

Diagnosis and Treatment of Pre-diabetes

Introduction

Pre-diabetes is a relatively new term coined by the American Diabetes Association (ADA) and the Department of Health and Human Services in 2002.^{1,2} It includes both “impaired glucose tolerance” and “impaired fasting glucose” and was designed to bring attention to the significance of the disease.³ The ADA defines pre-diabetes as a fasting blood glucose (no caloric intake for at least eight hours) between 100 mg/dL (5.6 mmol/L) and 125 mg/dL (6.9 mmol/L) (impaired fasting glucose [IFG]) and/or a postprandial blood glucose between 140 mg/dL (7.8 mmol/L) and 199 mg/dL (11.0 mmol/L) two hours after a 75 gram oral glucose challenge (impaired glucose tolerance [IGT]).^{1,2} The Canadian Diabetes Association (CDA) defines IFG as a fasting glucose between 110 mg/dL (6.1 mmol/L) to 125 mg/dL (6.9 mmol/L). The CDA definition of IGT is the same as ADA.⁴ This document reviews the screening, diagnosis, and treatment of pre-diabetes.

Risk Factors for Pre-diabetes

Diabetes is a common disease that often goes undiagnosed for many years. It is estimated that about one-third of patients with diabetes do not know they have the disease.⁵ The average time from disease onset to diagnosis is an average of seven years. There were approximately 314 million people world wide with pre-diabetes in 2003, and by the year 2025, this number could increase to 472 million, or 9% of the adult population.³ Given the morbidity and mortality associated with diabetes, this is not acceptable.

There are a number of risk factors which increase the risk of pre-diabetes and diabetes. These include a family history of type 2 diabetes, obesity (especially around the waist), age greater than 45 years old, hypertension, dyslipidemia, ethnicity (African American, East Asian, Aboriginal, Latino, or Pacific Islander), mothers who develop gestational diabetes, and a sedentary

lifestyle.^{3,4} Other risk factors which have been identified include polycystic ovary syndrome, acanthosis nigricans, and schizophrenia.⁴

Importance of Detecting Pre-diabetes and Diabetes

Early identification of patients with pre-diabetes and diabetes is crucial. An elevated A1c has been associated with an increased risk of macrovascular and microvascular complications usually associated with overt diabetes. In addition, left untreated, pre-diabetes often progresses to diabetes.

For example, in the Diabetes Prevention Program (DPP), even in patients with pre-diabetes, diabetic retinopathy was noted in 8% of patients.^{3,8,9} Neuropathy has also been noted in patients with pre-diabetes. In population-based studies, it is estimated that peripheral neuropathy is seen in up to 14% of the general population. However, a number of studies have shown that the prevalence of peripheral neuropathy is much higher in those with pre-diabetes. For example, in a group of 187 sequential patients with idiopathic neuropathy, 45% had pre-diabetes, and 15% had unrecognized diabetes.¹⁰ In terms of nephropathy, the prevalence of nephropathy was assessed in more than 5,000 Pima Indians who had pre-diabetes over a ten-year period. In patients with pre-diabetes, the rate of nephropathy was found to be related to higher fasting plasma glucose or two-hour post glucose load levels.²¹

In a study of 47,904 persons in New Zealand, A1c testing was offered as part of a screening campaign for hepatitis B. The goal of the study was to determine the association between A1c and mortality. For patients without a diagnosis of diabetes, the risk of all-cause mortality increased steadily as the A1c value increased. In fact, each 1% increase in A1c in patients without diabetes over the reference range of 4% to <5% was associated with a 16% increase in rate of mortality.¹¹

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Two additional studies also show that A1c concentration is associated with mortality. In a study by Khaw and colleagues of over 10,000 patients in England, the risk of cardiovascular disease and total mortality associated with A1c concentrations increased as A1c increased over 5%. An increase in A1c of 1% (using less than 5% as a baseline) was associated with a 24% and 28% increase in the relative risk of death in men and women, respectively.¹⁵

More recently, as a secondary analysis of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) study, it was noted that in both diabetic patients and nondiabetic patients with symptomatic chronic heart failure, that A1c concentration was an independent risk factor for cardiovascular death, hospitalization for heart failure, and total mortality.¹⁶

A number of studies evaluating pharmacotherapy of pre-diabetes have found that treatment of pre-diabetes can positively benefit both surrogate markers of cardiovascular disease and actual cardiovascular events. For example, in the DPP trial, lifestyle changes in patients with pre-diabetes had a beneficial effect on blood pressure and plasma lipids.¹² In other trials, both troglitazone (*Rezulin*, no longer marketed) and acarbose (*Precose*) were associated with a reduced rate of carotid intima-media thickness in patients with pre-diabetes.¹³ Finally, a single study comparing acarbose to placebo in patients with pre-diabetes, showed that acarbose was associated with a reduced risk of composite cardiovascular outcome.¹⁴

Screening and Diagnosis for Pre-diabetes and Diabetes

According to the ADA, testing to detect pre-diabetes and type 2 diabetes in asymptomatic people should be considered in adults who are overweight or obese (body mass index 25 kg/square meter or greater), and who have one or more additional risk factors for diabetes. In those without these risk factors, testing should begin at age 45.⁶ Similarly, the Canadian Diabetes Association recommends that screening for diabetes using a fasting plasma glucose should be performed every three years in individuals 40 years of age or older. However, more frequent and/or earlier testing with either a fasting plasma

glucose or two-hour plasma glucose test following a 75 gram oral glucose load should be considered in people with additional risk factors for diabetes.⁴

Hyperglycemia that does not meet the criteria for diabetes is considered pre-diabetes. As previously mentioned, ADA defines pre-diabetes as a fasting blood glucose between 100 mg/dL (5.6 mmol/L) and 125 mg/dL (6.9 mmol/L) and/or a postprandial blood glucose between 140 mg/dL (7.8 mmol/L) and 199 mg/dL (11.0 mmol/L) two hours after a 75 gram oral glucose challenge.^{1,2,4,6} The fasting glucose range defined as pre-diabetes by the CDA differs slightly from ADA and is between 110 mg/dL (6.1 mmol/L) and 125 mg/dL (6.9 mmol/L).⁴ The recommendations by the ADA go on to state that the use of the A1c for the diagnosis of diabetes is not recommended at this time due to lack of evidence on prognostic significance and diagnostic thresholds.⁶ Although not included in the recommendations, some experts suggest that a random glucose greater than 130 mg/dL may suggest pre-diabetes.⁵

Recently, however, the recommendations for screening and the optimal test to determine the presence of pre-diabetes have been questioned. In June 2008, the United States Preventative Services Task Force (USPSTF) recommended that screening for type 2 diabetes be conducted in asymptomatic adults with sustained blood pressure (treated or untreated) greater than 135/80 mm Hg.⁷ But they do not give any specific screening recommendations for adults with normal blood pressure including those with risk factors such as obesity and dyslipidemia. This is based on the fact that there is insufficient evidence to evaluate the benefits and risks of assessing routine screening for type 2 diabetes in asymptomatic adults without high blood pressure.

The exclusion of adults with other risk factors for diabetes in these guidelines is controversial. As discussed earlier in the document, early detection of pre-diabetes and diabetes is beneficial. Opponents of the new recommendation cite that a lack of evidence does not mean there is no benefit in screening, especially in patients with other risk factors for diabetes. In addition, the test for determining pre-diabetes, a fasting plasma glucose, is simple and inexpensive.

A second controversy in the screening for pre-diabetes is the optimal test. While both the ADA and the Canadian Diabetes Association

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recommend a fasting plasma glucose or 75 gram oral glucose tolerance test, recent evidence suggests that an A1c can also be used. A recent consensus statement discusses the potential benefits of the A1c test in screening and diagnosing diabetes.⁵ Benefits of the A1c test over the fasting plasma glucose or oral glucose tolerance test include lack of effect of recent calorie intake (test does not need to be performed in the fasting state) and better representation of the last three months rather than the last few days.⁵

Proponents of the A1c test note that the A1c assay has undergone widespread laboratory standardization. In the U. S., more than 99% of clinical laboratories use the National Glycohemoglobin Standardization Program-certified method for measuring A1c. In addition, a number of studies have established the accuracy of the A1c test, using the oral glucose tolerance test or the fasting plasma glucose as the reference standard.⁵

If the A1c test is used as a method of screening, an A1c greater than 6.0% (estimated average glucose or eAG 126 mg/dL [7 mmol/L]) but less than 6.5% (estimated average glucose or eAG 140 mg/dL [7.8 mmol/L]) indicates a positive screen and warrants assessment of fasting plasma glucose or an oral glucose tolerance test. In a patient with an A1c between 6.5% and 6.9% and a subsequent fasting plasma glucose of 126 mg/L or greater or a two-hour plasma glucose of 200 mg/dL following a 75 gram oral glucose load confirms the diagnosis of diabetes.⁵

Treatment of Pre-diabetes

A number of controlled clinical trials have shown the benefit of lifestyle modification with or without pharmacotherapy to prevent or delay the progression to diabetes in patients with pre-diabetes.

The greatest benefit occurs with lifestyle modification. Consequently, a modest weight loss (5% to 10%) and moderate-intensity physical activity (30 minutes daily) is the mainstay of treatment for patients with pre-diabetes [Evidence level B; lower quality RCT].⁹ In the DPP trial, lifestyle modification reduced the incidence of diabetes by 58% over the 2.8 year follow-up period, compared with placebo. In comparison, metformin therapy reduced the incidence of

diabetes by 31% during the same follow-up period.⁹

Pharmacotherapy can be considered in patients who are unable or unwilling to engage in lifestyle modification and in those that have had an inadequate response to lifestyle change. It may also be considered in patients that are at very high risk for progression to diabetes such as those with both impaired fasting glucose and impaired glucose tolerance.^{13,20} Drawbacks of pharmacological therapy include potential for adverse effects, cost, and lack of proven positive long-term outcomes.

A number of antidiabetes agents have been studied and can be considered in the treatment of pre-diabetes. Metformin was the first drug shown to be effective for treating pre-diabetes [Evidence level B; low quality RCT].⁹ As mentioned previously, the DPP trial showed that metformin reduced the incidence of diabetes by 31% during a 2.8 year follow-up period.⁹ This effect was greatest in patients who were younger and obese. Given the low cost of the agent, relative safety, and long history of use in the treatment of diabetes, metformin has gained widespread use for this indication.¹³

Acarbose has also been shown to have beneficial effects in the treatment of patients with pre-diabetes [Evidence level B; low-quality RCT].¹⁴ In the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial, acarbose was found to reduce the rate of increase in carotid-intima-media thickness compared with placebo.¹⁴ However, many patients are unable to tolerate acarbose due to gastrointestinal effects.¹³

The glitazones (troglitazone [no longer available], rosiglitazone [*Avandia*]) have also been studied in patients with pre-diabetes. In the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial, rosiglitazone was shown to reduce the progression of pre-diabetes to type 2 diabetes and reduce blood pressure [Evidence level B; low quality RCT].¹⁷ However, concerns about the potential for congestive heart failure limit its use.¹⁷

A different group of antidiabetes medications, the dipeptidyl peptidase-4 (DPP-4) inhibitors, are another class of agents which may prove beneficial in the treatment of pre-diabetes. These agents appear to preserve beta-cell function and increase beta-cell mass. These mechanisms in

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combination with the low-risk of hypoglycemia and lack of significant adverse effects may prove to be beneficial in patients with pre-diabetes. However, no clinical trials have been published, so it is difficult to assess their usefulness in this indication.¹²

Although not usually considered “antidiabetes” agents, the angiotensin-converting-enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) may also prevent the development of diabetes [Evidence level B; lower quality RCT].^{17,18} It is thought that ACE inhibitors and ARBs may preserve pancreatic function, especially in patients who have hypertension and pre-diabetes. In a number of secondary analyses of large ACE inhibitor clinical trials (i.e., Captopril Prevention Project [CAPPP], Heart Outcomes Prevention Evaluation [HOPE], and the Studies of Left Ventricular Dysfunction [SOLVD] trial), the development of new-onset diabetes was reduced. Similarly, the development of diabetes was reduced in several secondary analyses of large ARB trials (i.e., Losartan Intervention For Endpoint reduction in hypertension study [LIFE], Study on Cognition and Prognosis in the Elderly [SCOPE], and Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity Program [CHARM]).²² However, these analyses were secondary analyses and used a variety of diagnostic guidelines to define diabetes. Also, other medications which may have affected the rate of diabetes development were employed. Furthermore, one recent trial, DREAM, found that ramipril did not reduce the development of diabetes in pre-diabetes patients without cardiovascular disease.¹⁷ Large, long-term, controlled studies designed to evaluate the effect of ACE-inhibitors and ARBs on the progression of pre-diabetes to diabetes are on-going.¹⁸

Orlistat, a medication used for weight loss, has been studied in a single trial of high-risk patients with and without pre-diabetes. It was found that after four years of treatment, orlistat plus lifestyle changes reduced the progression of impaired glucose tolerance to diabetes better than placebo (6.2% versus 9.0%). Additional studies are needed.¹⁹

In addition to treating high blood glucose concentrations in patients with pre-diabetes, hypertension and dyslipidemia should be aggressively treated, using the same goals as those

used in patients with overt diabetes.²⁰ These patients should also receive daily aspirin therapy.

Conclusion

Pre-diabetes is a common condition which occurs in millions of people worldwide. Even before the development of diabetes, microvascular and macrovascular complications typically associated with diabetes can occur. Screening of patients at high risk of diabetes is warranted in order to reduce the morbidity and mortality associated with diabetes. Once patients are identified, lifestyle modification is crucial in order to prevent or delay the progression to diabetes. A number of pharmacologic agents have been studied and appear to be promising in the treatment of pre-diabetes, but long-term outcomes are not known. Larger, long-term clinical trials are needed to determine the optimal role of medications in the treatment of pre-diabetes.

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Levels of Evidence

In accordance with the trend towards Evidence-Based Medicine, we are citing the **LEVEL OF EVIDENCE** for the statements we publish.

Level	Definition
A	High-quality randomized controlled trial (RCT) High-quality meta-analysis (quantitative systematic review)
B	Nonrandomized clinical trial Nonquantitative systematic review Lower quality RCT Clinical cohort study Case-control study Historical control Epidemiologic study
C	Consensus Expert opinion
D	Anecdotal evidence In vitro or animal study

Adapted from Siwek J, et al. How to write an evidence-based clinical review article. *Am Fam Physician* 2002;65:251-8.

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