What Is the Proper Use of Hemoglobin A1c Monitoring in the Elderly?

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Diabetes mellitus (DM) is a major health problem for the aging population. Glycemic control is fundamental to the management of diabetes, as glycemic levels are closely linked to development of diabetes-related complications. Measurement of the hemoglobin A1c (A1c) to assess chronic glycemic control is an integral component of diabetes care. Currently, there is no clear evidence that age alters the relationship between A1c and average blood glucose. The Diabetes Control and Complications trial and the United Kingdom Prospective Diabetes Study are the 2 main studies that have provided evidence leading to the widespread recommendation of A1c monitoring. The American Diabetes Association recommends achieving an A1c level of 7% or lower. However, older diabetics represent a heterogeneous population ranging from frail nursing home residents to active community-dwelling elderly with variable life expectancies. One needs to look at the individual in order to best balance risk versus benefit associated with tight glycemic control. Benefits of intensive therapy in an effort to lower A1c must always be weighed against the greater risk of disabling and unpredictable hypoglycemia, as the geriatric population is less likely to benefit from reducing the risk of microvascular complications and more likely to suffer serious adverse effects from hypoglycemia. **(J Am Med Dir Assoc 2006; 7: S60–S64)**

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Diabetes mellitus (DM) is a major health problem for the aging population. Nearly one fifth of adults older than age 60 in the United States have diabetes.[1] Some reports predict that by the year 2025, two thirds of the diabetic population will be elderly.[1,2] Little information is available on the percentage of nursing home residents with diabetes, although in 2 studies the prevalence of DM among this group was reported in the range of 15%.[3,4]

In community-dwelling older adults, diabetes is a strong predictor of disability and poor physical performance.[5] Geriatric syndromes, such as polypharmacy, depression, cognitive impairment, urinary incontinence, falls, and persistent pain, are more common in older persons with diabetes.[6–11] Diabetic elderly are also reported to have higher rates of premature death and coexisting illnesses such as hypertension, coronary heart disease, and stroke.[10,12]

Glycemic control is fundamental to the management of diabetes, as hyperglycemia is closely linked to the development of diabetes-related complications. Measurement of the hemoglobin A1c (A1c) to assess chronic glycemic control is an integral component of diabetes care and is being used increasingly by quality assurance programs to assess the quality of diabetes care. This article focuses on A1c as a glycemic marker and its clinical utility in the management of diabetes, with special considerations in the elderly.

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WHAT IS HEMOGLOBIN A1c?

Carbohydrates such as glucose bind nonenzymatically to proteins (such as hemoglobin, albumin) in a process called glycation. Glycation of hemoglobin occurs over the entire 120-day life span of red blood cells. The A1c fraction exhibits glycation at the N-terminal valine of the hemoglobin beta-chain. The A1c value is thought to represent average glycemia over the past 3 months. However, recent glycemia has the largest influence, with plasma glucose levels in the preceding 30 days contributing about 50% to the final A1c result.[13] Hence, the higher the ambient blood glucose, the greater the rate of glycation and the higher the A1c value. Each 1% change in A1c reflects a change in mean plasma glucose of about 35 mg/dL.

The best correlation of A1c with mean plasma glucose comes from the Diabetes Control and Complication trial (DCCT), which compared 26,056 A1c values with corresponding 7-point plasma glucose profiles from 1439 subjects over a period of 6.5 years.[14] According to the DCCT data, an A1c value of 7% represents a mean blood glucose level of about 170 mg/dL and an A1c value of 9% represents a mean blood glucose value of about 240 mg/dL.[15]

Although A1c is a good indicator of average blood glucose level, it does not give an indication of the stability of glycemic control. One patient with fluctuating values

could have the same A1c measurements as one whose glucose varies little throughout the day. Hence, both A1c and plasma glucose profiling are needed to truly ensure good glycemic control.

WHAT IS THE CLINICAL EVIDENCE FOR A1c MONITORING?

There are 2 main studies that have provided an evidence-based approach leading to the widespread recommendation of A1c monitoring. The DCCT was a study done in 1441 type 1 patients with diabetes, mean age 27 years with mean follow-up of 6.5 years. Herein, the intensively treated group achieved a median A1c of 7% as compared to 9% in the conventionally treated group. Subsequent analyses showed that A1c measurement could be used as a tool to stratify the risk of a patient developing microvascular complications; in fact, there was an exponential rise in the rate of these complications with increasing A1c values. These findings were confirmed by the United Kingdom Prospective Diabetes Study (UKPDS)[16] in 1998, which enrolled 3867 new-onset type 2 patients with diabetes (mean age, 54 years) and followed them over 10 years. Although A1c separation was not as impressive as in the DCCT (A1c 7.0% versus 7.9% over 10 years), there was still a 25% risk reduction in microvascular endpoints. Subsequent analyses in the UKPDS also demonstrated that A1c gives an indication of macrovascular risk as well.[17] A recent meta-analysis suggests a moderate increase in cardiovascular risk with increasing levels of A1c in persons with diabetes mellitus, however the independent effect of A1c in predicting cardiovascular outcome is unclear.[18]

WHAT ARE THE RECOMMENDED A1c GOALS?

The American Diabetes Association (ADA) recommends achieving an A1c level of 7% or lower,[19] whereas the American Association of Clinical Endocrinologists recommends a goal A1c of 6.5% or less.[20] According to the American Geriatrics Society, target A1c should be individualized for older persons.[21] A reasonable goal for relatively healthy adults with good functional status is 7% or lower. For frail older adults, persons with life expectancy of less than 5 years, and others in whom the risks of intensive glycemic control appear to outweigh the benefits, a less stringent target such as 8% is appropriate.[21] The Veterans Affairs goals are consistent with those of the American Geriatrics Society, and suggest higher A1c goals in patients who have limited life expectancy (<15 years), or significant comorbidities; however, they recommend that all patients have an A1c maintained below 9% in order to avoid symptoms or complications referable to hyperglycemia.[22]

HOW OFTEN SHOULD A1c TESTING BE DONE?

There is no consensus on the optimal frequency of A1c testing. The ADA recommends that for any individual patient, the frequency of A1c testing should be dependent on the judgment of the physician. In the absence of well-controlled studies that suggest a definite testing protocol, expert opinion recommends A1c testing at least 2 times a year in patients who are meeting treatment goals (and who have stable glycemic control) and more frequently (quarterly assessment) in patients whose therapy has changed or who are not meeting glycemic goals.[19] In nursing home residents with diabetes, it is recommended that A1c should be measured at least every 12 months, or care goals or medical records should indicate why this is not appropriate.[23]

DOES AGING INFLUENCE A1c RESULTS?

Dunn et al[24] and Graf et al[25] in the 1970s reported a positive correlation between age and A1c. This was further supported by a study done by Arnetz et al[26] (1982) in a sample consisting of 48 community-dwelling subjects between the ages of 50 and 89 with no history of diabetes. Patients with impaired glucose tolerance tests were excluded. The study reported increased values of A1c with aging, with the oldest having the highest values. The Telecom Study[27] (1989) in 3240 healthy individuals concluded that age independently influenced A1c. These studies are consistent with the finding that fasting glucose levels increase with age by about 1 to 2 mg/dL per decade.[28] The reported relationship of increasing A1c with age has been attributed to the greater incidence of impaired glucose tolerance and diabetes among older people.

In contrast, Kabadi[29] (1988) reported no significant association between age and A1c. Wiener and Roberts[30] also did not detect any direct relationship between age and A1c in 3 groups of 399 patients carefully characterized by oral glucose tolerance test as nondiabetic, patients with impaired glucose tolerance, and diabetic.

Currently, there is no clear evidence that age alters the relationship between A1c and average blood glucose. Current recommendations do not take into account age while interpreting the results of A1c, and the reference ranges are not age specific.

WHAT IS THE RELATIONSHIP OF A1c TO FASTING AND POST-PRANDIAL BLOOD GLUCOSE?

In type 2 diabetes patients, correlation between fasting blood glucose and A1c values is reasonably good.[31] However, the majority of patients have exaggerated glucose excursions after meals, due to loss of first-phase insulin secretion. Nonetheless, A1c is more closely related to preprandial than postprandial glucose levels.[32] This indicates that many diabetic patients with apparently good metabolic control as inferred from A1c or fasting glucose values indeed have high glucose levels after meals. Recently El-Kebbi et al[33] (2004) suggested that a single casual plasma glucose level of greater than 150 mg/dL may be used to identify patients with inadequate glycemic control when A1c value is not available. A better cardiovascular outcome has been reported with control of postprandial sugars.[34] Whether controlling postprandial sugars will lead to a better outcome in older patients per se needs to be explored.

CAN A1c BE USED AS A SCREENING TEST FOR DIABETES?

At present, the ADA does not recommend A1c for screening or diagnosis of diabetes secondary to lack of standardization and limited sensitivity for mild elevations of blood glucose. However, the issue of standardization has largely been overcome by the use of the National Glycohemoglobin Standardization Program (NGSP)–certified assay by the majority of US laboratories. As such, many studies have argued for its diagnostic utility. Greci et al[35] (2003) showed that in acutely ill patients with random hyperglycemia (random plasma glucose of more than 125 mg/dL) at hospital admission, A1c of more than 6% can reliably diagnose diabetes, and levels less than 5.2% reliably exclude it. Davidson et al[36] (1999) suggested measurement of A1c level in patients with fasting plasma glucose of 110 to 139 mg/dL instead of repeating fasting glucose on another day. They suggested that patients whose A1c level is less than 1% above the upper limit of normal would be considered as having impaired fasting glucose, not diabetes. Nonetheless, A1c is still not considered the standard of care for either screening or diagnosis of diabetes.

WHAT ARE THE LIMITATIONS IN A1c ANALYSIS?

Similar to all tests used in patient care, A1c analysis is subject to certain limitations. Numerous previous analytical problems such as lack of standardization have been overcome by US laboratories switching to use of A1c assays certified by the NGSP. A1c is also affected by turnover of red blood cells and structure of hemoglobin. Falsely high A1c values can be obtained when red cell turnover is low, resulting in a disproportionate number of older red cells. Rapid red cell turnover leads to a greater proportion of younger red cells and falsely low A1c values, as in patients with hemolytic anemia and those treated for iron, vitamin B12, or folate deficiency.[37] In patients with chronic renal failure, values of A1c can be variable depending on the assay used and whether or not the patient is on erythropoietin therapy, which affects red blood cell turnover.

WHAT ARE THE BARRIERS TO ACHIEVING RECOMMENDED A1c LEVELS IN THE ELDERLY?

In elderly patients, the fear of iatrogenic hypoglycemia makes achievement of optimal glycemic control and A1c levels complex and generally only partially successful. Hypoglycemia often causes recurrent physical or psychosocial morbidity, or both, and sometimes death.

In the UKPDS, 2.4% of those using metformin, 3.3% of those using a sulfonylurea, and 11.2% of those using insulin reported major hypoglycemia over 6 years of follow-up.[38] The incidence of hypoglycemic events in nursing home residents is unclear. In a study comparing nursing home diabetic patients with ambulatory diabetic patients, incidence of hypoglycemic events over a 6-month period was lower in nursing home residents as compared to community-dwelling diabetic patients.[4] However, the study was done in an academic nursing home and cannot be generalized to community nursing homes.[39]

Table 1. *Barriers to Achieving Recommended A1c Levels in the Elderly*

Iatrogenic hypoglycemia/hypoglycemia unawareness
Polypharmacy
Drug-drug interactions
Drug-disease interactions
Personal belief of provider or patient

Elderly patients with a long-standing history of type 2 diabetes are likely to be insulin deficient due to the duration of their disease. They exhibit glucose counter-regulatory defects similar to type 1 diabetic patients in the form of impaired glucagon secretory response and hypoglycemia-associated autonomic failure, making them more vulnerable to hypoglycemic events.[40] Hence, the longer the duration of diabetes, the more difficult it becomes to maintain lower A1c levels without exposing the patient to the dangers of hypoglycemia.

Administration of excessive doses of insulin secondary to cognitive impairment or visual problems, missed meals, renal insufficiency, alcohol consumption, and ill-timed insulin or exercise can also lead to hypoglycemic events with devastating consequences. Last, dementia is a unique form of diminished hypoglycemic awareness, in which the patient can no longer appropriately recognize and respond to low blood sugars. Table 1 lists some of the common barriers in achieving recommended A1c level.

WHY SHOULD A1c GOALS BE MODIFIED IN A GERIATRIC POPULATION?

Older diabetics do not represent a uniform group. They represent a spectrum ranging from frail nursing home residents with multiple chronic conditions, substantial diabetes-related comorbidities, and limited cognitive and physical functioning to active community-dwelling elderly with little comorbidity. Life expectancies are also highly variable.

Quality of life is another important consideration. Seeking lower A1c numbers, which may result in complicated, costly, or uncomfortable treatment regimens may be associated with reduced quality of life.

Also, aging per se is a strong, unmodifiable risk for mortality and, therefore, the relative contribution of any modifiable risks associated with diabetes would progressively be smaller with aging. The Nagano study[41] in 2003 reported a similar mortality rate in a cohort of elderly Japanese diabetic patients as compared to an age- and sex-matched general population. Rosenthal et al[42] performed a prospective analysis of risk factors in 137 elderly patients with diabetes and concluded that depression was the best predictor of mortality.

There is no clinical trial data available exclusively in the geriatric population establishing the value of strict glycemic control. The goals have been set by extrapolating data from young or middle-aged patients. Benefits such as enhancement of wound healing, reduction of symptoms associated with

hyperglycemia such as polyuria and fatigue, and possibly maximizing of cognitive function may possibly be achieved with less aggressive glycemic targets for A1c than those recommended in most of the guidelines. Hence, one needs to look at the individual in order to best balance risk versus benefit associated with tight glycemic control. In older persons with diabetes, greater reductions in morbidity and mortality may result from control of all cardiovascular risk factors rather than tight glycemic control to get the optimal A1c number.

CONCLUSIONS

Despite its inherent limitations, A1c continues to be a valuable marker of glycemic control. In managing frail elderly and nursing home residents with DM, individual preferences, comorbidities, and other patient factors may require modification of goals and frequency of monitoring. Benefits of intensive therapy in an effort to lower A1c must always be weighed against the greater risk of disabling and unpredictable hypoglycemia, as the geriatric population is less likely to benefit from reducing the risk of microvascular complications and more likely to suffer serious adverse effects from hypoglycemia.

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