Summary Robert Wagner

Pathophysiology-based subphenotyping of individuals at elevated risk for type 2 diabetes[1]

Diabetes is defined by high glucose levels. In case of type 2 diabetes, this definition pools heterogenous pathologic entities, each leading to glycemic elevation with potentially different fates for metabolic stability and the development of complications. A recent subphenotyping approach of adult-onset diabetes separated subphenotypes with primary insulin deficiency and primary insulin resistance that had different risks for complications such as diabetic retinopathy and nephropathy. However, glycemic elevation is a continuum, and the diagnosis of type 2 diabetes is often delayed and/or preceded by years spent in intermediary hyperglycemia. By clustering individuals who are at elevated risk for type 2 diabetes for the variables insulin secretion, insulin sensitivity, glycemia, HDL-cholesterol, liver fat content, visceral fat, subcutaneous fat and genetic type 2 diabetes risk, we identified 6 distinct metabolic groups. Three of these clusters (1,2 and 4) had low risk for diabetes. Three other clusters (3, 5 and 6) had elevated diabetes risk. Cluster 3 was characterized by low insulin secretion and cluster 5 by high insulin resistance. Cluster 5 had the highest diabetes risk. On the other hand, cluster 6 had marked insulin resistance with high compensatory insulin secretion and hyperinsulinemia. Despite the considerably lower diabetes risk than in cluster 3 and 5, cluster 6 had the highest nephropathy risk and the highest all-cause mortality among the groups. The crucial metabolic alteration of cluster 6 could be a long-standing hyperinsulinemia in combination with severe insulin resistance and an adverse body-fat distribution with expanded renal sinus fat. Disentangling the heterogenous pathology of type 2 diabetes starts in the prediabetic stage, and further research is needed to test if targeted prevention can help avoid some of the most severe complications of diabetes.