

Approach to the Patient with Prediabetes

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Prediabetes consists of impaired fasting glucose and/or impaired glucose tolerance and is a significant risk factor for the development of type 2 diabetes, microvascular, and macrovascular disease. The values used to define prediabetes are arbitrary, because prediabetes represents an intermediary category along the continuum from normal glucose levels and tolerance to overt hyperglycemia. The progression from prediabetes to type 2 diabetes occurs over many years, strong evidence to support intervention to delay the progression from prediabetes to diabetes. Large, randomized prospective studies with lifestyle intervention and/or various modes of pharmacotherapy have demonstrated successful delay of diabetes. Several issues in the management of prediabetes remain controversial, such as the role of pharmacotherapy and when to escalate treatment. This article will review some of the issues surrounding the identification and treatment of prediabetes, with an interpretation of the available data to help guide management. (*J Clin Endocrinol Metab* 93: 3259–3265, 2008)

A 46-yr-old female is referred to you for an abnormal fasting glucose of 115 mg/dl (6.4 mmol/liter). She has no significant past medical history. She takes several vitamins but no prescribed medications. Her family history is remarkable for type 2 diabetes in her father. Her physical examination is notable for a height of 152.5 cm (60 inches), weight of 64.9 kg (142.8 lb), body mass index (BMI) of 27.9 kg/m², and blood pressure of 121/80 mm/Hg. A 75 gram oral glucose tolerance test (OGTT) is performed to evaluate her for undiagnosed diabetes, revealing a fasting plasma glucose (FPG) of 117 mg/dl (6.5 mmol/liter) and 2-h glucose of 153 mg/dl (8.5 mmol/liter). A hemoglobin A1c (HbA1c) is 6.4%, and lipid panel reveals a total cholesterol of 278 mg/dl (7.2 mmol/liter), low-density lipoprotein cholesterol (LDL-c) of 218 mg/dl (5.6 mmol/liter), high-density lipoprotein cholesterol (HDL-c) of 40 mg/dl (1.0 mmol/liter), and triglycerides of 99 mg/dl (1.1 mmol/liter). Intensive lifestyle recommendations, including a goal weight loss of 7% through a healthy low-calorie, low-fat diet and increased physical activity of 150 min/wk, are recommended. The patient is seen every 6 months with FPG performed semiannually and HbA1c and OGTT performed annually. Over the next few years, the patient complied with the lifestyle recommendations and lost 6 kg (9%) of her body weight, with fasting glucoses ranging from 95–108 mg/dl (5.3–6 mmol/liter), HbA1c in the range of 6.1–6.3%, and annual OGTT revealing isolated impaired fasting glucose (IFG). With this intervention, her LDL-c decreased to 115 mg/dl (3.0 mmol/liter)

and total cholesterol to 175 mg/dl (4.5 mmol/liter). By age 54, the patient's weight steadily climbs to 68.2 kg (150 lb), and she reports less diligence with her lifestyle changes. An OGTT reveals FPG of 123 mg/dl (6.8 mmol/liter) with 2-h glucose of 252 mg/dl (14 mmol/liter) and HbA1c of 6.9%. The OGTT is repeated within 6 wk, revealing a FPG of 148 mg/dl (8.2 mmol/liter) and 2-h glucose of 224 mg/dl (12.4 mmol/liter), consistent with a diagnosis of type 2 diabetes. Her total cholesterol is 286 mg/dl (7.4 mmol/liter), LDL-c 206 mg/dl (5.3 mmol/liter), HDL-c 42 mg/dl (1.1 mmol/liter), and triglycerides 189 mg/dl (2.1 mmol/liter). She is started on metformin 850 mg twice daily, a statin, and aspirin. Blood pressure is 138/80 mm Hg, urine microalbumin level is normal, and she has no evidence of retinopathy.

Clinical question no. 1: What is prediabetes?

Prediabetes broadly refers to an intermediate stage between completely normal glucose levels and the clinical entity of type 2 diabetes, encompassing both IFG and impaired glucose tolerance (IGT).

As defined by the American Diabetes Association (ADA), prediabetes is a FPG of at least 100 mg/dl (5.6 mmol/liter) but less than 126 mg/dl (7.0 mmol/liter), which is frequently termed IFG, or an abnormal 2-h response to a 75-g OGTT of at least 140 mg/dl (7.8 mmol/liter) and less than 200 mg/dl (11.1 mmol/liter),

0021-972X/08/\$15.00/0

Printed in U.S.A.

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doi: 10.1210/jc.2008-1091 Received May 20, 2008. Accepted July 21, 2008.

Abbreviations: ADA, American Diabetes Association; BMI, body mass index; DPP, Diabetes Prevention Program; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL-c, high-density lipoprotein cholesterol; 2hPG, 2-h postchallenge plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LDL-c, low-density lipoprotein cholesterol; OGTT, oral glucose tolerance test; QALY, quality-adjusted life years.

which is often termed IGT. The World Health Organization defines IGT similarly as the ADA, but IFG is defined as a fasting glucose of at least 110 mg/dl (6.1 mmol/liter) (1, 2).

The definitions of diabetes and prediabetes are based on assessments of disease risk as well as population distributions of plasma glucose (2). Data suggesting a threshold of plasma glucose above which the incidence of retinopathy significantly increases has been used to help define diabetes (3, 4). This has been brought into question with recent data, with the Diabetes Prevention Program (DPP) showing that 7.9% of participants with IGT had findings consistent with diabetic retinopathy, and 12.6% of patients with diabetes had evidence of diabetic retinopathy early in the conversion to diabetes (5). In addition, the primary cause of morbidity and mortality in diabetes is cardiovascular disease. Multiple prospective studies have demonstrated that cardiovascular events increase linearly with 2-h postchallenge plasma glucose (2hPG) at levels well below the levels diagnostic of diabetes. The DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) study, for example, demonstrated a graded increase between 2hPG and cardiovascular disease mortality and a J-shaped relation between fasting glucose and mortality (6). Such data suggest evidence of disease before the official diagnosis of diabetes. Thus, we should reconsider the approach of viewing isolated values of glucose with a threshold model, but instead view glucose as a continuous variable in risk factor assessment for both cardiovascular and diabetic microvascular disease.

Clinical question no. 2: Does this patient have prediabetes at presentation?

This patient meets criteria for IFG, consistent with prediabetes, even before performing an OGTT. However, it is difficult to exclude the possibility that this patient does not already have type 2 diabetes by FPG alone. Fasting glucose alone is reported to miss the detection of approximately 30% of cases of type 2 diabetes (2, 3, 7). This percentage may be even higher as reported in the Rancho Bernardo cohort and in the DPP. In the Rancho Bernardo cohort, 70% of women and 48% of men aged 50–89 had new diabetes diagnosed on the basis of an elevated 2-h plasma glucose alone (8). In the DPP, 87% of cases of new diabetes were detected based on initial elevation of 2hPG, as opposed to only 34% that were detected based on initial elevation of FPG (9).

Upon presentation, an OGTT should be considered to definitively diagnose whether the patient has prediabetes or has unrecognized type 2 diabetes mellitus. Diagnosis impacts prognosis, because patients diagnosed with both IFG and IGT develop diabetes approximately twice as often as individuals with either isolated IFG or isolated IGT (10, 11). In addition, cardiovascular risk is greater in those with IGT or diabetes based on the 2hPG (6, 12). The OGTT, however, requires additional time and resources, is considered less reproducible than the FPG, and thus would require an additional confirmatory test if abnormal (9, 13).

Alternatively, there is growing acceptance for the role of HbA1c in the screening, diagnosis, and prognosis of diabetes (14–16). According to a recent panel recommendation, an HbA1c of 7% or higher would suggest the presence of diabetes, along with a confirmatory test, whereas an elevated HbA1c of at least 6.5–6.9%

should prompt further investigation with a FPG or OGTT (14). Thus, in this patient, an initial FPG and HbA1c followed by an OGTT if FPG was less than 126 mg/dl (7 mmol/liter) and HbA1c was less than 7% would complete her diagnostic evaluation. All were performed initially, confirming the patient's diagnosis of prediabetes (IFG with IGT) and excluding the possibility of undiagnosed diabetes.

Clinical question no. 3: What is the natural course of untreated prediabetes?

The progression from prediabetes to type 2 diabetes occurs over many years before the development of overt hyperglycemia seen in diabetes (17). The risk of progressing to diabetes is greater in individuals with both IFG and IGT compared with isolated IFG or isolated IGT alone (10, 11). The risk of progressing to diabetes depends on the degree of insulin resistance and deficiency of insulin secretion as well as other diabetes risk factors, such as age, family history, overweight/obesity, or history of gestational diabetes or polycystic ovary syndrome.

The average annual risk of developing diabetes for someone with normoglycemia is approximately 0.7% per year (18). In contrast, this risk is about 5–10% per year in individuals with IFG or IGT (10). In the DPP, which enrolled subjects with elevated fasting glucose (≥ 95 mg/dl, or ≥ 5.3 mmol/liter) and IGT, 11% of individuals in the standard arm progressed to diabetes annually (19). Over the lifetime, a majority of patients with IFG, IGT, or both would develop type 2 diabetes in the absence of intervention.

Prediabetes is not only a significant risk factor for progression to type 2 diabetes but is also considered a risk factor for macrovascular disease and for retinopathy. Some of this risk may be associated with progression to overt diabetes, but there is still increased risk in individuals who have not yet progressed to diabetes. A metaanalysis of 38 prospective studies, for example, suggests that postchallenge blood glucose levels in the nondiabetic range appear to have a linear relationship with cardiovascular disease risk and a possible threshold risk with fasting plasma glucose of about 100 mg/dl (5.6 mmol/liter) (20).

Clinical question no. 4: What is the evidence supporting intervention for prediabetes, and does treatment alter the natural course of prediabetes?

There is ample evidence that intensive lifestyle intervention and various modes of pharmacotherapy reduce the risk of progression to diabetes, but is the progression to diabetes truly being prevented, or is the hyperglycemia of diabetes being treated early? Are the treatment interventions sustainable? And finally, is there any impact of treatment of prediabetes on long-term microvascular and macrovascular comorbidities?

Lifestyle approaches or metformin therapy for diabetes prevention?

Lifestyle changes have consistently demonstrated benefit in preventing or delaying the progression from IGT to diabetes. The Chi-

nese Da Qing study of more than 500 IGT subjects was one of the first to show the benefit of long-term diet and exercise intervention to prevent diabetes (21). Both the Finnish Diabetes Prevention Study and the DPP demonstrated a 58% reduction in the progression from IGT to diabetes with intensive lifestyle changes compared with standard lifestyle advice (19, 22). In the DPP, lifestyle intervention with a goal of at least 7% weight loss and at least 150 min of physical activity per week appeared to have greater impact on older persons and those with a lower BMI (19). With a BMI goal of less than 22 kg/m² in the intensive lifestyle group compared with less than 24 kg/m² in the standard group, a Japanese study in males with IGT resulted in a 67.4% risk reduction in diabetes over 4 yr (23).

The interventions involved are intense, and require a firm commitment from patient, provider, and society alike. Even with the multifaceted approach of lifestyle intervention in the DPP, only 38% of the participants in the lifestyle intervention group achieved the weight loss goal of at least 7% at the end of the study, while only 58% met the goal of at least 150 min of moderate intensity activity (19). Yet, there was clear benefit in the intervention. Encouraging is the follow-up of the Finnish Diabetes Prevention Study, in which participants were followed for an additional median 3 yr after the 4-yr intervention period. No diet or exercise counseling was provided in the annual follow-up visits. During the total follow-up, the intervention group maintained a 43% reduction in relative risk of developing diabetes compared with the standard control group. The risk reduction was greatest, however, in those who maintained the lifestyle goals of weight loss, reduced fat intake, increased fiber intake, and increased physical activity (24).

On the other hand, metformin at 850 mg twice daily resulted in a 31% reduction in progression to diabetes in the DPP, being more effective in younger individuals and in participants with a higher BMI (19). In addition, after a 1- to 2-wk washout period, metformin demonstrated a persistent reduction in diabetes by

25%, suggesting the possibility that metformin was not just masking a diagnosis of diabetes but also helped to delay the progression of prediabetes (25). Whether metformin was really changing the natural history of the disease would have been better delineated if the washout period had been longer.

Does the combination of lifestyle intervention and metformin confer additive benefit? The Indian Diabetes Prevention Programme (IDPP-1), which showed a very high progression rate to diabetes of 55% over 3 yr in subjects with IGT, evaluated the combination of metformin with intensive lifestyle changes compared with either treatment alone. Although the tolerated level of metformin was only 250 mg twice daily compared with the 850 mg twice daily in the DPP, a combination of metformin with lifestyle change had no additional benefit compared with the treatment with either metformin or lifestyle changes alone (26).

Computer modeling from the DPP estimates that over a lifetime, 83% of participants treated with standard intervention would develop diabetes, compared with 63% of those treated with lifestyle intervention and 75% of those treated with metformin. Lifestyle intervention would delay the onset of diabetes by 11.1 yr, and metformin would delay the onset of diabetes by 3.4 yr (Fig. 1). Lifestyle intervention would increase life expectancy by 0.5 yr and reduce the incidence of blindness by 39%, end-stage renal disease by 38%, amputation by 35%, stroke by 9%, and coronary heart disease by 8% (27). Supportive of this, both traditional (hypertension and dyslipidemia) and nontraditional (C-reactive protein and fibrinogen) risk factors were significantly reduced with intensive lifestyle treatment in the DPP (28, 29).

Despite such intriguing data from computer modeling, improvements in long-term health outcomes (*i.e.* mortality and reduction in cardiovascular events) from diabetes prevention efforts have yet to be proven. The longest follow-up outcomes study to date is the Da Qing Diabetes Prevention Outcome Study, evaluating participants 14 yr after the initial 6-yr intervention

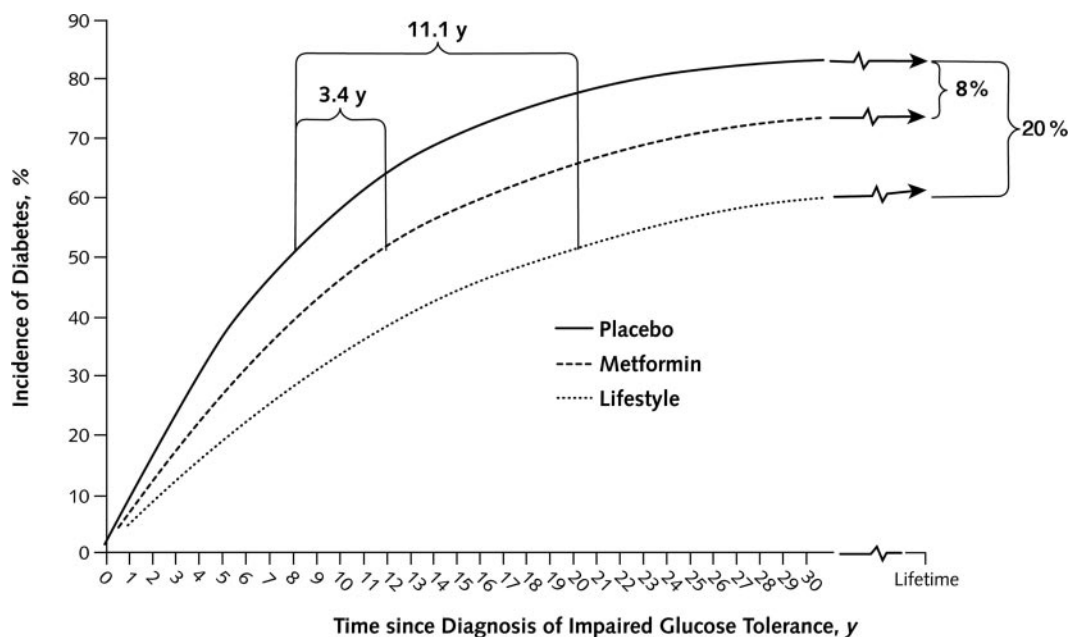


FIG. 1. Simulated cumulative incidence of diabetes among adults with impaired glucose tolerance by the Diabetes Prevention Program treatment group. [Reproduced with permission from W. H. Herman *et al.*: Ann Intern Med 142:323, 2005 (27) ©American College of Physicians.]

period. Participants in the intensive lifestyle intervention arm sustained a 43% reduction in diabetes incidence over the 20-yr period. There was no reported difference in cardiovascular disease events or mortality, although the study had limited power to address these outcomes (30).

Pharmacological intervention in diabetes prevention

Other methods of pharmacotherapy have also demonstrated prospective benefit in disease prevention. Acarbose was associated with a 25% reduction in progression from IGT to diabetes after 3 yr in the STOP-NIDDM (Study to Prevent Non-Insulin-Dependent Diabetes Mellitus) trial. This effect disappeared with discontinuation of the acarbose, suggesting that acarbose may have masked the progression to diabetes (31). This trial also demonstrated a 49% relative risk reduction in cardiovascular disease with acarbose, reduction in hypertension, and a reduction in progression of carotid intima-media thickness (32, 33). These data suggest that maintenance of normoglycemia may help prevent long-term macrovascular morbidity.

The most enticing data to suggest a biological delay in the progression from prediabetes to diabetes with pharmacotherapy are from Buchanan and colleagues (34, 35). In both the TRIPOD (Troglitazone in Prevention of Diabetes) and PIPOD (Pioglitazone in Prevention of Diabetes) studies in Hispanic women with a history of gestational diabetes, Buchanan *et al.* (34, 35) showed that troglitazone and pioglitazone, respectively, stabilized pancreatic β -cell function compared with placebo. Women in the placebo arm of TRIPOD had a decline in β -cell function. Pioglitazone stabilized this decline in β -cell function in the PIPOD study, and this effect persisted after an extended washout period of the pioglitazone (35). The TRIPOD and PIPOD studies also demonstrated decrease in carotid intima-media thickness with troglitazone and pioglitazone, respectively, suggesting a cardioprotective effect (36, 37).

In the DREAM study (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication), rosiglitazone increased the regression of IFG or IGT to normoglycemia and reduced the incidence of the composite outcome of diabetes or death by 60% over 3 yr (38). After a washout period, the incidence of diabetes in the placebo and rosiglitazone groups were similar (39). Of note, rosiglitazone also reduced the risk of renal disease, suggesting that maintenance of normoglycemia may impact development of microvascular disease (40). Although there was no effect on cardiovascular outcomes, there was an increase in congestive heart failure events compared with placebo (0.5 vs. 0.1%) (38). The increased risk of weight gain, congestive heart failure, fractures (41), and cost associated with rosiglitazone must be weighed against its potential benefits in prediabetes.

The recently reported ACT NOW (ACTos NOW for the Prevention of Diabetes) study demonstrated a remarkable 81% reduction in the conversion of IGT to type 2 diabetes over a mean 2.6 yr with pioglitazone compared with placebo. Improvements in insulin sensitivity and β -cell function were seen despite a weight gain of 3.9 kg with pioglitazone compared with 0.8 kg with placebo. The results from the washout period will help determine whether the improvements seen were due to biological delay of diabetes or early treatment of hyperglycemia (42).

Back to the patient . . . clinical question no. 5: Should this patient's prediabetes be treated?

The evidence is undisputable that diabetes can be delayed or prevented by either intensive lifestyle modification and/or a variety of pharmacotherapies. This patient should have her prediabetes addressed, diabetes diagnosed or excluded, and should be treated. The risks of treatment, particularly with lifestyle intervention, are low and the benefits extend beyond the prevention of diabetes. In addition, lifestyle intervention is a highly cost-effective method of treating prediabetes. Elegant cost analyses of the DPP showed that compared with placebo, lifestyle intervention would cost \$635 more over a lifetime and produce a gain of 0.57 quality-adjusted life years (QALY), or a cost per QALY gained of about \$1100. The estimated cost per QALY gained for metformin intervention extended over the lifetime compared with placebo was approximately \$31,300 but was substantially lower at \$1755 if the cost of generic metformin was substituted in the calculation (27). Eddy and colleagues (43) have estimated higher cost-effectiveness ratios, but several other models have now demonstrated the relative cost-effectiveness of lifestyle interventions as well as metformin (44).

Thus, there is no significant deterrent to treating this patient's prediabetes, and a detailed conversation between provider and patient should ensue. Factors such as the availability of resources for participation in an intensive lifestyle program and the patient's commitment of time toward dietary and lifestyle changes should be reviewed. If pharmacotherapy is considered, a detailed discussion of the goals, available data, and potential side effects should be reviewed.

Clinical question no. 6: How should prediabetes be treated?

Published guidelines on the approach to the patient with prediabetes include a consensus statement from the ADA, the Indian Health Services (IHS) Guidelines for care of the adults with prediabetes and/or metabolic syndrome, and a position statement from the Australian Diabetes Society and Australian Diabetes Educators Association (Table 1). The recommendations on treatment of prediabetes differ slightly. The ADA consensus statement stratifies therapy based on whether the patient has isolated IFG, isolated IGT, or a combination of IFG and IGT, allowing for consideration in differences in the underlying physiology and disease progression. Lifestyle modification with a weight loss goal of 5–10% is recommended along with moderate physical activity of about 30 min daily. Recommendations for use of metformin are tailored around individuals who may have greater benefit from metformin as seen in the DPP and those who are at greater risk of progression to diabetes. Thus, metformin is considered in individuals less than 60 yr of age, individuals with a BMI of at least 35 kg/m², and individuals with increased risk such as family history of diabetes in first-degree relatives, elevated triglycerides, reduced HDL-c, hypertension, or HbA1c more than 6.0% (11). The IHS guidelines similarly advocate lifestyle changes with consideration for metformin on an indi-

TABLE 1. Key features of selected published recommendations on prediabetes

	ADA consensus statement (2007) (11)	Indian Health Services Guidelines for care of adults with prediabetes and/or the metabolic syndrome in clinical settings (2006) (45)	Australian Diabetes Society and Australian Diabetes Educators Association position statement (2007) (46)
Definition			
IFG	FPG >100 mg/dl (5.6 mmol/liter) but <126 mg/dl (7.0 mmol/liter) and 2hPG <200 mg/dl (11.1 mmol/liter)	FPG >100 mg/dl (5.6 mmol/liter) but <126 mg/dl (7.0 mmol/liter)	FPG >110 mg/dl (6.1 mmol/liter) and <126 mg/dl (7.0 mmol/liter) with 2hPG <140 mg/dl (7.8 mmol/liter)
IGT	FPG <126 mg/dl (7.0 mmol/liter) and 2hPG >140 mg/dl (7.8 mmol/liter) but <200 mg/dl (11.1 mmol/liter)	2hPG >140 mg/dl (7.8 mmol/liter) but <200 mg/dl (11.1 mmol/liter)	FPG <126 mg/dl (7.0 mmol/liter) and 2hPG >140 mg/dl (7.8 mmol/liter) but <200 mg/dl (11.1 mmol/liter)
Who should be screened for prediabetes?	Individuals with risk factors for diabetes should be screened for prediabetes	Annual testing of individuals at risk for developing diabetes	Incidental detection when screening for diabetes
Method of screening	1) FPG 2) 2-h OGTT if metformin therapy is considered	1) FPG 2) Optional 2-h OGTT if resources permit	Incidental detection when screening for diabetes
Recommended treatment	Lifestyle modification for IFG or IGT Lifestyle modification and/or metformin for IFG and IGT and at least one of the following: age <60 yr, BMI >35 kg/m ² , family history of diabetes in first-degree relatives, elevated triglycerides, reduced HDL-c, hypertension, HbA1c >6.0%	Lifestyle changes Consideration of metformin on an individualized basis; depression screening and cardiovascular risk reduction also recommended	Intensive lifestyle intervention for a minimum of 6 months before consideration of pharmacotherapy
Follow-up	1) Metformin treatment: semiannual HbA1c 2) Lifestyle intervention: annual follow-up	Monitor glucose values every 6 months	75-g OGTT, initially performed annually, then individualized retesting every 1–3 yr

vidualized basis (45). The Australian guidelines recommend lifestyle intervention as first-line therapy for a minimum of 6 months before consideration of pharmacotherapy (46).

In this patient's case, intensive lifestyle changes were recommended, and the patient's commitment to these changes were reviewed. Metformin therapy was not considered as initial therapy but may be considered in higher-risk patients as outlined by the ADA. Metformin was added when there was clear evidence of glycemic deterioration, or progression of underlying disease, as evidenced by increase in FPG, increase in HbA1c, and increase in 2hPG.

If pharmacotherapy for prediabetes is initiated, it is important for both patient and provider to realize that any therapy will require a long-term commitment. In addition, it is important to review with the patient that there are limited data demonstrating the long-term health benefits of pharmacological intervention compared with lifestyle intervention. Furthermore, one might debate which drug is the appropriate choice. The use of metformin is supported by its relative safety, cost effectiveness, and long-term data in the DPP. The ideal pharmacological intervention must demonstrate long-term safety, health benefit (reduced incidence of diabetes, macrovascular and microvascular complications, and mortality), cost effectiveness, and the ability to halt the biological progression from prediabetes to diabetes. These factors will remain the subject of current and future research endeavors in diabetes prevention.

Clinical question no. 7: When should one escalate interventions for prediabetes?

The issue of when one should escalate intervention depends on the goals of treatment of prediabetes. Is the primary goal complete normalization of glucose levels or rather deterring progressive β -cell dysfunction? How will the primary goal reduce long-term mortality and morbidity? We look toward goals in type 2 diabetes to address these important questions. In their 2006 joint consensus statement, the ADA and the European Association for the Study of Diabetes (EASD) espoused an HbA1c goal as close to the nondiabetic range as possible, or at least less than 7%. The consensus statement recommended a "call to action to initiate or change therapy" for an HbA1c of at least 7% (47). This HbA1c recommendation was based on issues of practicality and projected reduction in long-term complications. However, the recent ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial also brings to light issues of safety in intensification of therapy. In this trial of more than 10,000 subjects with type 2 diabetes, intensive therapy with a goal HbA1c less than 6.0% compared with a standard HbA1c goal of 7.0–7.9% resulted in increased mortality after a mean 3.5 yr of follow-up (48). Given these findings, reasonable goals in prediabetes include 1) prevention of glycemic deterioration as an indicator of preservation of β -cell function and 2) modification of nonglycemic risk factors (e.g. dyslipidemia and hypertension) to minimize long-term car-

diovascular risk. Should this involve pharmaceutical intervention, safety and avoidance of hypoglycemia are imperative.

Which measures would alert the practitioner to deterioration of glycemic control, or need for further intervention, over time? There are several options to consider, including FPG, repeat OGTT, HbA1c, or any combination of these tests.

Although FPG is convenient and can be coupled with fasting lipid tests, FPG alone has limitations. As previously stated, FPG provides an incomplete picture of chronic glycemic control and change, providing poor sensitivity (~40–60%) in detecting diabetes (49). Postprandial hyperglycemia due to insulin resistance and insufficient β -cell compensation are often more prominent in prediabetes than fasting hyperglycemia. At lower levels of HbA1c (e.g. <7.3%), postprandial glucose contributes more to the overall diurnal hyperglycemia than FPG (50).

The Australian guidelines in prediabetes recommend an annual OGTT initially with individualized monitoring every 1–3 yr thereafter (Table 1). In addition, participants in the DPP had annual OGTTs to detect conversion from IGT to diabetes. Although the OGTT with repeat confirmatory testing proved its merit in detecting new conversions to diabetes in the DPP (9), escalation of therapy was based primarily on significant changes in glycemic control as measured by elevations in FPG of at least 140 mg/dl (7.8 mmol/liter) (19). Thus, used primarily to label the conversion to diabetes, a periodic OGTT would not provide any additional information in the decision to escalate therapy.

The use of HbA1c as a diagnostic and monitoring test in prediabetes is debated. On the one hand, HbA1c is not standardized across various populations. In the DPP, for example, after correcting for factors that would affect glycemia, HbA1c levels were consistently higher across ethnic minorities compared with Caucasians (51). Furthermore, HbA1c by itself lacks sufficient sensitivity to diagnose diabetes. However, HbA1c correlates well with long-term complications and is a good indicator of chronic glycemic control (2). In consideration of many of these issues, the recent panel discussion by Saudek *et al.* (14) suggested that an HbA1c at least 7%, confirmed by another test (repeat HbA1c \geq 7%, FPG, or OGTT), would establish the diagnosis of diabetes and that an HbA1c of at least 6.5–6.9% would indicate diabetes with a confirmatory glucose-dependent test.

In this patient, baseline labs included FPG, HbA1c, and OGTT. Based on our discussion, one strategy for follow-up would be to measure both FPG and HbA1c on a periodic basis (e.g. every 6 months) to decide whether intervention should be escalated. If FPG and HbA1c remain stable, no additional intervention is required. If HbA1c increases to 7.0% or higher or if FPG increases to at least 140 mg/dl (7.8 mmol/liter) (19), pharmacotherapy should be advanced to minimize long-term complications. An OGTT would help time the conversion to an arbitrary diagnosis of diabetes and may influence treatment targets for blood pressure and lipids. The information provided by a periodic OGTT should be weighed against the practical issues of inconvenience, time, and need for a confirmatory test if abnormal.

Clearly, many of these long-debated issues remain unresolved. In this article, we have offered our interpretation of the existing data in an effort to guide the practitioner. The decision with each patient must factor in availability of resources, patient

and provider commitment to diagnosis and treatment, and level of adherence with recommended treatment. Although there may be debate on the details of management of prediabetes, there is no longer any controversy that prediabetes needs to be addressed and treated. Preventing diabetes is the only way of decreasing the immense current and future burden of diabetes and the attendant complications. The time is now.

Acknowledgments

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Disclosure Statement: The authors have nothing to disclose.

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