

Subphenotyping Obesity in Pursuit of Personalized Medicine: The Devil is in the Details

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Thousands of years ago, when originally recognized in Egypt, China, India, and Greece, diabetes mellitus was a disorder with a single phenotype, sugar in the urine. With the discovery of insulin, Sir Harold Himsworth noted distinct populations that were sensitive and relatively insensitive to insulin, ultimately resulting in the recognition of Types 1 and 2 Diabetes Mellitus (T1DM and T2DM). These subtypes have obvious and major implications for screening, prognosis, prevention, and treatment, as observed in the 1950s in terms of response to sulfonylureas. Phenotyping also led to the recognition that many adults with “adult onset diabetes” in fact had Type 1 diabetes (latent autoimmune diabetes in adults or LADA), recognition of which also had clear therapeutic implications.

Since then, it has become clear that the broad category of T2DM is heterogeneous. Distinct features are observed when T2DM-like syndrome occurs during pregnancy, for example (gestational diabetes). The lack of homogeneity is underlined by the fact that over 600 genetic loci contribute to diabetes risk, possibly implying the presence of thousands of subtypes. Currently, the widely recognized subtypes include monogenic diabetes (also known as maturity-onset diabetes of the young or MODY), pancreatic diabetes (such as that seen in chronic pancreatitis or cystic fibrosis), glucocorticoid-induced diabetes in Cushing’s syndrome or iatrogenic cases, and iron-related diabetes (as seen in hereditary hemochromatosis or transfusional iron overload).¹

The categories listed above, however, account for a relatively small proportion of the large T2DM population, and treatment algorithms still have a significant component of “trial and error.” The ideal strategy would be to identify the key pathophysiological factors in a given patient’s diabetes and deliver targeted therapy to that factor or pathway. In the absence of this information, however, others have taken a more empirical approach, for example, looking for key phenotypic features or clusters of such features to identify distinct populations that might better respond to a given therapy or may have a different natural history. One group identified subgroups of patients with prediabetes that differed in the risk of progression to T2DM and response to metformin.²

The current field of obesity medicine is in many ways similar to that of T2DM. A few subtypes of obesity have been identified based on fat distribution (eg, visceral vs subcutaneous), and these features predict comorbidities. Rare forms of monogenic obesity have illuminated and/or validated the pathophysiological pathways involved in this disorder. In parallel with the story for diabetes, there are new and effective treatments of obesity, but they are most often used in the same “shotgun” or “trial and error” fashion as antidiabetic drugs. Furthermore, these treatments are expensive and have serious side effects; therefore, better targeting strategies are required. As is the case with diabetes, further subphenotyping of obesity (based on biochemical, anthropomorphic, demographic, and other criteria) is a promising tool that allows us to better target weight loss interventions to those more at risk for complications such as major cardiovascular events (MACE). As two of the many examples, identifying obese subjects with distinct clusters of cardiometabolic risk markers identifies individuals with the most and least chances of decreasing the risk of MACE with intervention,³ and the same is true for quantifying different patterns of fat deposition by MRI.⁴

Several recent studies on *Diabetes, Metabolic Syndrome and Obesity* have made significant contributions to this field, including adjunctive therapies and improved predictions of risk and responses to specific therapies. We can also call out an excellent review of the obesity mechanisms and treatments that have appeared in this journal recently.⁵ Among the most recent studies relevant to sub-phenotyping,

- El-Aghbary et al (*Exploring the Relationship Between Inflammatory Biomarkers and Anthropometric Measures of Obesity in Healthy Adults: A Case Control Study*) showed the value of a simple complete blood count in identifying those who may have a significant inflammatory component in their obesity;⁶
- Cai et al (*Effects of Different Exercise Interventions on Health Status in Overweight and Obese Children and Adolescents: A Network Meta-Analysis*) show that different exercise regimens differentially target overall fitness, body composition, lipid abnormalities, and glycemic control;⁷
- Tang et al (*Uric Acid Metabolism and Its Relationship with Glucose and Lipid Metabolism in Overweight and Obese Children and Adolescents: A Cross-Sectional Study in South China*) showed that the serum uric acid level was a predictor of dyslipidemia and insulin resistance;⁸
- Wang et al (*The Impact of Sarcopenic Obesity on Weight Loss Outcomes and Recurrent Weight Gain Following Laparoscopic Sleeve Gastrectomy*) showed fewer weight loss benefits of sleeve gastrectomy in a recognized obese subtype, namely sarcopenic obesity;⁹
- Qu et al (*Impact of Pathological Grades of Metabolic Dysfunction-Associated Steatotic Liver Disease [MASLD] on Weight Loss Following Laparoscopic Sleeve Gastrectomy*) showed differences in surgical outcomes between patients with and without MASLD, a common concomitant of obesity.¹⁰
- Hu et al (*Serum LncRNA SNHG16: A Biomarker for Diagnosing Childhood Obesity and Predicting Its Progression to Metabolic Syndrome*) identify a long non-coding RNA that is a biomarker for childhood obesity and predictor of progression to metabolic syndrome in children.¹¹

Some of the above studies await further study of long-term outcomes, effects of interventions, and generalization to other populations, but others are currently at or close to the stage of translation to the practice of medicine. We await other studies like these, and deeper studies prompted by them, to lead us to the ultimate goal of “personalized medicine”, namely, providing the right treatment to the right patient at the right time.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

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