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Beta-cell dysfunction and insulin resistance in relation to abnormal glucose tolerance in African populations: can we afford to ignore the diversity within African populations?

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The pathogenesis of type 2 diabetes (T2D) in sub-Saharan Africans is incompletely understood despite the rapid increase in T2D prevalence in sub-Saharan Africa. T2D and its precursor, pre-diabetes, are characterized by abnormal glucose tolerance resulting from a complex inter-relationship between beta-cell dysfunction and insulin resistance. The roles of beta-cell dysfunction and insulin resistance in T2D among sub-Saharan African populations are understudied.

In a recent publication by Ishimwe *et al*,[1] the relative contributions of insulin resistance and beta-cell dysfunction to abnormal glucose tolerance were evaluated in African migrants in the USA. The authors used robust methods for assessment of abnormal glucose tolerance and compared two methods for determining insulin resistance and beta-cell failure. They conclude that beta-cell failure rather than insulin resistance is the major cause of abnormal glucose tolerance in Africans. Although their work presents an important addition to the literature, caution is warranted with regard to extrapolating their findings from African migrants in the USA to other African populations and geographical contexts.

Africa is a large continent with a varying disease experience. Previous studies have shown large regional and sex-specific variations in T2D in Africa, including substantial differences between rural and urban settings.[2] There are data that indicate substantial differences in insulin action between African populations even within rural areas. For example, a study in rural Kenya found 32% higher insulin resistance among Maasai compared with the Luo and 17% higher compared with the Kamba.[3]

African populations are exposed to a wide range of environmental exposures and lifestyle factors that can affect insulin sensitivity and beta-cell function. Lifestyle factors such as dietary intake, physical activity, alcohol consumption, and smoking differ greatly between population groups within Africa and between Africans in Africa and African migrants in Europe and the USA. For example, the prevalence of smoking ranges from 1.8% in Zambia to 25.8% in Sierra Leone.[4] Nicotine has been demonstrated to impair beta-cell function and beta-cell mass[5] and thus variations in smoking between African regions could impact the contribution of beta-cell dysfunction between African populations. As another example, environmental chemical agents, such as chemical contaminants from food, plastic, and air, may produce injury in beta-cells,[6] and exposure to these chemical agents is likely to differ greatly between African migrants and non-migrants, as well as between urban and rural dwellers.

In addition to large variation in the environment, Africa also represents the highest level of genetic diversity in the world.[7] Genomic studies in Africans have successfully replicated T2D-associated variants in genes involved in insulin resistance as well as in genes involved in beta-cell dysfunction, indicating that both mechanisms are important in Africans.[8 9] In addition, it is plausible that differences in genetic factors between African populations, possibly driven by local adaptation pressures, contribute to variations in the interplay between insulin resistance and beta-cell dysfunction in abnormal glucose tolerance. For example, hunter-gatherer populations from East Africa were found to

have strong signatures of local adaption for genes that encode for proteins involved in insulin resistance.[10]

The study by Ishimwe *et al*[1] is cross-sectional, and without data on glucose tolerance among these African migrants at the time of US entry the relative contributions of African and US environmental influences over time cannot be determined. The authors measured insulin sensitivity and secretion by both Oral Glucose Tolerance Test (Matsuda Index and Insulin Secretion Index) and fasting measures (homeostatic model assessment). Insulin clamps may have provided better physiologic clarification. However, it is to be recognized that insulin clamps are often not feasible in studies of this size and cannot diagnose glucose tolerance status.

To conclude, the available evidence indicates that both insulin resistance and beta-cell dysfunction are important in the pathogenesis of T2D in Africans. While one mechanism may be more important in a specific study, this is by no means generalizable to other African cohorts due to substantial variations in disease experience, environmental exposures, and genetic adaptation across African populations. There is a need for studies exploring the contributions of insulin resistance and beta-cell dysfunction to abnormal glucose tolerance in diverse African populations living in diverse geographical contexts. Research and clinical protocols designed to address the etiology and prevalence of abnormal glucose tolerance in African ancestry populations should include testing not only for insulin resistance, as is commonly done, but also for beta-cell function.

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