

Management Strategies for Patients with Prediabetes

Kathy Seritena, Pharm D, OSU College of Pharmacy, Drug Use Research and Management

Introduction

The term prediabetes refers to a gray zone that includes patients with mild abnormalities of glucose tolerance who do not meet criteria for diabetes. There is no consensus on how to define this population, or what to call them. Terms include prediabetes, impaired fasting glucose, intermediate hyperglycemia, impaired glucose regulation, or high risk of diabetes.¹ Prediabetes is considered to be an impaired fasting glucose (IFG) of 100-125 mg/dL or a hemoglobin A1c (HbA1c) 5.7 to 6.4%.² A 2017 report from the Centers for Disease Control (CDC) cited the incidence of prediabetes in the United States to be more than 84 million people, based on 2015 data.³ Pharmacotherapies have been promoted for the delay or prevention of type 2 diabetes mellitus (T2DM) in individuals with prediabetes without strong evidence. The purpose of this newsletter is to discuss evidence regarding management strategies of patients with prediabetes.

Delaying or preventing the onset of T2DM is desirable. However, there is no evidence that treatment of prediabetes with medication reduces or prevents mortality or any complications of diabetes.^{4,5} The course of prediabetes is variable. The development of T2DM is dependent on a variety of risk factors. Positive family history, gestational diabetes, obesity, ethnicity, polycystic ovarian syndrome, impaired insulin secretion and insulin resistance, and elevated glucose levels have been shown to contribute to the increased risk.^{2,4} Some patients with prediabetes will convert to normal glucose levels without lifestyle or pharmacotherapy interventions.⁶ Guidelines recommend yearly screenings for T2DM in patients with prediabetes based on expert opinion.²

Lifestyle Modifications

Studies have shown that changes in lifestyle, such as diet modification, weight loss, and exercise, can slow the progression to diabetes in patients with impaired glucose tolerance (IGT).⁴ Benefits of lifestyle changes have been shown to persist beyond the initial intervention for up to 20 years.^{2,7} The Diabetes Prevention Program (DPP) studied overweight patients with IGT randomized to lifestyle interventions versus metformin, as well as both interventions versus placebo, over a mean follow up duration of 2.8 years.⁷ The incidence of diabetes, based on cases per 100 person-years, was 11 for placebo, 7.8 for metformin and 4.8 for the lifestyle intervention group. The reduction in risk was statistically significantly more for the lifestyle intervention group compared to metformin. The Diabetes Prevention Program Outcomes Study (DPPOS) was an open label 15-year follow-up on the DPP study.⁸ DPPOS found the incidence of diabetes to be reduced by 27% in the lifestyle intervention group compared to 18% in patients taking metformin.

A meta-analysis done by the CDC found that combined diet and physical activity interventions compared to usual care reduced the incidence of T2DM (risk ratio [RR] 0.59; 95% confidence interval [CI], 0.52 to 0.66), decreased body weight (-2.2%; 95% CI, -2.9% to -1.4%) and decreased fasting blood glucose levels (-2.2 mg/dL; 95% CI, -3.6 to -0.9 mg/dL).⁹ A Cochrane systematic review and meta-analysis

studied the effects of diet, physical activity, or both for prevention or delay of T2DM and its complications in people at increased risk.¹⁰ Twelve trials of 5,238 patients were included. Combinations of diet and exercise interventions in individuals with IGT were found to prevent or delay T2DM based on moderate evidence (RR 0.57; 95% CI, 0.50 to 0.64). The evidence for diet alone or physical activity alone was not conclusive. A separate meta-analysis of 28 prospective cohort studies demonstrated a 26% reduced risk of developing diabetes with 150 min/week of moderate activity compared to those individuals who were inactive.¹¹

Pharmacotherapy

Evidence suggests that metformin is more effective than placebo in reducing the transition from prediabetes to T2DM.⁷ A systematic review and meta-analysis of patients taking metformin, who were at risk of developing diabetes, identified 31 trials of at least 8 weeks in duration. The risk of new-onset diabetes was reduced with metformin compared to placebo or no treatment (OR 0.60; 95% CI, 0.5 to 0.8; absolute risk reduction 6% over 1.8 years).¹² The absolute risk with or without treatment was not analyzed and would be helpful to determine if the benefit of drug therapy outweighed the potential risk of adverse events. As reviewed previously, the DDP trial found a benefit of metformin compared to placebo in delaying T2DM in patients with prediabetes; however it was inferior to lifestyle modifications.⁷ Additionally, patients 60 years and older were found to only derive benefit from lifestyle changes and no benefit was associated with metformin.

Liraglutide was compared to placebo for T2DM risk reduction as an adjunct to diet and exercise.¹³ Liraglutide 3 mg once daily was studied in a double-blind, placebo-controlled, randomized trial of adults with prediabetes, a body mass index of 30 kg/m², or a body mass index of 27 kg/m² with comorbidities. At 3 years, 2% of patients treated with liraglutide compared to 6% of placebo treated patients were diagnosed with T2DM (CI and p-values not provided).¹³ Therefore, greater than 90% of patients did not develop diabetes, and had no benefit from treatment. Patients in the liraglutide group also lost a mean difference of -4.3 kg (95% CI, -4.9 to -3.7, p<0.001) compared to placebo. Liraglutide was also associated with more serious adverse events, 15% vs. 13%, respectively (p-value not reported), most commonly cholelithiasis, cholecystitis acute, and osteoarthritis.¹³

A 2016 Cochrane review evaluated the evidence for insulin secretagogues for the prevention and delay of developing T2DM; however, evidence was insufficient to draw any meaningful conclusions.¹⁴ A second Cochrane review studied glycoprotein-1 receptor agonists (GLP-1 RA) and dipeptidyl peptidase-4 (DPP-4) inhibitors for prevention of T2DM in patients at increased risk. There was no conclusive evidence that DPP-4 inhibitors or GLP-1 RAs prevent progression to diabetes when compared to placebo (based on low quality evidence).¹⁵

Guideline Recommendations

The National Institute for Health and Care Excellence (NICE) published guidance in 2012 for the prevention of T2DM in patients who are high risk.¹⁶ NICE recommends that patients determined to be at high risk (i.e. prediabetic) should be referred to an intensive lifestyle change program. Metformin, in addition to lifestyle modifications, is recommended for patients at high risk with worsening HbA1c or fasting plasma glucose levels when lifestyle modifications alone have failed or they are unable to participate in an intensive lifestyle change program. Yearly follow-up on glucose levels should also be assessed.

Limitations

The majority of evidence on the prevention of T2DM in individuals who have prediabetes is of low quality and does not provide evidence of a mortality benefit or prevention of complications. Observational and cohort studies are the source of most of the evidence, with limited evidence from randomized controlled trials. The use of varying definitions of prediabetes also prevents pooling data and drawing strong conclusions on findings.

There are no Food and Drug Administration (FDA) approved medications for the management of prediabetes. No pharmacotherapy has proved to be more effective than lifestyle modifications in the prevention of progression from prediabetes to T2DM. With the use of any pharmacotherapy, the risk of adverse events must be balanced with the potential benefit. Despite improvement in surrogate outcomes, there is no evidence of morbidity or mortality benefits of lifestyle or pharmacotherapy interventions in patients with prediabetes.

Oregon Health Plan Fee-For-Service Policy

OHP FFS does not recommend drug treatment for patients with prediabetes

Patient Resources

The CDC created the National Diabetes Prevention Program (National DPP) to provide lifestyle management programs to individuals at high risk of T2DM.³ A descriptive analysis of the program found 35% of participants achieved a goal of 5% weight loss and 41.8% met the goal of 150 minutes of physical activity a week.¹⁷ More information on the National DPP can be found at:

<https://www.cdc.gov/diabetes/prevention/index.html>.

Key Take Home Points

- There is a lack of high quality evidence on preventing or delaying T2DM in patients with prediabetes
- Lifestyle changes are the most appropriate option in individuals with prediabetes to prevent the transition to overt T2DM

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