Cognitive Dysfunction among Older Adults with Diabetes

Hsu-Ko Kuo, MD, MPH, *Department of Geriatrics and Gerontology, National Taiwan University; Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan.*

Yau-Hua Yu, DDS, DMSc, *Department of Medical Research, Veterans General Hospital, Taipei, Taiwan.*

Shin-Yu Lien, BS, *School of Nursing, Chang Gung University, Taoyuan, Taiwan.*

Yi-Der Jiang, MD, PhD, *Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan.*

There has been a substantial increase in total cases of diabetes mellitus in industrialized countries among older adults. Diabetes mellitus has been increasingly recognized as a risk factor for cognitive impairment and dementia. This article discusses the epidemiological evidence for diabetes to predict Alzheimer's disease, vascular dementia, and decline in various domains of cognition. We also address the features of diabetes-related executive dysfunction and its importance in the clinical care of diabetic older adults.

Key words: *diabetes mellitus, cognition, Alzheimer's disease, vascular dementia, frontal executive dysfunction*

Introduction

Diabetes mellitus (DM) is quiet enough at its onset but can have a toll on the body that causes immense and insidious damage to various organ systems, including microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (coronary heart disease, stroke, peripheral arterial disease) complications. As DM increasingly becomes a disease of older adults, some of its underappreciated cognitive manifestations must be addressed. Cognitive dysfunction—which imposes a direct impact on quality of life, loss of independence, and demands on caregivers—may ultimately be as great a concern to older adults with diabetes as the more traditionally recognized vascular complications.

Cognitive Dysfunction among Older Adults with Diabetes Mellitus

Cognitive decline has been variably related to a number of factors, including the apolipoprotein E epsilon 4 allele, years of formal education and other lifestyle factors, depressive symptoms, and cardiovascular risk factors. Diabetes mellitus, widely accepted as a risk factor for VaD, has a similar role in AD[3] and should be added to the list of risk factors associated with cognitive decline and dementia among older adults. Growing evidence suggests that the impact of DM on cognition may not be entirely due to the cerebrovascular damage that often accompanies DM.

The Relation of Diabetes Mellitus to Cognitive Dysfunction

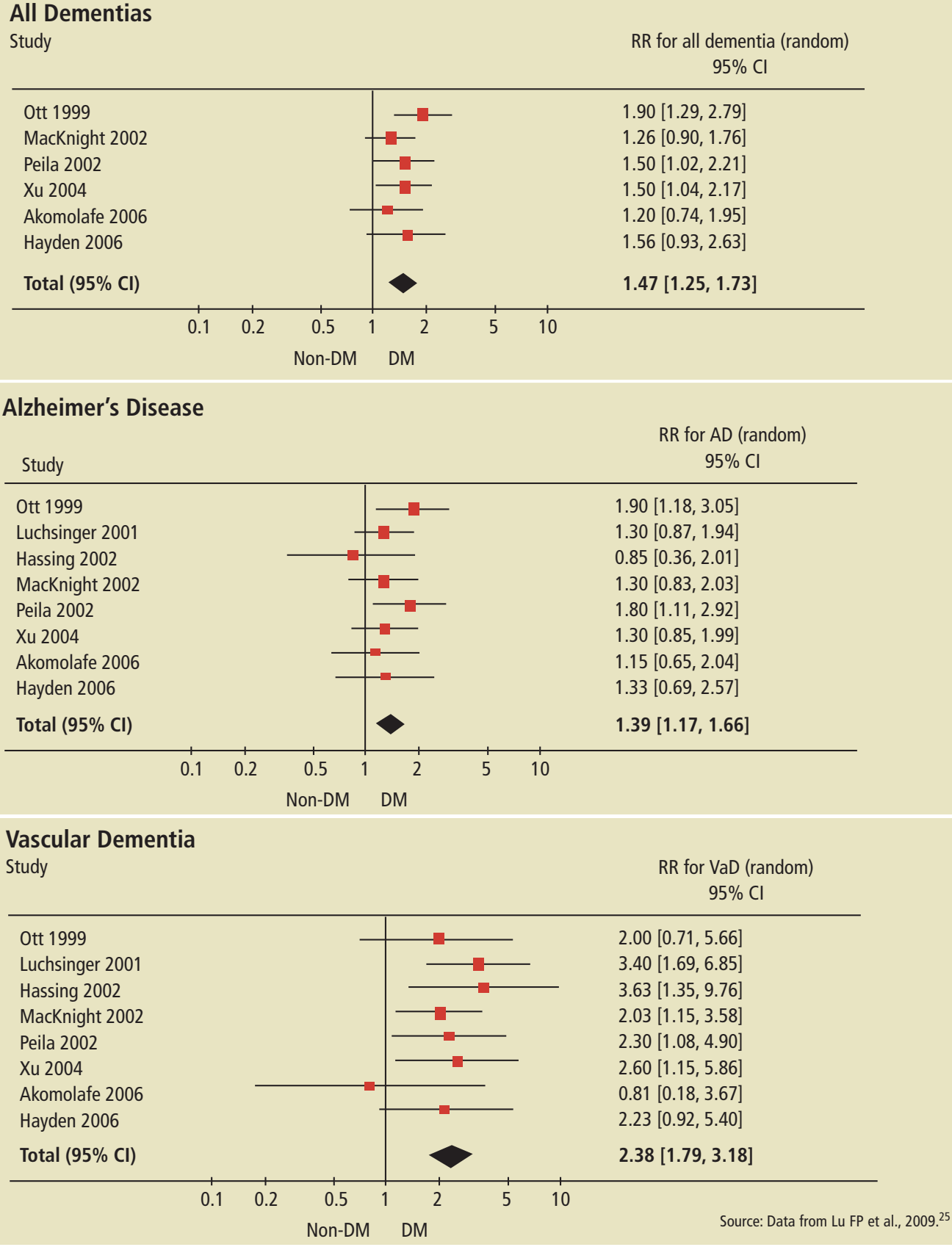
Global Cognition and Individual Cognitive Domains

Many prospective epidemiological studies have reported a relationship between DM and a decline in frontal lobe–mediated executive function, including psychomotor speed and attention, abstract thinking, mental flexibility, and multitasking.[4–6] The Trail Making Test (parts A and B), digit symbol substitution test, and word list generation test (verbal fluency)—which require strategy formation, behavioural spontaneity, and, to some extent, retrieval ability from long-term memory—assess frontal lobe–mediated cognitive abilities and are characterized as traditional measures of executive function. Many other studies have shown that a decline in executive function is an important feature in DM-related cognitive decline.[7–9] In addition to frontal lobe executive dysfunction, DM has been reported to be associated with a decline in other cognitive systems, including visuospatial ability,[7] verbal memory.[7,8] and global cognitive function.[8–11]

Dementia

Older adults with diabetes typically score lower on certain cognitive tests and have a faster pace of cognitive decline than do those without DM. Diabetic complications and comorbidities, such as stroke and hypertension, have been implicated as risk factors for dementia and AD.[12,13] A growing body of large-scale longitudinal studies has been performed to elucidate the role of DM in the development of incident dementia, AD, or VaD.[14–22] A recent systematic review of population-based studies suggested that the risk of dementia is generally increased in patients with DM.[23] Cukierman *et al.,* using meta-analytic technique, demonstrated that diabetic adults were 1.6 times more likely to develop all-cause dementia than were people without diabetes (95% CI 1.4–1.8).[24] Studies addressing the potential underlying mechanisms from DM to dementia could provide insight into both

Figure 1: Adjusted Relative Risk for All Dementias, Alzheimer's Disease, and Vascular Dementia in Diabetes Compared with Nondiabetic Older Adults in Prospective Population-Based Studies



Source: Data from Lu FP et al., 2009.[25]

Table 1: Commonly Seen Behaviour Signs of Diabetes Mellitus-Associated Executive Dysfunction

Problems	Examples
Stopping	Disinhibited behaviours, such as blurting out socially inappropriate remarks; frontal release signs, such as the grasp and palmomental reflex
Starting	Lack of spontaneous retrieval of previously learned information; needing repeated reminder and monitoring for treatment plans; problems with initiation; lack of motivation; inability to maintain effortful behaviour; mutism is a most extreme example
Switching	Lack of mental flexibility; inability to change strategies for solving problems; difficulty in switching habitual behaviour such as diet and lifestyle; self-management difficulty when there is a change in medical regimen such as dosage and schedule
Socialization	Poor interpretation of social cues; difficulties in socializing due to lack of motivation, personality changes, or uninhibited behaviours
Planning	Inability of volition, multitasking, and organizing; inability to manage polypharmacy and complex dosing regimen; inability to be compliant to suggestions from health care providers; "stubborn" or "uncooperative" patients not compliant with treatment advice
Judgment	Failure to anticipate consequences of behaviour, such as inability to self-monitor blood sugar and obtain hypoglycemia; inability to identify signs of medication adverse effects

the prevention and treatment of cognitive dysfunction in people with diabetes.

Given that DM is associated with an increased risk of developing dementia, some prospective studies have been designed to investigate the relationship of DM to common subtypes of dementia, specifically AD and VaD. Diabetes, a strong risk factor for the development of VaD after a comprehensive adjustment of various cardiovascular disease and risk factors, is consistently associated with a statistically significant 2.0- to 2.6-fold increase in risk of incident VaD among older adults.[15,18,20,21] Studies with DM as an exposure have generally suggested a 30–100% increased risk of AD. A recent meta-analysis by our group demonstrated that overall risk ratios for AD, VaD, and all dementias, comparing persons with DM to those without, were 1.39 (95% CI 1.17–1.66), 2.38 (95% CI 1.79–3.18), and 1.47 (95% CI 1.25–1.73), respectively (Figure 1).[25]

Pathophysiological Mechanisms of Diabetes-Related Cognitive Dysfunction

Hyperglycemia

Early reactions between glucose and protein amino acids proceed from nonenzymatic glycosylation (posttranslational modification) to reversible Schiff's bases, and to stable, covalently bonded Amadori rearrangement products.[26] Over weeks and months, these early products evolve further chemical reactions into irreversibly bonded advanced glycosylation end products (AGEs),[27] immunohistochemically identified in both senile plaques and neurofibrillary tangles.[28] It was also reported that AGE-modified beta-amyloid (Abeta) promotes Abeta aggregation, thus contributing to amyloidosis in AD.[29]

In addition to forming AGEs, three major pathways are associated with hyperglycemia: an increased flux of glucose through the polyol pathway, the activation of protein kinase C, and an increased flux of glucose through the hexosamine pathway.[30] Each of these pathways, along with the AGE modification, reflects the hyperglycemia-induced oxidative stress,[31] thus resulting in vascular endothelial damage, leading to lacunes, white matter changes (leukoaraiosis), large ischemic stroke, or brain atrophy. These changes are known risk factors for cognitive impairment.

Hypoglycemia

Extensive evidence in human studies demonstrated that acute hypoglycemia impaired cognitive performance in attentional flexibility,[32,33] logical reasoning,[34] and speed of information processing.[32,34–36] The most common cause of hypoglycemia among people with diabetes is the use of exogenous insulin and oral hypoglycemic agents. Depending on the magnitude and duration, hypoglycemia causes varying levels of cognitive and neurological impairment. However, study of the cognitive impact of recurrent hypoglycemia in diabetic patients has been hampered by the difficulty in controlling for prior hypoglycemic history and such competing influences as chronic exposure to hyperglycemia, cerebrovascular disease, depression, and other comorbidities. Moreover, most studies have been conducted in animals or middle-aged individuals with type 1 diabetes. More studies are needed to elucidate the role of hypoglycemia in the development of cognitive dysfunction in older diabetic patients.

Hyperinsulinemia and Insulin Resistance

Older adults with diabetes, most of whom have type 2 diabetes, are known to have insulin resistance or hyperinsulinemia. Hyperinsulinemia has an important role in the metabolism of Alzheimer's protein Abeta. Abeta is cleared through microglial low density lipoprotein–receptor mediated uptake or through proteolytic degradation. The proteolytic degradation of Abeta involves insulin-degrading enzyme (IDE). Insulin-degrading enzyme, in fact, demonstrates a strong preference for insulin over Abeta. Researchers incubated neurons in vitro with insulin and found that insulin increased extracellular Abeta both by reducing IDE-mediated Abeta degradation and by stimulating Abeta secretion.[37] In a human study, investigators experimentally raised plasma insulin to levels commonly encountered in many patients with type 2 DM and found that insulin infusion led to an increase in cerebrospinal fluid Abeta levels, most notably in older individuals.[38]

In short, diabetes in older adults, by chronic elevation of both serum glucose and insulin, may lead to excess oxidative stress and abnormal amyloid metabolism, thus resulting in generalized cerebral macro-/microvasculopathy, brain atrophy, and dementia.

Strategies for Prevention and Management

Diabetes mellitus in older adults is usually encountered in the context of multiple metabolic syndromes as well as cardiovascular disease and risk factors, namely, hypertension, coronary heart disease, stroke, smoking, physical inactivity, dyslipidemia, and obesity. Studies have suggested that vascular risk factors modify the association between diabetes and cognitive dysfunction and that an aggregation of vascular risk factors significantly increases the risk of developing dementia.[8,39,40] Moreover, the management of diabetes is associated with a better cognitive outcome. A controlled clinical trial conducted by Gradman *et al.* found that after 2 months of treatment with glipizide, older adults with DM were able to perform better in tests of verbal learning and memory.[41] In a 2-year prospective analysis, antidiabetic medications appeared to alleviate both physical and cognitive decline, especially for those with a longer diabetic duration.[42] Therefore, it is plausible to aggressively manage DM, along with other vascular risk factors, in midlife to prevent late-life cognitive dysfunction.

Many prospective studies have reported DM as an important predictor for executive dysfunction, including perceptual speed, attention, abstract thinking, and mental flexibility as assessed by such tests as the Trail Making Test, digit symbol substitution test, and verbal fluency test. Executive functions, abilities for multitasking, planning, and organizing, are essential for DM management and cardiovascular risk modification, which typically involve the management of multiple medications, dietary and lifestyle changes, self-monitoring of blood sugar, and frequent follow-up. A poor executive function impairs a diabetic patient's ability to manage his or her own disease. By analyzing 60 older adults with diabetes, Munshi *et al.* demonstrated that impaired executive function in this population was associated with poor diabetes control and that older diabetic adults had a high risk of depression and functional disabilities.[43] Unfortunately, older adults with diabetes with overlooked cognitive impairment, especially executive dysfunction, are often labelled as noncompliant or unmotivated. Clinicians are advised to assess older adults with diabetes for cognitive impairment using a standardized instrument during the initial evaluation and with any significant decline in clinical status, including increased difficulty with self-care. Although the Mini-Mental State Examination (MMSE), a commonly used screening instrument, has been recommended as a tool to detect cognitive impairment,[44] the test is not sensitive

Clinical Pearls

Older diabetic patients with cognitive dysfunction, less able to have multitasking ability and to flexibly apply acquired knowledge into their care, should not be labeled as "noncompliant."

Because diabetes care is largely multidisciplinary involving self-monitoring, medication adherence, and lifestyle changes, older patients with diabetes and cognitive dysfunction need to be evaluated for barriers to safe and effective diabetes control, especially when treatment regimens are somewhat complicated.

Family members or caregivers may benefit from education and support to enable them to effectively help older patients with diabetes and cognitive dysfunction.

Key Points

In addition to a decline in memory, visuospatial ability, and global cognitive function, diabetes mellitus is particularly associated with impairment in frontal lobe executive function, including psychomotor speed, attention, abstract thinking, mental flexibility, and multitasking.

Unrecognized cognitive impairment may interfere with a patient's ability to implement lifestyle modifications and take prescribed medications.

Clinicians should assess older adults with diabetes for cognitive impairment using a standardized screening instrument during the initial evaluation period and with any significant decline in clinical status.

If cognitive dysfunction is suggested, therapy should be simplified and prescribed in a clear step-by-step fashion to achieve the best possible outcomes.

enough to detect executive dysfunction. In addition to performing a cognitive screening instrument such as MMSE, clinicians should learn to recognize the signs of executive dysfunction, including problems with stopping, starting, switching, socialization, planning, and judgment (Table 1). Some tests such as the clock-drawing test, Trail Making Test, and word list generation, are easily administered and useful in identifying subtle executive dysfunction. From a primary care standpoint, it is crucial to be aware of a patient's cognitive status when formulating a treatment plan or prescribing antidiabetes medications. Newly developed difficulties with participating in diabetes self-care should be considered indicators of cognitive decline. If cognitive dysfunction is suspected from the associated behavioural signs or confirmed through cognitive tests, therapy should be simplified and prescribed in a clear step-by-step fashion to achieve better outcomes.

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