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# Serum multi-omics approach may help redefine management guidelines for patients with Glycogen storage disease type Ia

Glycogen storage diseases are inherited disorders of carbohydrate metabolism resulting from the deficiency of individual enzymes involved in the synthesis, transport and breakdown of glycogen [1]. In particular, glycogen storage disease type Ia (GSDIa) is caused by deficient activity of glucose-6-phosphatase, which plays a key role in glucose homeostasis by hydrolysing glucose-6-phosphate (G6P) to glucose and phosphate in the final step of gluconeogenesis and glycogenolysis. As a result, patients with GSDIa accumulate G6P, leading to excessive storage of glycogen and fat in the tissues. Specifically, the clinical picture of GSDIa includes a broad spectrum of biochemical alterations (e.g. hypoglycaemia, lactic acidemia, hyperlipidaemia, hyperuricaemia) and clinical manifestations (e.g. hepatomegaly, growth retardation, renal disease) that, if not properly managed, may lead to secondary metabolic disorders and/or disease complications (e.g. hepatic adenomas and carcinoma, chronic kidney disease). For patients with GSDIa, adherence to a highly individualised dietary regimen is the mainstay of treatment and has improved prognosis and long-term outcomes in recent decades. Nevertheless, the (re-)definition of guidelines for the management of patients with GSDIa remains a critical and essential priority [2]. To this end, an integrative multi-omics approach including mass spectrometry-based proteomics and metabolomics was carried out on serum samples from n. 12 patients with GSDIa (8 males and 4 females, median age 16.5 ± 9 years, age range 5-34 years) and n. 12 age- and sex-matched healthy controls (HC) to better dissect the metabolic perturbations occurring in GSDIa. Univariate and multivariate statistical methods were used for downstream data analysis. In addition, correlation analyses based on Pearson's coefficient were performed to define a GSDIa-specific multi-omics serum profile by examining the strength and direction of relationships between omics features. Overall, the analyses revealed a specific multi-omics serum profile and protein-metabolite network signature in patients with GSDIa in comparison to HC, shedding new light on the pivotal role of the liver in the pathogenesis of GSDIa and providing new insights into the metabolic alterations in GSDIa. Collectively, and combined with our previous lipidomics findings on GSDIa [3], our results may help to redefine recommendations for the management of GSDIa and develop strategies to counteract disease complications.

[1] Koeberl DD et al, J Inherit Metab Dis 2024, DOI: 10.1002/jimd.12654. [2] Derks TGJ et al, Nutrients 2021, DOI: 10.3390/nu13113828. [3] Rossi et al, J Lipid Res 2024, DOI: 10.1016/j.jlr.2024.100651

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