Editorials

Controversies in Family Medicine

Should Adults with Prediabetes Be Prescribed Metformin to Prevent Diabetes Mellitus?

No: Evidence Does Not Show Improvements in Patient-Oriented Outcomes

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Prediabetes is not a disease. It is a risk factor for a disease (diabetes mellitus). Most people with so-called prediabetes will not develop diabetes within five years.[1] The American Diabetes Association (ADA) definition of prediabetes now includes a threshold value in fasting glucose (100 to 125 mg per dL [5.5 to 6.9 mmol per L]), two-hour glucose tolerance test (140 to 199 mg per dL [7.8 to 11.0 mmol per L]), or A1C (5.7% to 6.4%). This definition dramatically expands the number of people who meet the definition of prediabetes; one-third of Americans older than 18 years meet the criteria.[2] In addition, many people will be mislabeled as having prediabetes. Compared with the reference standard of an oral glucose tolerance test, a single A1C measurement is 49% sensitive and 79% specific for prediabetes.[3] The ADA itself states that "prediabetes should not be viewed as a clinical entity in its own right but rather as an increased risk for diabetes and cardiovascular disease."[1] Cutoff values for diabetes and prediabetes are arbitrary.[4]

There is broad agreement that the first interventions for people with obesity, diabetes, or elevated blood glucose levels should be improving diet and exercise. A diagnosis is not needed to focus on these interventions to improve health and well-being. Studies of patients with borderline glucose values have shown a decreased incidence of crossing the threshold for a diabetes diagnosis with lifestyle intervention.[3] Those advocating for pharmacologic intervention for threshold glucose values cite randomized controlled trials that show a lower incidence of diabetes with metformin treatment. The landmark 2002 Diabetes Prevention Program studied metformin vs. placebo medication vs. a lifestyle modification program in patients without

diabetes who had elevated fasting and postload plasma glucose levels.[5] This study showed a decreased incidence of diabetes at 2.8 years. Using the ADA-defined threshold, 28.9% in the placebo group, 21.7% in the metformin group, and 14.4% in the lifestyle group were diagnosed with diabetes at three years. At four years, the average A1C was 5.9% in the metformin or lifestyle groups and 6.1% in the placebo group. Although these surrogate outcome differences are statistically significant, they are not clinically meaningful. Treating borderline glucose values does not improve quality of life, mortality, or any other patient-oriented outcomes.[5,6]

It is unlikely that initiating metformin before diabetes is diagnosed improves outcomes compared with waiting for a formal diagnosis. When the clinically meaningful benefit of a treatment is marginal, harms become more important to consider. Although metformin is inexpensive and simple to use, many patients experience gastrointestinal symptoms such as diarrhea, flatulence, nausea, and vomiting.[5] Long-term use is associated with vitamin B_{12} deficiency.[7]

Further, the labeling of patients with the diagnosis of prediabetes is an example of disease mongering (i.e., "the selling of sickness that widens the boundaries of illness in order to grow the markets for those who sell and deliver treatments"[8]). The impact of giving patients an unneeded disease label is not fully understood. It may encourage patients to make lifestyle changes. On the other hand, it leads to "medicalization" and may increase psychological stress and depression.[9,10]

Inevitably, some experts, led by commercial interests, will suggest other medication treatments for borderline glucose values. Recently published studies analyzed surrogate end points for prediabetes treatment in newer drug classes.[11-13] Many trials are ongoing to study pharmaceuticals in prediabetes.[4] No doubt the drumbeat recommending lucrative medication treatment for prediabetes will continue to get louder.

Discussing with patients the pros and cons of medications for borderline glucose values could distract us from more important topics such as lifestyle changes, smoking cessation, blood pressure control, and the possible benefit of medications for cardiovascular disease prevention. Time is the most valuable resource in a physician-patient partnership, and there are better ways to spend it.

This is one in a series of pro/con editorials discussing controversial issues in family medicine.

A collection of Editorials: Controversies in Family Medicine published in *AFP* is available at https://www.aafp.org/afp/pro-con.

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