The multiple faces of urinary glucose tetrasaccharide as biomarker for patients with hepatic glycogen storage diseases

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To the Editor

Hepatic glycogen storage diseases (GSDs) are rare inborn errors of carbohydrate metabolism.[1] Clinical presentations include severe fasting intolerance, growth failure, and hepatomegaly. Biochemical characteristics are (non)ketotic hypoglycemia, hyperlactatemia, increased liver enzymes, and hyperlipidemia. Strict dietary management is the cornerstone of treatment. Routine analysis in plasma (i.e., glucose, lactate, ketones, alanine and aspartate aminotransferases [ALT and AST], creatine phosphokinase [CK], uric acid, lipids) and urine (ketones) are essential for monitoring metabolic control.[1] Urinary glucose tetrasaccharide (Glc4) excretions, first described as a biomarker of GSDII (Pompe disease), can also be elevated in hepatic GSD patients.[2] Indeed, in our patient cohort, urinary Glc4 excretions were increased in 10/15 GSDIa (67%), 9/10 GSDIb (90%), 28/28 GSDIII (100%), 1/7 GSDIV (14%), 3/10 GSDIX (30%) and 8/9 GSDXI (89%), compared with 17/22 GSDII (77%) patient samples. Highest urinary Glc4 excretions were found in GSDIII patients.

GSDIII (OMIM 232400) is caused by a deficiency of debranching enzyme activity due to biallelic pathogenic *AGL* variants. The International Study on GSDIII described the dual phenotypes of this disease, ranging from a merely fasting intolerance associated liver disease in childhood to a chronic, progressive muscle disease during adulthood in an important subset of the patients, in whom also heart, skeletal muscle, and bones can be affected.[3] In a recent issue of *Genetics in Medicine*, the authors of "Liver fibrosis during clinical ascertainment of glycogen storage disease type III: a need for improved and systematic monitoring" described the natural history of liver disease in 26 pediatric GSDIII patients.[4] In their single-center, retrospective, longitudinal study, a major observation was that elevated markers of liver injury (ALT, AST), hyperlipidemia, and urinary Glc4 in childhood tended to normalize with age, while CK activities were elevated and did not decrease with age.

In our experience, a case-oriented analysis is important, emphasized by observations in a recently diagnosed GSDIII patient, homozygous for the pathogenic c.4529dupA *AGL* variant. We observed decreased liver enzyme activities and urinary Glc4 excretions after initiation of dietary management (Supplemental Table 1). CK activities increased in conjunction with reaching milestones of physical development, such as walking. A good positive correlation was found between urinary Glc4 and plasma AST and ALT, but there was no (or even a slightly negative) association with plasma CK, which parallels the results of Halaby et al.[4] In nine adult GSDIIIa patients, however, we found that urinary Glc4 was positively related to clinical signs of myopathy and plasma CK activities. In this cohort, three patients with CK activities below 250 U/L and six patients with CK above 750 U/L had median (range) urinary Glc4 excretions of 2.1 (1.7–3.2, ref <1) and 20 (16–29, ref <1) umol/mmol creatinine, respectively. Combining these observations, we therefore hypothesize that in pediatric GSDIII patients, decreasing Glc4 excretions reflect improved fasting tolerance (i.e., a liver function), whereas in adults, glc4 excretion may be associated with chronic, progressive skeletal muscle involvement.

Glc4 is a degradation product of glycogen and (other) branched chain starches, such as amylopectin, formed by the glycolytic activity of salivary and pancreatic α-amylases and neutral α-1,4-glucosidase activities.[5,6] Glc4 is associated with increased glycogen storage in both liver, as demonstrated in our patient and those of Halaby et al.,[4] and in muscle.[7] In this respect, it is interesting to note that Glc4 is also elevated in Duchenne muscular dystrophy and muscle trauma.[5,8] Glc4 may therefore be a good biomarker not only for GSD, but also for muscle disorders in general.

At the cellular level, Glc4 and other GSD biomarkers are at far biochemical distance from the enzymatic defect, and for some, including Glc4, the precise origin is yet unclear. Moreover, biomarkers may not adequately reflect the intracellular situation. In clinical care, blood or urine samples are usually obtained at relatively random moments, and the composition and the timing of the last meal versus acquiring the samples affects the results of many of these markers, including urinary Glc4.[5] Prospective studies on the clinical relevance of biomarkers for GSD are therefore highly welcomed and were recently prioritized.[9] It is important to clearly define biomarker use in different stages of the disease of interest: (1) identify the risk of developing an illness, (2) screen for subclinical disease, (3) diagnose disease, (4) categorize disease severity, and (5) predict prognosis. Metabolomics may allow us to study and identify new biomarkers for GSD patients, whereas stable isotope studies may provide a better insight in metabolic fluxes in individual patients. These studies are particularly important in the light of upcoming trials with novel therapies, including messenger RNA (mRNA) treatment and gene therapy.

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SUPPLEMENTARY INFORMATION

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