A Complex System Approach to the Assessment of Homeostasis Loss in Type 2 Diabetes

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Background. The role of individual circulating biomarkers in the development of Type 2 Diabetes (T2D) has been broadly studied, but interactions of such biomarkers as proxy of homeostasis dysregulation remain underexplored. The aim of the present study was to analyze biomarkers in the context of T2D development using Mahalanobis Distances (MDs), which are unitless measures of the dispersion of reduced dimensionality features (i.e. Principal Components).
Methods. We calculated the MDs of the Principal Components (PCs) containing information of 27 plasma biomarkers (comprehending glycemic, lipid, microbiome and one-carbon metabolism) measured in 4446 participants from the PREVEND study. Cox regression analyses were performed using the MDs as predictors of T2D.
Results. After a median follow-up of 8.6 years, incident T2D was ascertained in 227 subjects. PCs number 1,2,4,7,8,10, which incorporate the variability of iron metabolism and Branched Chain Amino Acids were associated with a reduced risk of T2D; and PCs number 6,9,11,12,13,17,22, accounting for hepatic, lipids and glucose metabolism were associated with an increased risk of T2D. The hazard ratio of the MDs calculated from the 27 PCs was 1.87 (95% CI, 1.53–2.29; $P<0.001$). The highest hazard ratio was obtained using the MDs calculated from the first 13 PCs (2.14 (95% CI, 1.77–2.59; $P<0.001$)). Such associations remained after the adjustment for age, being 1.91 (95% CI, 1.58–2.30; $P<0.001$) and 2.10 (95% CI, 1.75–2.53; $P<0.001$), respectively. Interestingly, the association of MDs calculated from all different subsets of PCs were stronger in women than in men ($P<0.01$).
Conclusion. This study suggests that MDs contain information about the homeostasis loss that precede the unset of T2D, and it is significantly associated with the risk of T2D independent of age and clinical risk factors.