Diabetes and Aging: Unique Considerations and Goals of Care

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Diabetes in older adults is a growing public health burden. The unprecedented aging of the world's population is a major contributor to the diabetes epidemic, and older adults represent one of the fastest growing segments of the diabetes population. Of impending concern is that these numbers are projected to grow dramatically over the next few decades (1,2). Almost one-third of U.S. adults over the age of 65 years have diabetes. Approximately half of those are undiagnosed, and an additional one-third of older adults have prediabetes (3). Persons with diabetes today are living much longer compared with those in the past. We also recognize that management of older adults with diabetes is clearly more complicated given the observation that they commonly have multiple coexisting medical conditions that can impact clinical management. While rates of diabetes-related complications have declined overall in the general population, the incidence rates of macrovascular complications such as acute myocardial infarction and stroke continue to be the highest in older age-groups. These individuals also have the highest rate of diabetes-related end-stage renal disease (4).

Heterogeneity in the health status of older adults (ranging from robust and otherwise healthy individuals to those with frailty and multiple comorbid conditions) and the paucity of evidence from clinical trials represent a challenge to making generalized treatment recommendations for older adults. Although many more individuals with type 1 diabetes are living longer (5), type 2 diabetes remains the most common type in older age-groups. Furthermore, older adults with diabetes may either have elderly onset disease (diagnosed at age 65 years or older) or long-standing diabetes with onset in middle age or earlier years (6), adding to the complexity of managing diabetes in older adults. Consequently, the American Diabetes Association (ADA) organized a Consensus Development Conference on Diabetes and Older Adults in February 2012. A Consensus Report was published that same year emphasizing the importance of individualizing treatment recommendations for older adults with diabetes and, in particular, to consider the patient's life expectancy, comorbidities, functional status, and risk for hypoglycemia when determining goals of care (7).

Thus, given the importance of the topic of diabetes in older adults, our editorial team has featured 11 articles in this issue of *Diabetes Care* that provide a comprehensive overview of the topic. In this issue, we feature narratives that report on novel research and expert perspectives related to diabetes and aging. The topics range from addressing hospital management of older adults, including innovative methods to measure the quality of care offered to older patients hospitalized with diabetes, to the safety of specific glucose-lowering therapies and potential consequences of overtreatment (i.e., hypoglycemia) of diabetes in older patients. We also feature narratives discussing the importance of addressing cognitive status in clinical practice, the significant financial burden of treating diabetes in the elderly, and a review of the pathophysiology of diabetes in aging that may impact goals of care for this population—including the determination of glycemic targets and strategies to reduce cardiovascular disease and mortality.

Impaired glucose intolerance is associated with aging, and postprandial hyperglycemia is a prominent characteristic of type 2 diabetes in older adults (8). In fact, oral glucose tolerance testing detects many more older persons with undiagnosed diabetes who would otherwise be missed compared to using fasting plasma glucose testing alone (3). Age-related insulin resistance is associated with changes in body composition and physical inactivity

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among other factors (9), which may partially explain the greatest relative benefits of the intensive lifestyle intervention observed among older participants in the Diabetes Prevention Program (DPP) (10). In this issue of *Diabetes Care*, Lee and Halter (11) provide an updated current perspective on the pathophysiology of type 2 diabetes among older adults and the implications for hyperglycemia management in this population. Specifically, they state that "usual defects contributing to type 2 diabetes are further complicated by the natural physiological changes associated with aging as well as comorbidities and functional impairments often present in older people."

Though older adults have the highest prevalence of diabetes of any age-group, these individuals have traditionally not been included in randomized controlled trials for diabetes treatments. As a result, existing clinical trial data on glucose control may not be directly applicable or generalizable to most older adults with diabetes. The UK Prospective Diabetes Study (UKPDS) enrolled middle-aged adults with newly diagnosed type 2 diabetes and excluded those aged >65 years (12), limiting interpretation of these results in older adults. Of greater concern, an analysis of 440 clinical trials among persons with type 2 diabetes suggests that older adults continue to be excluded from two-thirds of these trials (13), further hindering the ability to generalize ongoing trial results to the older population with diabetes. Following the publication of the main UKPDS results, three major randomized controlled trials (the Action to Control Cardiovascular Risk in Diabetes [ACCORD] trial, the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation [ADVANCE] trial, and the Veterans Affairs Diabetes Trial [VADT]) specifically investigated the role of glycemic control (<6.0 or <6.5%) in preventing cardiovascular events in middle-aged and older patients with type 2 diabetes. Mean ages at enrollment were in the 60s, and most participants had established diabetes for approximately a decade. While the ACCORD trial was terminated early because of unexpectedly excessive deaths in the intensive glucose control arm (14), the ADVANCE and VADT trials found no statistically significant effect of intensive glucose control on major cardiovascular events or death (15,16).

In the absence of randomized controlled trials specifically in older adults with diabetes, more sophisticated observational studies have sought to explore differences in cardiovascular outcomes for older adults with diabetes at lower versus higher HbA_{1c} targets. In the article by Palta et al. in this issue (17), the authors examine the associations between HbA_{1c} and mortality specifically in a nationally representative population of older U.S. adults. They report that the risk of all-cause, cardiovascular, and cancer mortality appeared to increase significantly among older adults with diabetes and an HbA_{1c} >8.0%. The authors also state that their results support current recommendations for older adults with diabetes put forth by the ADA and other professional societies, suggesting a need for individualized HbA_{1c} targets and less aggressive glycemic goals for older adults with diabetes based on the patient's characteristics and health status.

In addition to macrovascular and microvascular diseases, geriatric syndromes occur at higher frequency in older adults with diabetes and may affect health outcomes, including quality of life, that are particularly important in aging (18). These geriatric syndromes include falls and fractures, depression, polypharmacy, vision and hearing impairment, and urinary incontinence. Persons with diabetes also have greater declines in functional status and muscle loss with aging (9). Consideration of these geriatric syndromes is a unique aspect of care for the older population. The cognitive status of the patient is particularly important to consider in the older adult with diabetes and can dramatically impact the ability to self-manage diabetes. In the article by Munshi (19), the need for increased awareness and recognition of cognitive dysfunction is emphasized. Common challenges faced by clinicians and suggested strategies to improve the management of diabetes in older adults with cognitive dysfunction are described.

The risks of overtreatment of hyperglycemia in older adults are significant and include hypoglycemia and increased treatment burden. Age may affect counterregulatory responses to hypoglycemia (20). Avoiding drug-induced hypoglycemia in older adults with type 2 diabetes may also dramatically reduce unnecessary costs (21). In the study by Lipska et al. (22), temporal trends in the utilization of glucose-lowering medications, glycemic control, and rates of severe hypoglycemia (defined as requiring an emergency department visit, hospital admission, or observation stay) among Medicare Advantage patients were examined in the U.S. between 2006 and 2013. While the use of glucose-lowering drugs has substantially changed over this 8-year period, including an increased use of metformin, dipeptidyl peptidase 4 inhibitors, and insulin and decreased use of sulfonylureas and thiazolidinediones, only a modest decline was observed in the rate of severe hypoglycemia among older patients (2.9 to 2.3 per 100 person-years). Further, the rate of severe hypoglycemia remained particularly high among those with two or more comorbidities at 3.5 per 100 person-years in 2013. The results of this study raise the concern that older adults with multiple comorbidities are particularly vulnerable to having severe hypoglycemic events.

There are also risks to untreated or undertreated hyperglycemia, particularly over the renal threshold for glycosuria, including symptoms of dehydration, dizziness, and falls. Long-term mortality after hyperglycemic crises are significantly higher in older adults (23). In the Perspective by Korytkowski and Forman (24), the authors point out that although older adults are at higher risk of atherosclerotic cardiovascular disease, most of the studies examining the benefits for aggressive glucose-lowering and cardiovascular risk factor modification (i.e., lipid-lowering, hypertension, and antiplatelet therapies) are in nonelderly adults. A compelling summary of the rationale and practical recommendations for atherosclerotic cardiovascular disease risk factor reduction in older adults is presented, as is the importance of considering whether the benefits outweigh the risks in this heterogeneous population.

Comparative effectiveness studies of medications to treat diabetes in older adult populations are lacking. Type 2 diabetes is also characterized by defects in β-cell function that may become more manifest later in life. The safety of therapies in older adults with diabetes is important to consider in clinical practice to minimize polypharmacy and potential adverse side effects. Meneilly et al.

(25) conducted a phase III, double-blind, randomized, placebo-controlled trial (lixisenatide GetGoal-O trial) in patients ≥70 years of age with type 2 diabetes uncontrolled on their current antidiabetic treatment and evaluated the efficacy and safety of lixisenatide versus placebo on glycemic control. They concluded that "in nonfrail older patients uncontrolled on their current antidiabetic treatment, lixisenatide was superior to placebo in HbA_{1c} reduction and targeting postprandial hyperglycemia, with no unexpected safety findings." In the article by Bethel et al. (26), baseline data from the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) among participants ≥75 years of age with well-controlled type 2 diabetes and cardiovascular disease were examined. Over 2.9 median years of follow-up, older adults had higher rates of the primary composite cardiovascular outcome, death, severe hypoglycemia, and fractures. However, sitagliptin appeared to have neutral effects on cardiovascular risk compared with placebo without any significant safety concerns.

As the problem of diabetes among older adults grows, so too does the cost of providing diabetes-related care. In 2013, the ADA estimated that the total costs of diagnosed diabetes in the U.S. have risen to $245 billion in 2012 (from $174 billion in 2007). The majority of these costs were via Medicare (which provides coverage to older adults) and Medicaid (27). Also, a large portion of these diabetes-related costs involves treating diabetes-related complications, which are more frequent in older adults with diabetes. In the article by Choi et al. (28), the impact of Medicare Part D on reducing the financial burden of prescription drugs for older adults with diabetes was investigated between 2006 and 2011. Part D enrollment of Medicare beneficiaries with diabetes increased to more than 50% of the eligible population during this period. In parallel, out-of-pocket pharmacy expenses decreased by 13.5% for Medicare beneficiaries with diabetes following Part D implementation. However, while the overall coverage gap fell between these years, in 2011 there remained approximately 40% of Part D beneficiaries with diabetes who experienced the coverage gap. Future strategies to reduce this coverage gap could have particular benefits for older adults with diabetes.

The prevalence of diabetes in hospitalized patients represents a growing concern. Older adults have a more than three times higher prevalence rate of diabetes compared with younger adults who are discharged from hospitals in the U.S. (29). In the Perspective by Umpierrez and Pasquel (30), the authors highlight the potential risks of hyperglycemia for older patients in the hospital, including longer length of stay and increased mortality. Additionally, they emphasize that inpatient glycemic targets should be individualized and that insulin is the preferred treatment for older patients hospitalized with diabetes. A smooth transition to outpatient diabetes care is critical and facilitated by appropriate education in skills for home self-management. The quality of care offered to patients with diabetes in the inpatient setting is also an important concern. Novel methods to measure inpatient quality of care were investigated by Pogach et al. (31), who describe the use of a proposed out-of-range (OOR) measure (HbA_{1c} <7% or >9%) in high-risk older adults in the Veterans Health Administration population. Among almost 200,000 patients receiving therapy for diabetes other than metformin with at least one significant medical, neurological, or mental health condition, approximately half of those aged 65 years and over were OOR by this measure, with overtreatment being much more common than undertreatment. There was significant variation in facility-level rates for OOR, suggesting that this measure may help focus quality improvement efforts for hospitalized patients with diabetes. However, Bloomgarden et al. (32) questioned the supposition by Pogach et al. (31) that "age per se represents a suitable marker of risk, given the evidence of increasing population life expectancy, even into the ninth decade." Bloomgarden et al. also state that comorbidities, in their opinion, appear to be "better predictors both for the risk of and the risk from hypoglycemia for a given individual and should remind us to avoid agents likely to cause hypoglycemia." Given the controversy in this area, we felt it fair as an editorial team to present both narratives and viewpoints.

As outlined above, we as a medical community continue to struggle with how best to manage diabetes in older adults. In large measure, the difficulty results from having continued gaps in research that investigates diabetes in older adults, the age-group with the highest prevalence rates of diabetes and the fastest growing segment of the population. We also recognize that given the exclusion of older participants from most traditional randomized controlled trials of diabetes interventions, treatment decisions are often made with much uncertainty and need to be individualized. Therefore, future research should allow and account for the complexity of older adults. Beyond broadening the inclusion criteria for randomized controlled trials, we will increasingly need comparative effectiveness studies to assess safety and efficacy of therapies in older adults with diabetes who are particularly vulnerable to adverse effects from overtreatment. Older adults with diabetes are a heterogeneous population ranging from the robust to the frail and represent unique challenges and considerations for both the clinician and researcher that will need to be urgently addressed in the future. On the basis of the considerations cited above and the goal of *Diabetes Care* to disseminate the latest on this topic, we are proud to feature this special issue devoted to this most complicated topic.

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