COMMENTARY

Diabetes in Normal-Weight Individuals: High Susceptibility in Nonwhite Populations

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Type 2 diabetes is one of the most prevalent diseases of our time. There are an estimated 425 million people with diabetes worldwide, and 625 million people are projected to have the disease by 2045 (1). Over the next three decades, the largest increases in diabetes prevalence and overall numbers of people with the disease are expected to occur in low- and middle-income countries and among nonwhite ethnic minorities living in high-income nations (1). Overweight and obesity are well-established risk factors for diabetes; however, evidence suggests that the relationship between body weight and diabetes risk may differ by race/ethnicity (2–4), which has implications for the prevention, screening, and treatment of individuals who develop diabetes with a BMI below the overweight or obesity range.

In their article in this issue of *Diabetes Care*, Zhu et al. (5) examined racial/ethnic disparities in the prevalence of diabetes by BMI category in a large, racially/ethnically and geographically diverse cohort of 4.9 million adults. Individuals enrolled in the cohort were members of three integrated health care systems in the U.S. in the years 2012–2013 and were from six racial/ethnic groups including white, black, Hispanic, Asian, Hawaiian/Pacific Islander, and American Indian/Alaskan Native. They found that the age-standardized prevalence of diabetes increased across BMI categories among all racial/ethnic groups. However, compared with whites, all other racial/ethnic groups had a higher prevalence of diabetes at any given BMI, and these differences were more pronounced in lower BMI categories. Strikingly, in those with a normal weight, the prevalence of diabetes was 5.0% in whites, 10.1% in Asians and American Indians/Alaskan Natives, 13.0% in Hispanics, 13.5% in Blacks, and 18.0% in Hawaiians/Pacific Islanders. Furthermore, when they examined the relative risks for diabetes for each BMI category by race/ethnicity, Zhu et al. reported that across all racial/ethnic groups whites had the steepest BMI gradient, followed by Asians, American Indians/Alaskan Natives, Hispanics, Hawaiians/Pacific Islanders, and blacks.

This study by Zhu et al. (5) has several notable strengths. It included a large cohort of 4.9 million adults that was racially/ethnically, geographically, and socioeconomically diverse. All participants were members of integrated health care systems, which reduced confounding due to health care access. However, the study is not without limitations. Because of its cross-sectional nature, the temporal association between BMI and diabetes could not be assessed. Furthermore, it is possible that those who develop diabetes in underweight or normal-weight categories do so through different pathophysiological mechanisms than those who are overweight or obese. For example, obesity-driven insulin resistance may not be sufficient to explain the high prevalence of diabetes in nonobese people, and other factors, such as poor insulin secretion, may be at play in the early natural history. However, no measures of insulin secretion or insulin resistance were available in the study by Zhu et al. Therefore, the relative contributions and timing of these factors for diabetes risk by BMI category could not be assessed. In addition, differences in deposits of ectopic fat (e.g., fat deposition in the liver or in the pancreas) may confer a large role on diabetes risk and may be particularly associated with diabetes risk in normal-weight or underweight individuals (6,7). However, no direct measures of ectopic fat were available. Lastly, there is considerable heterogeneity in diabetes prevalence within ethnic groups, such as Asians (8–10), but this was not examined.

By assessing the age-standardized prevalence of diabetes by BMI category in a racially/ethnically diverse population with similar health care access, Zhu et al. were able to demonstrate a high risk of diabetes even at low BMI in all racial/

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ethnic minority groups compared with whites. These results suggest that factors beyond obesity and access to health care may be contributing to the disproportionate burden of diabetes, especially in nonwhite populations. This phenomenon is seen globally, and people with ancestry from low- and middle-income countries, especially parts of the world where the industrial revolution occurred more recently and rapidly, exhibit a high risk of diabetes at lower body weight (11). It is therefore important not only to acknowledge the elevated risk of diabetes at low BMI in many large populations but also to conduct additional studies to better understand the mechanistic and pathophysiological processes behind this risk. Such studies may include longitudinal assessments of the relative contributions and timing of impaired insulin secretion and insulin resistance to diabetes development in nonoverweight individuals as well as the role of ectopic fat accumulation or other factors, such as low lean mass, environmental pollution, or stress.

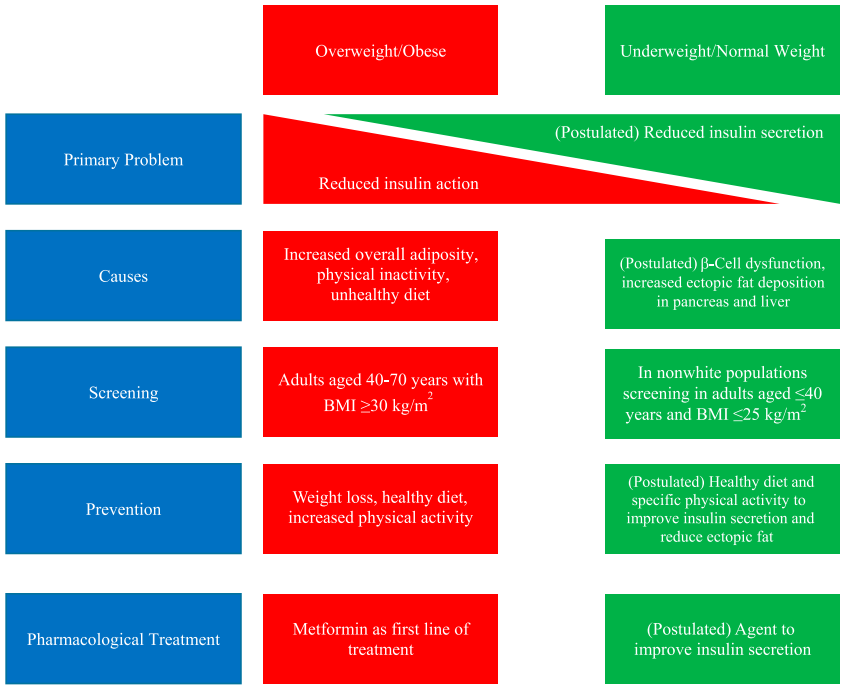

Figure 1—Postulated differences in type 2 diabetes mechanisms, causes, screening, prevention, and treatment between those who are overweight/obese and those who are underweight/normal weight.

In addition, the majority of global diabetes prevention trials have enrolled people in the overweight or obese category and largely those with impaired glucose tolerance (12–15). Trials on diabetes prevention in nonoverweight, high-risk individuals are lacking but are of importance given the elevated global prevalence of diabetes exhibited in this group. There is some evidence to suggest that high-intensity interval training can improve insulin secretion (16,17), and moderate weight loss of 5% was shown to be effective in reducing ectopic fat accumulation in a small sample of normal-weight individuals (18). However, additional research is necessary to identify the most beneficial methods of prevention in those who are at high risk for hyperglycemia in the absence of overweight or obesity. Furthermore, the U.S. Preventive Services Task Force for Diabetes Screening currently recommends using overweight/obesity as the main screening criteria in adults aged 40–70 years (19). However, doing so will likely lead to missing a substantial number of racial/ethnic minorities at risk for diabetes. While the U.S. Preventive Services Task Force does recommend screening at younger ages in racial/ethnic minority populations, screening in normal-weight/underweight individuals in these populations is an important consideration. A BMI cut point of 23 kg/m^2 has been suggested as a more appropriate cut point for screening in Asian populations (20). However, it is possible that a lower BMI cut point may identify more high-risk individuals in other racial/ethnic groups as well. Data are also scarce as to the most appropriate treatment strategies in nonoverweight individuals. While metformin is currently the first-line pharmaceutical treatment for type 2 diabetes in many settings (21), among nonoverweight individuals treatments promoting the preservation and recovery of β-cell function might potentially be a more prudent strategy (22).

In conclusion, the article from Zhu et al. (5) details a substantial burden of diabetes at nonobese levels of BMI in all populations, but especially in racial/ethnic minorities in the U.S. These results echo previous studies pointing to a high prevalence of diabetes in normal-weight groups in nonwhite populations, both in high- and low-income settings (2,23–25). Given that the largest increases in diabetes prevalence are expected in nonobese, nonwhite individuals (1), who represent the majority of the world, it is important to understand the factors other than obesity driving risk posed in this sizable population. There are likely differences in the mechanisms, causes, effectiveness of screening, and treatment between those who have obesity-driven diabetes compared with those without (Fig. 1). Therefore, not only should screening practices be tailored to better identify high-risk individuals in the absence of obesity, but additional research focusing on more effective interventions in this population is warranted, as are mechanistic studies to identify pathophysiological pathways contributing to the natural history of diabetes incidence in normal-weight individuals.

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