EDITORIAL

Prediabetes Diagnosis and Management

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The Diabetes Prevention Program (DPP) was a multicenter, randomized clinical trial that demonstrated that people at high risk for type 2 diabetes could delay or prevent diabetes with healthy dietary changes combined with moderate physical activity or by taking metformin.[1]

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Since the DPP was published in 2002, the medical and public health communities have been challenged to translate its results into clinical and public health practice. The term *prediabetes*, defined as an intermediate state of glycemia between normal glucose regulation and diabetes that is associated with an increased risk of diabetes and cardiovascular disease, was coined to identify individuals at high risk for type 2 diabetes who might benefit from interventions that prevent diabetes. However, the imprecise definition of the term *prediabetes* has impeded efficient and cost-effective translation of the DPP results.

In 1979, the National Diabetes Data Group defined impaired glucose tolerance (IGT) as a glucose level of 140 through 199 mg/dL (7.8-11.0 mmol/L), measured 2 hours after a 75-g oral glucose load, and indicated that people with IGT had a higher risk of developing diabetes than people without IGT.[2] Approximately 1% to 5% of people with IGT developed overt diabetes annually, but many returned to normal glucose regulation spontaneously.[2] Screening for IGT was recommended only when it was feasible to intervene to prevent diabetes. At the time, no effective and safe interventions for diabetes prevention had been identified.

Randomized clinical trials subsequently used the oral glucose tolerance test to identify eligible participants and demonstrated that diabetes prevention was feasible.[1,3,4] Because of logistical difficulties performing oral glucose tolerance tests in routine clinical practice,[5] simpler criteria were sought to identify people at increased risk for developing diabetes. The term *prediabetes* was coined to identify people at increased near-term risk of diabetes. However, prediabetes was defined without the scientific rigor used to conduct the diabetes prevention clinical trials, and definitions differed across organizations and countries.

In 1997 and 1998, the American Diabetes Association (ADA) and the World Health Organization (WHO) introduced the concept of impaired fasting glucose (IFG) as a category of increased risk for diabetes analogous to IGT.[6,7] Initially, both the ADA and WHO defined IFG as a fasting plasma glucose (FPG) level of 110 to 125 mg/dL (6.1-6.9 mmol/L). In 2003, after results of the DPP clinical trial were published, the ADA recognized that an FPG of 110 to 125 mg/dL identified fewer people than were identified with the oral glucose tolerance test and changed its diagnostic criterion for IFG to 100 to 125 mg/dL (5.6-6.9 mmol/L).[8] In 2009, an International Expert Committee studied the relationships among FPG, 2-hour plasma glucose (2h-PG), and glycated hemoglobin (HbA_{1c}) and prevalent retinopathy.[9] The committee recognized that an HbA_{1c} level of 6.5% or higher, like the criteria for IFG and IGT, was associated with an increased risk of retinopathy and recommended this threshold to diagnose diabetes. The group also concluded that in individuals with HbA_{1c} levels of 6% to less than 6.5% were "likely to be at the highest risk for progression to diabetes."[9]

In this issue of *JAMA*, a Review by Echouffo-Tcheugui and colleagues discusses the diagnosis and management of prediabetes.[10] The Review summarizes 5 different definitions of prediabetes proposed by international organizations. The FPG criterion recommended by the ADA is 100 to 125 mg/dL whereas that recommended by the WHO is 110-125 mg/dL. Similarly, the HbA_{1c} criterion recommended by the ADA is 5.7% to 6.4% whereas that recommended by the International Expert Committee is 6.0% to 6.4% (to convert HbA_{1c} to mmol/mol, use the equation [10.93 × HbA_{1c}] − 23.50). Consensus exists only for the definition of IGT. The differences between these criteria are sizable and result in large differences in the prevalence of prediabetes, the risk of progression to diabetes, and the effectiveness and cost-effectiveness of interventions for diabetes prevention. In an effort to increase enrollment in lifestyle change programs, eligibility criteria for inclusion in the National Diabetes Prevention Program were expanded by the Centers for Disease Control and Prevention (CDC) to include a positive result on the CDC-ADA Prediabetes Risk Questionnaire. However, the risk questionnaire has relatively low sensitivity (72%-76%) and specificity (54%) in identifying people with prediabetes.[11]

The prevalence of prediabetes in the US varies substantially when FPG, HbA_{1c}, and 2-hour PG diagnostic criteria are used (28.3%, 21.7%, and 13.3%, respectively),[12] and concordance between diagnostic criteria is poor. An analysis of National Health and Nutrition Examination Survey data from 2015-2016 demonstrated that 51.3% of the US population met the criteria for at least 1 of the ADA recommended definitions of prediabetes, but only 2.5% of the US population met criteria for all 3 criteria.[13] The risk of progression to type 2 diabetes varied substantially according to the criterion that defined prediabetes. At 5-year follow-up, 18% of individuals with IFG of 100 to 125 mg/dL, 26% of those with IFG of 110 to 125 mg/dL, 39% of those with IGT, 50% of those with IFG and IGT, 25% of those with HbA_{1c} 5.7% to 6.4%, and 38% of those with HbA_{1c} 6.0% to 6.4.% progressed to type 2 diabetes.[14]

In secondary analyses, the DPP research group evaluated HbA_{1c} as a criterion for eligibility for the DPP clinical trial and

assessed the effects of the lifestyle, metformin, and placebo interventions on diabetes incidence defined by HbA_{1c} of 6.5% or higher. Of the DPP participants without diabetes who had FPG of 95 mg/dL or more and 2-hour PG 140 to 199 mg/dL with HbA_{1c} levels measured at baseline, 13% had diabetes at baseline defined by HbA_{1c} of 6.5% or higher and 38% had normal glucose regulation defined by HbA_{1c} of less than 5.7%.[15] Of the 49% of DPP participants deemed eligible to participate based on HbA_{1c} levels of 5.7% to 6.4% at baseline, the metformin and lifestyle interventions each prevented HbA_{1c}-defined diabetes.[15]

The term *prediabetes* is problematic because it suggests that individuals with the condition will develop diabetes and that individuals who do not meet the criterion for prediabetes are unlikely to develop diabetes. Neither of these assumptions is completely true. When more sensitive and less-specific criteria such as FPG 100 to 125 mg/dL are used to define prediabetes, the likelihood of reverting to normal glucose values is greater than the risk of developing diabetes.[16] Classification of individuals as high-risk or low-risk based on a single measure of glycemia is suboptimal because the risk for progression to diabetes is a continuum, and when assigning risk to implement prevention strategies, risk factors other than diabetes must be considered.[9]

Although randomized clinical trials such as the DPP can demonstrate whether treatments are effective, response to treatment varies.[17] Focusing on aggregate results from the randomized treatment groups may lead to the faulty inference that an effective treatment provides equal benefits to everyone. Understanding this phenomenon, termed "heterogeneity of treatment effects,"[18] requires knowledge about which participants do and do not benefit from the treatment. Treatment benefits generally increase as an individual's baseline risk increases. Sussman et al[19] reported that among participants in the DPP randomized to metformin, the risk of progression to diabetes at 3 years was reduced by 22 percentage points (60% in the control group vs 38% in the metformin group) in the one-fourth of participants at highest risk for developing diabetes. No benefit was observed in the one-fourth of participants at lowest risk. Among participants randomized to the lifestyle intervention, the 3-year risk of developing diabetes was reduced by 40 percentage points (59% in the control group vs 19% in the lifestyle intervention group) among those at highest risk compared with 8 percentage points (12% in the control group vs 4% in the lifestyle intervention group) among those at lowest risk of developing diabetes.[20] Benefit-based tailored treatment uses multivariable models to predict an individual's risk of progression to diabetes and regression to normal glucose regulation based on clinical characteristics including measures of glycemia. Only by considering multiple risk factors can an individual's level of risk and likelihood of responding to a treatment be assessed. Although all 3 diagnostic criteria (FPG, HbA_{1c}, and 2-hour PG) for prediabetes are useful, none by itself is adequate to define individual risk.[20]

The effectiveness and cost-effectiveness of an intervention depend on an individual's baseline risk.[21] Intervening for an individual at no risk will not change the outcome and the resources spent for the intervention will not add value. Intervention effectiveness and cost-effectiveness are greatest when individuals at higher risk receive the intervention. Current thresholds for defining prediabetes using fasting glucose, HbA_{1c}, and 2-hour PG levels do not identify a homogeneous population. The imprecise term "prediabetes" should be abandoned and replaced with simple multivariable risk models that include measures of glycemia and sociodemographic and clinical information to estimate each individual's risk. Such models should be used to select the optimal intervention strategy for diabetes prevention for each individual.

ARTICLE INFORMATION

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