Cognitive Dysfunction in Older Adults With Diabetes: What a Clinician Needs to Know

Medha N. Munshi

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One of the challenges of managing older adults with diabetes is the individualization of care in people with multiple comorbid conditions. Although macrovascular and microvascular complications of diabetes are well recognized, there is a lack of awareness regarding other conditions such as cognitive dysfunction, depression, and physical disabilities. Cognitive dysfunction is of particular importance because of its impact on self-care and quality of life. In this Perspective, I discuss common and practical questions faced by clinicians managing diabetes in older adults who also have cognitive dysfunction.

As the population ages, all clinicians, whether they are primary care providers or specialists, are faced with challenges on how to manage diabetes in the context of many other coexisting conditions. Although patient-centric management strategies are recommended for everyone, some age-related conditions are not well understood and their impact on diabetes management in the aging population is still evolving. Traditional diabetes management strategies stress the role of the patient as an important member of the diabetes management team and focus on the self-care education needed to care for diabetes and related syndromes. Thus, the presence of cognitive dysfunction (also commonly referred to as cognitive impairment) is an important condition to recognize as it interferes with patients' participation in their diabetes management. Cognitive dysfunction is a broad term that includes many domains, such as memory, learning, mental flexibility, attention, and executive function. In addition, patients with cognitive dysfunction can be on a spectrum that extends from a mild cognitive impairment (defined as cognitive dysfunction without difficulty performing daily activities) to severe dysfunction (commonly referred to as dementia). Although mild cognitive dysfunction may not cause difficulty in self-management activities in many patients, progression of this condition needs to be carefully observed. Mild cognitive impairment also puts the patient at risk for delirium, which is a sudden worsening in the cognitive function in the presence of acute medical illness. For patients with diabetes, executive functions are particularly important as they involve behaviors, such as insight into a particular problem, problem-solving, judgment, stopping or changing old habits, and starting new habits. All of these behaviors are important when patients are asked to do complex tasks such as matching insulin dose with carbohydrate content, predicting the impact of physical activity on blood glucose, or even recognizing and treating hypoglycemia appropriately. In the younger population, acute cognitive dysfunction is typically seen as an immediate manifestation of hypoglycemia. In the older population, in addition to acute cognitive dysfunction during hypoglycemic episodes, there is also the long-term impact of both hyperglycemia and hypoglycemia on cognitive function. In this Perspective, I will discuss important aspects of managing diabetes in the older population with coexisting cognitive dysfunction.

Beth Israel Deaconess Medical Center, Joslin Diabetes Center, Harvard Medical School, Boston, MA

Corresponding author: Medha N. Munshi, mmunshi@bidmc.harvard.edu.

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IS DIABETES ASSOCIATED WITH COGNITIVE DYSFUNCTION IN OLDER ADULTS?

Diabetes is a risk factor for the development of dementia of both vascular as well as neurodegenerative (Alzheimer) etiology. Type 2 diabetes is associated with approximately a 1.5- to 2.5-fold increase in the risk of dementia (1,2). A large community-based prospective cohort study followed patients over a 20-year period and found that diabetes in midlife was associated with a 19% greater cognitive decline over a 20-year period. Prediabetes, poor control, and longer duration of the disease were associated with greater late-life cognitive decline (3). The prevalence of dementia in type 1 diabetes is less clear. A recent Kaiser Permanente Northern California registry analysis found an 80% (hazard ratio 1.8) higher likelihood of developing cognitive dysfunction in people with type 1 diabetes, compared with those without diabetes (4). A smaller cohort study of 200 older patients with type 1 diabetes found a 35%–44% prevalence of cognitive dysfunction (5). In general, the etiology of cognitive dysfunction in the aging population is likely to be the combination of ischemic and degenerative pathology (6). In vascular dementia, small vessel disease exacerbated by diabetes affects cognitive function. It is also believed that insulin regulates neurons in the central nervous system and affects amyloid β metabolism, in addition to many other effects, which accelerates Alzheimer-related pathology (7).

Although cognitive dysfunction is associated with both type 1 and type 2 diabetes, there are several distinct differences observed in the domains of cognition affected in patients with these two types. Patients with type 1 diabetes are more likely to have diminished mental flexibility and slowing of mental speed, whereas learning and memory are largely not affected (8). Patients with type 2 diabetes show decline in executive function, memory, learning, attention, and psychomotor efficiency (9,10). Imaging studies are also distinctive in these two types of diabetes. MRI studies in a small group of patients have shown that the cognitive profile and MRI rating of patients with type 1 diabetes of more than 30 years of duration match that of type 2 diabetes of around 7 years of duration (11). This finding might be due to the fact that the patients with type 2 diabetes are predisposed to both vascular and Alzheimer types of dementia. MRI studies of patients with type 2 diabetes have shown atrophy and vascular lesions, suggesting this additive effect (12).

Aging also has an independent impact on patients with diabetes. A longitudinal study of asymptomatic older patients over the course of 6 years showed increased brain volume loss with aging and elevated A1C, suggesting a clustering impact of the metabolic syndrome in the aging population (13). So far, it seems that the risk of cognitive dysfunction in type 2 diabetes may be influenced by glycemic control, hypoglycemia, inflammation, depression, and macro- and microvascular pathology (14). The cumulative impact of these conditions on the vascular etiology may further decrease the threshold at which cognition is affected by other neurological conditions in the aging brain. In patients with type 1 diabetes, it seems as though diabetes has a lesser impact on cognitive dysfunction than those patients with type 2 diabetes. Although patients with type 1 diabetes performed lower than age-matched control subjects, the test results showed that the cognitive test values remained in the normal range (15). Thus, the cognitive decline in patients with type 1 diabetes may be mild and may not interfere with their functionality until later years, when other aging-related factors become important.

HOW DOES COGNITIVE DYSFUNCTION IMPACT DIABETES?

The presence of cognitive dysfunction has an impact on the risk of both hypoglycemia and hyperglycemia in patients with diabetes.

Hypoglycemia

The impact of cognitive dysfunction on hypoglycemia is most critical due to its poor consequences in the older population. There is a bidirectional relationship between dementia and the risk of hypoglycemia. In a prospective population-based study, patients with any hypoglycemic episode had a twofold higher risk of developing dementia (16). Similarly, patients with dementia had a three times higher risk of having subsequent hypoglycemic episodes. The association between cognitive dysfunction and the risk of hypoglycemia is seen in patients with both type 1 and type 2 diabetes. In a post hoc analysis of a large prospective cohort of the Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) trial, cognitive decline over a 20-month period was associated with an increased risk of subsequent hypoglycemia in patients with type 2 diabetes, whether these patients were in the standard or an intensive glycemic control group (17). Other cross-sectional population-based studies in patients with type 2 diabetes have also shown an association between a history of severe hypoglycemia and poor cognitive function in later life (18,19). In a younger cohort, the Diabetes Control and Complications Trial (DCCT) follow-up study over 18 years has been reassuring in showing no evidence of long-term cognitive decline in a large group of patients with type 1 diabetes with a history of severe hypoglycemia (20). However, recent studies have shown a higher prevalence of cognitive dysfunction in older patients (>60 years of age) with type 1 diabetes (5).

Hyperglycemia

There has been some evidence to also suggest a bidirectional relationship between the degree of hyperglycemia and cognitive dysfunction. Presence of cognitive dysfunction is associated with poor glycemic control (21). As described in the previous section, this is likely due to the patients' inability to perform various components of self-management. On the other hand, hyperglycemia-mediated advanced glycosylated end product production and oxidative stresses are cited as the factors that can damage neurons and vascular endothelium leading to cognitive dysfunction (22). However, more work is needed to identify the impact of glycemic and nonglycemic factors associated with diabetes on the progression of cognitive dysfunction. Patients with type 1 diabetes enrolled in the DCCT trial were reassessed after 18 years and this assessment showed that long-term poor metabolic control was associated with cognitive decline (23). The ACCORD-MIND study evaluated this relationship in patients with type 2 diabetes and also showed an association between the poor glycemic control and lower cognitive function (24). The decline in cognitive function was the same in this population, whether

the patients were treated with an intensive regimen or standard care (25). However, this association between A1C and cognitive function was not observed in another large prospective cohort study (26). Small studies have also evaluated the impact of glucose excursions on cognitive function and found an association between the diurnal variation and postprandial elevation of glucose levels with a cognitive decline (27,28). Some preliminary data suggest short-term improvement of cognitive function in patients with type 2 diabetes treated with intranasal insulin via the impact on anterior brain vasodilatation (29). Further research is needed to understand this area more clearly so that a targeted approach can be developed for the older adults at risk for cognitive dysfunction.

HOW DO PATIENTS WITH DIABETES PRESENT WITH COMORBID COGNITIVE DYSFUNCTION?

Unlike other chronic diseases, diabetes self-care involves many behaviors that require various degrees of cognitive pliability and insight to perform proper self-care coordination and planning. Glucose monitoring, medications and/or insulin injections, pattern management, and diet and exercise timing require participation from different domains of cognitive function. In addition, the recognition, treatment, and prevention of hypoglycemia, which are critical for the older population, also depend in large part on having intact cognition.

The reason a clinician needs to recognize different domains of cognition affected in patients with diabetes is to understand which self-care behavior will be affected in that individual. Table 1 shows different behaviors affected by cognitive dysfunction, their impact on self-care, and the strategies to improve diabetes management in these patients. The cognitive domain affected, in turn, impacts the clinical presentation (30). For example, a patient with memory problems may forget to take insulin doses, forget to take medications/insulin on time, or forget to eat on time. In general, a patient with executive dysfunction has preserved working memory and is able to remember the instructions given by the provider. However, it is difficult for him or her to stop old behaviors and start a new behavior. Thus, the behavior in a patient with executive dysfunction might be misconstrued as "noncompliance" when the changes recommended by the providers are not actually integrated into the day-to-day practice. In small studies, executive dysfunction was associated with adherence-related issues and difficulty learning to safely administer an insulin injection, whereas a deficit in general cognition was associated with missed clinic appointments and inaccuracies in blood glucose reporting (31–33). Cognitively impaired patients using insulin are more likely to not know what to do in the event of low blood glucose or how to manage medication on sick days (34). Patients with diminished mental flexibility and processing speed may do well with a simple regimen but may fail if the regimen is too complex. In general, older patients with diabetes with cognitive dysfunction are less likely to be involved in diabetes self-care and glucose monitoring compared with age-matched control subjects (35).

Other comorbidities associated with aging and diabetes also add to the burden of cognitive impairment and its impact on self-care abilities. For example, depression is associated with a greater decline in cognitive function in patients with type 2 diabetes (36). Depression also can independently negatively impact the motivation to practice self-care. In addition, conditions such as vision impairment, hearing loss, physical disabilities, and chronic pain, even in a mild form, may add to difficulty performing self-care in the presence of cognitive dysfunction.

Thus, the clinical presentation of patients with cognitive dysfunction and associated comorbidities is frequently subtle but has a large impact on overall diabetes management. That is why periodic assessment of these conditions (the so-called geriatric syndrome) is recommended in all older patients with diabetes (37).

HOW DO WE RECOGNIZE COGNITIVE DYSFUNCTION?

As the aging patient population gets medically more complex, the time constraints seem to get worse for the clinicians caring for them in the clinics. Medicare guidelines recommend that the primary care physician should perform some type of cognitive assessment in all individuals over 65 years of age as part of an annual wellness visit. This is an ideal situation to identify gradual change in cognition in an individual over the years. In clinical practice, moderate-to-severe decline in cognition is usually identified by patients and/or their family members or caregivers. It is important that we pay attention to these complaints and assess how they impact diabetes management. Mild cognitive dysfunction in many older individuals who are on a simple diabetes regimen may remain unrecognized and may not interfere with self-care. However, mild or subtle dysfunctions in patients who are on complex insulin regimens are more likely to interfere with their ability to perform self-management. Thus, attention should be paid and cognitive function should be assessed in the population on a complex regimen who are having difficulty managing their diabetes (38,39). Executive dysfunction is frequently subtle in its presentation and often goes unrecognized by patients themselves, their family members, and clinicians. Executive function includes behaviors such as judgment, problem-solving, starting new behaviors, or stopping old behaviors. These behaviors are critical when patients need to match carbohydrate with the insulin dose, pick the right time and dose for insulin injections and diet, or identify the impact of physical activity on glucose levels. Thus, it is important to identify executive dysfunction before prescribing a complicated insulin regimen or making new major changes in regimen. Various short screening tests, such as Montreal Cognitive Assessment (MoCA), Mini-Cog, or Mini-Mental State Examination (MMSE), are useful to assess overall cognition, although MMSE typically misses executive dysfunction (38–40). MoCA is available in the public domain. The Mini-Cog is a short screening tool that is found to be useful in a busy clinical practice to screen for cognitive dysfunction including executive dysfunction (40). It combines a three-word recall and a clock-drawing test.

However, the specialist clinicians may not have access to cognitive evaluations performed at other facilities and may not be able to perform screening regularly due to time constraints. For these clinicians, the challenge in managing older patients with diabetes is to identify cognitive decline when these problems start to interfere with diabetes management. Certain clinical changes

Table 1—Clinical presentations of patients with diabetes and cognitive dysfunction and strategies for management

Affected behavior	Impact on diabetes self-care	Strategies to improve management
Memory loss	• Forget to monitor glucose	• Decrease frequency of self-monitoring, check when caregivers are available
	• Forget to take medications	• Pillboxes, alarms
	• Forget to take insulin injections	• Long-acting formulations to decrease frequency of pills/day
	• Forget to eat on time	• Decrease number of insulin injections
	• Forget to eat before exercise	• Involve caregivers
	• Forget to attend clinic visits	• Choose supervised exercise programs
		• More than one clinic visit reminders
Problem-solving difficulty	• Seems to remember instructions but unable to integrate into practice	• Repeated education and instructions at each visit
	• Unable to recognize or treat hypoglycemia	• Avoid labels such as "noncompliant"
		• Make small changes at a time
		• Avoid complex regimens
Difficulty stopping old behavior and starting new behavior	• Seems to be "stubborn"	• Avoid changes if possible
	• Refuses any new therapy	• Ask for help from caregivers with reminders when behavior is being changed
	• Errors occur when old routines are changed	• May need to restrict access to insulin (especially in type 1 patients) if too much insulin is taken due to old habits
Difficulty with mental flexibility	• Feel anxious regarding "failing" the treatment plans	• Avoid difficult tasks such as sliding scales
	• Too much focus on diabetes management	• Simplify regimen
		• Decrease the need for frequent snacks or monitoring

could serve as red flags suggesting the possibility of cognitive decline and the need for further assessment or referral to appropriate providers such as a neurologist, a psychiatrist, or a geriatrician. In older patients, sudden worsening of glycemic control in a patient with a good track record, difficulty achieving glycemic goals in spite of reasonable efforts, feeling overwhelmed, disease-related distress, or new nonadherence with monitoring and medications may suggest cognitive decline. Whether patients are identified as having cognitive dysfunction by screening or by the clinical picture, they should be referred for definitive evaluation of their cognitive function for diagnosis and management.

HOW SHOULD A CLINICIAN APPROACH THE CARE OF AN OLDER PATIENT WITH DIABETES AND COGNITIVE DYSFUNCTION?

Management of patients with diabetes and cognitive dysfunction raises two related questions.

Can We Prevent Further Decline in Cognitive Function in the Patient With Diabetes?

At present, it is not clear whether improving glycemic control or using specific therapeutic agents can improve the risk of cognitive decline. The studies to evaluate the impact of glycemic control on the progression of cognitive impairment in patients with diabetes have shown conflicting results. Some of these differences in the results may be due to the difference in the age of the cohorts. A study of a middle-aged population showed that the management of prediabetes and diabetes with tight glycemic control during the midlife may protect against cognitive decline in late life (3). These results are encouraging and strengthen recommendations for tighter glycemic control in middle-aged populations with diabetes (29). On the other hand, there is clear evidence that the intensive control of blood glucose, blood pressure, or cholesterol levels in the older population is not beneficial in preventing cognitive decline (25,41). Intensive treatment regimens require diligent self-care and insight into insulin function and its relationship with carbohydrates and physical activity. In patients with cognitive dysfunction, if patients' coping abilities are limited, the complex regimens may lead to treatment failure and hypoglycemia, which in turn increases the risk of cognitive decline. Thus, with the current level of evidence, it is prudent to avoid both stricter glycemic control and extreme glucose levels in the older population.

Whether cognitive decline can be prevented at the level of prediabetes or metabolic syndrome is unclear and is the focus of several studies. The roles of medications, nutrition, and nutritional supplements are being investigated and have shown some initial beneficial effects in small studies (42–44). However, larger studies in this area are needed to help in the development of clear recommendations and guidelines.

Are There Better Strategies to Manage Diabetes in the Presence of Cognitive Dysfunction?

Before discussing better strategies for managing diabetes in older patients with cognitive decline, it is important to define the appropriate glycemic goals in these patients.

Glycemic Goals

Recently, there is an increasing discomfort with the use of A1C as a sole parameter to define glycemic goals in the older population. Studies have shown that A1C values in the older population may not reflect the same estimated mean glucose as in the younger population.

Table 2—Simplification strategies for older patients with diabetes

Difficulty with regimens	Possible strategies
Forget to take mealtime insulin	• Use basal insulin once daily to control fasting glucose. • Replace mealtime insulin with once-daily noninsulin agents to control postprandial hyperglycemia (e.g., long-acting formulation of metformin or sulfonylurea, pioglitazone, once-a-day GLP-1 analog, dipeptidyl peptidase 4 inhibitors, sodium–glucose cotransporter 2 inhibitors).
Make errors in insulin scale	• Avoid insulin sliding scale. Replace with fixed insulin dose before meals. • If scale is not avoidable, use simple one- or two-dose scale. For example, glucose >250 mg/dL, use two units; glucose >350 mg/dL, use four units.
Hypoglycemia at fasting but high glucose during the daytime	• Use basal insulin in the morning and titrate the dose up to get fasting glucose control the next morning. • Combine insulin with noninsulin agents as described above for postprandial glucose control during the day.
Need caregiver for insulin injections	• Choose strategies with less frequent insulin administration. For example, use basal insulin in the morning to titrate for fasting glucose control. At the same time, use long-acting oral agents or mixed insulin in the morning to control postprandial glucose during the daytime. • Coordinate with caregivers to see when they are available to assist the patient.
Forget to take medications scheduled several times/day	• Use pillbox. • Try long-acting formulations once daily.

Possible reasons for this discrepancy are the commonly present comorbidities that impact red cell life span (e.g., anemia, uremia, renal dysfunction, blood transfusion, erythropoietin therapy) (45,46). In addition, A1C level does not reflect glucose excursions and variability. Continuous glucose monitoring used in the studies involving older adults has shown that higher A1C levels (liberating the glycemic goals) are not associated with a lower risk of hypoglycemia (47). This scenario can be worse in patients with cognitive dysfunction on complex insulin regimens who may have wide glucose excursions. In addition, excursions leading to hypoglycemia can cause further decline in cognition. Thus, it is prudent to avoid A1C as the sole measure of glycemic goal in this population. In those older patients who are suspected to have comorbid conditions that make A1C unreliable, self-monitoring of glucose levels should be considered to define glycemic goals.

A consensus report on the management of diabetes described three variables that need to be considered before goals are decided (37): moderate-to-severe comorbidities, cognitive function, and functional status. Given these three factors, a patient can be considered healthy, complex/intermediate, or very complex/poor health category. The glycemic goals (A1C) then can be <7.5%, <8%, or <8.5%. Thus, in patients with mild-to-moderate cognitive dysfunction, an A1C goal of <8% is recommended. An A1C goal of <8.5% is recommended for those individuals with severe cognitive dysfunction.

Treatment Strategies

Although the goal-setting framework described here considers the patient's overall health, it does not consider the type of treatment modality used to take patients to their goals. As we know, some agents, such as insulin and sulfonylurea, are more dangerous for older patients than other glucose-lowering medications because of their higher risk of hypoglycemia and subsequent risk of cognitive dysfunction.

When deciding on a treatment strategy, consideration of cognitive function, caregiver support, and coexisting comorbidities are important. Using medications with a lower risk of hypoglycemia is one clear way to approach this problem in patients with type 2 diabetes. Contraindications because of other comorbidities, such as renal and hepatic dysfunction, and the high cost of new classes of drugs are barriers to this approach. When medications with a low risk of hypoglycemia are not an option, insulin can be used safely at all ages in patients with diabetes and have fewer contraindications than other noninsulin agents. However, insulin can also be a dangerous medication, particularly in older patients with cognitive dysfunction who may make unrecognized errors in doses, timing of injections, or timing

Table 3—Take-home message for management of older patients with diabetes and cognitive dysfunction

- Consider cognitive dysfunction when older adults fail to perform self-care without obvious reasons.
- Older patients with cognitive dysfunction may fail to identify, report, or treat hypoglycemic episodes correctly. To avoid poor outcomes, aim for the best glycemic goal that can be achieved without putting the patient at risk for hypoglycemia.
- Select glucose-lowering agents with a low risk of hypoglycemia, if possible.
- Assess and modify glycemic goals periodically based on changes in overall health.
- Avoid the use of A1C as a sole measure of glycemic control. Finger-stick readings may provide a more accurate assessment of current blood glucose levels.
- A simplified regimen can improve the risk of hypoglycemia without compromising glycemic control and may improve quality of life.
- Repeated education in areas that are critical for safety, such as hypoglycemia recognition and treatment, is important.
- Caregivers should be educated and their welfare and convenience should be incorporated into treatment strategies.

and content of meals. These errors can lead to wide glucose excursions, which are more dangerous in the older population with a high risk of hypoglycemic unawareness. However, insulin can be used safely in appropriate settings, such as if caregivers are available or if the patient is in a supervised setting such as a long-term care facility (48).

In patients who need insulin therapy, simplification, also known as de-intensification of the regimen, is generally recommended in all frail patients, especially if they have cognitive dysfunction (37,49). However, the practice has not caught up with the recommendations as shown by large observational studies showing unnecessary intensive control in patients with diabetes and dementia (50–52). The lost opportunity to simplify regimens is possibly due to the lack of guidance or algorithm that directs nonspecialist clinicians who care for the majority of these frail older patients with diabetes. We have developed a simplification algorithm that can be used to de-intensify complex insulin regimens by continuing basal insulin and replacing mealtime insulin with noninsulin agents (53). The simplification regimen in this study led to decreased duration of hypoglycemia in these patients without compromising glycemic control. The use of basal insulin to lower the baseline and use of noninsulin agents to control postmeal hyperglycemia is an effective way to manage diabetes and lower the risk of hypoglycemia and glucose excursions. The use of extended-release formulations for oral or noninsulin injectable agents is also useful and decreases the frequency of dosing, resulting in a decreased chance of missing doses. Some clinically useful strategies for patients with advancing cognitive dysfunction are shown in Table 2. It is important to remember that such strategies are unlikely to result in excellent glycemic control. It is meant to avoid severe hypo- and hyperglycemic episodes and to improve stress and quality of life in patients who are unable to cope with complex regimens.

With advances in the past few decades, we now see a larger number of patients with type 1 diabetes who are aging successfully and facing the new challenges that aging brings. There are subtle differences in how management issues present in patients with type 1 versus type 2 diabetes with cognitive decline. Patients with type 1 diabetes are typically proactive in their disease management and highly disciplined. Cognitive dysfunction in these patients creates significant distress for the first time in their lives; they suddenly feel a "lack of control" over the disease they have managed for many decades. The addition of autonomic dysfunction, gastropathy, or neuropathy may result in wider glucose excursions. These patients are usually more afraid of hyperglycemia than hypoglycemia—both of which they have managed for many years. However, cognitive dysfunction in older adults with type 1 diabetes has been found to be associated with hypoglycemic unawareness and glucose variability (5), which in turn increases the risk of severe hypoglycemia (54). The need for goal changes to avoid hypoglycemia and accept some hyperglycemia can be very difficult for many of these patients. It is important that clinicians recognize this need to "not let go" and take an approach with patience providing repeated education. Family members and caregivers become important for supervision to avoid errors in insulin dosing and to avoid severe hypoglycemia with falls and unconsciousness. With newer advances in technology, the careful use of continuous glucose monitoring and Bluetooth-enabled insulin pens may help patients with type 1 diabetes manage their disease safely.

Finally, it is important to remember that diabetes and its self-care requirement have an impact on quality of life in all age-groups. However, the presence of cognitive dysfunction significantly decreases the quality of life because of the difficulty in participating in self-care and other behavioral changes that frequently accompany this disease. Management plans that overwhelm patients physically, emotionally, or financially should be carefully avoided. In addition, it is important to care for the caregivers who are also distressed and overwhelmed. Treatment regimens should also consider convenience and the ability of the caregivers of older individuals with cognitive dysfunction.

SUMMARY

Identification of cognitive dysfunction and modification of treatment regimens to accommodate it in older patients is important for successful diabetes management. Table 3 delineates the overarching principles of managing diabetes in the older population with coexisting cognitive dysfunction.

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