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# Orthotopic Liver Transplantation in Glycogen Storage Disease Type Ia: Perioperative Glucose and Lactate Homeostasis

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## Abstract

Glycogen storage disease type Ia (GSD Ia) is a rare inborn error of metabolism. It causes severe fasting intolerance and lactic acidosis due to the deficiency of glucose-6-phosphatase enzyme. Blood glucose and lactate concentrations from 2 patients with GSD Ia were retrospectively compared to a control group of patients with familial amyloid polyneuropathy. Carbohydrate intake and infusions were compared to experimental data based on stable isotope studies. Perioperative lactate concentrations were significantly higher in our 2 patients with GSD Ia (median 15.0 mmol/L; range 9.9–22.0 mmol/L) versus 8 controls. In one patient, despite normal blood glucose concentrations, lactate acidosis was probably caused by a combination of the disease itself, insufficient (par)enteral carbohydrate intake, Ringer lactate infusions, and circulatory insufficiency. Patients with GSD Ia carry an increased risk of lactic acidosis during orthotopic liver transplantation compared to non-GSD patients. Multidisciplinary perioperative care is essential to prevent significant complications.

## Keywords

glycogen storage disease type Ia, liver transplantation, familial amyloid polyneuropathy, glucose blood, hypoglycemia, lactic acidemia

## Introduction

Glycogen storage disease type Ia (GSD Ia; Mendelian Inheritance in Man [MIM] 232200) is a rare autosomal recessive inborn error of metabolism caused by deficient activity of glucose-6-phosphatase (G6Pase; Enzyme Commission number [EC] 3.1.3.9) in liver, kidney, and intestine.<sup>1,2</sup> Glucose-6-phosphatase is coded by the glucose-6-phosphatase, catalytic subunit (*G6PC*) gene located at chromosome 17q21. In GSD Ia, endogenous glucose production (EGP) is impaired by defects in both glycogenolysis and gluconeogenesis. Clinically, patients present with severe fasting intolerance, failure to thrive, and hepatomegaly. Biochemically, the disorder is associated with nonketotic hypoglycemia, hyperlactacidemia, hyperuricemia, and hyperlipidemia. Dietary treatment aims to maintain normoglycemia and normolactatemia and prevent long-term complications, including short stature, osteoporosis, gout, anemia, renal disease, and hepatic adenomas, with potential for transformation into hepatocellular carcinoma.<sup>3,4</sup>

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When the adenomas are resistant to regular medical therapy or not amenable to resection alone, orthotopic liver transplantation (OLT) can be considered.<sup>5</sup> Data on perioperative care in patients with GSD 1a are scarce, especially in OLT.<sup>5,6</sup> The small time window to reach optimal metabolic control before OLT in patients with GSD type 1a is very challenging and may affect perioperative glucose and lactate homeostasis.

Based on experiences with 2 cases, we performed a retrospective, observational study on glucose and lactate concentrations before and during OLT with implications for perioperative management.

## Materials and Methods

### Data Retrieval Methodology

In this retrospective study, we described patients with GSD 1a ( $n = 2$ , aged 19 and 27) and compared them to patients with familial amyloid polyneuropathy (FAP; MIM 105210;  $n = 8$ , 5 females, mean age at transplantation:  $43 \pm 8$  years) who underwent OLT between 1991 and 2013 in our hospital. Familial amyloid polyneuropathy is an autosomal dominant disorder characterized by slowly progressive peripheral sensorimotor neuropathy and autonomic neuropathy, cardiomyopathy, nephropathy, vitreous opacity, and central nervous system amyloidosis, which starts at adulthood. Orthotopic liver transplantation halts the progression of peripheral and/or autonomic neuropathy.<sup>7</sup> Patients with FAP were selected as a control group because of their similarity in clinical physical condition, namely, the absence of cirrhosis, portal hypertension, clotting disorders, and other factors that could influence glucose and lactate homeostasis. The local medical ethics committee approved the study. All clinical and laboratory data were retrieved from electronic and paper medical records.

### Case Presentations

Case A (body weight: body mass index =  $26 \text{ kg/m}^2$ , 80 kg) was a female patient with GSD 1a who underwent OLT in June 2013 at the age of 19 years because of multiple hepatic adenomas. The diagnosis was confirmed both enzymatically after liver biopsy and genetically (ie, homozygote for the common *p.R83H* mutation in the *G6PC* gene). During metabolic follow-up, the blood parameters of metabolic control in the 5 years before OLT are reflected by median lactate and triglyceride concentrations of 6.9 mmol/L (range: 2.3–12.2) and 7.9 mmol/L (range: 5.7–11.1 mmol/L), respectively. The patient was not considered completely adherent to the treatment. In the transition phase to adult medicine, radiologic imaging showed multiple hepatic adenomas with progressive growth, despite intensive dietary treatment. Due to the number of the hepatic adenomas and their locations, she was accepted for liver transplantation listing, with a nonstandard exception after a multidisciplinary discussion.

Due to the emergency nature of an OLT from a postmortal donor, the patient was called for immediate hospital admission

to startup the procedure. No formal change in the dietary management was performed before arrival at the hospital. Blood laboratory parameters upon admission were analyzed 8 hours before surgery, including glucose 6.7 mmol/L, triglycerides 6.3 mmol/L, and total cholesterol 5.0 mmol/L. The first lactate measure was 7.6 mmol/L, 7 hours and 30 minutes before OLT. She was admitted at the surgical ward receiving her regular continuous gastric drip feeding. Two hours before the surgery, she displayed a hypoglycemia of 2.7 mmol/L that was treated with an additional bolus (30 mL of 50% glucose) intravenously. Due to a delay in the organ procurement procedure, she entered the operating room 3 hours later than expected, with a lactate concentration of 10 mmol/L.

Anesthesia was induced with thiopental (5 mg/kg), sufentanil (0.2  $\mu\text{g/kg}$ ), and esmeron (0.6 mg/kg) and maintained with desflurane (0.8 Maximum Allowable Concentration [MAC]), sufentanil (effect target 0.3  $\mu\text{g/mL}$ ), and esmeron (0.3 mg/kg). Multiple blood samples were taken during preanhepatic, anhepatic, postreperfusion phases, and at the end of surgery for assessment of glucose, lactate, blood gasses, electrolytes, and coagulation parameters. Circulatory support was given by noradrenaline infusion (0.05–0.2  $\mu\text{g/kg/min}$ ) to maintain a mean arterial pressure above 60 mm Hg. During preparation phase, nitroglycerine infusion (0.05–0.15  $\mu\text{g/kg/min}$ ) was given to maintain a central venous pressure below 5 mm Hg, and immunosuppressive management started with 80 mg of dexamethason. Orthotopic liver transplantation was performed with a heart beating graft from a postmortem donor. Standard piggyback implantation with end-to-end portal and arterial anastomoses was done with duct-to-duct reconstruction. Total operation time was 7 hours and 22 minutes, cold ischemia time was 5 hours and 58 minutes, warm ischemia time was 39 minutes, anatomic anhepatic phase time was 89 minutes, and revascularization time was 51 minutes. The hepatectomy was difficult due to the liver size ( $33 \times 25 \times 15 \text{ cm}$ , 3500 g), and estimated blood loss was 1500 mL (350 mL in the preanhepatic phase, 270 mL in the anhepatic phase, and 880 mL in the postreperfusion phase including the evacuated recirculation of 500 mL). The donor graft functioned immediately. During the entire procedure, fluid replacement was made with 8.5 L of Ringer lactate (RL), 1.5 L of colloids, and 1 unit of red blood cell concentrate.

Case B was a male patient with GSD 1a (also homozygote for the common *p.R83H* mutation in the *G6P* gene) who underwent an OLT in 2004 at the age of 27 years for the same indication with an identical surgical procedure. Detailed perioperative data on glucose homeostasis and management were not available anymore, but blood lactate concentrations could be retrieved and were included for the analysis.

### Calculations of Glucose and Lactate Homeostasis

Perioperative lactate concentrations in 2 transplanted patients with GSD 1a were compared to a control group, consisting of 8 patients with FAP who underwent OLT in our center between 1991 and 2011.

The (par)enteral intake of carbohydrates before and during the surgery was compared to the minimal estimated EGP as determined experimentally by stable isotope studies.<sup>8</sup> The intravenous treatment with RL during the surgery was compared to the minimal estimated endogenous lactate production through the Cori cycle.<sup>9</sup> The RL solution (Baxter Healthcare Corporation, Deerfield, Massachusetts) contains 0.32 g/dL sodium lactate.

### Statistics

Statistical analyses were performed using SPSS version 18.0 (International Business Machines Corp, Armonk, New York). Normality of data was assessed using the Shapiro-Wilk normality test. Wilcoxon Mann-Whitney *U* test was used to test for statistical significance of lactate concentrations between the groups of patients. For all statistical analyses,  $P < .05$  was considered significant.

### Results

During OLT, median blood lactate concentrations in patients with GSD 1a were significantly higher compared to controls, that is, 15.0 mmol/L (range 9.9-22 mmol/L) versus 5.3 mmol/L (range 1.3-10.4 mmol/L), respectively (Mann-Whitney *U* test,  $P < .0001$ ). During the anhepatic phase (ie, removal of the liver and venovenous bypass), median (range) blood lactate concentrations in GSD 1a case A and controls were 20.0 mmol/L (range 19.0-21.0 mmol/L) and 5.4 mmol/L (range 5.2-6.8 mmol/L), respectively.

Case A could be studied in more detail, and Figure 1 presents perioperative data on glucose and lactate homeostasis. During the entire perioperative period, the (par)enteral carbohydrate intake did not meet the minimally estimated glucose requirements. Interestingly, we observed normoglycemia during the entire OLT procedure, despite insufficient carbohydrate intake. A severe lactic acidosis (minimum pH 7.18) was also observed during the surgery. Blood loss was estimated as 350, 270, and 880 mL in the 3 consecutive phases of OLT.

### Discussion

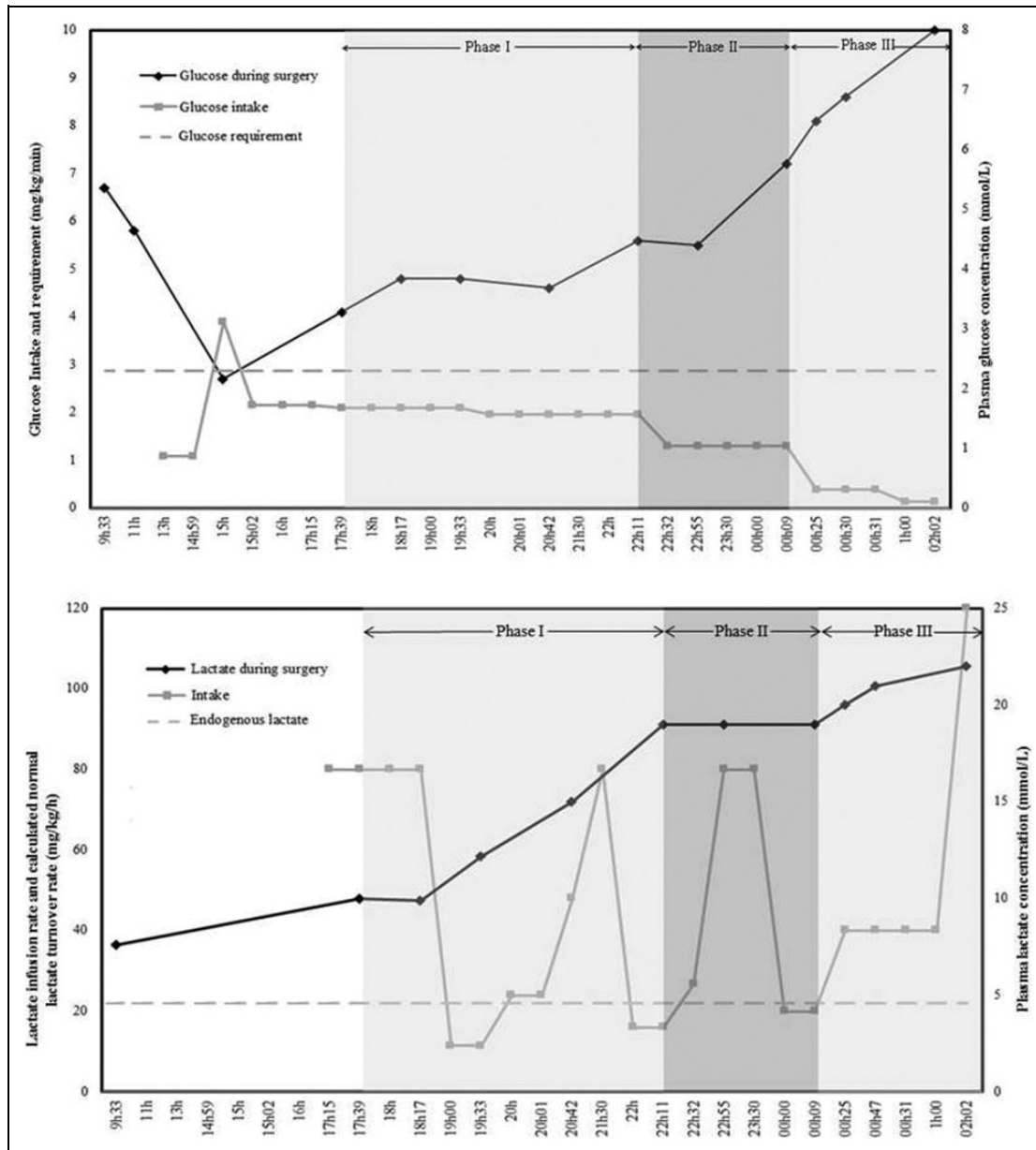
We demonstrate that OLT is associated with increased risks of lactic acidosis in patients with GSD 1a. Perioperative management of OLT in patients with GSD 1a is challenging, as there is limited time to achieve a normal metabolic state. These cases emphasize the importance of a multidisciplinary perioperative approach with specific considerations for treatment, which are outlined subsequently.

Glucose and lactate metabolism are intimately related, and different factors may have contributed to lactic acidosis (during OLT) in patients with GSD 1a, when compared to the patients with FAP. First, lactate concentrations increase in fasting patients with GSD 1a, hence exogenous carbohydrate intake should exceed the estimated glucose requirements.<sup>8</sup> Second, stress and medication (ie, vasopressor and dexamethason) may

increase either endogenous lactate production and/or energy demands unpredictably. Vasopressors may cause lactate production by different mechanisms. On one hand, vasoconstriction causes relative ischemia and secondary anaerobic oxidation. On the other hand, adrenalin, for example, exerts many metabolic effects on the islet cells of the pancreas (alpha 2 receptor inhibition of insulin secretion; beta 2 receptor stimulation of glucagon secretion) and the liver/muscle (beta receptor glycogenolysis, which causes secondary lactate production by shunting towards glycolysis), whereas metabolic responses are less pronounced with noradrenalin or phenylepinephrine (a selective alpha1 agonist). Glucocorticoid effects of dexamethason are stimulation of both glycogenolysis and gluconeogenesis. Third, patients with GSD 1a cannot convert lactate into glucose by gluconeogenesis in the liver, kidney, and intestine, that is, these patients depend on a combination of renal clearance of lactate via the blood compartment, metabolic clearance in the brain,<sup>10</sup> and respiratory compensation to maintain physiological pH. Last, RL infusion has served as an important additional source of lactate (Figure 1). The contribution of blood loss during each different phase of OLT is difficult to quantify. It may have both increased lactate production by increased anaerobic metabolism and increased lactate clearance directly from the circulation.

The normoglycemic episode during OLT in case A, despite the insufficient carbohydrate intake (Figure 1) cannot be completely explained. Upon fasting, in general, blood glucose concentrations depend on both EGP and the metabolic clearance rate of glucose by peripheral tissues. In patients with GSD 1a, there is a deficiency of G6Pase  $\alpha$ , the final common pathway of glycogenolysis and gluconeogenesis, the 2 main components of EGP. Experimental data indicated that EGP is not completely absent in patients with GSD 1a and may reach  $\sim 60\%$  of normal.<sup>11-15</sup> Theoretically, residual *in vivo* G6Pase  $\alpha$  activity next to the (muscle) G6Pase  $\beta$  and/or alternative glycogenolysis (by the  $\alpha$ -glucosidase or debranching pathway) may contribute to whole-body EGP in patients with GSD 1a.<sup>16</sup> The magnitude of surgery affects the severity of the hyperglycemic response in OLT.<sup>17</sup> A reduced metabolic clearance rate of glucose by insulin resistance offers an alternative hypothesis, but more recently, we observed an identical hyperglycemic episode during partial hepatectomy in a patient with GSD 1a who did not respond to exogenous insulin therapy (unpublished observation). Surgery is associated with an inflammatory response wherein glucose uptake by the cell is inhibited by cortisol and endogenous insulin secretion is inhibited by the  $\alpha$ -adrenergic response.<sup>18</sup>

Follow-up of adult patients with GSD 1a is associated with relatively new challenges. Case A demonstrates the importance of a multidisciplinary follow-up and management after transition from pediatric to adult medicine, especially under emergency and complex circumstances such as the perioperative phase of OLT. Dedicated metabolic physicians need to be involved before, during, and after OLT, as specific knowledge on the disorder is required to optimize outcome. The importance of metabolic follow-up of patients with GSD 1a after



**Figure I.** Perioperative data on glucose (A) and lactate homeostasis (B) during orthotopic liver transplantation (OLT) in case A. The white area represents the pre-OLT phase, whereas the different gray areas represent the 3 consecutive phases of the OLT (the preanhepatic, anhepatic, and postreperfusion phase, respectively). A, Black solid diamonds denote blood glucose concentrations and gray squares indicate administered glucose. B, Black solid diamonds denote blood lactate concentrations and gray squares indicate administered lactate. A, The dotted line corresponds to calculated experimental reference data for endogenous glucose production (EGP).<sup>8</sup> B, The dotted line corresponds to calculated experimental reference data for the Cori cycle.<sup>9</sup>

OLT is emphasized again by extrahepatic complications. In the collaborative European study on GSD 1a, the overall prevalence of proteinuria was 13%, and additional 31% of the patients had microalbuminuria.<sup>3</sup> In a recent systematic review on OLT in the GSD 1 population including 58 patients, renal failure was the most common complication in 24% (14 of 58) of patients with GSD 1a, 21% (3 of 14) requiring dialysis.<sup>5</sup> Hence, extrahepatic symptoms of the disorder may not be prevented and/or reversed by OLT. For this highly specific cohort of patients with GSD 1a, still many questions remain about the

possibility to completely abandon dietary restrictions of fructose and lactose after OLT, the effect of immunosuppressive therapy on renal function, and the effect on bone density. Answering these questions requires systematic follow-up and data collection.

## Conclusions and Recommendations

In patients with GSD 1a, OLT is associated with severe increased risk of lactic acidosis compared to non-GSD patients.

Multidisciplinary perioperative care is essential to prevent significant complications. Before OLT, total exogenous carbohydrate intake should exceed estimated glucose requirements (for adults starting at  $\pm 2.5$  mg/kg/min corresponding with 1.5 mL/kg/h dextrose 10%). Immediately after hospital admission, a continuous intravenous supply of glucose should be started, and blood glucose and lactate concentrations should be monitored. Optimal metabolic control (aiming at blood concentrations of glucose  $>4$  mmol/L and lactate  $<2$  mmol/L, respectively) decreases the risk of excessive bleeding. Ringer lactate should be avoided, since the conversion of lactate into glucose by gluconeogenesis is impaired. During surgery, lactate and pH should be closely monitored and buffered according to the base deficit, by bicarbonate or red blood cells. To maintain normal blood pressure, Ringer malate and acetate are preferred solutions for volume therapy, and metabolically inactive vasopressors (such as phenylephrine) are preferred.

### Authors' Note

All authors confirm the absence of previous similar or simultaneous publications. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study. The funding source had no influence in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

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