RESPONSE TO COMMENT ON NARAYAN

Type 2 Diabetes: Why We Are Winning the Battle but Losing the War? 2015 Kelly West Award Lecture. Diabetes Care 2016;39:653–663

K.M. Venkat Narayan

Diabetes Care 2016;39:e182 | DOI: 10.2337/dci16-0018

Reacting to the hypothesis that the pathogenesis of type 2 diabetes may be fundamentally different in "thin" people developing the disease, Reaven (1) expresses concern that this position does not acknowledge the evidence from his group and others that there may be significant differences in the degree of insulin resistance across racial/ethnic groups that is independent of obesity. Insulin resistance is clearly a major factor in the pathogenesis of type 2 diabetes in all racial/ethnic groups. Furthermore, there is considerable individual variation in the role of obesity on the risk of type 2 diabetes even within ethnic groups. Some have even hypothesized a "personal fat threshold" to explain this variation, suggesting that individuals have a personal fat threshold above which their risk for type 2 diabetes increases, independent of BMI, and below which remission is possible (2).

Importantly, however, there may also be relative differences in the importance of "poor insulin action" versus "poor insulin secretion" in the pathophysiology of type 2 diabetes (1), and this is what our group hypothesizes and was conveyed in the 2015 Kelly West Award Lecture (3). We believe that "poor insulin action" and "poor insulin secretion" are continuums and are present in each of the two hypothesized phenotypes (which we have termed diabetes type 2A and 2B), although their relative importance varies depending on the type 2 diabetes phenotype. This is depicted using overlapping bars across these two primary problems (insulin action versus insulin secretion) in Fig. 6 of the 2015 Kelly West Award Lecture article (3).

Asian Indians and Pima Indians, two high-risk ethnic groups that markedly differ in levels of obesity, may represent two extremes in the relative importance of insulin action (type 2A diabetes) versus insulin secretion (type 2B diabetes) in the development and progression of diabetes. Defects in insulin secretion and action are both required for the development of type 2 diabetes in all populations, but the timing and concentration of these perturbations may differ across ethnicities (e.g., some populations are at high risk even at younger ages or lower adiposity or progress more rapidly through the natural history even at earlier stages). These differences across ethnicities seem insufficiently explained by insulin action alone, and a wider understanding of the drivers of metabolic perturbations is needed. So, in addition to insulin sensitivity, one factor in the big picture is insulin secretion. Etiological factors, screening and diagnostic tests, and prevention and treatment may also well vary by different phenotypes defined by relative importance of insulin action (type 2A diabetes) versus insulin secretion (type 2B diabetes) defects (3).

With the predominant burden of type 2 diabetes shifting to the developing countries, it would be productive to conduct careful investigations of the populations in these settings or in migrant populations from these settings in whom the frequency of phenotypes with early abnormalities of insulin secretion (type 2B diabetes) may potentially be large. Such investigations in global settings, overwhelmingly underrepresented in type 2 diabetes research, may offer new insights on the role of β-cell function and the factors affecting it (e.g., epigenetics, nutrition, lipotoxicity, microbiomes, and pollution). In a globalizing world, science needs to go where the epidemic is growing.

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

References

1. Reaven G. Comment on Narayan. Type 2 diabetes: why we are winning the battle but losing the war? 2015 Kelly West Award Lecture. Diabetes Care 2016;39:653–663 (Letter). Diabetes Care 2016;39:e181. DOI: 10.2337/dc16-1067
2. Taylor R, Holman RR. Normal weight individuals who develop type 2 diabetes: the personal fat threshold. Clin Sci (Lond) 2015;128:405–410
3. Narayan KMV. Type 2 diabetes: why we are winning the battle but losing the war? 2015 Kelly West Award Lecture. Diabetes Care 2016;39:653–663

Emory Global Diabetes Research Center, Hubert Department of Global Health, Rollins School of Public Health, and Department of Medicine, School of Medicine, Emory University, Atlanta, GA

Corresponding author: K.M. Venkat Narayan, knaraya@emory.edu.