro-inflammatory cytokines in individuals with type 2 diabetes.

Inflammation is thought to play a role in cognitive impairment through direct effects on the brain (cytokines can cross the blood–brain barrier), and/or by accelerating the progression of vascular disease. In individuals with type 2 diabetes, there is an association between high levels of inflammatory cytokines, and poorer scores on neuropsychological tests of memory and executive functioning, even after controlling for other variables known to affect cognition such as vocabulary, education level, cardiovascular dysfunction, duration of diabetes, and glycemic control. Similarly, older adults with type 2 diabetes who have lower levels of the pro-inflammatory cytokine TNF-α (because of a polymorphism on the TNF-α gene that acts to suppress its expression), have higher neuropsychological test scores, and show more preserved cognitive functioning when tested one year later. Central adiposity is also associated with lower hippocampal volumes, and an increased risk of cognitive decline in older patients with diabetes.

**Hypercortisolemia and hypothalamic pituitary adrenal (HPA) axis dysfunction**

The HPA axis is the neuroendocrine system involved in the body’s response to stress: physical, emotional, or psychological. In such ‘fight or flight’ conditions, the HPA axis initiates the release of cortisol, which functions to mobilize resources and respond to the stressor; for example, by suppressing ‘background’ bodily processes like digestion or the immune system, or by stimulating gluconeogenesis, which raises blood sugar levels to support increased energy expenditure. The HPA axis is also involved in the regulation of other processes such as thirst, hunger, and mood.

In type 2 diabetes, negative
feedback control of the HPA axis may be impaired, resulting in chronically high cortisol levels\(^7\) (i.e., these individuals may have difficulty ‘turning off’ the stress response during non-stressful periods). Cortisol has adverse effects within the brain; the hippocampus and related medial temporal lobe structures are particularly sensitive to the deleterious effects of glucocorticoids. Individuals with type 2 diabetes and impaired HPA regulation show deficits on hippocampal-dependent declarative memory tasks.\(^{26}\) Similarly, higher fasting cortisol in elderly people with type 2 diabetes has been linked to cognitive declines on many different types of neuropsychological tests, not just those measuring declarative memory.\(^{27}\) There are also links between cognitive impairment and hippocampal atrophy in this population.\(^{26}\)

**Putting it all together**

Although attempts have been made to characterize the independent effects of vascular and metabolic changes in type 2 diabetes, in reality these factors link together intricately to create an environment that promotes Alzheimer’s disease pathology. Figure 3 attempts to provide a clear, but comprehensive depiction of these complex interactions. To summarize, low brain insulin levels and disrupted insulin signalling contribute to A\(\beta\) and tau pathology, chronic hyperglycemia exacerbates the production of AGEs beyond ‘normal’ levels, and AGEs activate inflammatory pathways and enhance oxidative stress. Hypertension causes cellular and atherosclerotic damage, which, in turn, activates the immune system and contributes further to the environment of inflammation and oxidative stress. Chronic activation of this immune response adds to the vascular damage that initiated the response in the first place, and exacerbates the effects associated with metabolic dysregulation—A\(\beta\) and tau pathology, and increased AGE production. Interactions within and between these vascular and metabolic factors ultimately create a positive feedback system that promotes vascular and neuronal dysfunction, and contributes to cognitive declines through the progressive accumulation of damage.

**Clinical Management**

At present there are only a handful of clinical trials looking at changes in cognitive functioning associated with better management of type 2 diabetes. Initial findings do, however, suggest that cognitive declines can be minimized or delayed. Lower intake of saturated and trans fats, and higher relative intake of polyunsaturated fats may reduce cognitive declines.\(^{28}\) Physical activity is also an important factor for maintaining quality of life in patients with type 2 diabetes.

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**Key Point**

In patients with type 2 diabetes, macro- and microvascular changes, insulin dysfunction, poor glycemic control, inflammation, and heightened hypothalamic-pituitary-adrenal axis activity interact to create an environment that promotes Alzheimer’s disease pathology.
The adverse effects of vascular dysfunction on brain health remain a concern; however, it is now acknowledged that other metabolic disturbances in type 2 diabetes are equally harmful to brain health and function.

Macro- and microvascular pathology in the brain can impact the delivery of nutrients and oxygen to meet metabolic demand. Adults with diabetes show global decreases in cerebral blood flow and reduced response to vasodilatory stimuli (e.g. hypercapnia), particularly in frontal regions.

In patients with type 2 diabetes, disrupted brain insulin levels and dysfunctional insulin signalling may contribute to beta-amyloid (Aβ) plaque deposition and the formation of neurofibrillary tangles; processes that are inextricably linked to Alzheimer’s disease.

Prolonged hyperglycemia—the hallmark of type 2 diabetes—increases oxidative stress, and thus exacerbates the production of advanced glycation end-products (AGEs) beyond ‘normal’ levels. AGEs can reduce insulin signalling, and thus may have a direct negative impact on cognitive function.

Inflammation is thought to play a role in cognitive impairment through direct effects on the brain, and/or by accelerating the progression of vascular disease.

Cortisol has adverse effects within the brain; the hippocampus and related medial temporal lobe structures are particularly sensitive to the deleterious effects of glucocorticoids. In type 2 diabetes, negative feedback control of the HPA axis may be impaired, resulting in chronically high cortisol levels.

In patients with type 2 diabetes, macro- and microvascular changes, insulin dysfunction, poor glycemic control, inflammation, and heightened hypothalamic pituitary adrenal axis activity interact to create an environment that promotes Alzheimer’s disease pathology.

It is important to make patients with type 2 diabetes aware of the fact that proper management of metabolic and vascular complications can help minimize the adverse effects of diabetes on brain health, cognitive function, and quality of life.
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Clinical Pearls

Beyond the age of 65 years, type 2 diabetes conveys the highest risk for progression to dementia, over and above that of hypertension, dyslipidaemia, and obesity.

Individuals with type 2 diabetes with a history of vascular dysfunction perform more poorly on neuropsychological tests.

Even in otherwise-healthy adults, decreased brain insulin signalling can impair aspects of cognitive functioning.

Higher fasting cortisol in people with type 2 diabetes has been linked to cognitive declines on many different types of neuropsychological tests.

It remains unclear whether type 2 diabetes is a causal pathway for Alzheimer’s disease, or if it simply produces an environment where Alzheimer’s disease pathology is exacerbated.

Interactions within and between the vascular and metabolic complications associated with type 2 diabetes ultimately creates a positive feedback system that promotes dysfunction, and contributes to cognitive decline through the progressive accumulation of damage.

At this point, however, it is still too early to propose best practices related to the management of type 2 diabetes-induced cognitive change. Anxiously awaited are results from ongoing trials exploring standard diabetic care versus intensive diabetic care, and others using pioglitazone, a thiazolidinedione with hypoglycemic action. On balance, we can speculate that stringent control of insulin and blood sugar levels will minimize the cognitive deficits that result from diabetes-related metabolic disturbances, and that control of hypertension will minimize vascular dysfunction. A healthy diet, regular exercise, adequate stress management, and continued social engagement will counteract deleterious effects associated with inflammation, oxidative stress, and chronic HPA activation, and may even promote the maintenance of intact cognitive abilities. All things considered, it is important to make patients with type 2 diabetes aware of the fact that proper management of metabolic and vascular complications can help minimize the adverse effects of diabetes on brain health, cognitive function, and quality of life.

References

Dementia Risk in Older Adults with Type 2 Diabetes

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