Alterations of Central Liver Metabolism of Pediatric Patients with Non-Alcoholic Fatty Liver Disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in children and is associated with overweight and insulin resistance (IR). Almost nothing is known about in vivo alterations of liver metabolism in NAFLD, especially in the early stages of non-alcoholic steatohepatitis (NASH). Here, we used a complex mathematical model of liver metabolism to quantify the central hepatic metabolic functions of 71 children with biopsy-proven NAFLD. For each patient, a personalized model variant was generated based on enzyme abundances determined by mass spectroscopy. Our analysis revealed statistically significant alterations in the hepatic carbohydrate, lipid, and ammonia metabolism, which increased with the degree of obesity and severity of NAFLD. Histologic features of NASH and IR displayed opposing associations with changes in carbohydrate and lipid metabolism but synergistically decreased urea synthesis in favor of the increased release of glutamine, a driver of liver fibrosis. Taken together, our study reveals already significant alterations in the NASH liver of pediatric patients, which, however, are differently modulated by the simultaneous presence of IR.