Patient-specific effects of metformin on the hepatic metabolism in adolescents with metabolic dysfunction-associated steatotic liver disease (MASLD)

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Abstract

Metformin is a commonly prescribed antidiabetic drug that inhibits hepatic glucose production (HGP). Recent studies examining the use of metformin for the treatment of children with metabolic dysfunction-associated steatotic liver disease (MASLD) showed controversial results. To evaluate the patient-specific impact of metformin on hepatic glucose, lipid, amino acid, and energy metabolism in a cohort of 70 paediatric patients with biopsy-proven MASH. We parametrized our mathematical model HEPATOKIN1 of liver metabolism with patient-specific proteomics data of liver enzyme abundances and simulated metformin-induced diurnal changes of a large panel of metabolic functions. On average, a single dose (250 mg) of metformin reduced diurnal HGP by 19%. Based on a Z-score of 1, 15% of patients were classified as low responders or high responders. During elevated metformin plasma levels within four after metformin ingestion, energy metabolism, cytosolic and mitochondrial redox potential, urea synthesis and ketone body synthesis were reduced by 10–30%, but averaged over 24 h, these metabolic side effects were not significant. In particular, there was no significant impact of metformin on hepatic fat storage. Baseline lactate and insulin activity at 90 min after glucose challenge (OGTT) correlated significantly with the reduction in HGP and may serve as predictors of effective therapy. On a daily average, metformin selectively affects hepatic glucose production, glycogen storage and lactate uptake, while numerous other metabolic functions are significantly altered only for several hours after administration of the drug. Our method provides a patient-specific analysis of the potential effects of metformin therapy on central hepatic metabolism and may therefore help guide the physician's therapeutic decision.