Implications of Rising Prediabetes Prevalence

Given the burden of type 2 diabetes and its complications, much attention has been given to prevention, beginning with identifying at-risk individuals prior to diagnosis. This has led to the designation of "prediabetes," which is an intermediate form of dysglycemia on a spectrum ranging from normal to overt diabetes. The American Diabetes Association defines prediabetes as a fasting glucose of 100 to <126 mg/dL (impaired fasting glucose [IFG]), a 2-h plasma glucose of 140 to <200 mg/dL after a 75-g oral glucose tolerance test (impaired glucose tolerance [IGT]), or HbA_{1c} 5.7% (39 mmol/mol) to <6.5% (48 mmol/mol) (1). Fasting glucose ≥100 mg/dL portends an increased risk of diabetes (2,3), cardiovascular disease (CVD) in women (2), and mortality (4). HbA_{1c} levels 5.5% (37 mmol/mol) to <6.5% (48 mmol/mol) are associated with an increased risk of diabetes and CVD compared with levels <5.5% (37 mmol/mol) even after adjustment for fasting glucose and key CVD risk factors (3). Because of these associated risks, surveillance of prediabetes allows better prediction of diabetes trends and of the resources that will be required to treat rising diabetes.

In the current issue of *Diabetes Care*, Bullard et al. (5) review secular trends in U.S. prediabetes prevalence using National Health and Nutrition Examination Surveys (NHANES) data from 1999 to 2010. Prediabetes was defined as HbA_{1c} 5.7% (39 mmol/mol) to <6.5% (48 mmol/mol) or fasting glucose 100 to < 126 mg/dL; oral glucose tolerance tests (OGTTs) were not used. Participants completed a household interview followed by physical examination at mobile centers. A total of 19,182 participants ages ≥12 years were included in the analysis.

The authors report an increase in overall age-adjusted prediabetes prevalence from 27.4% in 1999–2002 to 34.1% in 2007–2010. Notably, the increase was solely the result of more individuals fulfilling the HbA_{1c} criterion, which was met by 9.5% in 1999–2002 and 17.8% in 2007–2010, whereas the prevalence of IFG remained essentially unchanged (23.8–25.9%). The findings were similar after adjustment for important covariates including BMI. Analyses of ethnic subgroups revealed an increasing prevalence of prediabetes HbA_{1c} levels among non-Hispanic whites (8.5–15.9%), non-Hispanic blacks (16.3–28.3%), and Mexican Americans (9.7–17.1%), whereas IFG prevalence did not change significantly. The authors conclude that prediabetes is increasing in prevalence and that demographic subgroups may benefit from targeted diabetes prevention efforts.

These important findings should be addressed in the broader context of the current obesity and diabetes epidemics. The prevalence of prediabetes was highest among overweight and obese individuals, and the prevalence increased in all BMI subgroups. Thus, the rise in prediabetes is closely linked to worsening obesity and possibly even to weight within the normal BMI range.

These findings raise several issues for consideration. First, in terms of absolute numbers, more people were classified as having prediabetes based on fasting glucose than based on HbA_{1c} (23.8 vs. 9.5% in 1999–2002 and 25.9 vs. 17.8% in 2007–2010). However because IFG did not change significantly over the interval, the increase in prediabetes prevalence would have been missed if fasting glucose had been the only surveillance metric. Thus, in terms of identifying the burden of prediabetes, including both fasting glucose and HbA_{1c} in the definition of prediabetes is valuable.

An important question is whether individuals identified with prediabetes based on HbA_{1c} or fasting glucose are similar to those identified via OGTT. This distinction is crucial because most major diabetes prevention trials, whose findings have led to current recommendations for management of prediabetes, used IGT to identify prediabetes (6–9). A prior cross-sectional analysis of NHANES data concluded that an HbA_{1c} range of 5.7% (39 mmol/mol) to <6.5% (48 mmol/mol) identifies individuals at a level of risk for diabetes (based on Stern risk score) and CVD (based on Framingham risk score) comparable with that of those enrolled in the Diabetes Prevention Program (DPP) (10). Compared with a reference range of 5% (31 mmol/mol) to <5.5% (37 mmol/mol), HbA_{1c} levels of 5.5% (37 mmol/mol) to <6% (42 mmol/mol) and 6% (42 mmol/mol) to <6.5% (48 mmol/mol) have been shown to be associated with higher odds of coronary disease (odds ratios 1.23 and 1.78, respectively) (3). IFG, while a risk factor for development of diabetes, is often discordant with OGTT results (11). The combination of IFG and IGT is associated with an increased mortality risk; however, this is less clear for IFG in the absence of IGT, particularly for fasting glucoses in the 100–109 mg/dL range (12,13). Thus, individuals with HbA_{1c} 5.7% (39 mmol/mol) to <6.5% (48 mmol/mol) or IFG may be comparable with those with IGT in major prevention trials, but this remains an open question.

Another notable point to consider with the current findings is that there were changes in the measurement of both HbA_{1c} and plasma glucose in NHANES over the study interval that may have affected the results. For HbA_{1c}, there were two instrument changes: a change in laboratory site and a change in high-performance liquid chromatography method. Importantly, however, the HbA_{1c} assay at all study points in time was calibrated to the Diabetes Control and Complications Trial assay. However, the Centers for Disease Control and Prevention could not determine whether the increase in HbA_{1c} in NHANES resulted from a change in laboratory protocol or survey design or a true population change (14).

There were also instrument changes in plasma glucose measurement, necessitating corrections of the measured values from 2005–2006 and 2007–2010. These corrections served to reduce the measured glucose values in the latter years, which would tend to decrease the estimated prevalence of IFG. This may partly explain why IFG prevalence did not increase concurrently with HbA_{1c}.

A final limitation is that HbA_{1c} levels may be affected by medical conditions other than diabetes such as hemoglobinopathies, iron-deficiency anemia, and chronic kidney disease and thus unreliable for assessment of dysglycemia in those settings (15). It is unlikely, however, that the prevalence of such conditions changed

significantly in the studied time interval to account for the increase in prediabetes.

Of note, the question has been raised of whether HbA_{1c} has the same correlation with glycemia in different ethnic groups (16–19). African Americans have higher HbA_{1c} levels than Caucasians, even after adjustment for fasting glucose, and it has been postulated that this difference might be due to nonglycemic factors such as variations in hemoglobin glycation or erythrocyte turnover. However, analysis from a large community-based sample found that other serum markers of glycemia (fructosamine, glycated albumin, and 1,5-anhydroglucitol) paralleled the HbA_{1c} differences between ethnicities (20). Because these markers are unrelated to hematologic factors, this finding suggests that the higher HbA_{1c} among African Americans truly reflects systematically worse glycemic control, perhaps due to postprandial glucose excursions.

Once prediabetes is identified, the question of how best to reduce progression to diabetes and CVD remains. Both lifestyle changes and metformin can delay progression from IGT to diabetes (6–9,21,22). Lifestyle modification can also reduce CVD risk factors (23,24) up to 10 years later. To prevent progression of prediabetes, the American Diabetes Association recommends weight loss, moderate exercise, consideration of metformin (for those with BMI >35 kg/m^2, age <60 years, or women with a history of gestational diabetes mellitus), and treatment of modifiable CVD risk factors (25).

Recognition of prediabetes is critical, given the risk of progression to diabetes. Identifying individuals with prediabetes offers the opportunity to modify their risk prior to development of significant sequelae. Preventing diabetes remains a challenge but one that is both feasible and imperative. Close surveillance of rising prediabetes prevalence is critical to projecting the future burden of diabetes and the resources that will be required to combat diabetes going forward.

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