COMMENTARY

Metformin Should Be Used to Treat Prediabetes in Selected Individuals

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In this issue of *Diabetes Care*, Dr. Mayer Davidson proposes that prescription of metformin for patients with prediabetes is inappropriate (1). We respectfully disagree. Hyperglycemia is a continuous risk factor for adverse health outcomes. Both the degree and duration of hyperglycemia are associated with the development and progression of diabetic microvascular and macrovascular complications (2), and early aggressive management of hyperglycemia in both type 1 and type 2 diabetes confers lifelong health benefits (3,4). We believe that Dr. Davidson's approach to watchful waiting, "to follow [high-risk individuals] closely and immediately introduce metformin when their glycemia meets the criteria for diabetes. . .," is inadequate. Numerous studies have demonstrated that there is a delay of 3–8 years between the onset and the diagnosis of type 2 diabetes (5), and at the time of diagnosis as many as 8–16% of patients have diabetic retinopathy, 17–22% have microalbuminuria, and 14–48% have peripheral polyneuropathy (6,7). A recent epidemiologic analysis of new-onset diabetes in the U.K. demonstrated a statistically significant increased risk of microvascular complications at diagnosis among individuals identified previously with prediabetes compared with those with previous normal glucose tolerance (adjusted odds ratio of 1.76 for retinopathy and 1.14 for nephropathy) (8). Therefore, there is no reason to withhold metformin, a safe, effective, and cost-saving treatment to delay or prevent the development of type 2 diabetes, from individuals at high risk. That said, a number of caveats apply.

First, the Diabetes Prevention Program (DPP) and indeed most of the other major diabetes prevention trials studied individuals at extremely high risk for progression to type 2 diabetes (9). Eligibility required that subjects have overweight or obesity and impaired glucose tolerance (2-h glucose after a 75-g oral glucose load of 140–199 mg/dL) and fasting hyperglycemia (fasting glucose 95–125 mg/dL). As pointed out by Dr. Davidson, a series of consensus panels made pragmatic decisions to align simpler and more commonly used diagnostic criteria (HbA_{1c}, fasting glucose) with impaired glucose tolerance as defined by the 2-h oral glucose tolerance test (1). Although perhaps identifying comparable numbers of individuals with "prediabetes," it is well documented that the American Diabetes Association fasting glucose and HbA_{1c} criteria do not identify the same individuals as the criteria used for enrollment in the DPP. Compared with the gold standard 2-h glucose criterion of 140–199 mg/dL, fasting glucose of 100–125 mg/dL lacks specificity and results in many false-positive diagnoses, whereas HbA_{1c} of 5.7–6.4% lacks sensitivity and results in many false-negative diagnoses (10,11). Applying either lifestyle or metformin therapy to individuals at lower risk for type 2 diabetes will reduce the effectiveness and cost-effectiveness of the therapy and, with regard to metformin, may lower the benefit-to-risk ratio. A precision medicine approach, with metformin therapy reserved for individuals at high risk for progression to type 2 diabetes, is optimal.

Second, even within the seemingly homogeneous DPP study population, there was substantial heterogeneity of treatment effect. The DPP Research Group reported that metformin was more effective in participants <60 years of age, with BMI ≥ 35 kg/m^2, with greater degrees of fasting hyperglycemia, and in women with histories of gestational diabetes mellitus (12,13). Individuals selected for treatment with metformin should have a high likelihood of benefiting. This approach to precision medicine, termed "benefit-based tailored treatment," calculates an individual's absolute risk reduction as the difference between the individual's risk without treatment and with treatment (14). The DPP Research Group developed risk equations that use clinical variables measured at DPP baseline to predict risk of progression to diabetes and demonstrated that the benefits of metformin therapy were limited to approximately one-half of the metformin treatment group who were at higher risk

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for progression to type 2 diabetes (15). Thus, although the DPP demonstrated that metformin treatment works, focusing solely on aggregate treatment results may lead to the faulty inference that metformin treatment provides equal benefits to everyone who receives it. Personalized medicine demands understanding heterogeneity in treatment effects, allowing one to quantify benefits and risks to facilitate benefit-based tailored treatment and ensure that the individuals selected for treatment with metformin are likely to benefit.

Third, Dr. Davidson uses data from the DPP metformin washout study and from the Diabetes Prevention Program Outcomes Study (DPPOS) to argue that because metformin may not cause long-lasting changes in the pathophysiology of prediabetes, it should not be used for diabetes prevention. We disagree with this argument. Antihypertensive and lipid-lowering therapy are effective only so long as they are continued. No one would argue that they should not be used because their effects on blood pressure and cholesterol disappear when treatment is discontinued. The complications and comorbidities of diabetes occur as a function of the degree and duration of hyperglycemia. Computer simulation modeling has demonstrated that metformin delayed the onset of diabetes by 3.4 years and potentially provided an 8% absolute reduction in the risk of development of type 2 diabetes over 30 years, thereby reducing the cumulative lifetime glycemic exposure and, by doing so, delaying or preventing the development of complications and their attendant decrements in health-related quality of life (16).

Fourth, Dr. Davidson's argument that "use of metformin... would increase drug costs considerably for payers as well as for many individuals" is not supported by the evidence. Metformin is inexpensive, and economic analyses of the DPP and DPPOS have demonstrated that in an intention-to-treat analysis over 10 years, metformin therapy is cost-saving compared with placebo—that is, it both reduces costs and improves health outcomes (15). It is reasonable to expect that selective use of metformin in individuals with the greatest likelihood of benefit would yield even greater cost savings.

Finally, we would point out that there is a nationwide demand for pharmacotherapy to improve health. In 2018, 70% of the U.S. population in every age-group reported that they used dietary supplements for their health and wellness benefits (17). Revenues from vitamin and nutritional supplement production in the U.S. exceeded $32 billion in 2019 (18). Many of these supplements including cinnamon, chromium, α-lipoic acid, and bitter melon are specifically marketed for diabetes and diabetes prevention. Allowing the marketing and sale of these unproven therapies for diabetes prevention and denying high-risk individuals metformin, a proven safe, effective, and cost-saving treatment, is wrong.

In conclusion, we believe that metformin should be used to treat prediabetes selectively. The efficacy, safety, and cost-effectiveness of metformin therapy were demonstrated among very high-risk individuals. Assurance of achieving the same beneficial effects is most secure when metformin therapy is prescribed to individuals who meet eligibility criteria for the DPP. Recognizing the heterogeneity of treatment effect, metformin therapy should also be limited to individuals who are at highest risk and most likely to benefit, including those who are younger, more obese, more hyperglycemic, or who have histories of gestational diabetes mellitus. We reject Dr. Davidson's argument that there is no benefit to the early aggressive treatment of prediabetes in people at very high risk for developing diabetes if the underlying pathophysiologic process is not altered. Early use of metformin can delay the emergence of overt but often unrecognized hyperglycemia that causes microvascular and neuropathic complications and is associated with increased cardiovascular risk. By delaying or preventing the onset of diabetes, metformin therapy is likely to have direct benefits on long-term complications and health-related quality of life.

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