Cognitive and Physical Disabilities and Aging-Related Complications of Diabetes

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Diabetes has gained notoriety as a major chronic disease epidemic in the United States and is threatening to undo some of the success in coronary heart disease (CHD) and stroke mortality prevention made during the past several decades. An increase in the prevalence of type 2 diabetes among youth has been a particularly alarming aspect of this epidemic, but the diabetes epidemic in developed countries affects the entire age range, and the greatest absolute increase and total numbers of diabetes cases are actually occurring among the elderly. Currently, 42% of the diabetic population in the United States is 65 years old or older; this proportion is projected to increase to 53% by 2025 and to 58% by 2050.

The increase in diabetes among the elderly is concerning because, in addition to the wide range of traditional diabetes complications (including acute hyperglycemic and hypoglycemic events and vascular complications that may lead to vision loss, renal failure, foot ulcers and amputation, myocardial infarction, stroke, and cardiovascular death), evidence has been growing that diabetes is associated with increased risk of cognitive decline, physical disability, falls and fractures, and other conditions associated with geriatric syndromes. These less traditional complications are common and may be as damaging as the commonly recognized vascular outcomes of the disease to older diabetic people because of their direct influence on quality of life. Indeed, for older people with diabetes, the threat of loss of independence due to progressing cognitive and physical decline may be of greater direct concern than the clinical progression of diabetes complications.

Unfortunately, few epidemiological studies have examined the impact of diabetes on functional outcomes, and almost no randomized clinical trials (RCTs) have examined the effect of treatments on these outcomes. In this review, we summarize the research associating diabetes with these aging-related outcomes and comment on the potential for clinical and public health interventions to reduce the burden of these outcomes among elderly people with diabetes.

ASSOCIATIONS BETWEEN DIABETES AND COGNITIVE DECLINE OR DEMENTIA

Numerous cross-sectional and case-control studies dating back to the 1980s have shown positive associations between diabetes and cognitive impairment. Many overlapping mechanisms for this association have been proposed. Chronic hyperglycemia and the production of advanced glycated end products may damage vascular tissue and endothelial function, DNA, and mitochondria in the brain and increase free radicals, inflammatory responses, and amyloid deposition. Chronic hyperglycemia may also influence cerebral blood flow, neurotransmitter function, or nutrient delivery to the brain. In addition, diabetes could influence cognitive function by leading to cardiovascular events, transient ischemic attacks, and strokes. Repeated hypoglycemic events and related metabolic and vascular disruption might influence long-term cognitive function. Diabetes may also be a marker of other factors, such as insulin resistance and hypertension, or may represent a common genetic susceptibility to both diabetes and Alzheimer’s disease dementia.

Regardless of the mechanism, several large prospective studies have associated diabetes with cognitive decline and clinical dementia during the past 5 years. Four found a significant association between diabetes and rate of cognitive decline as measured by cognitive tests over 4–6 years. Two of these studies found a 60–100% greater risk of cognitive decline among people with diabetes than among those without diabetes. Associations were observed for a range of cognitive domains, including attention, concentration, visuo-spatial reasoning, memory, and psychomotor speed, but tended to not be associated with decline on the modified mini-mental state exam.
Two earlier studies failed to find any association between diabetes and change in cognitive function. However, the first study had limited power,18 and the second study used only the mini-mental state exam, a screening test with high specificity but poor sensitivity, to study change in cognitive function.19

Recent studies have also addressed the effect of diabetes on clinically defined dementia. The findings have varied depending on the type of dementia. At least three studies have found diabetes to have a 50–200% greater risk for overall dementia and Alzheimer’s disease.20–23 Other studies have found diabetes associated with about twice the risk of vascular dementia but not of Alzheimer’s disease.24–26 The study by Luchsinger et al.25 found that diabetes was particularly associated with stroke-mediated dementia, wherein the relative risk was >3.

Although no formal quantitative meta-analyses have been conducted on this issue, these studies suggest that diabetes is associated with both subtle declines in cognitive function (as measured by neuropsychological tests) and more profound declines in function (as assessed by clinical dementia criteria). Associations with Alzheimer’s disease appear relatively weak, indicating that the association with dementia is driven by vascular factors. Separation of vascular dementia from Alzheimer’s disease dementia remains difficult, however, especially because Alzheimer’s disease may be influenced by vascular factors.27,28

On the whole, these studies lacked data to determine the specific mechanisms underlying the association between diabetes and cognitive decline or dementia. Similarly, it is unknown whether aspects of metabolic and cardiovascular risk control among people with diabetes play any role in increasing the risk of cognitive impairment and decline.

**Associations Between Diabetes and Physical Disability or Functional Status**

Levels of disability, assessed according to difficulty with mobility, walking, and carrying out complex and simple daily activities, have emerged as key indicators of morbidity for older adults.29,30 For an individual, measures of disability and independence are directly influenced by the number and severity of chronic diseases present and are central components of quality of life. At the population level, disability measures are key indicators of overall health status and whether improved medical care and longevity are accompanied by reduced morbidity.

Although there are many reasons to suspect that diabetes could lead to increased physical disability, the magnitude or key factors explaining such a relationship have rarely been examined. In the Third National Health and Nutrition Examination Survey (NHANES III), women and men aged ≥60 years with diagnosed diabetes were ~2–3 times more likely to be unable to walk one-fourth of a mile, climb stairs, and do housework than similar-aged adults without diabetes.31 Women with diabetes also had significantly slower walking speed, worse balance, and a 58% higher likelihood of falling than did nondiabetic women. In a prospective study of women in the Study of Osteoporotic Fractures,32 women with diabetes had twice the yearly incidence of becoming unable to walk one-fourth of a mile (4.3 vs. 1.9% among nondiabetic women), doing heavy housework (8.5 vs. 4%), or preparing meals (1.5 vs. 0.7%). Recent analyses from the Women’s Health and Aging Study have found similar degrees of association between diabetes and mobility problems, activities of daily living disabilities, and balance among a cohort of older women at high risk for disability.33,34

The mechanisms explaining the association between diabetes and physical disability are probably multifactorial. In NHANES III, CHD and high body mass index (BMI) were the strongest explanatory factors among women, accounting for 52% of their excess risk for disability.31 Among men, CHD and stroke were the most important explanatory factors, explaining 25 and 21% of the excess disability risk, respectively. In the Study of Osteoporotic Fractures, age, CHD, arthritis, physical inactivity, BMI, and visual impairment were key predictors of disability among the women with diabetes.32 And in the Women’s Health and Aging Study,34 where more information on lower-extremity disease was collected, peripheral nerve dysfunction, peripheral arterial disease, and depression were the main predictors of physical disability. In each of these studies, however, a significant excess risk of disability associated with diabetes remained, even after controlling for diabetes-related complications. This indicates either that diabetes has an intrinsic influence on disability or that other unmeasured or undiscovered diabetes-related complications influence the risk for disability.

The effects of diabetes on physical disability may extend to other adverse aging-related outcomes. At least four large studies have found an increased risk of falling among older adults with type 2 diabetes.35–38 Schwartz et al.35 found that, although women with type 2 diabetes had a significantly higher bone mineral density than did nondiabetic women, the increased risk of falls (53% greater risk of at least one fall per year) apparently outweighed this advantage, resulting in a 49% increased risk of fractures. Other studies have supported this finding, indicating that women with diabetes may be at particularly increased risk of hip or foot fractures.39–42

**Interventions to Reduce Cognitive and Functional Decline**

As a result of numerous large RCTs conducted during the past decade, clinicians are now armed with the knowledge that aggressive management of glycemia, blood pressure, and lipids; aspirin use; smoking cessation; and regular screening for foot, eye, and kidney problems may prevent and delay the complications of diabetes.43 Some of these and other interventions might also influence the risk for aging-related diabetes outcomes, such as cognitive and physical disabilities. Unfortunately, most
large effectiveness studies were conducted among middle-aged populations, and almost no RCTs examined the effect of interventions on cognitive or functional decline.

Management of glycemia and blood pressure could conceivably ameliorate cognitive decline among patients with diabetes. Two short-term, nonrandomized studies suggested that improved glycemic control improves cognitive function over 3–6 months. Another study found that people who received intensive inpatient management had improved concentration and psychomotor function compared to patients who received regular home-based care, but the two groups did not differ in glycated hemoglobin concentration, making it unclear which aspect of care influenced cognitive function. An RCT of more than 500 men and women with type 2 diabetes showed that glycemic management over 12 weeks was associated with improvement in several acute symptoms, as well as subjectively reported confusion and cognitive function. Finally, the Diabetes Control and Complications Trial found no difference in change in overall cognitive function between younger people with type 1 diabetes randomized to intensive glycemic management versus regular care. Thus, although glycemic control remains a possible approach to prevent or reduce cognitive decline, the lack of long-term RCTs in older diabetic populations makes it unclear whether such benefits are likely to occur.

Several studies have examined the effects of antihypertensive use on cognitive function as part of large RCTs examining cardiovascular disease outcomes. Two of these studies found no effect of antihypertensive treatment on the rate of cognitive decline, but another, the Systolic Hypertension in Europe trial, found a 50% reduction in the incidence of dementia among treated hypertensive adults aged ≥60 years after 2 years of follow-up. In a further analysis (median follow-up 3.9 years), patients originally randomized to combination antihypertensive treatment using calcium-channel blockers had a net 7.0/3.2 mmHg lower blood pressure and a 55% lower incidence of dementia than did control subjects. Treatment-related reductions were greater for Alzheimer’s dementia (62%) than for mixed or vascular dementia (48%). The treatment group also had a lower rate of disability measured by difficulty carrying out activities of daily living. None of these analyses were conducted primarily among people with diabetes.

For patients with Alzheimer’s disease, cholinesterase inhibitors and vitamin E supplements have emerged as standards of care. In addition, clinical research is actively underway examining the long-term effects of these drugs and is exploring the effects of anti-inflammatory drugs and agents aimed at blocking and clearing amyloid plaques.

Several potential interventions could reduce the risk of physical disability, but none have been tested in RCTs among older diabetic people. In recent observational studies of diabetic adults, physical inactivity, obesity, depression, CHD, lower-extremity disease, and arthritis were identified as factors associated with physical disability. Structured exercise programs involving walking and strength and balance training have been associated with improved functional status and reduced incidence of disability among older adults. Weight loss has also been associated with improved physical function in obese people, but it is unclear whether weight loss is likely to improve long-term outcomes among obese older people with diabetes.

**Barriers to Primary Care Management**

Although the clinical goals and guidelines for people with diabetes are similar for older and younger adults, several factors make the care of older diabetic patients particularly complex. The functional status of older people with diabetes is more heterogeneous than that of younger people because the older population ranges from people with newly diagnosed diabetes to those with decades of poorly controlled diabetes. Some older people have few or no comorbid conditions, whereas others have years of diabetes-related complications.

Similarly, life expectancies vary considerably, which means that different interventions may have different value for different patients depending on their anticipated effect on quality of life. For frail older adults with diabetes who have a short life expectancy, substantial comorbidity, or significant difficulty adhering to treatment recommendations, aggressive targets for blood pressure, lipids, or glucose levels may not be appropriate or attainable. Moreover, aggressive management of these conditions may not provide the same benefit as observed for younger people and can instead result in harm, such as episodes of hypoglycemia or hypotension. The goals of therapy might instead be to enhance quality of life through less aggressive targets aimed at reducing and managing bothersome symptoms.

Polypharmacy is common among the elderly because of the desire to simultaneously manage glycemia, hyperlipidemia, hypertension, and other associated conditions. Yet polypharmacy can affect cognitive ability, physical functioning, and depression through drug-drug or drug-disease interactions. The use of medications, particularly those with sedating effects, is a risk factor for falls and cognitive impairment. Other medications have been associated with urinary incontinence, depression, and failure to thrive. One RCT found that withdrawal of psychotropic medications significantly reduced the risk of falling. For these reasons, it is important for clinicians to carefully review medications, have a clear rationale for why each medication is indicated, consider costs and dosing schedules when prescribing medications (once-daily dosing is generally preferred), and discuss the benefits and potential side effects of each medication.
with elderly patients and their family members or caregivers.

Depression is more common among people with diabetes than without it and may be a key mediator of the association between diabetes and cognitive or physical decline. Depression is also likely to impede diabetes self-management and to increase the risk for diabetes-related morbidity and death. Older adults have high rates of underdiagnosis and undertreatment of their depressive symptoms, and <10% of depressed older adults and <5% of older adults with high levels of depressive symptoms receive antidepressant medications. Evidence from two carefully conducted meta-analyses of RCTs revealed that pharmacological or psychological treatment of older adults (age >55 years) is effective in reducing depressive symptoms, and a systematic review of RCTs found similar findings among physically ill people.

Data on the relationship between screening for depression in the clinical setting and patient outcomes are mixed, however. One RCT found that middle-aged patients screened with a single question or a longer survey were significantly more likely to recover from depression than were patients not screened for depression, but mean improvement in depressive symptoms was not significantly different from the control group. Another partially RCT found no improvement in depression among patients aged ≥70 years who were screened by office staff before their initial visit.

Summary and Future Needs
The high cumulative incidence of cognitive decline, physical decline, and related geriatric syndromes among older diabetic adults indicates the need for more focused attention on clinical and public health approaches to reduce this burden. Inclusion of older segments of the population and measurement of functional outcomes in major diabetes intervention studies is a major step in this direction. Development of guidelines specific to the management of older patients with diabetes may also help reduce some of their functional decline.

Among the unanswered questions that warrant examination are when and how to prioritize interventions targeting blood pressure, glycemia, elevated lipids, and aspirin use and how to stratify older adults by their likelihood of risk or benefit from intensive therapies. The heterogeneity of older people with diabetes may mean that interventions that address screening, prevention, or treatment of age-associated syndromes such as cognitive or functional decline, depression, and disability may enhance diabetes management.

Finally, office-based and system-level approaches could improve long-term functioning of older people. These approaches include screening for dementia, impaired physical functioning, depression, and frailty to help focus treatment approaches, identify preventable causes, and better organize caregivers. Broader system-based approaches include case management, home geriatric assessment, and disease management programs. Systematic research into the effectiveness of these varied approaches will help prioritize their use and facilitate implementation in the form of public health policy.

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