ACE/AACE Consensus Statement

DIAGNOSIS AND MANAGEMENT OF PREDIABETES IN THE CONTINUUM OF HYPERGLYCEMIA—WHEN DO THE RISKS OF DIABETES BEGIN? A CONSENSUS STATEMENT FROM THE AMERICAN COLLEGE OF ENDOCRINOLOGY AND THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS*

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Abbreviations:
AACE = American Association of Clinical Endocrinologists; **ACE** = American College of Endocrinology; **CVD** = cardiovascular disease; **IFG** = impaired fasting glucose; **IGT** = impaired glucose tolerance; **NCEP** = National Cholesterol Education Program; **QALY** = quality-adjusted life-year

INTRODUCTION

A worldwide pandemic of obesity and diabetes is well advanced. In the United States alone, diabetes now affects an estimated 24.1 million people, an increase of more than 3 million in approximately 2 years. Twenty-five percent of persons with diabetes in the United States do not know they have diabetes. Another 57 million people in the United States have prediabetes (1), defined as people with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), some of whom in fact already have the characteristic microvascular changes resulting from diabetes itself (2,3). Worldwide, the number of people with prediabetes is estimated to be 314 million and is projected to be 418 million in 2025 (4). As the prevalence of and progression to diabetes continue to increase, diabetes-related morbidity and mortality have emerged as major public health care issues. Diabetes is expensive—the associated yearly cost of diabetes in the United States is $174 billion. Direct costs related to diabetes, diabetes complications, and general medical care are $116 billion, and indirect costs are $58 billion from illness, disability, and premature mortality (5).

Prediabetes raises short-term absolute risk of type 2 diabetes by 3-to 10-fold, with some populations exhibiting greater risk than others (6,7). People with diabetes are vulnerable to multiple and complex medical complications. These complications involve both cardiovascular disease (CVD) (heart disease, stroke, and peripheral vascular disease) and microvascular disease (ie, retinopathy, neuropathy, and microalbuminuria). Most patients with diabetes die of CVD (8).

Epidemiologic evidence suggests that the complications of diabetes begin early in the progression from normal glucose tolerance to frank diabetes. Early identification and treatment of persons with prediabetes have the potential to reduce or delay the progression to diabetes (9-13) and related CVD (14,15) and microvascular disease (16).

Despite the clear origins of diabetes-related complications early in the prediabetic state, few recommendations have been made for the diagnosis and management of patients with prediabetes. No medications are approved by the US Food and Drug Administration for addressing either IFG or IGT. Most insurance companies deny payment for lifestyle treatment to prevent diabetes. There are differences in opinion among health care professionals regarding the therapeutic approach to treating people with prediabetes. Many of these people already have diabetes-related complications, yet there are no defined goals and targets of treatment in prediabetes for the many risk factors, which include glucose levels, weight, blood pressure, and lipid levels.

It is clear that the risks and adverse consequences of high blood glucose occur at much lower glucose levels than those at which we currently define as diabetes. Acknowledging these many challenges, there are major questions that health care professionals must address such as: “When do the risks of diabetes begin?”; “What can we do to prevent diabetes?”; “What strategies are necessary to reduce the vascular complications related to diabetes?”; and “How does society pay for the preventive costs of diabetes in the large number of patients at risk?”

CONSIDERATIONS

The American College of Endocrinology (ACE) Task Force on the Prevention of Diabetes was convened under the auspices of ACE. This group formulated 6 specific diagnostic and management questions. Over a 2-day period, 23 international experts reviewed all available scientific data to assist the committee in addressing these questions (Appendix 1).

The consensus conference examined the current status of prediabetes, the facts about related complications, what happens to people who progress to diabetes, available intervention trials, economic implications of early intervention, and what future studies are needed.

The consensus conference’s recommendations are primarily based upon analysis of the available scientific evidence; expert opinion was used when necessary.

These recommendations are aimed at the general medical community and are especially directed at general primary care physicians, health care providers, and educators because they are at the forefront of treating this condition. The message also calls upon national and local community leaders and governments to increase efforts to curtail the obesity and diabetes epidemics and for further research in this high-risk population.

ACE and the American Association of Clinical Endocrinologists (AACE) are available to support medical societies and public efforts in implementing these recommendations.

QUESTION 1

What is the spectrum between normal glucose tolerance, prediabetes, and diabetes, and what should be the diagnostic criteria for each?

Prediabetes currently refers to people who have IFG (100-125 mg/dL [5.6-6.9 mmol/L]), IGT (2-hour postglucose load, 140-199 mg/dL [7.8-11 mmol/L]), or both.

There is a continuous spectrum of glucose levels between those considered normal (fasting <100 mg/dL [<5.6 mmol/L]; postchallenge <140 mg/dL [<7.8 mmol/L]) and those that are considered diagnostic for diabetes (fasting ≥126 mg/dL [≥7 mmol/L]; postchallenge ≥200 mg/dL [≥11.1 mmol/L]). IGT should be considered more important for risk than IFG.

Presently, diabetes is diagnosed somewhat arbitrarily on the basis of the glucose level associated with the eventual appearance of characteristic end-organ complications, specifically retinopathy. Currently, diabetes may be diagnosed at a fasting plasma glucose level of 126 mg/dL (7 mmol/L) or higher or a 2-hour postglucose challenge plasma glucose concentration of 200 mg/dL (11.1 mmol/L) or higher (17,18). However, in large population studies, values for both normal fasting and 2-hour plasma glucose levels are considerably lower than these thresholds for diagnosing diabetes. The upper limit of normal fasting plasma glucose is widely believed to be 99 mg/dL (5.5 mmol/L) although metabolic and vascular abnormalities have been described recently at values less than that. Similarly, 2-hour postglucose levels less than 140 mg/dL (7.8 mmol/L) are believed to be within the reference range. Whatever label is given to the "gap" in glycemic status between normal and diabetes, the data indicate that, for many individuals, these glucose levels are not benign and may herald overt type 2 diabetes and CVD (19,20), as well as microvascular complications (2,3). Thus, the ill-defined area in fasting glucose of 100 to 125 mg/dL (5.6-6.9 mmol/L) and 2-hour levels of 140 to 199 mg/dL (7.8-11 mmol/L) is thought to describe a prediabetic range, where some degree of increased microvascular and macrovascular complications of diabetes has been described (21,22).

This intermediate state of prediabetes constitutes inherent disease risk. The progression to diabetes for patients with IGT is 6% to 10% per year, and for persons with both IFG and IGT, the cumulative incidence of diabetes by 6 years may be as high as 65% (compared with levels on the order of 5% for those with normal glucose levels at baseline) (23). Approximately half of patients with IGT meet the National Cholesterol Education Program (NCEP) criteria for the diagnosis of metabolic syndrome (24).

Numerous investigations indicate that the risk of CVD maintains a linear association with glycemia well below the present diagnostic threshold for type 2 diabetes and extends to lower glucose levels than those defined by the criteria for the diagnosis of IFG and IGT (25,26) into the range of glucose otherwise considered normal (27). In addition, the CVD event rate in epidemiologic studies, such as AusDiab (Australian Diabetes, Obesity, and Lifestyle Study) (25) and Framingham (20) and intervention studies such as STOP-NIDDM (Study to Prevent Non–Insulin-Dependent Diabetes Mellitus) (14) and DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) (10), suggest nearly a doubling of cardiovascular risk in prediabetes compared with what would be expected for individuals without IFG or IGT. The Nurses' Health Study demonstrated that women destined to convert to type 2 diabetes (a "true" prediabetes population) have nearly 3 times the risk of a cardiovascular event compared with those who remained nondiabetic over an extended follow-up period (28).

Conversion of IFG to diabetes further increases CVD mortality 2-fold (29). Similarly, the DECODE study (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) found a higher coronary heart disease risk with elevated 2-hour postglucose levels even in the presence of normal fasting glucose levels (22). The syndrome of multiple cardiovascular risk factors or the metabolic syndrome described by NCEP characterizes a group of individuals at increased risk of diabetes, as well as CVD. The age-adjusted risk in the Framingham offspring study with metabolic syndrome was 2.54 for coronary heart disease and 6.92 for diabetes in men, whereas in women, coronary heart disease risk was lower at 1.5 while diabetes risk was similar at 6.5 (7). Thus, IFG, IGT, and metabolic syndrome may each describe a prediabetic state that appears to have coincident heightened coronary heart disease risk. For example, in the San Antonio Heart Study, IGT increased future diabetes risk by approximately 5-fold, as did a diagnosis of the metabolic syndrome (30). Individuals with combinations of these high risk states have increased absolute risk for type 2 diabetes compared with individuals who meet criteria for only a single risk category. In the Insulin Resistance Atherosclerosis Study, Haffner et al (unpublished data, 2008) found that patients with a diagnosis of IGT, IFG, or metabolic syndrome converted to diabetes at a rate of 8% to 10% per year, and if all 3 diagnoses were present, conversion rates far exceeded 10% per year.

More traditional diagnoses of prediabetes are future-based risk predictions and include women with a history of polycystic ovary syndrome or gestational diabetes, offspring of parents with type 2 diabetes, and individuals with abdominal adiposity. Patients with CVD also have an increased prevalence of prediabetes. Type 2 diabetes is also being observed with increased frequency in adolescents, but is uncommon in children younger than 10 years (31).

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

- Family history of diabetes (18)
- Cardiovascular Disease (18)
- Being overweight or obese (18)
- Sedentary lifestyle (18)
- Non-white ancestry (18)

- Previously identified IGT, IFG, and/or metabolic syndrome (18)
- Hypertension (18)
- Increased levels of triglycerides, low concentrations of high-density lipoprotein cholesterol, or both (18)
- History of gestational diabetes (18)
- Delivery of a baby weighing more than 9 lb (4 kg) (18)
- Polycystic ovary syndrome (18)
- Receiving antipsychotic therapy for schizophrenia and severe bipolar disease (32)

A diagnosis of prediabetes can be made by any of 3 criteria (3): (a) IFG with glucose levels of 100 to 125 mg/dL (5.6-6.9 mmol/L). IFG should be determined after an overnight fast (8 hours minimum). Patients should not be active or have had caffeine or any other factor known to affect carbohydrate metabolism. (b) IGT with glucose levels of 140 to 199 mg/dL (7.8-11 mmol/L) after a 75-g oral glucose load given in the morning (after an appropriate overnight fast) (33). Patients should be on an adequate carbohydrate intake before the test, should not be physically active during the test, and must not smoke. For purposes of diagnosing IGT, a single sample drawn after a 2-hour glucose load is sufficient. The benefit to be gained by a 2-hour glucose tolerance test was considerable in the EUROHEART survey. Patients with impaired glucose metabolism identified by 2-hour oral glucose tolerance testing were greater in number than patients identified by routine determination of fasting glucose alone (34). In patients with IFG, a 2-hour glucose tolerance test may further clarify the level of risk while also detecting undiagnosed diabetes. (c) Metabolic syndrome diagnosed by the NCEP criteria (24) should be considered a prediabetes equivalent. It predicts future diabetes better than IFG. Three of 5 metabolic syndrome criteria are sufficient; recent evidence suggests even 2 of 5 metabolic syndrome criteria may be adequate as well.

Thus, it seems clear that prediabetic states may represent heterogeneous etiologies. These states not only entail increased risk of diabetes, but also increased risk of CVD. Progression rates of metabolic syndrome, IFG, or IGT to diabetes vary according to degrees of initial hyperglycemia, racial and ethnic backgrounds, and environmental influences. The higher the glucose values, the greater the risk of progression to diabetes and diabetic complications (35).

QUESTION 2

What are the clinical risks of not treating prediabetes?

In order to assess the clinical risk of not treating prediabetes, there are 2 obvious sources of data: (a) observational data from populations of patients with prediabetes and (b) data from interventional studies comparing placebo with active treatment.

Most, if not all, diabetic complications progressively worsen as glycemia worsens. In the DECODE study of more than 22 000 patients, 2-hour postload glucose levels were associated with a linear increase in hazard ratio for all-cause mortality as the 2-hour blood glucose concentration increased from 95 to 200 mg/dL (5.3-11.1 mmol/L) (36). Over this range of 2-hour glucose levels, the risk doubled and approached that of patients treated for diabetes. A 10-year follow-up of a population-based cohort of Finnish subjects (37) comparing participants with normal glucose tolerance with participants who had IGT at baseline, participants with nonprogressive IGT, and participants with IGT that progressed to diabetes, showed a 130% increase in cardiovascular mortality in those who did not progress to diabetes compared with only a 70% increase in individuals who developed diabetes during follow-up. In a 23-year follow-up of the Honolulu Heart Study, an increase in sudden death was associated with postchallenge hyperglycemia (38).

With regard to interventional trials, in the Diabetes Prevention Program, diabetic retinopathy was observed in 7.9% of patients with IGT compared with 12.6% in patients with IGT that later progressed to diabetes. Furthermore, in the placebo IGT group, there was a progressive increase in the prevalence of hypertension from 29% to 38%, an increase in the prevalence of dyslipidemia from 6% to 16% (15), and an increase in the prevalence of clinical CVD events by approximately 50% (relative risk 0.47 over 4 years) (14). IGT was also associated with impaired indices of autonomic function (39).

In other recent studies, the incidence of retinopathy in IFG has been higher (9% to 16%) than that described for the Diabetes Prevention Program (7.9% to 12.6%) (3). The prevalence of retinopathy has been observed to increase dramatically in the highest deciles of each glycemic measure. In the STOP-NIDDM trial, there was a 16% cumulative increase in hypertension (>140/90 mm Hg) in the placebo-treated IGT participants over a 3-year period. More gradual increases in microalbuminuria prevalence for patients with IGT have also been observed (2). In patients presenting with idiopathic peripheral neuropathy, approximately 40% have IGT (40).

Findings from these studies suggest that patients with IGT are at risk when IGT is identified, and when untreated, these patients experience progression in their incidence of diabetes, as well as in microvascular and macrovascular risk.

QUESTION 3

What goals and treatment modalities should be the focus of prediabetes management?

The management of prediabetes involves a set of global treatment measures designed to address its abnormalities and cardiometabolic disease risks. The preferred treatment approach for all the abnormalities is intensive lifestyle management, given its safety and the strength of evidence for its effectiveness in improving glycemia and reducing cardiovascular risk factors.

However, as prediabetes progresses, drug therapies directed towards hyperglycemia and the individual coronary heart disease risk factors may be required. Strict control of all known risk factors for CVD and microvascular complications in patients with type 2 diabetes by aggressive management of hypertension, dyslipidemia, and glycemia and use of aspirin (as well as smoking cessation) has proved to be highly beneficial (41).

We propose a set of treatment goals for blood pressure and lipid control matching those for diabetes, given the strong evidence of increased cardiovascular risk for persons with prediabetes. These interventions, after or with lifestyle changes, may reduce CVD risks independently of treatments focused on the issue of glucose control and the prevention of microvascular risk.

Much of our approach has been based on the possibility that glucose control in overt diabetes may not improve the coronary heart disease risk of diabetes (41-44); therefore, glucose-directed therapies alone will not suffice for prediabetes. The failure of late treatment strengthens the argument for early treatment. This provides the rationale for the 2-track approach to complication prevention, specifically interventions to lower glucose to prevent microvascular complications and progression to diabetes and interventions that address vascular disease risk factors to prevent CVD.

Lifestyle

Lifestyle modification should be the cornerstone of treatment; it should be attempted with all patients and reinforced in every visit with the health care professional. Lifestyle is a fundamental management approach that can effectively prevent or delay progression from prediabetes to diabetes, as well as reduce both microvascular and macrovascular disease risks. Importantly, lifestyle interventions improve the panoply of risk factors for diabetes and components of the metabolic syndrome: obesity, hypertension, dyslipidemia, and hyperglycemia.

Persons with prediabetes should reduce weight by 5% to 10%, with long-term maintenance at this level, on the basis of the Diabetes Prevention Program findings. Even this modest degree of weight loss results in decreased fat mass, blood pressure, glucose, low-density lipoprotein cholesterol, and triglycerides. These benefits can also translate into improved long-term outcome, especially if weight loss and lifestyle alterations are maintained (12,45-47). In long-term follow-up from the Finnish Diabetes Prevention Program (12), lifestyle intervention in people at high risk for type 2 diabetes resulted in sustained lifestyle changes and reduction in diabetes incidence, which persisted after individual lifestyle counseling was stopped. A program of regular moderate-intensity physical activity for 30 to 60 minutes daily, at least 5 days weekly, is recommended. A diet that includes calorie restriction, increased fiber intake, and possible limitations in carbohydrate intake is advised. Specifically for blood pressure, dietary recommendations include lower sodium intake and avoidance of excess alcohol. Lifestyle modification is recommended for all ages, although adjustments in the prescription may be necessary on an individual basis.

While lifestyle management may be difficult to maintain, the following have been shown to increase the likelihood of success: patient self-monitoring, realistic and stepwise goal setting, stimulus control, cognitive strategies, social support, and appropriate reinforcement. Physicians should focus on reinforcing maintenance of weight loss as the long-term goal.

Medical Weight-Loss Strategies

In addition, one could consider pharmacologic treatment for obesity. There is evidence that orlistat prevents progression from prediabetes to diabetes (48,49). Sibutramine has an effectiveness similar to orlistat with regard to reducing weight, improving lipid levels, and improving glycemic control, but may have adverse blood pressure effects in some patients that must be considered (50). Cannabinoid receptor antagonists, although effective in reducing weight and improving glycemia (51), may cause anxiety and depression (52) and are not currently approved in the United States.

Bariatric surgery also is effective in reducing the likelihood of diabetes development in patients who are morbidly obese (body mass index greater than 40 kg/m^2) or who have other significant risk factors, but the members of the committee did not believe that a general recommendation was appropriate for patients with prediabetes.

Pharmacotherapy in Prediabetes

Glycemia

Currently, there are no pharmacologic therapies that have been approved by the US Food and Drug Administration for the prevention of diabetes in adults, nor are there any approved pharmacologic options for use in children or adolescents. Thus, any decision to implement pharmacologic therapy for prediabetes, and specifically in children/adolescents, is off-label and requires careful judgment regarding the risks and benefits of each specific agent in each individual patient. Pharmacologic drug therapy should be considered for higher-risk patients rather than lower-risk patients unless there is evidence for progressive deterioration of blood glucose levels despite lifestyle modification. Before prescribing pharmacologic agents to high-

risk patients, an individual assessment of risk and benefit should be done.

The goals of early glucose-directed therapies are to normalize glucose levels, to prevent or delay progression to diabetes, and to prevent microvascular complications. For patients at particularly high risk, pharmacologic glycemic treatment may be considered in addition to lifestyle strategies. Such high-risk patients include those with (a) some combination of IFG, IGT, and/or metabolic syndrome (ie, any 2 of these risk categories) and (b) worsening glycemia, cardiovascular disease, nonalcoholic fatty liver disease, history of gestational diabetes, or polycystic ovary syndrome.

There is strong evidence from randomized multicenter interventional trials that metformin or acarbose reduce the progression of prediabetes to diabetes (9,53). While both agents are less effective than intensive lifestyle interventions, they do have relatively good safety profiles. Additionally, acarbose may be associated with a reduced risk of coronary heart disease as shown in the STOP-NIDDM trial (14).

There is robust published clinical trial evidence demonstrating that thiazolidinediones decrease the likelihood of progression from prediabetes to diabetes including findings from DREAM (10), Diabetes Prevention Program (54), and possibly ACT-NOW (unpublished data, 2008). Because concerns have developed regarding the safety of long-term use of these agents in a low-risk patient population, their use should be reserved for the higher-risk populations and those for whom other lower-risk strategies have failed.

Incretin-based therapies may eventually prove to effectively prevent diabetes because of their effects in maintaining or improving β-cell function and mass in experimental animals and in light of their beneficial effects on insulin secretion and β-cell function in humans (55-57). Since β-cell defects appear to drive the progression from prediabetes to diabetes, incretin-based therapies and thiazolidinediones, which also have β-cell benefits, should in theory be effective for diabetes prevention. However, long-term clinical trials are clearly needed to evaluate both the efficacy and safety of glucagonlike peptide 1 agonists and dipeptidyl peptidase IV inhibitors for long-term use in diabetes prevention.

Lipids

The committee believes that persons with prediabetes should have the same lipid goals as those with established diabetes. Although data are limited, the safety and ease of therapy for blood pressure and lipids is such that being proactive is defensible. Certainly, long-term clinical studies should be done to evaluate this. As such, statin therapy is recommended to achieve low-density lipoprotein cholesterol levels of 100 mg/dL or below (≤2.59 mmol/L). In addition, attention should be given to achieving goals for non–high-density lipoprotein cholesterol of 130 mg/dL (3.367 mmol/L) or less (and/or apolipoprotein B ≤90 mg/dL [≤0.9 g/L]). Additional use of fibrates, bile-acid sequestrants, ezetimibe, and other agents should be considered as appropriate. Bile-acid sequestrants may play a unique role in prediabetes because one of the drugs in this class, colesevelam, reduces glucose levels and is, in fact, approved for the treatment of diabetes, addressing both cardiovascular and diabetes risk factors. Although niacin is recognized as having important lipid benefits, its potential for adverse glycemic effect must be considered, especially for prediabetic patients in whom safety has not been studied.

Blood Pressure

Recognizing the limitations of data in prediabetes, the committee recommends that prediabetic patients achieve the same target blood pressure currently recommended for persons with diabetes—that is, a systolic pressure less than 130 mm Hg and a diastolic pressure less than 80 mm Hg. Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers should be first-line agents, with calcium channel blockers as appropriate second-line treatment approaches. Thiazides, β-adrenergic blockers, or their combination, should be used with caution because of adverse effects on glycemia. Controlling blood pressure mitigates many of the vascular complications of diabetes.

Antiplatelet Therapy

Low-dose aspirin is recommended for all persons with prediabetes for whom there is no identified excess risk for gastrointestinal, intracranial, or other hemorrhagic condition.

Considerations in the Child and Adolescent

The management of the child or adolescent at increased risk for the development of type 2 diabetes in childhood or later in life should use many of the measures recommended to prevent or delay the progression to diabetes in adults at increased risk. In the young patient at risk, emphasis must be placed primarily on lifestyle change, which can be beneficial in improving glycemic and cardiovascular risk parameters. Although there have been few intervention studies in children that are directed at reducing diabetes and/or cardiovascular risk, the increased incidence of type 2 diabetes in this age group has paralleled the increase in obesity, which has been attributed to increased caloric consumption and diminished exercise/activity. Reduction of body mass index and the benefits of increased exercise and physical activity are at least as important in this age category as they are in adults at risk. Interventions to achieve a healthier lifestyle have been family based (58) and school based (59), as well as those used with individuals. In the growing child, one must be cautious about recommending weight loss, being more attentive to achieving and pre-

serving appropriate weight for height or body mass index appropriate for age and sex. Guidelines for treating hypertension and dyslipidemia in children have been established by other expert groups (60,61).

QUESTION 4

What are the appropriate measures to monitor prediabetes and its treatment? Should we measure parameters of glucose, and if so, which ones?

This depends to an extent on risk stratification of the individual, with more monitoring appropriate for those at the highest levels of risk based on many factors including glucose, lipid, and blood pressure abnormalities and family history, etc. In general, monitoring of patients with prediabetes to assess for worsening glycemic status should include annual measurement of fasting glucose and hemoglobin A_{1c}, with 2-hour postchallenge glucose tolerance testing for those in whom progression is suspected and a more sensitive measure is needed. Patients with prediabetes should also have assessment for microalbuminuria, measurement of fasting lipid concentrations, and measurement of blood pressure at least annually. Those patients at highest risk (more than 1 of IGT, IFG, or metabolic syndrome) should be monitored more frequently.

In the future, biomarkers and genetic markers may allow more targeted interventions and even lead to suggested therapeutic options in appropriately selected individuals at high risk.

QUESTION 5

Can society afford the costs of treating or not treating the prediabetic state?

Prevention of diabetes is a key strategy for reducing patient suffering and the high social costs of the disease. Diabetes costs are driven by vascular complications (62), which account for more than 50% of total costs largely through expenses incurred during hospitalizations (5). The health care costs of diabetes increase with disease duration, and, even though the costs of macrovascular complications predominate, microvascular complications command a progressively greater proportion of cumulative costs over time, amounting to 48% after 30 years of diabetes (63). Diabetes prevention will delay diabetes onset and predictably result in decreased disease exposure and fewer complications. Thus, the costs of diabetes prevention can be balanced against cost savings realized from fewer patient-years of the disease, reduction in complications, and decreased need for hospitalization.

The cost-effectiveness of diabetes prevention has been assessed for several different interventions. In these analyses, costs pertain to both interventions and outcomes, with health outcomes expressed as quality-adjusted life-years (QALYs) that adjust length of life for quality of life. In particular, the Diabetes Prevention Program has provided a rich source of data that can be used to assess cost-effectiveness of lifestyle intervention or metformin to prevent the development of diabetes in patients with IGT (63,64). Cost-effectiveness analyses have been performed using a Markov lifetime simulation model for diabetes progression developed by the Centers for Disease Control and Prevention and the Research Triangle Institute International. The model follows a patient from onset of IGT until death, uses Diabetes Prevention Program intervention costs and quality of life measurements, presupposes a 10-year interval between IGT onset and appearance of diabetes, and assumes vascular disease complication rates based on the UKPDS (United Kingdom Prospective Diabetes Study). Compared with placebo, metformin was found to delay onset of diabetes by 3 years and to reduce cumulative incidence of diabetes by 8% after 30 years, while lifestyle intervention delayed diabetes onset by 11 years with a 20% diminution in diabetes cumulative incidence. Lifestyle intervention led to a net increase in 0.57 QALY relative to placebo at a net increase in cost of $635 per individual, resulting in a cost of $1124 per QALY. This cost for quality life-year saved compares quite well to accepted interventions for other illnesses, as it is only between 1% and 10% of the cost per QALY achieved for antihypertensive treatment, coronary artery–bypass graft, and cholesterol-lowering therapy. Another study analyzed Diabetes Prevention Program data using the Archimedes model to predict outcomes and complication rates based on Kaiser Permanente patient care data, epidemiologic observations, and clinical trials (64). These authors found that cost per QALY was much higher for lifestyle intervention at $143 000 per QALY; this higher cost estimation can be explained by multiple differences in assumptions (eg, assuming a stable hemoglobin A_{1c} of 7% associated with lower complication rates as opposed to increasing hemoglobin A_{1c} as in the UKPDS). Compared with no program, these latter authors concluded that lifestyle modification for high-risk people could result in actual cost savings over 30 years if the annual cost of the intervention can be reduced to about $100 and/or be provided in a group format. This may amount to generic medications and large-group interventions.

Multiple other cost-effectiveness studies addressing lifestyle interventions demonstrate a net cost savings for life-year gained (66-69). Importantly, there are also current initiatives to translate the Diabetes Prevention Program into lower-cost interventions in communities, and these efforts, if successful in achieving comparable weight loss, will dramatically enhance cost-effectiveness. Thus, vigorous efforts are warranted in communities and health care systems to develop lifestyle interventions that effectively delay or prevent progression of IGT to diabetes. Current

data suggest that these programs can prevent diabetes in high-risk patients in a cost-effective manner.

Cost-effectiveness analyses have similarly been performed for drug interventions to prevent diabetes. In the Diabetes Prevention Program, metformin is predicted to achieve only approximately one-third of the extended health benefits of lifestyle intervention, which detracts from relative cost-effectiveness. Even so, studies demonstrate that metformin or acarbose can result in net cost savings per life-year gained (65,70,71). The cost-effectiveness for pharmacologic interventions will vary as a function of drug properties that include effectiveness, cost compared with usual care, impact on quality of life, and safety.

Thus, it seems clear that preventing the progression of prediabetes to diabetes is cost-effective, even at the present time. Diabetes prevention may be cost saving if the cost of lifestyle interventions is lowered through the availability of group or Web-based programs and by the coming availability of an expanded number of generic medications.

Given the current basis of evidence, it is incumbent upon health care systems and health care providers to develop lifestyle intervention programs that prevent diabetes. Many physicians in the United States are unable to provide the team of health care professionals that can effectively engineer lifestyle changes in their patients because health systems fail to provide sufficient compensation. Health care systems that emphasize acute care to the exclusion of disease prevention or chronic disease management will continue to fail patients with diabetes and patients at high risk of diabetes. A restructuring of health care remuneration to reward disease prevention will be necessary to counteract the increasing burden of diabetes. Furthermore, our patients' health depends on built environments in communities that promote healthy lifestyles, necessitating collaboration among civic and governmental partners to achieve this goal.

QUESTION 6

What future research is needed to further clarify the diagnosis and management of the prediabetic state?

The diagnosis of prediabetes has been made on the basis of glucose criteria alone, namely, the categories of IFG and/or IGT. The adequacy of the cutoff points for establishing these diagnoses has been a subject of considerable discussion and was a focus of much attention in this conference. It is recognized that both these conditions are part of a continuum of risk, and there might be justification for use of even lower glucose cutoffs to capture individuals at equal levels of risk for developing type 2 diabetes and its cardiovascular sequelae. However, after much discussion, the committee agreed that there is insufficient evidence to warrant a recommendation for any change of current diagnostic guidelines for prediabetes on the basis of glucose levels.

Persons with prediabetes have 3 possible outcomes in long-term follow-up: (a) one-third convert to type 2 diabetes; (b) one-third remain in a prediabetic state; and (c) one-third revert to normoglycemia. Accordingly, the following areas of future research are recommended:

- *Recommendation 1*. We recommend that a retrospective analysis of data from previous long-term prevention studies be performed to determine whether there are unique characteristics that might distinguish with greater clarity the determinants of different levels of risk for conversion to diabetes.
- *Recommendation 2*. To determine if there are specific characteristics that predict the development of cardiovascular outcomes in persons with prediabetes, we recommend that the retrospective analysis include assessment of the metabolic risk profiles of those persons who have developed CVD vs those who have not.
- *Recommendation 3*. Since there are no conclusive studies to date that show that lowering of fasting or postprandial glucose prevents CVD in prediabetes, we recommend a clinical trial in which intensive control of all cardiovascular risk factors plus pharmacologic glucose lowering is achieved in prediabetic participants. The primary outcomes would be major cardiovascular events, microvascular complications, and death.

There are currently no approved pharmacologic treatments for prediabetes. Conclusive evidence exists for using lifestyle intervention to prevent progression of prediabetes to diabetes. This has been demonstrated in multiple clinical trials, including the Diabetes Prevention Program (9), the Finnish Diabetes Prevention study (48,68), and the Da Qing study (11). There are few data on the simultaneous use of lifestyle modification and preventive pharmacotherapy compared with either intervention alone. Since the failure of lifestyle modification is marked by development of diabetes, and since such failure is perhaps a requirement for pharmacologic intervention, it would be useful to know if a greater percentage of prevention could be achieved by the simultaneous use of both interventions.

- *Recommendation 4*. We recommend a clinical outcomes study that would test the hypothesis that simultaneous use of intensive lifestyle modification plus preventive pharmacotherapy results in the greatest degree of diabetes prevention in prediabetic participants, taking into account safety and cost-effectiveness.

Most persons with prediabetes have multiple risk factors that predict development of subsequent diabetes in addition to CVD. Data from the Diabetes Prevention Program have shown that treatment of prediabetes through lifestyle intervention improves multiple risk factors, including blood pressure lowering, improvement of dys-

lipidemia, and weight loss (16). There is a need to identify those patients with prediabetes who are at highest risk for CVD outcomes. Thus, the challenge is to develop a risk assessment that can be completed by patients and attached to the laboratory order form. The laboratory can then convert this information to a risk score for diabetes, which could trigger performance of a glucose tolerance test and other necessary diagnostic tests that would indicate higher levels of cardiovascular risk.

To develop more specific and targeted interventions to preserve β-cell function, which has been demonstrated to be a critical component in progression of glucose intolerance (72), the following areas of future research are recommended:

- *Recommendation 5*. We encourage further development of noninvasive methods of analyzing β-cell mass and more sensitive assessments of β-cell function in humans.
- *Recommendation 6*. We encourage the identification of novel therapeutic agents for preservation of β-cell function.
- *Recommendation 7*. We encourage further research in identifying unique genetic markers to specify unique β-cell therapeutic targets.

In addition to assessing fasting and 2-hour postchallenge glucose concentrations, we recommend the use of metabolic syndrome in identifying patients with prediabetes based on the documented risk for future diabetes and CVD and the compounded risk for diabetes when metabolic syndrome (defined by NCEP Adult Treatment Panel III criteria) (24) exists in combination with IFG or IGT. This approach recognizes that the prediabetic state involves the presence of other cardiovascular risk factors in addition to elevated blood glucose. However, there are limitations to the optimal use of the metabolic syndrome as a diagnostic or predictive entity. These limitations include the fact that multiple sets of criteria for the metabolic syndrome have been proposed, that there exists a lack of studies empirically testing various combinations of risk factors for optimal prediction of future diabetes and CVD, and that existing criteria may not reflect cardiometabolic disease risk with similar accuracy in different racial/ethnic groups. Thus, additional research is needed to optimize and refine clinical paradigms for assessing cardiometabolic disease risk.

- *Recommendation 8*. Diagnostic tests should be developed to better distinguish patients who will progress to diabetes from those who will not.
- *Recommendation 9*. Greater understanding of the role of insulin resistance (eg, liver and/or fatty liver insulin resistance, mitochondrial dysfunction) in the conversion of prediabetes to diabetes is needed.

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APPENDIX 1

Topics and Expert Speakers

Topic	Expert
Identifying prediabetes	Michael Stern, MD
Evidence-based prevention of diabetes and vascular complications—the Hoorn Study	Jacqueline M. Dekker, PhD, MSc
Impaired glucose vs diabetes: affect on cardiovascular disease and its risk factors	Barbara V. Howard, PhD
Spectrum of glucose tolerance in youth: from normal to type 2 diabetes	Silva Arslanian, MD
The cardiovascular complications of not treating prediabetes	Jaako Tuomilehto, MD, MPolSc, PhD
Impact of diabetes prevention on microvascular and macrovascular disease	Robert E. Ratner, MD, FACE
Nephropathy—hypertension: an update	George L. Bakris, MD, FACP, FAHA, FASN
Neurovascular dysfunction in prediabetes	Aaron I. Vinik, MD, PhD, FCP, MACP
Goals for obesity, blood pressure, and lipid management in patients with dysglycemia	Scott M. Grundy, MD, PhD, MD [Hon]
Early treatment of prediabetes and diabetes: role of thiazolidinediones	Ralph A. DeFronzo, MD
Effects of lifestyle intervention on glucose, weight, lipids, and blood pressure in people with prediabetes	David G. Marrero, PhD
Implications of medical treatment of lipid disorders in prediabetes	Christie Ballantyne, MD
Regulatory issues in prediabetes	Mary H. Parks, MD
Effects of drug-induced or surgical weight loss on glucose, weight, lipids, and blood pressure in people with prediabetes and diabetes	George A. Bray, MD, MACP, MACE
The effectiveness of pharmaceutical modalities in treatment of early hyperglycemia and the prevention of diabetes and complication	Jean-Louis Chiasson, MD
Glycemic implication of blood pressure medications	Carl J. Pepine, MD, MACC
Should we manage people with prediabetes	Edwin Gale, MD
Prediabetes from the community perspective	Peter W.F. Wilson, MD
What to monitor: glucose and nonglycemic parameters review	Lawrence Blonde, MD, FACP, FACE
The rate and determinants of conversion from prediabetes to type 2 diabetes	Steve M. Haffner, MD
The cost effectiveness of diabetes prevention	William H. Herman, MD, MPH
Role of the muscle	Gerald I. Shulman, MD, PhD, FACE
β-Cell	Jack L. Leahy, MD
What future research is needed to further clarify the diagnosis and management of the prediabetic state?	K. G. M. M. Alberti, DPhil, BM, MRCP, FRCP