Pathophysiology-based subphenotyping of individuals at elevated risk for type 2 diabetes

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# Abstract

The state of intermediate hyperglycemia is indicative of elevated risk of developing type 2 diabetes1. However, the current definition of prediabetes neither reflects subphenotypes of pathophysiology of type 2 diabetes nor is it predictive of future metabolic trajectories. We used partitioning on variables derived from oral glucose tolerance tests, MRI measured body fat distribution, liver fat content, and genetic risk in a cohort of extensively phenotyped individuals who are at increased risk for type 2 diabetes2,3 to identify six distinct clusters of subphenotypes. Three of the identified subphenotypes have increased glycemia (clusters 3, 5 and 6), but only individuals in clusters 5 and 3 have immanent diabetes risks. By contrast, those in cluster 6 have moderate risk of type 2 diabetes, but an increased risk of kidney disease and all-cause mortality. Findings were replicated in an independent cohort using simple anthropomorphic and glycemic constructs4. This proof-of-concept study demonstrates that pathophysiological heterogeneity exists before diagnosis of type 2 diabetes and highlights a group of individuals who have an increased risk of complications without rapid progression to overt type 2 diabetes.