Hypophosphatemia after Hepatectomy or Pancreatectomy: Role of the Nicotinamide Phosphoribosyltransferase

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BACKGROUND: Postoperative hypophosphatemia is common and is associated with a lower risk of liver failure after hepatectomy, but higher morbidity after pancreatectomy. Whether different physiologic mechanisms underlie the hypophosphatemia associated with these very different clinical outcomes is unclear. This study aims to evaluate the underlying mechanism in postoperative hypophosphatemia.

STUDY DESIGN: We prospectively enrolled 120 patients who underwent major hepatectomy (n = 30), minor hepatectomy (n = 30), pancreatectomy (n = 30), and laparotomy without resection (control group, n = 30). Preoperative and postoperative serum and urinary phosphorus, calcium, and creatinine, as well as phosphaturic factors, including serum nicotinamide phosphoribosyltransferase (NAMPT), fibroblast growth factor-23, and parathyroid hormone were measured. In addition, we evaluated urinary levels of nicotinamide catabolites, N-methyl-2-pyridone-5-carboxamide and N-methyl-4-pyridone-3-carboxamide.

RESULTS: We found that significant hypophosphatemia occurred from postoperative day (POD) 1 to POD 2 in all 4 groups and was preceded by hyperphosphaturia from preoperative day to POD 1. Phosphate level alterations were associated with a significant increase in NAMPT levels from preoperative day to POD 2 in all 3 resected groups, but not in the control group. The fibroblast growth factor-23 levels were significantly decreased postoperatively in all 4 groups, and parathyroid hormone levels did not change in any of the 4 groups. Urine levels of N-methyl-2-pyridone-5-carboxamide and N-methyl-4-pyridone-3-carboxamide decreased significantly in all 4 groups postoperatively.

CONCLUSIONS: This study demonstrates that the mechanism of hypophosphatemia is the same for both liver and pancreas resections. Postoperative hypophosphatemia is associated with increased NAMPT. The mechanism that upregulates NAMPT and its role on disparate clinical outcomes in postoperative patients warrant additional investigation. (J Am Coll Surg 2017;225: 488–497. © 2017 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

Hypophosphatemia has been reported after several types of operations and is associated with increased morbidity and mortality, but the underlying mechanisms involved remain uncertain.[1-3] After partial hepatectomy, the absence of hypophosphatemia or lack of early nadir is associated with increased rates of liver insufficiency and

Disclosure Information: Nothing to disclose.

Support: This work was supported by NIH/NCI P30 CA008748 Cancer Center Support Grant. Dr Jaimes received Byrne Research Fund from Memorial Sloan Kettering Cancer Center.

Poster presentation at American Society of Nephrology meeting, Chicago, IL, November 2016.

Received May 9, 2017; Revised June 20, 2017; Accepted June 20, 2017.

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http://dx.doi.org/10.1016/j.jamcollsurg.2017.06.012
ISSN 1072-7515/17

Abbreviations and Acronyms

eNAMPT = extracellular nicotinamide phosphoribosyltransferase
FGF-23 = fibroblast growth factor-23
iNAMPT = intracellular nicotinamide phosphoribosyltransferase
NAD = nicotinamide adenine dinucleotide
NAM = nicotinamide
NAMPT = nicotinamide phosphoribosyltransferase
POD = postoperative day
PTH = parathyroid hormone
2-PY = N-methyl-2-pyridone-5-carboxamide
4-PY = N-methyl-4-pyridone-3-carboxamide

increased 30-day mortality.[4-6] However, after pancreatectomy, the presence of hypophosphatemia is linked to a higher rate of postoperative complications, including pancreatic leaks and abscess formations.[7] Given their differences in clinical implication, the role of postoperative phosphate alteration and its underlying mechanism warrant investigation.

Phosphate participates in several critical biologic processes, including signal transduction and energy transfer, and alterations in its homeostasis are often linked to serious complications, such as respiratory failure, arrhythmias, renal insufficiency, and metabolic acidosis.[3] The pathophysiology of postoperative hypophosphatemia is likely multifactorial. Phosphate levels are regulated by a network of various organs, including bone, parathyroid glands, small intestine, liver, and kidneys.[8] For years, it was believed that in patients undergoing hepatectomy, liver regeneration and subsequent increased hepatic uptake of phosphate were responsible for the phosphate depletion.[9-11] However, increased urinary phosphate excretion is also observed, suggesting that renal mechanisms of phosphate handling play an important role in the development of postoperative hypophosphatemia.[3,12,13]

Several phosphaturic factors, including parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF-23), have been proposed as potential mediators of postoperative phosphaturia.[3,12,13] More recently, a novel phosphaturic factor, nicotinamide phosphoribosyltransferase (NAMPT), was also investigated as a mediator of hypophosphatemia after hepatectomy in rats.[14] Nicotinamide phosphoribosyltransferase is the rate-limiting enzyme in the metabolic pathway converting nicotinamide (NAM) to nicotinamide adenine dinucleotide (NAD), an essential coenzyme in many cellular redox reactions, such as those involved in DNA repair and regulation of cellular energy metabolism.[15-18] A 70% partial hepatectomy in rats results in an increased expression of NAMPT in the kidney cortex and systemic circulation.[14] These changes were associated with decreased expression of sodium-dependent phosphate transporters in the renal proximal tubules, thereby causing hyperphosphaturia and hypophosphatemia.[14]

Based on the experimental finding, this prospective study was initiated to test the hypothesis that NAMPT is a key factor in the metabolic pathway responsible for hypophosphatemia in patients after hepatectomy, but a different mechanism in patients after pancreatectomy given different clinical outcomes. We characterized the effect of operation on serum and urinary phosphate and several phosphaturic factors, including NAMPT, FGF-23, and PTH, as well as on urinary catabolites of nicotinamide, including N-methyl-2-pyridone-5-carboxamide (2-PY) and N-methyl-4-pyridoen-3-carboxamide (4-PY).

METHODS

Study patients

After approval by the IRB at Memorial Sloan Kettering Cancer Center, 120 consecutive and eligible patients who underwent open operations for liver and pancreas tumors were prospectively enrolled in the study from August 2015 to September 2016. We obtained written informed consent from each patient, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The patients were divided in 4 groups of 30 patients each: major hepatectomy, minor hepatectomy, pancreatectomy, and control. Major hepatectomy was defined as a resection of $\geq$3 Couinaud's segments, and minor hepatectomy was defined as a resection of $<$3 segments. Pancreatectomy included patients who underwent pancreaticoduodenectomy, central pancreatectomy, or distal pancreatectomy with splenectomy. Control patients were those who were deemed unresectable before or during exploratory laparotomy, and who had biopsies with or without placement of a hepatic artery infusion pump for regional, hepatic arterial chemotherapy. Control patients did not undergo any resection of liver or pancreas tissue other than biopsies in some cases. All patients in this study underwent elective open operation. Laparoscopic and robotic operations were excluded to eliminate the potential effects of minimally invasive operation on electrolyte alterations.

All patients enrolled in this study were 18 years of age or older and had preoperative glomerular filtration rates of $>$60 mL/min/1.73 m^2 as calculated using the Chronic Kidney Disease Epidemiology Collaboration formula.[19] All eligible patients, based on planned operation, age, and glomerular filtration rate, were approached for consent to this prospective protocol. Patients were then