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Review

Diabetes, Dementia and Hypoglycemia

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ABSTRACT

We are experiencing an epidemic of both diabetes and dementia among older adults in this country. The risk for dementia appears to be increased in patients with diabetes, and patients with dementia and diabetes appear to be at greater risk for severe hypoglycemia. In addition, there may be an increased risk for developing dementia by older patients with diabetes who have had episodes of severe hypoglycemia, although this issue is controversial. In this article, we review the factors that contribute to the increased risk for dementia in older adults with diabetes and outline the complex relationships between hypoglycemia and dementia.

RÉSUMÉ

Dans notre pays, nous faisons face à une épidémie de diabète et de démence chez les personnes âgées. Le risque de démence semble augmenter chez les patients diabétiques, conséquemment les patients souffrant de démence et de diabète semblent être exposés à un plus grand risque d'hypoglycémie grave. De plus, il existe une augmentation du risque de développer la démence chez les patients âgés diabétiques qui ont eu des épisodes d'hypoglycémie grave, bien que ce problème soit controversé. Dans le présent article, nous passons en revue les facteurs qui contribuent à l'augmentation du risque de démence chez les personnes âgées diabétiques et soulignons les relations complexes entre l'hypoglycémie et la démence.

Introduction

It appears that diabetes, dementia and hypoglycemia are inextricably linked in older patients with diabetes. In order to understand the magnitude of this problem, we undertook the following narrative review.

Diabetes and Dementia

We are experiencing an epidemic of diabetes in older adults. Health Canada reports that the current prevalence of diabetes in patients over the age of 65 is approximately 17%, a total of nearly 900 000 Canadians. Given that diabetes is often asymptomatic, this probably under-represents the actual figure. In addition, there are at least as many patients with prediabetes as diabetes, so the numbers of Canadians afflicted with abnormalities of glucose metabolism is staggering. We are also facing an epidemic of dementia. The current prevalence of dementia in the elderly is 15%, or about 800 000 people. This is expected to increase to 1.4 million by the year 2030.

There is evidence that older patients with type 2 diabetes without dementia have impairments in brain function and cognition (1–3), although the exact nature of the cognitive deficits is somewhat controversial (4). Current information from neuropathologic and neuroimaging studies implies that patients with diabetes without dementia have evidence of cerebral atrophy and subclinical infarction (4,5). It is interesting that imaging and neuropathology studies have also shown that there may be changes in the brains of patients with diabetes that are very similar to those seen in early Alzheimer disease, although this finding is more controversial (4,6).

Dementia is often preceded by a stage in which patients have objective evidence of cognitive dysfunction and memory complaints, but their functioning is intact. This is referred to as mild cognitive impairment (MCI). Many patients with MCI progress to dementia, and the coexistence of diabetes may increase the risk for progression (5). The differences among normal aging, MCI and dementia are outlined in the Table 1.

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Table 1
Cognitive changes in the elderly

	Impairment in function	Impairment in cognition
Normal aging	No	No
Mild cognitive impairment	No	Yes
Dementia	Yes	Yes

Early investigations did not identify an increased risk for dementia in elderly patients with type 2 diabetes. More recently, a number of prospective and retrospective population-based studies have demonstrated that the prevalence of dementia is increased in patients with diabetes by a factor of 2. This topic has been extensively reviewed (4–14). The risk for dementia in diabetes increases in relation to age, ethnicity, education, the presence of depression, microvascular and macrovascular disease, lower-extremity complications and longer duration of diabetes (4,11,15), although the relative risk for dementia in diabetes may decrease with age (7). Recently, a risk score has been validated; it allows the prediction of dementia risk in patients with type 2 diabetes (16). There has been some suggestion that certain classes of diabetes medication increase or decrease the risk for dementia, but this has not been clarified (11,12).

The most common forms of dementia are Alzheimer disease and vascular dementia, and there are a substantial number of patients who have mixed dementia. It makes perfect sense to assume that diabetes would contribute to an increased risk for vascular or mixed dementia, given its impact on the vascular system (see below), and the incidence of vascular dementia is clearly increased in patients with type 2 diabetes. However, the prevalence of Alzheimer disease may also be higher in patients with diabetes, although the odds ratios are less than those for vascular dementia (7).

There are several factors that may contribute to the increased risk for dementia in patients with diabetes (Figure 1). First, patients with diabetes are known to be at risk for small-vessel disease and stroke, which can contribute to vascular or mixed dementia. In support of this finding, it is known that the presence of hypertension, microvascular or macrovascular complications increases the risk for dementia (11). Chronic hyperglycemia, as reflected by higher levels of glycated hemoglobin (A1C), is associated with poorer cognition in patients with diabetes (9,10,17). Presumably, microvascular changes, alterations in synaptic plasticity, oxidative stress and the accumulation of advanced glycation end products are contributing factors to these cognitive effects. Interestingly, there appears to be a very strong correlation between levels of postprandial hyperglycemia and the risk for dementia (6). Conversely, severe hypoglycemia may also increase the risk for dementia (see below).

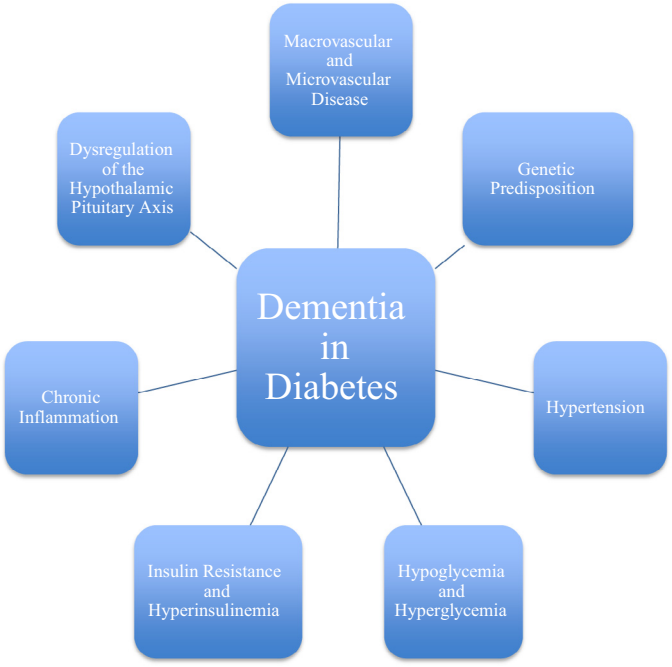

Figure 1. Pathophysiologic factors associated with dementia and diabetes in the elderly.

There is an association between insulin resistance, hyperinsulinemia and cognitive impairment (18,19). Insulin has neurotropic properties. It is rapidly transported across the blood-brain barrier. Insulin receptors are localized mainly in the parts of the brain that are associated with learning and memory. Insulin is involved in the production of important neurotransmitters, and nasal insulin has been shown to improve memory in patients with cognitive impairment (12,20). How do hyperinsulinemia and insulin resistance contribute to memory loss? Insulin resistance results in downregulation of insulin receptors, which may lead to a reduction in the neurotropic impact of insulin on the brain. Insulin resistance is associated with increased levels of inflammatory cytokines (see below), reduced glucose uptake and reduced blood flow. In addition, hyperinsulinemia may alter metabolism of amyloid, leading to its accumulation and toxic effects (6).

Chronic inflammation is present in many patients with diabetes, and elevated levels of inflammatory cytokines are associated with worse cognition in patients with diabetes (9,10). It is possible that increased levels of cytokines contribute to dementia by having a direct effect on the brain, by contributing to vascular disease or by causing insulin resistance, with the impacts noted above (18). Patients with type 2 diabetes have dysregulation of the hypothalamic pituitary axis and high levels of cortisol (9,10). There is an association between increased levels of cortisol and cognitive dysfunction in patients with type 2 diabetes. Increased levels of cortisol are associated with microvascular abnormalities in patients with diabetes. In addition to the impact on the circulation, high levels of cortisol may have detrimental effects on the hippocampus.

Brain changes and reductions in cognitive scores are most pronounced in patients with diabetes who have the ApoE4 allele, providing a further link between diabetes and dementia and implying that genetic factors may play a prominent role in this association (21). Rheologic abnormalities may also play a role. Increased levels of rheologic factors may increase the resistance to flow and are associated with vascular disease. For example, there is some evidence for an association between increased plasma viscosity and impaired cognition in patients with type 2 diabetes (9,10).

What are the implications of these findings for the prevention of dementia or for slowing its progression? Better glycemic control would seem to be a good idea, but the Action to Control Cardiovascular Risk in Diabetes (ACCORD) follow-up study Memory in Diabetes (ACCORD-MIND) found that although better control resulted in less brain atrophy, it had no impact on changes in cognitive function (22). Exercise may improve cognition in patients with impaired glucose tolerance, a precursor to diabetes, and physical activity may negate some of the impact of diabetes on cognitive function in the elderly (23,24). Good control of cardiovascular risk factors would be expected to reduce the risk for dementia, but conventional strategies for risk reduction (statins, antiplatelet agents) do not appear to reduce the incidence of dementia in elderly patients without diabetes (9,10). However, the Hypertension in the Very Elderly Trial-Cognitive Function Assessment (HYVET-COG) study did suggest that treatment of hypertension may have some beneficial impacts on cognition (25) in elderly patients without diabetes, and there is some evidence that treatment of hypertension, particularly with angiotensin converting enzyme inhibitors and angiotensin receptor blockers, may prevent cognitive decline in patients with diabetes (26,27).