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Diabetes and Prediabetes: New Guidelines for Diagnosis and Controversy Over Treatment Goals

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ABSTRACT: The American Diabetes Association now recommends hemoglobin A_{1c} (HbA_{1c}) as an additional criterion for the diagnosis of diabetes and prediabetes. The test should be done using a method certified by the National Glycohemoglobin Standardization Program. Patients with HbA_{1c} levels of 6.5% or higher are considered diabetic. Prediabetes or increased risk of diabetes is diagnosed at levels of 5.7% to 6.4%. For prediabetes levels, inform such patients of their elevated risk, and counsel them about lifestyle modification; also consider the use of metformin. For patients with recently diagnosed diabetes (HbA_{1c} level of 6.5% or higher), aggressive treatment (HbA_{1c} goal of as close to 6.0% as possible) will lower cardiovascular risk in addition to significantly reducing the risk of retinopathy, neuropathy, and nephropathy. If a patient has had diabetes for 10 to 15 years, is older, and also has a history of significant cardiovascular events, less aggressive treatment is indicated (with an HbA_{1c} goal of 7.0% or higher).

Key words: diabetes, prediabetes, hemoglobin A_{1c}, cardiovascular disease

Recent guidelines from the American Diabetes Association (ADA) recommend hemoglobin A_{1c} (HbA_{1c}) as an additional standard for the diagnosis of diabetes and prediabetes.[1] The guidelines include the results of recent studies that question the value of aggressive treatment to attain HbA_{1c} goals. The American Association of Clinical Endocrinologists' (AACE) recent publication of Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan agrees with the ADA position on diagnosis of diabetes but not with the position on prediabetes.[2]

Following the release of these guidelines, additional studies have been published that raise questions about blood pressure and lipid goals in patients with diabetes. A recent newsletter for diabetes professionals stated, "Key results from a landmark federal study are in and the results are disappointing for diabetes patients: adding drugs to drive blood pressure and blood-fats lower than current targets did not prevent heart problems, and in some cases caused harmful side effects."[3] In this article, I discuss these recent publications and offer some suggestions to help you sort through the data and make informed decisions in your daily practice.

DIAGNOSIS OF DIABETES

In January 2010 and again in January of 2011, the ADA published guidelines that recommend measurement of HbA_{1c} as an option for making the diagnosis of diabetes.[1] This set aside the previous recommendation that only blood glucose levels be used for diagnosis. The following is a list of the various options and values the ADA recommends for the diagnosis of diabetes:

- HbA_{1c} of 6.5% or higher.

- Fasting plasma glucose of 126 mg/dL or higher.
- 2-Hour post glucose load plasma glucose of 200 mg/dL or higher.
- Random plasma glucose of 200 mg/dL or higher with symptoms of hyperglycemia.

Previous ADA recommendations have not recommended measurement of HbA_{1c} for the diagnosis of diabetes because of the lack of standardization of the assay. Because HbA_{1c} assays are now highly standardized, their results can be uniformly applied. The International Expert Committee, after extensive review of the evidence, recommends the use of the HbA_{1c} test to diagnose diabetes, with a threshold of 6.5%.[4] The ADA now supports that recommendation. The diagnostic HbA_{1c} cut point of 6.5% is associated with increased prevalence of retinopathy. The test should be performed using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP). As of January 2011, point-of-care HbA_{1c} assays were not considered sufficiently accurate for diagnostic purposes.

In 2011 the AACE published guidelines agreeing that HbA_{1c} should be considered as an additional criterion for the diagnosis of diabetes.[2] The AACE also added that if blood glucose levels are normal, the HbA_{1c} should be repeated. The AACE guidelines also included these other recommendations:

- Traditional glucose criteria should be used for diagnosis when feasible.
- HbA_{1c} is not recommended for the diagnosis of type 1 diabetes or the diagnosis of gestational diabetes.
- Only standardized, validated assays should be used for HbA_{1c} measurement.
- The HbA_{1c} value may be misleading in any condition associated with hemolysis, anemia, and severe hepatic or renal disease.

For patients who have conditions associated with normal red cell turnover, such as sickle cell trait, an HbA_{1c} assay without interference from abnormal hemoglobin should be used (a list is available at www.ngsp.org/prog/index3.html). If a patient has an anemia associated with abnormal red cell turnover (hemolysis and iron deficiency), the diagnosis of diabetes should depend on glucose levels.

The use of HbA_{1c} for the diagnosis of diabetes has several advantages. It does not require fasting or special preparation, and it can be obtained at any time. Blood glucose levels vary from day to day, but the HbA_{1c} level is more stable. Some authors believe that HbA_{1c} measurement will identify fewer patients than a fasting or 2-hour post-load glucose measurement, but the convenience of obtaining an HbA_{1c} value may actually increase early identification.

My recommendations. Use HbA_{1c} for the diagnosis of diabetes. Be sure the laboratory or instrument you use is certified by the NGSP. In patients who may have sickle cell trait, an HbA_{1c} assay without interference from abnormal hemoglobins should be used (an updated list is available at www.ngsp.org/interf.asp). Repeat the HbA_{1c} if the blood glucose levels are normal. Never allow one value to make the diagnosis. If the patient has iron deficiency anemia, hemolysis, or anemia of chronic disease, use glucose levels to make the diagnosis.

DIAGNOSIS OF PREDIABETES

Since 1997, the ADA has recognized the existence of intermediate levels of glucose elevation that are out of the range of normal but have not yet reached diagnostic levels for diabetes. These intermediate levels are defined as impaired fasting glucose (IFG), 100 mg/dL to 125 mg/dL, and impaired glucose tolerance (IGT), 2-hour post-load values of 140 mg/dL to 199 mg/dL. Persons with these levels are considered at high risk for diabetes (prediabetic). These persons are also at risk for cardiovascular disease (CVD), and some may already have early signs of retinopathy, nephropathy, and neuropathy. Hypertension, elevated triglyceride levels, lower high-density lipoprotein (HDL) levels, and abdominal obesity are often present in this group. The new ADA guidelines now recommend HbA_{1c} levels of 5.7% to 6.4% for the diagnosis of prediabetes.

In contrast, the new AACE guidelines do not support the use of HbA_{1c} alone to identify patients who have prediabetes or who are at high risk for diabetes. Although they do state that an HbA_{1c} value of 5.5% to 6.4% can be used as a screening test, it should be followed by measurement of a fasting glucose level or a post–glucose load glucose level to confirm the diagnosis.

The International Expert Committee did not formally identify HbA_{1c} as a tool for the diagnosis of prediabetes, but it emphasized that patients with HbA_{1c} levels of 6.0% to 6.5% are at very high risk for diabetes.[4] Other studies indicate that persons with HbA_{1c} levels in this range are 10 times more likely to develop diabetes.[5,6] These studies also point out that some patients who are at risk are not always identified at these levels and that levels of 5.5% to 6.0% indicate increased risk.

Most of the enthusiasm for identifying patients at risk for diabetes results from the Diabetes Prevention Program (DPP).[7] This study demonstrated a significant delay in the onset of diabetes with lifestyle changes or pharmacological therapy in patients with a mean HbA_{1c} value of 5.9%.

My recommendations. For patients whom you believe are at risk for diabetes, obtain an HbA_{1c} level

and, if desired, add a fasting blood glucose level as well. If the HbA_{1c} level is 5.7% to 6.4%, inform the patient of the increased risk of diabetes and all of its complications. Counsel the patient about strategies for weight loss and increased physical activity. Consider the use of metformin as an adjunct to the lifestyle changes.

TREATMENT GOALS FOR GLYCOHEMOGLOBIN

Recent studies have challenged the ADA treatment goals for HbA_{1c}. It has long been believed that the incidence of CVD would decrease with lower HbA_{1c} levels. Two landmark studies, the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC)[8] and the United Kingdom Prospective Diabetes Study (UKPDS),[9] provide excellent evidence that lowering HbA_{1c} levels to 7% or less reduces the incidence of CVD. Both of these studies were done with patients who were recently diagnosed with diabetes.

In the DCCT/EDIC, patients with type 1 diabetes were followed up for an average of 17 years. The patients in the intensive therapy group had a 42% reduction in risk of any cardiovascular event even after intensive therapy was stopped. The researchers concluded that the initial 6.5 years of intensive treatment created a "metabolic memory" that provided protection against CVD.

In the UKPDS, patients with newly diagnosed type 2 diabetes were followed up for 10 years. They experienced statistically significant reductions (15% to 33%) in the risk of myocardial infarction. The investigators dubbed the protection of early intensive therapy the "legacy effect."

In 2008 two studies, Action to Control Cardiovascular Risk in Diabetes (ACCORD)[10] and Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE),[11] were published that contradicted the results of trials that showed that lowering HbA_{1c} had a cardiovascular protective effect. The ACCORD study was stopped early because reducing HbA_{1c} to near normal levels seemed to increase mortality. The ADVANCE investigators concluded that lower to near-normal blood glucose levels did not reduce cardiovascular events.

In January 2009 the Veterans Affairs Diabetes Trial (VADT) was published.[12] This study found that intensive therapy in patients with poorly controlled type 2 diabetes had no significant effect on the rates of major cardiovascular events.

At the annual ADA meeting in June 2009, the lead authors of the ACCORD and VADT studies concluded that intensive glycemic control does not account for the increase in cardiovascular deaths.[13] Rapid changes in blood glucose levels, older age, and co-morbidities accounted for the increased cardiovascular mortality in patients who received intensive treatment. In the ACCORD trial, a decline in HbA_{1c} was associated with a lower risk of death. "Patients with the lowest A_{1c} levels had the lowest risk. The excess mortality risk was in those patients who failed to achieve and sustain A_{1c} levels between 6% and 7%."[10]

In May 2009 a meta-analysis was published that reviewed 5 prospective, randomized, controlled trials (33,040 patients) to assess the effect of an intensive glucose-lowering regimen on death and cardiovascular outcomes compared with a standard regimen.[14] The meta-analysis included the UKPDS, ACCORD, ADVANCE, and VADT studies. The authors concluded, "Intensive compared with standard glycemic control significantly reduces coronary events without an increased risk of death. However, the optimum mechanism, speed, and extent of A_{1c} reduction might be different in differing populations."[14]

Weighing the evidence. Before making a clinical decision on the basis of these trials, consider that the patients in the UKPDS trials had *newly diagnosed diabetes;* moreover, they were younger and only 7.5% had a history of CVD. In the ACCORD and ADVANCE trials, 33% of participants had a history of CVD; they were 8 to 10 years older than the patients in UKPDS, and they had been treated for diabetes for 8 to 10 years. The populations were different, and decisions need to be made with these facts in mind.

My recommendations. Treatment decisions should be individualized. For patients with recently diagnosed diabetes, aggressive treatment (HbA_{1c} goal of as close to 6.0% as possible) will lower cardiovascular risk in addition to significantly reducing the risk of retinopathy, neuropathy, and nephropathy. If a patient has had diabetes for 10 to 15 years, is older, has difficulty in sensing hypoglycemia, and also has a history of significant cardiovascular events, less aggressive treatment is indicated (HbA_{1c} goal of 7.0% to 7.5%). It is also important *not to reduce* HbA_{1c} *rapidly* with medications, especially insulin. Gradual lowering over 6 months to a year is advised. Patients' resources and ability to cope should also influence decision making. Patients with good support systems, self-confidence, and motivation are more likely to be able to understand and adapt to an aggressive treatment plan.[15]

VALUE OF EARLY AGGRESSIVE TREATMENT

The day a patient receives a diagnosis of type 2 diabetes, he or she has been living with significant metabolic abnormalities for 10 to 12

CLINICAL HIGHLIGHTS

❑ Use hemoglobin A_{1c} (HbA_{1c}) done by a certified laboratory for the diagnosis of diabetes. Repeat the HbA_{1c} if the blood glucose values were normal. Point of care HbA_{1c} machines are helpful for following up patients with diabetes. Be sure the laboratory or instrument used is certified by the National Glycohemoglobin Standardization Program (NGSP).

❑ Patients' resources and ability to cope should also influence decision making. Patients with good support systems, self-confidence, and motivation are more likely to be able to adapt to an aggressive treatment plan.

❑ For patients whom you believe are at risk for diabetes, obtain an HbA_{1c} level and a blood glucose level as well. If the HbA_{1c} level is 5.7% to 6.4%, or the blood glucose value is abnormal, inform the patient of the increased risk of diabetes and its complications.

❑ For patients with recently diagnosed diabetes, aggressive treatment (HbA_{1c} goal of as close to 6.0% as possible) will lower cardiovascular risk in addition to significantly reducing the risk of retinopathy, neuropathy, and nephropathy.

❑ If a patient has had diabetes for 10 to 15 years, is older, has difficulty in sensing hypoglycemia, and also has a history of significant cardiovascular events, less aggressive treatment is indicated (HbA_{1c} goal of 7.0% to 7.5%). It is also important not to reduce HbA_{1c} rapidly with medications, especially insulin. Gradual lowering over 6 months to a year is advised.

❑ Continue to use statins in patients with diabetes. If triglycerides are elevated and/or the HDL-cholesterol level is low, consider niacin. If triglycerides remain over 500 mg/dL, add fibrates and fish oil to decrease the risk of pancreatitis

❑ It is still reasonable to attempt to achieve a goal of 130/80 mm Hg in all patients with diabetes. As always, we need to monitor our older patients for undesirable side effects.

years. Increasing resistance to the effects of insulin in muscle, the liver, and adipose tissue starts the process. The pancreas responds by secreting more insulin. Eventually, the beta cell is unable to secrete sufficient insulin to overcome the hyperglycemia of insulin resistance, and hyperglycemia appears. In other words, the pancreas is beginning to "burn out."

At the time of diagnosis, beta cell function may be decreased by up to 50% and beta cell mass is lost as a result of cell apoptosis.[16] The apoptosis is secondary to glucotoxicity, lipotoxicity, and inflammatory cytokines.[17] Glucotoxicity results from elevated levels of glucose for a prolonged period, and lipotoxicity is caused by elevated free fatty acids (eg, triglycerides). Both are toxic to the beta cell. Insulin drives free fatty acids into the fat cell; insulin resistance decreases that movement, resulting in elevations of plasma free fatty acids and triglycerides. Uncontrolled diabetes is associated with an increased secretion of inflammatory cytokines from adipose tissue. This causes further toxicity to the beta cell.

In addition to lifestyle changes, several drugs may aid in preserving beta cell function. Animal studies conducted with thiazolidinediones[18,19] and glucagon-like peptide-1 agonists[20] indicate that they contribute to prolonged beta cell survival.

LIPID AND BLOOD PRESSURE GOALS

The ACCORD trial included a lipid arm and a blood pressure (BP) arm.[21,22] Both arms produced surprising results. The lipid arm compared the combination of fenofibrate and simvastatin, to simvastatin alone. Although the addition of fenofibrate decreased triglycerides and increased HDL-cholesterol levels, no reduction in cardiovascular events occurred in the majority of patients with type 2 diabetes who were at high risk for CVD. Although statins are effective in patients with type 2 diabetes, residual risk remains, especially in patients with elevated triglycerides and lower HDL-cholesterol levels. Other studies that attempt to show a decrease in cardiovascular events with fibrate therapy have produced mixed results.

My recommendations. Continue to use statins in patients with diabetes. If triglycerides are elevated and/or the HDL-cholesterol level is low, consider niacin. If triglycerides remain over 500 mg/dL, add fibrates and fish oil to decrease the risk of pancreatitis.

In the ACCORD BP arm, patients with type 2 diabetes who were at high risk for CVD were compared at two systolic BP targets (140 mm Hg and 120 mm Hg). Reaching the target of 120 mm Hg did not reduce the rate of fatal and nonfatal major cardiovascular events; however, there was a decreased occurrence of stroke. The interpretation of the ACCORD BP results is complicated by the fact that the event rate observed in the standard-therapy group was

almost 50% lower than the expected rate. This result may have been a consequence of the frequent use of statins and of inclusion criteria that directed participants with dyslipidemia into the ACCORD lipid trial, leaving participants who were at lower risk in the BP trial. Additional methodological problems with the ACCORD BP trial make it difficult to generalize the results.

My recommendations. It is still reasonable to attempt to achieve a goal of 130/80 mm Hg in all patients with diabetes. A sufficient number of other good studies support the value of this goal. As always, we need to monitor our older patients for undesirable side effects. ■

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