Advances in Geriatrics

Laura Bonner, PhD and Suzanne Craft, PhD

Uncontrolled Diabetes Plus Hypertension: A Recipe for Dementia?

It's an all too familiar scenario: You have been treating "Mr. X," an 85-year-old man, for hypertension and diabetes for several years. Lately, however, you have been feeling very frustrated because his blood pressure has been rising, his hemoglobin A_{1c} (HbA_{1c}) level has exceeded 11%, and he seems not to appreciate the importance of taking his medications as prescribed. In fact, during his most recent appointment with you, he seemed forgetful and even mildly disoriented. You resolve that, next time you see him, you will administer a brief mental status examination to determine whether further evaluation of cognitive status is needed.

Diabetes and hypertension are independent risk factors for a host of unwanted outcomes, such as stroke, amputation, and early death. Furthermore, diabetes and hypertension—especially when poorly controlled and especially in combination with one another—are found increasingly to be key risk factors for Alzheimer disease (AD) and other forms of dementia. Because of the importance of AD and its impact on the lives of so many older adults, this topic is the focus of intense research attention throughout the scientific community. Several studies currently being conducted at the VA Puget Sound Health Care System Geriatric Research, Education and Clinical Center (VAPSHCS GRECC) in Seattle, WA are part of this research effort.

INGREDIENTS FOR POOR HEALTH

Hypertension, which is highly prevalent among VA patients (and Americans generally), increases the risk of cognitive impairment and dementia for many patients.[1,2] Diabetes, also a prevalent condition among the VA population, likewise puts patients at risk for dementia.[3] Diabetes also has been linked to mild cognitive impairment (MCI), which is defined as a decline in cognitive performance that can be detected by cognitive testing but that does not cause significant impairment in daily activities.[4] MCI is considered to be a risk factor for future development of dementia.

Unfortunately, hypertension and diabetes often are comorbid, and the combination may be especially dangerous, especially when either condition is poorly controlled.[5] Both clinical observation and physiologic research suggest that the combination of disorders constitutes a significant risk factor for many patients. When the brain is deprived of glucose (due to diabetes) and has suboptimal oxygen delivery (due to hypertension), neural circuits lack the ability to respond efficiently to cognitive demands.

Compounding the problem is the fact that patients with MCI may struggle to take medications as directed and may have significant problems following diet and exercise programs recommended by their health care providers.[6] These adherence challenges put patients at greater risk for disease complications and increased cognitive impairment. In this way, cognitive and vascular risk factors interact to create a dangerous cycle of worsening health (Figure).

CAN TREATMENT OF DIABETES AND HYPERTENSION PREVENT DEMENTIA?

Given the strong interrelationship between hypertension, diabetes, and cognitive impairment, many researchers and clinicians wonder whether effectively treating the first two can prevent or delay the third. A recent basic science study found lower neu-

Dr. Bonner is a psychologist and **Dr. Craft** is a neuropsychologist and the associate director, both at the VA Puget Sound Health Care System Geriatric Research, Education and Clinical Center, Seattle, WA. In addition, Dr. Bonner is an acting instructor and Dr. Craft is a professor, both in the department of psychiatry and behavioral sciences at the University of Washington School of Medicine, Seattle, WA.

The VHA's Geriatric Research, Education and Clinical Centers (GRECCs) are designed for the advancement and integration of research, education, and clinical achievements in geriatrics and gerontology throughout the VA health care system. Each GRECC focuses on particular aspects of the care of aging veterans and is at the forefront of geriatric research and clinical care. For more information on the GRECC program, visit the web site (http://www1.va.gov/grecc/). This column, which is contributed regularly by GRECC staff members, is coordinated and edited by Kenneth Shay, DDS, MS, director of geriatric programs for the VA Office of Geriatrics and Extended Care, VA Central Office, Washington, DC.

ritic plaque densities among patients with diabetes who had received insulin and oral hypoglycemic treatment than among those who had received only one or no medication.[7] At this time, diabetes treatment studies have not demonstrated definitively a reduced risk of dementia. A literature review performed in 2003 concluded that: "Future research on treatments for diabetes should include standardized assessments of cognitive function as outcome measures."[8] An ongoing study, the Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes Study (ACCORD-MIND), currently is examining this question.[9]

The results of recent, large-scale hypertension treatment studies also have been mixed,[10,11] but there is some evidence that treatment with antihypertensive agents can reduce the incidence of dementia. For example, the Systolic Hypertension in Europe (Syst-Eur) study and the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) both found that antihypertensive treatment reduced cognitive decline.[12,13] Although the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG) study found that antihypertensive treatment did not reduce cognitive decline, the authors note that the trial was terminated early for unrelated reasons (reduced incidence of stroke and reduced mortality), which may have obscured a longer-term effect on dementia.[14] Another trial, the Study on Cognition and Prognosis in the Elderly (SCOPE), found that treatment of hypertension with the angiotensin receptor blocker candesartan was associated with decreased decline in some but not all cognitive functions when compared with usual care (which could include antihypertensive medication).[15] While more research is required, the results of these studies suggest that control of hypertension has cognitive benefits.

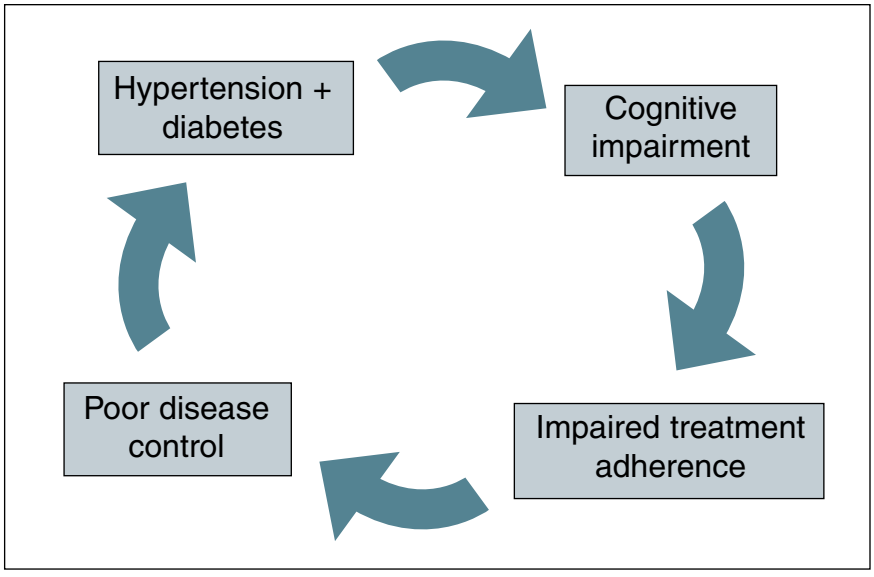

Figure. The cycle of worsening health that can result from the interaction of cognitive and vascular risk factors in patients with comorbid hypertension and diabetes.

CONTRIBUTIONS OF GRECC RESEARCH

Research conducted through the VAPSHCS GRECC's Memory Wellness Program has focused on the connections between diabetes, hypertension, and cognitive impairment for the past decade, including both basic science and treatment studies aimed at improving our understanding of the physiologic mechanisms at work in patients like "Mr. X."

Insulin action and cognitive function

A recent treatment study demonstrated that a six-month course of insulin sensitizing medication (rosiglitazone) improved cognitive performance in patients without diabetes who had AD or amnestic MCI.[16] These results suggest that subtle alterations in insulin action have a positive effect on cognitive function. Currently, the Memory Wellness Program is conducting a related, larger-scale study in which cognitively impaired patients without diabetes are randomly assigned to take rosiglitazone or placebo for 18 months and participate in cognitive testing at specified time points during and after the medication trial.

In another ongoing study, participants with AD or amnestic MCI take intranasal insulin or placebo for four months. Insulin administered using the device developed for this study is conducted directly to the brain and does not have significant systemic effects on plasma insulin or glucose levels. A pilot study showed acute improvement in verbal memory for patients with AD after one dose of intranasal insulin,[17] suggesting that insulin acts directly and rapidly to improve cognitive function.

Lifestyle factors

Two exciting studies are examining the effects of lifestyle factors—specifically, diet and exercise—on glucose metabolism and cognitive performance. In one recently completed study, participants with MCI took part in a supervised six-month

aerobic exercise program. Their cognitive test performance and glucose metabolism were then compared to that of a group of patients who participated only in a stretching program. Data from this study will be published soon. Another study examines the effects of diet on cognitive test performance, glucose metabolism, and other biomarkers. This ongoing study is comparing participants who are eating a low saturated fat and low glycemic index diet with others who are eating a high saturated fat and high glycemic index diet to determine whether changes in insulin activity caused by dietary macronutrient intake affect cognition and biomarkers of AD. Together, these studies address important questions about the relationships between lifestyle factors, overall health, and cognitive impairment.

Care management

A new translational research study, conducted by the VA's VISN 20 and the VAPSHCS GRECC, will intervene in the care of patients who have both diabetes and hypertension and in whom one or both conditions are poorly controlled. These patients will be tested for cognitive impairment, including either dementia or MCI. Patients with cognitive impairment will be randomly assigned to take part in a care management intervention or to continue receiving usual care. In the intervention group, patients and caregivers will work with a VA nurse care manager to improve treatment adherence and address other needs. Patients in the usual care group will continue to receive care from their regular VA primary care providers but will not work with the nurse care manager. The researchers predict that patients assigned to the care management program will exhibit improved cognitive performance and physical health compared to those assigned to the usual care group at the end of the six-month intervention period.

WHAT CAN WE DO NOW?

Our goal at the VAPSHCS GRECC is to conduct research that will lead to effective preventive measures in the future. But what can a primary care provider do right now to help prevent dementia in patients at risk? Our studies suggest that keeping blood pressure and diabetes under control will benefit cognition as well as overall health. If a patient seems to be developing problems with medication adherence, investigation of his or her mental status may be indicated. Our hope is to encourage patients to maintain a healthy body and a healthy brain.

Author disclosures

Dr. Craft reports being a consultant for and receiving grant support from GlaxoSmithKline. Dr. Bonner reports no actual or potential conflicts of interest with regard to this column.

Disclaimer

The opinions expressed herein are those of the authors and do not necessarily reflect those of Federal Practitioner, *Quadrant HealthCom Inc., the U.S. government, or any of its agencies. This article may discuss unlabeled or investigational use of certain drugs. Please review complete prescribing information for specific drugs or drug combinations—including indications, contraindications, warnings, and adverse effects—before administering pharmacologic therapy to patients.*

REFERENCES

1. Reitz C, Tang MX, Manly J, Mayeux R, Luchsinger JA. Hypertension and the risk of mild cognitive impairment. *Arch Neurol*. 2007:64(12):1734–1740.
2. Li G, Rhew IC, Shofer JB, et al. Age-varying association between blood pressure and risk of dementia in those aged 65 and older: A community-based prospective cohort study. *J Am Geriatr Soc*. 2007;55(8):1161–1167.
3. Whitmer RA. Type 2 diabetes and risk of cognitive impairment and dementia. *Curr Neurol Neurosci Rep*. 2007;7(5):373–380.
4. Roberts RO, Geda YE, Knopman DS, et al. Association of duration and severity of diabetes mellitus with mild cognitive impairment. *Arch Neurol*. 2008;65(8):1066–1073.
5. Elias PK, Elias MF, D'Agostino RB, et al. NIDDM and blood pressure as risk factors for poor cognitive performance. The Framingham Study. *Diabetes Care*. 1997;20(9):1388–1395.
6. Sinclair AJ, Girling AJ, Bayer AJ. Cognitive dysfunction in older subjects with diabetes mellitus: Impact on diabetes self-management and use of care services. All Wales Research into Elderly (AWARE) Study. *Diabetes Res Clin Pract*. 2000;50(3):203–212.
7. Beeri MS, Schmeidler J, Silverman JM, et al; Insulin in combination with other diabetes medication is associated with less Alzheimer neuropathology. *Neurology*. 2008;71(10):750–757.
8. Areosa SA, Grimely EV. Effect of the treatment of Type II diabetes mellitus on the development of cognitive impairment and dementia. *Cochrane Database Syst Rev*. 2002;(4):CD003804.
9. Williamson JD, Miller ME, Bryan RN, et al; and ACCORD Study Group. The Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes Study (ACCORD-MIND): Rationale, design, and methods. *Am J Cardiol*. 2007;99(12A):112i–122i.
10. McGuinness B, Todd S, Passmore P, Bullock R. The effects of blood pressure lowering on development of cognitive impairment and dementia in patients without apparent prior cerebrovascular disease. *Cochrane Database Syst Rev*. 2006;(2): CD004034.
11. Poon IO. Effects of antihypertensive drug treatment on the risk of dementia and cognitive impairment. *Pharmacotherapy*. 2008;28(3):366–375.
12. Forette F, Seux ML, Staessen JA, et al; for Systolic Hypertension in Europe Investigators. The prevention of dementia with antihypertensive treatment: New evidence from the Systolic Hypertension in Europe (Syst-Eur) study. *Arch Intern Med*. 2002;162(18):2046–2052.
13. Tzourio C, Anderson C, Chapman N, et al; and PROGRESS Collaborative Group. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. *Arch Intern Med*. 2003;163(9):1069–1075.
14. Peters R, Beckett N, Forette F, et al; for HYVET Investigators. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): A double-blind, placebo controlled trial. *Lancet Neurol*. 2008;7(8):683–689.
15. Saxby BK, Harrington F, Wesnes KA, McKeith IG, Ford GA. Candesartan and cognitive decline in older patients with hypertension: A substudy of the SCOPE trial. *Neurology*. 2008;70(19 pt 2):1858–1866.
16. Watson GS, Cholerton BA, Reger MA, et al. Preserved cognition in patients with early Alzheimer disease and amnestic mild cognitive impairment during treatment with rosiglitazone: A preliminary study. *Am J Geriatr Psychiatry*. 2005;13(11):950–958.
17. Reger MA, Watson GS, Green PS, et al. Intranasal insulin administration dose-dependently modulates verbal memory and plasma amyloid-beta in memory-impaired older adults. *J Alzheimers Dis*. 2008;13(3):323–331.