Metformin Should Not Be Used to Treat Prediabetes

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Diabetes Care 2020;43:1983–1987 | https://doi.org/10.2337/dc19-2221

Based on the results of the Diabetes Prevention Program Outcomes Study (DPPOS), in which metformin significantly decreased the development of diabetes in individuals with baseline fasting plasma glucose (FPG) concentrations of 110–125 vs. 100–109 mg/dL (6.1–6.9 vs. 5.6–6.0 mmol/L) and A1C levels 6.0–6.4% (42–46 mmol/mol) vs. <6.0% and in women with a history of gestational diabetes mellitus, it has been suggested that metformin should be used to treat people with prediabetes. Since the association between prediabetes and cardiovascular disease is due to the associated nonglycemic risk factors in people with prediabetes, not to the slightly increased glycemia, the only reason to treat with metformin is to delay or prevent the development of diabetes. There are three reasons not to do so. First, approximately two-thirds of people with prediabetes do not develop diabetes, even after many years. Second, approximately one-third of people with prediabetes return to normal glucose regulation. Third, people who meet the glycemic criteria for prediabetes are not at risk for the microvascular complications of diabetes and thus metformin treatment will not affect this important outcome. Why put people who are not at risk for the microvascular complications of diabetes on a drug (possibly for the rest of their lives) that has no immediate advantage except to lower subdiabetes glycemia to even lower levels? Rather, individuals at the highest risk for developing diabetes—i.e., those with FPG concentrations of 110–125 mg/dL (6.1–6.9 mmol/L) or A1C levels of 6.0–6.4% (42–46 mmol/mol) or women with a history of gestational diabetes mellitus—should be followed closely and metformin immediately introduced only when they are diagnosed with diabetes.

The Diabetes Prevention Program (DPP) studied the effect of an intensive lifestyle intervention and metformin on the development of diabetes in a cohort of people with an increased risk for diabetes (termed prediabetes). After a mean of 2.8 years of follow-up, 31% fewer metformin-treated individuals developed diabetes than individuals in the control group (1). Eighty-six percent of members of the metformin and placebo groups agreed to be followed and entered the Diabetes Prevention Program Outcomes Study (DPPOS). The placebo was discontinued and metformin (850 mg b.i.d.) was unmasked and continued. The 15-year follow-up results in the DPPOS metformin-treated group recently showed significantly less development of diabetes in participants with higher baseline fasting plasma glucose (FPG) concentrations (110–125 vs. 100–109 mg/dL [6.1–6.9 vs. 5.6–6.0 mmol/L]) (2), in those with A1C levels 6.0–6.4% (42–46 mmol/mol) vs. <6.0%, and in women with a history of gestational diabetes mellitus (2). An accompanying editorial (3) invited arguments discussing whether people meeting the criteria for prediabetes should be treated with metformin. Since 33.9% of the population over 18 years of age in the U.S., 84.1 million people, have prediabetes (4), use of metformin to treat them would increase drug costs considerably for payers as well as for many individuals. This Perspective will argue against doing so.

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Received 5 February 2020 and accepted 28 April 2020

See accompanying article, p. 1988.

It is instructive to review the history of diagnosing prediabetes. Before 1979, there were six different criteria for diagnosing diabetes. In that year, the National Diabetes Data Group (NDDG) published a single set of criteria for the diagnosis (FPG ≥140 mg/dL [7.8 mmol/L] or 2-h glucose concentration on an oral glucose tolerance test [OGTT] ≥200 mg/dL [11.1 mmol/L]) based on three prospective studies in subjects who had a baseline OGTT and were evaluated for diabetic retinopathy 3 to 8 years later (5). They also opined that individuals whose 2-h glucose value was ≥140 to 199 mg/dL (7.8 to 11.0 mmol/L) had impaired glucose tolerance (IGT), which indicated an increased risk for developing diabetes. No FPG criterion for diagnosing prediabetes was offered.

The NDDG criteria for diagnosing diabetes were not equally sensitive. Although 95% of all persons with an FPG concentration ≥140 mg/dL (7.8 mmol/L) also had a 2-h glucose concentration ≥200 mg/dL (11.1 mmol/L) on the OGTT, this level of concordance was not seen with all persons who had a 2-h glucose concentration ≥200 mg/dL (11.1 mmol/L). Only one-quarter to one-half of these individuals also had an FPG ≥140 mg/dL (7.8 mmol/L) (6). The American Diabetes Association (ADA) convened an Expert Committee to address this imbalance (7). Based on an analysis by the Expert Committee of the third National Health and Nutrition Examination Survey (NHANES III) and several other published studies, the new FPG criterion for diagnosing diabetes was set at ≥126 mg/dL (7.0 mmol/L), which yielded the same prevalence of diabetes as did a 2-h glucose value on the OGTT of ≥200 mg/dL (11.1 mmol/L). Since no studies defining a normal FPG concentration were known, the often-stated normal glucose value of <110 mg/dL (6.1 mmol/L) used by clinical laboratories was adopted. The FPG range of 110–125 mg/dL (6.1–6.9 mmol/L) was termed impaired fasting glucose (IFG) and joined IGT to diagnose prediabetes.

However, again there was an imbalance. Many fewer people with IFG subsequently developed diabetes compared with those who had IGT. The ADA convened another meeting of the Expert Committee to address this issue (8,9). They analyzed four populations and determined that lowering the IFG criterion to 100–125 mg/dL (5.6–6.9 mmol/L) would greatly reduce the predictive discrepancy between IGT and IFG for the subsequent development of diabetes.

In 2008, an invited expert panel (IEP) recommended that diabetes could be diagnosed by an A1C level of ≥6.5% (48 mmol/mol) and also suggested that values of 6.0–6.4% (42–46 mmol/mol) required close follow-up and testing (10). In response, the ADA, the European Association for the Study of Diabetes, and the International Diabetes Federation appointed an International Expert Committee that agreed with the invited expert panel regarding the diagnosis of diabetes (if the A1C level were confirmed) (11). However, that committee also opined that because of the progressive continuum of risk of increasing glycemia below the diagnostic levels of diabetes for the subsequent development of diabetes, it was inappropriate to define a specific prediabetes risk group. The ADA subsequently adopted the recommended A1C level for diagnosing diabetes but also included an A1C criterion of 5.7–6.4% (39–46 mmol/mol) for prediabetes (12). The lower bound of the prediabetes criteria was based on modeling the estimated composite risk of developing diabetes and cardiovascular disease (CVD) using cross-sectional data from the 2005–2006 NHANES (13). However, the glycemia of prediabetes is not independently associated with CVD (14–21). Furthermore, in people who experience an acute coronary syndrome, the outcomes (length of hospital stay, 28-day readmission rate, acute pulmonary edema, 12-month recurrent acute coronary syndrome, or mortality) are no different between those with prediabetes (A1C 5.7–6.4% [39–46 mmol/mol]) or with A1C levels <5.7% (39 mmol/mol) (22). Rather, the association between prediabetes and CVD is due to the other risk factors for CVD that people meeting the glycemic criteria for prediabetes also have. Restricting the modeling to only the risk for developing diabetes might have influenced the prediabetes A1C criterion.

The World Health Organization (WHO) accepted the 1997 ADA IFG criterion of FPG 110–125 mg/dL (6.1–6.9 mmol/L) for prediabetes (23) but not the 2003 ADA IFG criterion of FPG 100–125 mg/dL (5.6–6.9 mmol/L) (24). Regarding the A1C criteria, the WHO adopted the ADA A1C criterion of ≥6.5% (48 mmol/mol) for diagnosing diabetes (if confirmed) but stated that there was insufficient evidence to decide on A1C values <6.5% (48 mmol/mol) (25).

The Diabetes Canada 2018 Clinical Practice Guidelines recommended the criteria for prediabetes as IFG concentrations of 110–125 mg/dL (6.1–6.9 mmol/L) or A1C levels of 6.0–6.4% (42–46 mmol/mol) (26).

Although numerous studies have shown that glycemia is not an independent risk factor for CVD (14–21), it certainly is for the development of diabetes. However, there is no obvious threshold; the risk starts to increase beginning at FPG concentrations of 82–87 mg/dL (4.6–4.8 mmol/L) and progresses in a curvilinear fashion (27–29). For instance, the risk with the WHO IFG criterion of 110–125 mg/dL (6.1–6.9 mmol/L) is 2.1- to 11.3-fold higher than with the lower bound of the ADA IFG criterion of 100–109 mg/dL (5.6–6.0 mmol/L) (14,30,31). Similarly, the risk with the A1C IEP criterion of 6.0–6.4% (42–46 mmol/mol) is 2.0- to 6.5-fold higher than with the lower bound of the ADA A1C criterion of 5.7–5.9% (39–41 mmol/mol) (14,31).

Claims have been made that treating people with prediabetes with antihyperglycemic drugs (metformin, thiazolidinediones [TZD], α-glucosidase inhibitors, glucagon-like peptide 1 agonists, basal insulin) has delayed or even prevented the development of diabetes. This is a misinterpretation of the situation. These drugs have simply treated a level of glycemia lower than the diagnostic criteria for diabetes retarding its increase to the level at which a diagnosis of diabetes would occur. After these drugs were discontinued, the prevalence of diabetes in treated individuals mirrored that in the placebo group.

An argument has been made that the difference between the placebo and metformin groups in the DPP only decreased from 31% to 25% 1–2 weeks (mean 11 days) after discontinuing metformin (a period of time that encompassed more than five half-lives of the drug), indicating that metformin caused a long-lasting, fundamental change in the pathophysiology of prediabetes (32). However, the time course of action of a drug is much more related to its tissue biologic effects than to the pharmacokinetics of its concentration in the blood. It is well established that it takes 2–4 weeks for both metformin and sulfonylureas to

exert their maximal effects when started (33–35). Although the author could find no studies examining the time course of the effect of metformin wearing off, it takes 2–4 weeks for the effect of a sulfonylurea (tolazamide) to completely dissipate (33). The facts that in the 1- to 2-week period in which metformin was discontinued 64% more subjects who had received metformin developed diabetes than those who had received a placebo (32) and that in the DPPOS the incidence of developing diabetes was similar in the original three groups of the DPP (36) strongly suggest that metformin does not fundamentally change the pathophysiology of prediabetes

Troglitazone, a TZD that was removed from the market because of hepatic toxicity, was used for a mean of 0.9 years in the DPP (37). During this period, diabetes incidence was reduced by 75% compared with placebo but the incidence was identical to placebo after troglitazone was discontinued. In the DREAM (Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication) study, in which rosiglitazone was the TZD, 60% fewer persons developed diabetes compared with the placebo group (38). In those who had not developed diabetes during the intervention period, the rate of development of diabetes was the same in both groups during the 2- to 3-month washout period after both rosiglitazone and its placebo were discontinued (39) and 1.6 years later (40). The Outcome Reduction With Initial Glargine Intervention (ORIGIN) study compared people with CVD risk factors who also had IFG, IGT, or early type 2 diabetes and who were given either glargine insulin or placebo (41). In those who did not have diabetes at baseline, 30% and 35% developed diabetes in the glargine and placebo groups, respectively, approximately 3 months after the study ended. The pathophysiologic abnormalities of insulin resistance and progressive β-cell dysfunction that characterize prediabetes were not fundamentally altered by these drug treatments (42,43), which explains the lack of any long-term effects when these medications were discontinued (44).

Even so, should metformin treatment be offered to individuals whose glycemic parameters are near the diagnosis for diabetes, i.e., those with IGT or whose FPG meets the WHO IFG criterion of 110–125 mg/dL (6.1–6.9 mmol/L) or the IEP A1C criterion of 6.0–6.4% (42–46 mmol/mol)? There are three arguments against this. First, approximately two-thirds of people with prediabetes do not develop diabetes, even after many years. In the placebo arm of the DPPOS, 65% of participants had not developed diabetes 5.7 years after the DPP had ended (45). In the Framingham Offspring Study, 69% of the cohort with prediabetes had not developed diabetes 27–30 years later (46). In people >60 years of age with prediabetes who were followed for 12 years in the Swedish National Study on Aging (47), 23% died and 13% developed diabetes. Even if all of the individuals who died had developed diabetes before doing so (highly unlikely), this would still leave 64% who did not develop diabetes.

Second, approximately one-third of people with prediabetes return to normal glucose regulation (NGR). In the DREAM study, 30% of the participants in the placebo arm returned to NGR during the 3.0 years of the study (38). After the study ended, the percent of participants who returned to NGR 1.6 years later was 38% in the placebo arm and 42% in the rosiglitazone arm (40). In the DPPOS, 24% of individuals in the placebo arm returned to NGR 5.7 years after the DPP ended (45). In a Korean population, 36% of people with prediabetes returned to NGR within 10 years (48). Even in the older population of the Swedish National Study on Aging, 23% returned to NGR (47). It is unknown how many of the 23% who died might have returned to NGR. In the Whitehall II Cohort Study (49), in which the ADA criteria were used to diagnose prediabetes, of those with IFG or IGT or diagnosed with A1C levels, 45%, 37%, and 17%, respectively, returned to NGR in 5 years. Finally, in a Cochrane Database systemic review of 47 studies of prediabetes, return to NGR ranged from 33% to 59% within 1–5 follow-up years and from 17% to 42% within 6–11 years of follow-up (50).

Third, as described previously, the diagnostic criteria for diabetes were selected because the risk for microvascular complications increased beyond that level of glycemia. Metformin, the preferred initial drug for treating patients with diabetes, is started to lower glycemia to levels that are not associated with this risk. Five studies (51–55) have shown that the development or progression of retinopathy and microalbuminuria over a 6- to 10-year period was almost nil if A1C levels were kept below 7.0% (53 mmol/mol). So, given that two-thirds of people with prediabetes do not develop diabetes over many years (45–47), and in approximately one-third glycemia returns to normal (40,45,47–50), why put people who are not at risk for the microvascular complications of diabetes when prediabetes is diagnosed on a drug (possibly for the rest of their lives) that has no immediate advantage except to lower subdiabetes glycemia to even lower levels? The authors of the Cochrane Database systemic review (50) also concluded that "practitioners should be careful about the potential implications of any active intervention for people 'diagnosed' with [intermediate hyperglycemia]."

This Perspective is not arguing against the benefit of delaying the development of diabetes. Rather, it is pointing out that the benefit of delay achieved with medication must be weighed against the potential adverse effects of the drug, its cost, and the important fact that a large number of people with the diagnosis of prediabetes will not develop diabetes and metformin would be of no benefit for them. The argument is that lifestyle interventions, especially weight loss in overweight and obese individuals, should be pursued rather than use of a medication.

It seems more prudent to identify individuals at the highest risk for developing diabetes—i.e., those fulfilling the WHO FPG criterion of 110–125 mg/dL (6.1–6.9 mmol/L) or those meeting the IEP A1C criterion of 6.0–6.4% (42–46 mmol/mol) or women with a history of gestational diabetes mellitus—in order to follow them closely and immediately introduce metformin when their glycemia meets the criteria for diabetes (if confirmed). Meanwhile, these individuals should be intensely counseled on lifestyle interventions to reduce the risk of developing diabetes, and the risk factors for CVD should be aggressively addressed. Although the ADA (56) and the Endocrine Society (57) recommend metformin for treatment of prediabetes, apparently most clinicians agree with the views described above because currently only 1–4% of people with prediabetes are given metformin (58,59).

Duality of Interest. No conflicts of interest relevant to this article were reported.

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