COMMENTARY

Precision Prevention of Diabetes

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Prediabetes is defined as glycemia that is higher than normal but not high enough to warrant a diagnosis of diabetes. While it is not a disease in its own right, prediabetes is a risk factor for diabetes and cardiovascular disease (1). Unfortunately, as currently used, the term prediabetes encompasses a heterogeneous group of disorders. Prior studies have demonstrated that the prevalence of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) differ by age, sex, and geographic region; that the risk of progression from prediabetes to type 2 diabetes varies according to the diagnostic criterion used; and that subjects with prediabetes defined by either IFG or IGT differ with respect to their risk for cardiovascular mortality. The article by Sathish et al. (2) in this issue of *Diabetes Care* demonstrates that individuals with prediabetes defined by IFG and IGT respond differently to lifestyle intervention.

The authors identified four randomized controlled clinical trials that recruited people with isolated IFG, isolated IGT, and both IFG and IGT; pooled the data; and used random-effects models and the within-trial interactions approach to determine whether the effect of conventional lifestyle intervention on diabetes incidence differed by prediabetes phenotype. They found that with lifestyle intervention, diabetes incidence was reduced significantly in individuals with IGT with or without IFG but not in those with isolated IFG.

The strongest data that support the efficacy of lifestyle intervention for diabetes prevention come from studies of individuals with IGT (3). In a systematic review and meta-analysis of 32 randomized controlled trials that assessed 14 lifestyle and pharmacologic interventions for diabetes prevention, lifestyle modification was found to reduce the incidence of diabetes by 44% compared with control. Of the 14 trials that assessed lifestyle intervention compared with control, 10 exclusively randomized individuals with IGT. Only one trial randomized individuals with IFG, and three trials randomized individuals with prediabetes defined by various IFG, IGT, and A1C criteria (3).

What led to this confusion about the diagnosis of prediabetes? It arose from a well-intentioned desire to rapidly translate the results of the Diabetes Prevention Program (DPP) into routine clinical practice. In 1979, the National Diabetes Data Group first recommended that the 75-g oral glucose tolerance test be used to diagnose diabetes and that people with 2-h plasma glucose levels intermediate between normal ($<$140 mg/dL) and the level indicating diabetes ($\geq$200 mg/dL) be labeled as having IGT (4). It further recognized that individuals with IGT were at greater risk than the general population for developing diabetes but that many would return to normal spontaneously. For that reason, the National Diabetes Data Group discouraged use of the term prediabetes. They also discouraged testing for IGT, because at the time, there were no proven-effective interventions to prevent progression to diabetes.

In 1997, the International Expert Committee (5) recognized that the oral glucose tolerance test was infrequently performed and introduced the category of IFG, defined as fasting plasma glucose 110–125 mg/dL (IFG_{110}), to create a fasting glucose category analogous to IGT. In 2002, the results of the landmark DPP were published; they established the efficacy of lifestyle and metformin interventions in delaying or preventing the development of diabetes (6). In 2003, the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus lowered the cut point for IFG from 110 to 100 mg/dL (IFG_{100}) (7) in order to identify an at-risk population more similar in size to the population identified as having IGT. Subsequent research demonstrated that the pathophysiologies of IFG and IGT were different. Although both are associated with β-cell dysfunction, the pathophysiology of IFG is primarily associated with reduced hepatic insulin sensitivity, whereas that of IGT is related to reduced peripheral insulin sensitivity (8,9).

Analyses from the 2005–2008 National Health and Nutrition Examination Survey demonstrated that the prevalence of IFG and IGT differed in the population by age and sex (10). The prevalence of IFG_{100} alone was 26.2% and IGT alone was 13.7% in U.S. adults. The prevalence of IFG_{100} was substantially higher in men than women (33.1% vs. 19.7%), whereas the prevalence of IGT was similar in men (12.8%) and women (14.6%). Concordance was also poor: only 5.1% of U.S. adults $\geq$18 years of age had both IFG_{100} and IGT (10).

The prevalence of prediabetes also varies substantially by geographic region (11). The age-adjusted prevalence of IFG_{110} in adults 20–79 years of age is

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2.5% in the Western Pacific (including Japan), 3.3% in Europe (including the U.K.), and 8.8% in Southeast Asia (including India). In contrast, the age-adjusted prevalence of IGT is 12.9% in the Western Pacific, 7.1% in Europe, and 5.4% in Southeast Asia.

The risk of progression from prediabetes to type 2 diabetes also varies according to the diagnostic criteria used. In the DPP clinical trial, eligible subjects were adults >25 years of age with IGT, fasting hyperglycemia, and BMI >24 kg/m^2 (22 kg/m^2 in Asians) (6). Three years after randomization, the risk of progression to type 2 diabetes in the DPP placebo group was 110 per 1,000 person-years (6). The Obesity, Diabetes, and Cardiovascular Disease Collaboration performed an individual participant data meta-analysis of 16 studies from Asia, Australia, Europe, and North America to compare the ability of different diagnostic criteria for prediabetes to predict the 5-year incidence of diabetes (12). Progression from prediabetes to diabetes was 24 per 1,000 person-years for IFG_{100} and 44 per 1,000 person-years for IGT.

Additional studies have demonstrated that subjects with IGT but not isolated fasting hyperglycemia are at increased risk for cardiovascular mortality and that the risk may vary by geographic region (13). The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study pooled data from 10 European epidemiologic studies and assessed mortality among adults 30–89 years of age over a median of 8.8 years' follow-up (14). Compared with people with 2-h plasma glucose <140 mg/dL, those with IGT had an increased hazard ratio (HR) for death from cardiovascular disease (CVD) (HR 1.34 [95% CI 1.14–1.57]). In contrast, compared with people with fasting plasma glucose (FPG) <110 mg/dL, those with IFG_{110} had an insignificantly increased HR for death from CVD (1.09 [0.90–1.30]) (14). A second meta-analysis of five Asian epidemiologic studies involving Japanese and Asian Indian subjects 30–89 years of age over a median of 5.0 years' follow-up found that compared with people with 2-h plasma glucose <140 mg/dL, those with IGT had an insignificantly increased HR for CVD mortality (1.27 [0.86–1.88]), and compared with individuals with FPG <110 mg/dL, those with IFG_{110} had an insignificantly increased HR for CVD mortality (1.05 [0.67–1.65]) (15). The study by Sathish et al. (2) is limited by the small number of studies analyzed and by the age, sex, and regional differences across the studies. Two of the four studies focused exclusively on Asian Indians who were younger, less likely to be male, and more likely to have IFG. The third study included European subjects from the U.K. who were substantially more likely to have IGT. The fourth study included Japanese subjects and was not included in the meta-analysis of isolated IGT because all the subjects recruited had IFG.

A common approach to study interaction among treatment effects and covariates is to perform a two-stage individual participant data meta-analysis (16). In such analyses, the treatment effect is calculated separately for each subgroup and then compared using a statistical test or by calculating a difference. Figure 1 of Satish et al. (2) demonstrates that across trials and compared with the control groups that received standard care, the groups that had isolated IGT and IFG plus IGT and received lifestyle intervention had a reduced hazard for diabetes, whereas the group that had isolated IFG did not. This approach is simple and leads to a straightforward graphical display but amalgamates within-trial and across-trial information and is more likely to introduce aggregation bias. In contrast, Supplementary Fig. 2 is based on a better approach (meta-analysis with within-trial interaction [16]) and shows that the difference in treatment effects was significant only when isolated IFG was compared with IFG plus IGT. The difference between isolated IGT and IFG plus IGT was not significant. These results suggest an alternate conclusion, i.e., that lifestyle intervention for diabetes prevention should optimally target subjects with both IFG and IGT.

Based upon available evidence, it is not surprising that the effect of lifestyle intervention differs between individuals with IFG and IGT. This is consistent with both the differences in the presumed pathophysiology of IFG and IGT and the observed differences in the epidemiology of these conditions. While the results of the current study should be considered hypothesis generating and will require confirmation in other populations, they highlight the importance of more precise phenotyping of individuals with prediabetes and implementing proven-effective interventions for those most likely to benefit (17).

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