American College of Endocrinology Consensus Statement on Guidelines for Glycemic Control*

**Based on Consensus Development Conference, Washington, DC, August 20 and 21, 2001.*
See Appendix for consensus panel participants, presenters, and consensus statement writing committee.

INTRODUCTION

Diabetes is a global epidemic that affects more than 150 million people worldwide (1). In the United States, an estimated 16 million people have diabetes; more than 800,000 cases are diagnosed annually (2). With a 60% increase in adult obesity (body mass index ≥30 kg/m^2), together with rapid growth in the elderly and high-risk ethnic populations, diabetes prevalence within the total population in the United States now exceeds 7% (3). Because of its devastating chronic complications, diabetes has become the sixth leading cause of death in America and the major cause of disability from disease in the United States. Direct and indirect costs of diabetes in the United States were $98 billion in 1996 and are expected to exceed $100 billion in 2001 (2).

In light of the substantial evidence now available clearly in support of the benefits of "tighter" glycemic control, current US clinical practice guidelines may not adequately translate this new research-based knowledge to optimize reduction of microvascular and macrovascular complications of diabetes. Furthermore, despite the widespread use of self-monitoring of blood glucose, patients generally do not know their diabetes status and goals (4,5). In addition, a concern exists that recommendations for diagnosis and screening of diabetes are unclear relative to populations at greatest risk for developing diabetes. At the time of diagnosis of diabetes, an overall 50% prevalence of complications was seen in the United Kingdom Prospective Diabetes Study (UKPDS) population, an indication that diabetes was present long before the diagnosis was made (6). This finding has been reported in other studies as well (7).

The American College of Endocrinology (ACE) convened a consensus development conference on glycemic control on August 20 and 21, 2001, in Washington, DC. A panel of experts in endocrinology, diabetes, and metabolism heard presentations from invited speakers, who reviewed research from past and current studies on diabetes. The consensus committee statement that follows represents that panel's collective analyses, evaluations, and opinions based, in part, on the conference proceedings. The following questions were considered:

1. What is the goal of diabetes management?
2. To what extent does glycemic control attain that goal?
3. What factors should be used to assess glycemic control?
4. What are the guidelines for the attainment of glycemic control in patients with diabetes?
5. What further recommendations are needed regarding glycemic control and reduction of complications of diabetes?

CONSENSUS STATEMENT

Question 1. What is the goal of diabetes management?

The goal of diabetes management is the prevention of acute and chronic complications of diabetes mellitus. Traditional chronic complications of diabetes are viewed as the microvascular complications of diabetes, including retinopathy, nephropathy, and neuropathy. Nevertheless, the macrovascular complications of diabetes are more prevalent and are the major cause of disability and death in patients with diabetes.

Question 2. To what extent does glycemic control attain that goal?

Large-scale, randomized, prospective trials of various interventional therapies in patients with both type 1 and type 2 diabetes have clearly shown that reductions in hyperglycemia significantly decrease the microvascular complications of diabetes. Attempts at primary prevention of both eye and kidney disease by intensive diabetes management in the Diabetes Control and Complications Trial (DCCT) (8) and in the Kumamoto Study (9) reduced the incidence of these complications by 50 to 70%. In the intensive treatment cohort of the UKPDS, the incidence of microvascular complications was reduced by 25% (10). In general, all trials demonstrated a 30 to 35% reduction in microvascular complications per 1% absolute reduction of glycated hemoglobin (HbA1c). An epidemiologic analysis of the data from the UKPDS failed to demonstrate a threshold above which microvascular complications occur (6). In both the UKPDS and the DCCT, any reduction in high HbA1c levels was associated with a decrease in the risk of microvascular complications of diabetes.

In both the UKPDS and the DCCT, a trend toward a significant reduction in macrovascular complications was noted. In the overweight cohort of the UKPDS, a significant reduction in the incidence of macrovascular complications was achieved with metformin therapy only (11). An epidemiologic analysis of the entire patient population receiving intensive treatment, however, revealed a significant 14% reduction in macrovascular complications for every 1% reduction in HbA1c (6).

Fasting plasma glucose, postchallenge glucose, and postprandial glucose levels have been significantly associated with microvascular and macrovascular complications in several cross-sectional and prospectively followed epidemiologic studies. The associations have been most significant with regard to the classic microvascular complication of retinopathy and, to a lesser extent, nephropathy (12,13). The relationships between glycemia and macrovascular complications are more controversial. In general, many studies have noted significant associations of postchallenge and postprandial glycemia with

macrovascular risk; fewer studies, however, have reported such associations with fasting glycemia (14-22). A consistent feature in the literature has been the occurrence of increased cardiovascular risk at levels of plasma glucose far lower than those required for the diagnosis of diabetes. Furthermore, such increased cardiovascular risk appears much earlier in the evolution of type 2 diabetes than does the increased microvascular risk.

Question 3. What factors should be used to assess glycemic control?

It was the consensus of the panel that glycemic control be assessed primarily by periodic measurement of HbA1c levels. Secondary assessments should include regular measurement of both fasting preprandial and postprandial glucose levels.

Primary Assessment

HbA1c has become the "gold standard" for assessing and monitoring glycemic control in patients with type 1 and type 2 diabetes (8-10). HbA1c has been the independent variable against which rates of complications in all major trials have been assessed. Assays for HbA1c, traceable to the original DCCT methods, should form the basis for clinical determinations of glycated hemoglobin in medical practice. This methodology is generally based on high-performance liquid chromatography but may include other assays such as affinity chromatography as well. Currently, all laboratories determining HbA1c should use methods certified by the National Glycohemoglobin Standardization Program. The upper limit of normal for such methods is generally 6.0%.

Secondary Assessments

Before the development of glycated protein technologies, fasting plasma glucose levels were the primary basis for assessment of glycemic control. The utility of that approach is limited, however, because fasting glycemia can measure the glycemic burden only at a single point in time and may not accurately reflect overall glycemic control. With the advent of self-monitoring technology, assessments of fasting and preprandial plasma glucose levels have evolved into an important element of day-to-day decision making in the routine management of diabetes (23-27).

Postprandial hyperglycemia is a key component of the total glycemic burden in patients with diabetes; it is an important contributor to the HbA1c level, which can be viewed as reflecting the summation of both preprandial and postprandial glycemia (28). Thus, for maximal reduction of HbA1c levels, assessments of both preprandial and postprandial glucose levels are necessary as part of the diabetes management program (29).

Question 4. What are the guidelines for the attainment of glycemic control in patients with diabetes?

Hemoglobin A1c Target

In the epidemiologic analysis of the UKPDS data, the risk for occurrence of microvascular and macrovascular complications was shown to increase at HbA1c values of 6.5% or more (6). In the 6-year follow-up data of the UKPDS, the two-step progression of retinopathy was increased more than fourfold in the middle tertile of patients with HbA1c values of 6.2 to 7.5% in comparison with the tertile with HbA1c values <6.2%. HbA1c values >7.5% were associated with little additional progression of retinopathy beyond that seen for the range of 6.2 to 7.5% (30). A few smaller cohort trials further corroborate the significance of HbA1c elevations that exceed 6.5% (31-33). These findings are also consistent with several epidemiologic studies that have implicated the association of high HbA1c levels with the development of complications of diabetes, especially atherosclerosis (even in cohorts without diabetes) (34). No differential effect of hyperglycemia on rates of occurrence of microvascular complications could be observed between the data obtained in patients with type 1 and those with type 2 diabetes. The data from the DCCT (35) showed a relationship between HbA1c and the incidence of retinopathy, similar to that seen in the UKPDS. Moreover, in both studies, glycemic reductions yielded similar benefits with regard to the incidence of retinopathy and nephropathy for equal degrees of HbA1c reduction.

The panel recommends that HbA1c be universally adopted as the primary method of assessment of glycemic control. On the basis of data from multiple interventional trials, the target for attainment of glycemic control should be HbA1c values ≤6.5%. This level is three standard deviations above the mean HbA1c value in nondiabetic populations (34).

The panel further recommends that HbA1c assessments be performed at least twice per year in patients who are at target. Assessments should be performed quarterly or more frequently in patients who are above target, who are undergoing a change in therapy, or both. In addition, the panel recommends that, in agreement with the National Diabetes Education Program and the National Glycohemoglobin Standardization Program, the standard name for the HbA1c test should be "A1C."

Fasting Preprandial Glucose Targets

The treatment target for the UKPDS was a fasting blood glucose level <108 mg/dL (10). In the National Health and Nutrition Examination Survey (NHANES) III database, increased risk of retinopathy is clearly associated with fasting plasma glucose levels in the interval 110 to

119 mg/dL (36). Fasting plasma glucose levels >110 mg/dL are also associated with substantial cardiovascular risk. For example, in more than 3,500 patients without diabetes randomized in the Cholesterol and Recurrent Events (CARE) study, rates of recurrence of cardiovascular events increased as fasting plasma glucose levels increased above 90 mg/dL and had virtually doubled in the cohort with fasting plasma glucose levels of 110 to 115 mg/dL (37). Therefore, the panel recommends that laboratory assessments of fasting plasma glucose should target a value of <110 mg/dL. A similar value for preprandial plasma glucose seems reasonable. Values obtained by self-monitoring of blood glucose may or may not reflect plasma glucose. Accordingly, patients and health-care providers should become familiar with what the individual meters measure.

Postprandial Glucose Target

The published literature includes a relatively smaller body of evidence from which to draw conclusions about guidelines for postprandial glucose control. No interventional trials with outcome data have focused on postprandial glucose control per se. Many of the studies are epidemiologic, and data have been obtained with use of postchallenge glucose levels rather than postprandial loads. Some of the test meals have been liquid, which may yield outcomes that differ from those with solid food. These caveats notwithstanding, a large number of highly robust cross-sectional and prospective epidemiologic studies have clearly implicated a close association between postchallenge or postprandial hyperglycemia and cardiovascular risk (14,16-18,22,23,32,33,38). These studies encompass diverse populations and disparate geographic regions, from Honolulu to Chicago to Islington to Paris. A recent analysis of 25,000 patients in the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) Study (19) supports the concept of an important link between postchallenge glycemia and macrovascular risk. Furthermore, Hanefeld et al (15) showed that moderate postprandial hyperglycemia (148 to 199 mg/dL) not only is more indicative of atherosclerosis than fasting plasma glucose levels but also may exert direct detrimental effects on the endothelium.

Independent of complications per se, diabetes control targeting postprandial hyperglycemia proved more effective than use of fasting hyperglycemia in reducing HbA1c levels in pregnant and nonpregnant patients with type 2 diabetes (27,28). Indeed, investigators have suggested that postprandial glycemia may better correlate with HbA1c levels than fasting glycemia (28). In subjects without diabetes, blood glucose levels typically peak approximately 1 hour after the start of a meal and return to preprandial levels within 2 to 3 hours; 2-hour postprandial blood glucose levels rarely exceed 140 mg/dL (39,40). Therefore, the consensus panel recommends a treatment-targeted 2-hour postprandial blood glucose level of <140 mg/dL.

Risk-to-Benefit Ratio

Under some circumstances, these guidelines may be modified for individual patients whose functional state or risk for other adverse treatment effects (such as hypoglycemia unawareness) is thought to outweigh the benefits of optimal glucose control. All the aforementioned large prospective interventional studies demonstrated an increased risk of hypoglycemic episodes in patients with tight glycemic control—particularly with use of insulin or insulin secretagogues. Nonetheless, the panel believes that the current spectrum of therapeutic strategies and the available monitoring devices allow more precise titration of blood glucose, which is associated with a reduced risk of hypoglycemia. For example, the new rapid-acting insulin analogs (such as insulin lispro and insulin aspart) have been shown to produce higher serum insulin levels earlier with a shorter duration of action than regular human insulin (41,42). This effect not only decreases the degree and duration of postprandial hyperglycemia but also reduces the incidence and severity of hypoglycemia (41,42). Furthermore, Lalli et al (43) demonstrated that lower HbA1c levels can be achieved without an increased incidence of hypoglycemia when insulin lispro is used. The safety and efficacy of the new rapid-acting oral secretagogues (for example, repaglinide and nateglinide) have also been demonstrated in numerous clinical studies (44,45). In summary, new medications and technologies facilitate tighter control of glycemia without increasing the risk of hypoglycemia.

Question 5. What further recommendations are needed regarding glycemic control and reduction of complications of diabetes?

Case Finding

Patients with diabetes should be identified as early as possible in their illness. The consensus panel recognizes that the current screening guidelines for diagnosis of diabetes have resulted in an overall 50% prevalence of complications at the time of diagnosis; thus, diabetes is present long before the diagnosis is made (10).

The panel recommends targeted screening for populations at high risk for the development of diabetes. Risk factors include the following:

- Family history of diabetes
- Cardiovascular disease
- Overweight
- Sedentary lifestyle
- Latino/Hispanic, African American, Asian American, Native American, or Pacific Islander ethnicity
- Previously identified impaired glucose tolerance or impaired fasting glucose
- Hypertension
- Increased levels of triglycerides, low concentrations of high-density lipoprotein cholesterol, or both
- History of gestational diabetes

- Delivery of a baby weighing more than 9 pounds (4 kg)
- Polycystic ovary syndrome

The high frequency of complications at the time of diagnosis of diabetes, with use of current screening guidelines, makes earlier diagnosis imperative. Moreover, prevalence data on newly diagnosed cases of diabetes indicate a younger age at onset within the general population, and especially among high-risk ethnic minority populations. Recent data from the Centers for Disease Control and Prevention (2) showed a 76% increase in the prevalence of diabetes in adults 30 to 39 years old. Therefore, the panel recommends targeted case finding in high-risk persons 30 years of age or older.

Additional Research

Data about the impact of glycemic control on the development of microvascular complications suggest a differential sensitivity to hyperglycemia in some minority populations (46-49). This relationship seems to prevail even after adjustment for comorbid conditions (50). Further research quantifying this phenomenon and elucidating the mechanism (or mechanisms) by which such differential sensitivity could occur should be pursued. The differential sensitivity to hyperglycemia also seems to have a genetic component, which is independent of comorbid conditions (51). Additional research in this area should also be undertaken.

Finally, the epidemiologic evidence presented at the consensus conference suggested a robust relationship between postchallenge hyperglycemia and cardiovascular risk. Precise quantification of this finding should be explored in a large-scale, prospective, randomized, interventional trial, focusing on postprandial glycemic control as the principal intervention.

SUMMARY

Large, randomized, interventional trials have provided conclusive evidence that achieving and sustaining tight glycemic control significantly reduces the risk of developing diabetes-related microvascular and macrovascular complications (6,8-10). Because patients who participated in these trials failed to achieve target HbA1c values (<7%), it might be argued that the glycemic targets recommended by the consensus panel are unrealistic and perhaps unachievable by most patients and clinicians. This argument, however, contradicts sound clinical judgment. Studies have found no glycemic threshold beyond the normal range for reducing microvascular and macrovascular complications (6). In other words, patients who achieve *any* reduction in levels of HbA1c significantly decrease the risk for complications of diabetes—regardless of their ability to achieve the specific glycemic targets recommended by the consensus panel (6). Therefore, the consensus panel believes that the setting of clinical standards should reflect the best estimate of maximal benefit that may accrue from that care and should not depend on the ease or convenience of attaining such targets for either patients or clinicians. Furthermore, the consensus panel believes that establishing glycemic targets that assist and encourage patients and clinicians to achieve normoglycemia will result in improved health, augmented longevity, and enhanced quality of life. These are, after all, the goals of diabetes management.

APPENDIX

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