Improving Care in Older Patients with Diabetes: A Focus on Glycemic Control

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ABSTRACT

Diabetes affects more than 25% of Americans older than age 65 years. The medical care of older patients must differ from the care of their younger counterparts. Older patients are at high risk of drug toxicity. A hemoglobin A\textsubscript{1c} (HbA\textsubscript{1c}) level less than 7.0% has historically been the goal of all patients with diabetes, regardless of age. Recent research has demonstrated that using medications to achieve such tight glycemic control is not necessary and is often not safe.

This article discusses the seminal research findings that strongly suggest that HbA\textsubscript{1c} goals should be relaxed in older patients. The authors then recommend an age-specific and functionally appropriate HbA\textsubscript{1c} reference range for patients receiving medications to improve glycemic control. Other interventions are suggested that should make diabetes care safer in older patients receiving hypoglycemic medications.

INTRODUCTION

Care of Older Adult Patients

The medical care of older patients must differ from the care of their younger counterparts. Complications from "standard" medical care are much more common in the geriatric population because of reduced reserve physiologic capacity, leading to functional decline. For example, among the sickest patients—hospitalized older patients—lasting disability is more common compared with hospitalized younger patients because of at least three mechanisms:

1. Incomplete recovery from a classic medical diagnosis (eg, oxygen dependence after pneumonia or chronic dyspnea after a myocardial infarction)
2. Exacerbation of a preexisting geriatric syndrome (eg, heightening fear of falls caused by hospital-related deconditioning with leg weakness or worsening dizziness caused by additional polypharmacy from new medications)
3. Iatrogenic complications during a hospitalization (eg, nosocomial Clostridium difficile colitis leading to nursing home placement or hospital-acquired incident delirium leading to dementia).

Older patients are at high risk of drug toxicity. Because they are more likely than younger patients to have multiple medical problems, older patients take more medications, which often leads to incorrect and unnecessary administration of prescribed medications. Additionally, the metabolism of drugs is reduced in older patients because of decreased lean body mass with increased body fat and a higher likelihood of having renal, hepatic, and/or cardiac insufficiency. Finally, drug-drug and drug-disease interactions make older patients at high risk of iatrogenic complications of drug toxicity.

"Overuse" of medications has been categorized as when the benefits of the additional medication are negligible (eg, antibiotics for a sore throat), when the risks outweigh the benefits (eg, muscle relaxant for neck pain), or use of a medication that a competent patient would have otherwise declined after shared decision making (eg, morphine for mild knee pain). Use of hypoglycemic medications for the treatment of diabetes in older patients using standard guidelines often fit all three categories of "overuse." The clinical benefits of additional hypoglycemic medications are often minimal, the harms are common and lasting, and the patient often lacks understanding of the time needed to accrue benefits from hypoglycemic medications. Hypoglycemia occurs frequently in older patients with diabetes, more often contributing to functional decline and lasting disability compared with their younger counterparts. The goals of glycemic control and the treatment using hypoglycemic diabetic medications in patients with diabetes must differ depending on age and functional status.

Diabetes Care in Older Adult Patients

Since 2003, there has been general acceptance by geriatric-focused physicians that glycemic control should be tempered by a sense of life expectancy, goals of care, cognitive status, and physical functional status. The one-size-fits-all model is not appropriate in frail older patients receiving hypoglycemic medications, for whom the risks of these medications often outweigh their benefits. Rather, shared decision making is necessary.
Historically, glycemic goals target a hemoglobin A\textsubscript{1c} (HbA\textsubscript{1c}) level below 7.0% without differentiation by age. The 2013 American Association of Clinical Endocrinologists (AACE) executive summary for diabetes management states that the HbA\textsubscript{1c} goal is 6.5% or lower for healthy patients without concurrent illness and who are at low hypoglycemic risk. The AACE states that the goal should be individualized to an HbA\textsubscript{1c} measurement above 6.5% for patients with concurrent illness and who are at risk of hypoglycemia. Although this AACE position states that the goals should be individualized on the basis of age and comorbidity, guidance on comorbidity criteria is absent. We believe that the lack of clarity in the AACE’s statement perpetuates the “lower-is-better” myth and encourages the overuse of potentially dangerous hypoglycemic medications.

The American Diabetes Association’s (ADA’s) 9-page executive summary of its 67-page position statement, “Standards of Medical Care in Diabetes 2014,” states that an HbA\textsubscript{1c} under 7.0% is “a reasonable goal” for many nonpregnant patients. Also, the ADA recommends that “older adults who are functional, cognitively intact, and have significant life expectancy should receive diabetes care with goals similar to those developed for younger adults” and that “glycemic goals for some older adults might reasonably be relaxed, using individual criteria, but hyperglycemia leading to symptoms or acute hyperglycemic complications should be avoided ….” Like the 2013 AACE executive summary, the 2014 ADA executive summary possibly lacks proper guidance for clinicians on when HbA\textsubscript{1c} goals should be relaxed.

However, in the text of the ADA’s 2014 position statement, HbA\textsubscript{1c} goals of below 7.5%, below 8.0%, and below 8.5% are recommended for older patients who have, respectively, good health, complex/intermediate health, and very complex/poor health. This recommendation is more aligned with the position of the American Geriatrics Society (AGS), in which the target goal is set for an HbA\textsubscript{1c} between 7.5% and 8.0% in most older patients, and higher HbA\textsubscript{1c} targets between 8.0% and 9.0% are recommended with multiple comorbidities, poor health, and limited life expectancy. These recommendations from the AGS have been adopted and publicized by the “Choosing Wisely” campaign sponsored by the American Board of Internal Medicine (ABIM) Foundation. On the basis of results of pivotal historical trials, we strongly agree with the glycemic goal of having HbA\textsubscript{1c} below 7.0% in most patients under 65 years of age. In this article, we discuss the scientific foundation for treating hyperglycemia to the historic goal of less than 7.0% in patients older than age 65 years (still generally considered the threshold for proper glycemic control in patients with diabetes of all ages), and why we believe that these goals should be relaxed to the standards set by the AGS.

**Historical Context for Lower Glycemic Targets**

The Diabetes Control and Complications Trial (DCCT) was the first trial to establish that microvascular and macrovascular complications of hyperglycemia could be delayed with tighter glycemic control. In this seminal work published in 1993, a total of 1441 patients with Type 1 diabetes (mean age = 27 years), with and without microvascular complications, were randomly assigned to receive either standard control of blood glucose or intensive control (intervention). After an average follow-up of 6.5 years, the DCCT (conducted from 1983 to 1993) demonstrated that patients with tight glycemic control had a delay in onset (primary prevention) or progression (secondary prevention) of nephropathy, neuropathy, and retinopathy. The intervention group had a mean HbA\textsubscript{1c} of 7.4%; the conventional treatment group had a mean HbA\textsubscript{1c} of 9.1%. The 11-year, postintervention follow-up published in 2005 showed a 42% reduction in any cardiovascular disease event. (In 2004, the mean HbA\textsubscript{1c} in the intervention group was 7.9% compared with 7.8% in the control group.) Notably, the widespread applicability of the DCCT investigators’ conclusions to most patients with diabetes was properly questioned. Less than 10% of all patients with diabetes have Type 1 diabetes, and the pathophysiology of Type 1 diabetes (formerly called juvenile diabetes) is markedly different from that in most patients with Type 2 (formerly called adult-onset) diabetes, particularly those older than 65 years.

The UK Prospective Diabetes Study (UKPDS), whose results were published in 1998, attempted to mitigate these concerns and validate the importance of tight glycemic control in patients with Type 2 diabetes. In this study, 3867 patients with newly diagnosed Type 2 diabetes (mean age = 54 years) were randomly given intensive therapy or conventional treatment. Patients older than age 65 years were excluded from enrollment in the UKPDS. After 10 years of follow-up, the intensive therapy group (mean HbA\textsubscript{1c} = 7.0%) had delays in microvascular complications, with less retinopathy and nephropathy compared with those who received conventional treatment (mean HbA\textsubscript{1c} = 7.9%). Macrovascular complications were not shown to be prevented or delayed during the initial publication in 1998. After the end of the randomization of the 2 groups, shortly after the 1998 publication, the glycemic control equalized in both study groups. The 10-year postsurveillance results of the UKPDS, published in 2008, suggested there was a “legacy effect,” or long-delayed benefit, in preventing myocardial infarctions and death in the intensive therapy group compared with the conventional group. Earlier intensive glycemic control during the first 10 years after the diagnosis of diabetes could reduce macrovascular events 10 to 19 years later, the study found. The UKPDS influenced the adoption of HbA\textsubscript{1c} goals below 7.0% in adult patients with Type 2 diabetes.

**Fallacy of Applying these Studies to Older Adult Patients**

In 2014, Selvin et al published data from the National Health and Nutrition Examination Survey (NHANES, conducted by the Centers for Disease Control and Prevention). The authors labeled patients with diabetes of all ages who received hypoglycemic medications and had an HbA\textsubscript{1c} of 7.0% or greater as being suboptimally controlled. We think that an HbA\textsubscript{1c} below 7.0% should not necessarily be the goal in older patients with diabetes receiving hypoglycemic medications, and conclusions from influential articles such as NHANES mislead both clinicians and older patients with diabetes, potentially leading to harm. In NHANES, 40% of the patients with diabetes were older than age 65 years. We know that up to 57% of older
patients with diabetes have substantial comorbidities and geriatric syndromes, which often lead these patients to change their goals of medical care. Given the known reduced life expectancy in older patients, particularly in frail older patients, we believe that the age-neutral historic target of an HbA1c below 7.0% is fallacious. This target is based on results of studies (UKPDS and DCCT) that did not allow for enrollment of patients aged 65 years or older, and hence these glycemic goals should not translate to older patients.

The microscopic complications related to higher HbA1c concentrations may not be clinically relevant in older patients with new-onset diabetes. In a theoretical construct model comparing an HbA1c of 8.0% vs 7.0% in patients with the onset of diabetes at age 65 years, the additional lifetime risk of blindness caused by retinopathy was reduced by 0.2% (number needed to treat = 500) and the additional lifetime risk of end-stage renal disease was reduced by 0.2% (number needed to treat = 500). Therefore, the clinical significance of preventing microvascular disease is questionable. Later, the UKPDS showed that tight glycemic control might reduce the development of macrovascular disease by 10 to 19 years, but in a patient with limited life expectancy or onset of diabetes after the age of 65 years, the relevance of aggressive lowering of glucose levels becomes less clear. Furthermore, if microalbuminuria portends future macrovascular complications, the control of hypertension and hyperlipidemia with the appropriate use of cardioprotective medications (aspirin, angiotensin-converting enzyme inhibitors, and statins) plays an equal if not a more important role in the prevention of cardiovascular complications.

For older adult patients with long-standing diabetes and multiple medical problems, at least 3 randomized trials have demonstrated that an HbA1c of about 7.5% is appropriate and safe and that an HbA1c below 6.5% might be dangerous. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial published in 2008 assessed 10,251 patients (mean age = 62 years; average duration of diabetes = 10 years) with multiple comorbidities who received intensive treatment (mean HbA1c = 6.4%) or conventional therapy (mean HbA1c = 7.5%). The study was halted prematurely after 3.5 years because it showed that there was one additional death in the intervention group for every 95 patients over 3.5 years. In addition, 10% of the intervention group had hypoglycemic events that required medical assistance vs 3% for the control group, and 28% of the intervention group had more than 10-kg weight gain compared with 14% in the control group.

Also in 2008, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial took place in 11,140 older patients (mean age = 66 years; average duration of diabetes = 8 years) with severe cardiovascular disease or cardiovascular disease risk factors or preexisting microvascular complications. The ADVANCE trial found no macrovascular benefit or increased rate of death in the intense treatment group (mean HbA1c = 6.5%) vs conventional therapy (mean HbA1c = 7.3%) after 5 years. Severe hypoglycemia was significantly more common in the intervention group (2.7% vs 1.5% in the control group), which contributed to the significantly increased rate of hospitalization in the intervention group. The only microvascular benefit with intense treatment was a statistically significant reduction in albuminuria. In 2014, the follow-up study in ADVANCE demonstrated no reduction in macrovascular disease after the 6-year, postsurveillance follow-up. The legacy effect in preventing macrovascular disease seen in the UKPDS was not seen in ADVANCE.

In 2009, the Veterans Affairs Diabetes Trial assessed 1791 military veterans with suboptimally controlled Type 2 diabetes (mean age = 60 years; mean duration of diabetes mellitus = 11.5 years; 40% with vascular disease). The goal in the intervention group receiving intensive glucose control was to reduce the HbA1c by 1.5%. After 6 years, there were significantly more serious events in the intervention group (mean HbA1c = 6.9%), including hypoglycemia, vs the controls (mean HbA1c = 8.4%), which received standard glucose control. There were no statistically significant changes in composite microvascular outcomes, although a statistically significant reduction did occur in the progression of proteinuria. No statistical differences existed in the number of eye surgical procedures, but there was a trend for reduced retinopathy. There also were no significant reductions in macrovascular events (stroke, cardiac events and procedures) or amputations in the intervention group compared with the control group.

The age-neutral historic target of an HbA1c below 7.0% is fallacious. (and) based on results of studies ... that did not allow for enrollment of patients aged 65 years or older, and hence these glycemic goals should not translate to older patients.

Complications of Hypoglycemia

In 2011, the second most likely medication leading an older patient to be hospitalized through the Emergency Department because of an adverse drug event was insulin, and the fourth most likely medication was an oral hypoglycemic agent, according to authors from the Centers for Disease Control and Prevention. This group estimated that the numbers of hospitalizations in older patients occurring annually in the US because of insulin and oral hypoglycemic agents were 13,854 and 10,656 respectively. More than 94% of these hospitalizations were caused by complications of hypoglycemia, clearly demonstrating the potential dangers of these endocrine agents. This same group later published that patients older than age 80 years who were receiving insulin were twice as likely to go to the Emergency Department and 5 times as likely to be hospitalized because of insulin-related hypoglycemia and errors compared with 45- to 64-year-old patients, suggesting the need for looser glycemic targets based on age.

Kaiser Permanente Northern California (KPNC) data showed that hypoglycemia was the second most common nonfatal diabetic complication (after cardiovascular complications) in patients age 70 to 79 years with a duration of diabetes for more than 10 years and the third most common cause of nonfatal complications in patients with diabetes for less than 10 years (after cardiovascular
complications and eye disease). Additionally, among patients age 70 to 79 years, the incidence of hypoglycemia was 6 times more likely than acute hyperglycemic events in those who had diabetes for less than 10 years, and 19 times more likely in patients with diabetes for greater than 10 years.

As noted earlier, whether macrovascular disease can be prevented with tight glycemic control among older patients with a long-standing history of diabetes is questionable. Hypoglycemia might also increase the risk of dementia later in life. In a KPNC diabetic registry from 1980 to 2007, of 16,667 patients with a mean age of 65 years, 1,465 patients had at least 1 visit to the Emergency Department or hospital for a hypoglycemic event. The absolute risk in these patients of dementia developing per year of follow-up was 2.3%. Other KPNC data showed that hypoglycemia (as well as geriatric syndromes) more negatively affects an older patient's quality of life than do other diabetic complications (e.g., neuropathy, blindness, and end-stage renal disease).

Hypoglycemia Continues in Older Patients

As already discussed, the literature shows that an unexpected higher death rate was found in the intervention group of the ACCORD study and that hypoglycemic agents often lead to emergent hospitalizations in older patients, with hospitalizations frequently leading to lasting disability. Other research showed that older patients with multiple comorbid conditions and long-standing diabetes with an HbA1c between 6.4% and 6.9% did not have improved macrovascular outcomes or clinically significant improved microvascular outcomes compared with those with an HbA1c of 7.3% to 8.1%. Given this body of evidence, the physician mantra of "do no harm" would suggest that only a small percentage of patients older than 65 years would have an HbA1c below 7.0% and be receiving hypoglycemic medications. Yet, in published KPNC data, of 9,786 patients between age 70 and 79 years with a duration of diabetes mellitus for longer than 10 years, 41% had an HbA1c below 7.0%. Although only 7% of these patients were not receiving any hypoglycemic medication, 61% of these patients were on a regimen of a sulfonylurea and 39% were receiving insulin.

In a Veterans Affairs study in 2009 of 205,857 patients at high risk of hypoglycemia because of age older than 74 years, a creatinine level above 2.0 mg/dL, or presence of cognitive impairment while receiving a sulfonylurea and/or insulin, 50% of patients had a level of HbA1c under 7.0%, 27% had HbA1c below 6.5%, and 11% had HbA1c less than 6.0%. These findings suggest overtreatment with hypoglycemic medications.

DISCUSSION

Many hypoglycemic episodes are avoidable. Many patients may not know to take less hypoglycemic medication when their oral intake is reduced (because of, for example, poor access to food caused by an acute medical event such as an upper respiratory tract infection with consequent anorexia). All clinicians, while educating older adult patients with diabetes, should instruct them to reduce their hypoglycemic agents during times of poor nutritional intake and to carry candy and a glucagon injection with them in the event of a hypoglycemic episode. The first-line treatment of most diseases should be education and other nonpharmaceutical interventions. In Kaiser Permanente Southern California (KPSC), patients with diabetes mellitus have better glycemic control if they have taken health education classes at KPSC (personal communication; Ray Nanda, MD; 2016 Feb 22).

There may be financial ramifications to overtreatment with hypoglycemic agents. Medicare has been reducing reimbursements for care because of events thought to be avoidable ("never events" during a hospitalization or readmission). In 2012, it was estimated that in the US there was $213 billion of avoidable health care costs, of which $20 billion in costs were caused by medication errors and $1.3 billion was caused by mismatched polypharmacy in elderly individuals. Given the alarming rate

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<th>Table 1. Kaiser Permanente Southern California’s electronic medical record flag for elevated hemoglobin A1c in patients with diabetes, used through December 2015a</th>
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<td>Age</td>
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a As of October 12, 2012, a separate test was created in Kaiser Permanente Southern California for screening patients who did not have a diagnosis of diabetes. The reference range for that test is 4.8% to 5.6%.

b Patients of all ages were flagged as having elevated blood glucose levels if HbA1c measurement was ≥ 7.0%. HbA1c = hemoglobin A1c; RBC = red blood cell.

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<th>Table 2. Kaiser Permanente Southern California’s updated hemoglobin A1c reference range for different age bandsa</th>
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<td>Age, years</td>
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<td>65-75</td>
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<td>≥ 76</td>
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a Convened by the manuscript’s authors, multiple relevant Kaiser Permanente Southern California committees assisted in updating the HbA1c (diabetic monitoring) reference range. The consensus reference range is shown here. In use since January 2016, this updated reference range has been flagged as abnormal at an HbA1c level of ≥ 7.5% in patients with diabetes between 65 and 75 years of age and has been flagged as abnormal at an HbA1c ≥ 8.0 in patients with diabetes ≥ 76 years of age. The corresponding comments will allow clinicians to choose a more tailored HbA1c goal on the basis of the patient’s function and comorbidities.

HbA1c = hemoglobin A1c; RBC = red blood cell.
of possible overtreatment with hypoglycemic agents in older patients, the US Department of Health and Human Services is developing a National Action Plan for Adverse Drug Event Prevention that focuses on 3 classes of medications: opiates, warfarin, and hypoglycemic agents.29

We believe that the excessive burdens such as hypoglycemic episodes and other adverse medication reactions can be reduced through the following multi-interventional approach:

1. Establish a new reference range for HbA1c levels in older patients with diabetes that synthesizes the recommendations from the ADA, Choosing Wisely (sponsored by the ABIM Foundation), and the AGS.

2. Educate and encourage clinicians to reduce hypoglycemic medications in older patients at risk of functional loss or with multiple medical problems when their HbA1c level is below 7.0%. Accounting for risks of polypharmacy and the goals of care, for a healthy older patient with diabetes and an HbA1c level below 7.0%, prescribing metformin as the only agent may be appropriate. There is importance in using antidiabetes medications to reduce glucose burden because hyperglycemia can also cause substantial morbidity. Our (KPSC) updated reference range can guide physicians to prescribe on the basis of function and morbidity (Tables 1 and 2).

3. Prescribe metformin as the first-line agent when a physician initiates therapy with a hypoglycemic medication because of its low risk for hypoglycemia and its safety profile.

4. Use the electronic medical record to identify patients receiving hypoglycemic agents who have an HbA1c level below 7.0% and who are older than 80 years old or who have dementia or chronic kidney disease stage 4 or greater.

5. Educate patients and caretakers, as well as provide written instruction after the office visit, to decrease the dosing of hypoglycemic medications when the patient’s oral intake is reduced because of illness or poor access to food.

6. Prescribe glucagon for older patients with diabetes receiving hypoglycemic medications, which can be used emergently during symptoms of hypoglycemia.

7. Encourage older patients with diabetes who are receiving hypoglycemic medications to always carry glucose tablets or glucose-rich foods with them and to monitor their blood glucose level before driving.

8. Use the electronic medical record to identify older patients receiving hypoglycemic medications who have 2 consecutive HbA1c measurements below 6.5% in a period longer than 1 month.

By implementing the proposed interventions to reduce hypoglycemia, we can keep older patients with diabetes safer and more functional, without having any clinically significant health consequences from less intensive glycemic control. ✔

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

References

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Attending to Old People

Not only physicians, but everybody else attending old people, being accustomed to their constant complaints, and knowing their ill-tempered and difficult manners, realize how noble and important, how serious and difficult, how useful and even indispensable is that part of practical Medicine, called Gerocomica, which deals with the conservation of old people and the healing of their diseases.

—François Ranchin, MD, 1564-1641, French physician and professor and chancellor of the Université de Médecine, Montpellier, France