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Insulin resistance versus insulin deficiency: evidence of racial differences in the pathogenesis of type 2 diabetes

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Racial differences in the incidence of type 2 diabetes (T2D) are well established.[1] Southeast Asians living in Western countries as well as those living in their native countries are at a higher risk of developing T2D as compared with the Whites.[2 3] Similarly, Blacks and Native Americans in the USA are at a higher risk of developing T2D.[4] Many studies have been conducted to understand the racial differences in the pathogenesis of T2D. Insulin resistance and insulin secretion defects have been the focus of most of these studies. South Asians, known to have more body fat for the same body mass index (BMI), have been shown to be more insulin resistant than Whites.[5 6] Previous studies did not find South Asians to have higher degrees of insulin deficiency than Whites.[7] However, two epidemiological studies in the current issue of *BMJ-DRC* suggest otherwise.[8 9]

The first study compared the incidence of T2D in South Asians living in urban India and Pakistan with Blacks and Whites living in urban and suburban areas in the USA.[8] South Asian data were obtained from the Cardiometabolic Risk Reduction in South Asia Study that recruited healthy subjects in 2010–2011 and followed them until 2016–2017 with a median follow-up of 4.8 years. Data for Blacks and Whites were obtained form the Atherosclerosis Risk in Communities (ARIC) Study that recruited healthy subjects in 1987 and followed them through 1996–1998 with a median follow-up of 8.8 years. The comparison was limited to ages >45 years as the ARIC Study recruited only people >45 years of age. As previously shown, South Asians had lower prevalence of obesity based on BMI and waist circumference than Blacks and Whites but higher incidence of diabetes compared with Whites. However, contrary to current concepts, South Asians were less insulin resistant and more insulin deficient than Blacks and Whites. The second study compared the South Asian population from the same study with Pima Indians enrolled before 1989 and followed for a median of 6.7 years.[9] This study included only the age groups 20–44 years as very few Pima Indians developed diabetes after age 45 years. South Asians were significantly less obese than Pima Indians based on BMI and had overall lower incidence of diabetes compared with Pima Indians. However, in those with BMI <25 kg/m^2, the risk of diabetes was five times higher in South Asian men than in Pima Indian men. Again, the study suggested relatively low insulin resistance but more insulin deficiency in South Asian men. In both studies, lower insulin secretion at baseline was a stronger predictor of T2D in South Asians while higher insulin resistance was a stronger predictor of diabetes in Blacks, Whites and Pima Indians. Based on these two studies, the authors conclude that the dominant pathophysiological defect in South Asians may be insulin deficiency rather than insulin resistance. This may change our understanding of the pathogenesis of T2D in South Asians and affect the strategies for screening, prevention or treatment of diabetes in South Asians.

Although the studies suggest that overall South Asian population is less insulin resistant and more insulin deficient, drawing mechanistic conclusions from these epidemiological studies is problematic. The epidemiological data can only provide a correlation and cannot be considered equivalent to the carefully conducted mechanistic studies. Moreover, there are multiple limitations of these data. The population enrolled in the South Asian study was more recent than the other populations with a gap of almost two decades. The only indices of insulin resistance and insulin secretion available in these studies were HOMA-IR and HOMA-B, respectively, that are less accurate in South Asians.[10] Moreover, changes in insulin assays over the

last two decades would have had a tremendous effect on these indices. Even the definition of diabetes has changed over time that may affect how carefully glycated hemoglobin was measured across the studies. Only the baseline data were considered for analysis in these studies, missing out the changes happening over time. Indices of insulin secretion and insulin resistance may change over time and may be completely different by the time of developing diabetes. All data were adjusted for BMI that is not a good marker of obesity in South Asians.[11] Previous studies have shown that South Asians have more percentage of abdominal fat than other racial groups[12] and lower cut-offs for obesity have been suggested.[11]

I think the data presented in these studies are hypothesis generating and should be interpreted with caution. Insulin resistance and defects in insulin secretion are essential components of the pathophysiology of T2D. Therefore, within any healthy population, those with lower insulin secretion or higher insulin resistance at baseline will be more likely to develop T2D. The statistical strength of associations will change depending on the identified confounders within that population and the statistical adjustments. For example, including visceral fat rather than BMI may change the results. The evidence presented by authors is an interesting hypothesis but it does not mount to the level of pathophysiological studies showing higher insulin resistance in South Asians than Whites.[6] I would not consider the observations in these studies as clinically applicable or to have treatment implications at this time. There is definitely more to be learned about the racial differences in the pathogenesis of T2D.

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