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Editorial Board Member of *World Journal of Hepatology*, Dmitry Victorovich Garbuzenko, MD, PhD, DSc (Med), Professor, Department of Faculty Surgery, South Ural State Medical University, Chelyabinsk 454092, Russia. garb@inbox.ru

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MINIREVIEWS

Outcomes of patients with post-hepatectomy hypophosphatemia: A narrative review

Kai Siang Chan, Swetha Mohan, Vishal G Shelat

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Kai Siang Chan, Vishal G Shelat, Department of General Surgery, Tan Tock Seng Hospital, Singapore 308433, Singapore

Swetha Mohan, Vishal G Shelat, Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore 308232, Singapore

Corresponding author: Kai Siang Chan, MBBS, Doctor, Department of General Surgery, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433, Singapore.
kchan023@e.ntu.edu.sg

Abstract

Phosphate is an essential electrolyte for proper mineralisation of bone, buffering of urine, and diverse cellular actions. Hypophosphatemia (HP) is a clinical spectrum which range from asymptomatic to severe complications such as neuromuscular and pulmonary complications, or even death. Post-hepatectomy HP (PHH) has been reported to be 55.5%-100%. Post-hepatectomy, there is rapid uptake of phosphate and increased mitotic counts to aid in regeneration of residual liver. Concurrently, PHH may be due to increased urinary phosphorous from activation of matrix extracellular phosphoglycoprotein in the injured liver, which decreases phosphate influx into hepatocytes to sustain adenosine triphosphate synthesis. A literature review was performed on PubMed till January 2022. We included 8 studies which reported on impact of PHH on post-operative outcomes. In patients with diseased liver, PHH was reported to have either beneficial or deleterious effects on post-hepatectomy liver failure (PHLF), morbidity and/or mortality in various cohorts. In living donor hepatectomy, PHLF was higher in PHH. Benefits of correction of PHH with reduced post-operative complications have been shown. Correction of PHH should be done based on extent of PHH. Existing studies were however heterogenous; further studies should be conducted to assess PHH on post-operative outcomes with standardized phosphate replacement regimes.

Key Words: Hepatectomy; Hepatocellular Carcinoma; Hypophosphatemia; Phosphates; Liver neoplasms; Liver transplantation

Core Tip: Hypophosphatemia (HP) is a clinical spectrum which range from asymptomatic to severe complications such as neuromuscular and pulmonary complications, or even death. Post-hepatectomy HP (PHH) has been reported to be 55.5%-100%. Pathophysiologic mechanisms have been proposed. However, literature on the outcomes of patients following PHH is scarce. This is the first review to summarize existing literature on the pathophysiology of PHH in both healthy and diseased liver, and its impact on post-operative outcomes.

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INTRODUCTION

Phosphate is an essential electrolyte which is involved in several bodily functions. It is necessary for proper mineralisation of bone, buffering of urine, and diverse cellular actions such as energy metabolism, proliferation and specific functions of differentiated cells[1]. Given its essential roles, aberrancy in phosphate levels result in adverse impact on the body. Normal adult serum phosphate ranges from 0.81-1.45 mmol/L (2.5-4.5 mg/dL). Hypophosphatemia (HP) is defined as an adult serum phosphate level < 0.81 mmol/L (< 2.5 mg/dL)[2]. HP may also be subdivided according to its severity: mild (0.65-0.81 mmol/L, or 2.0-2.5 mg/dL), moderate (0.32-0.65 mmol/L, or 1.0-2.0 mg/dL) and severe (< 0.32 mmol/L, or < 1.0 mg/dL)[2]. The clinical presentation of HP is a spectrum; patients may be asymptomatic or present with mild symptoms such as fatigue, weakness or anorexia. However, HP may result in severe complications such as neuromuscular disturbances including encephalopathy, seizures, coma, pulmonary complications such as respiratory failure (in view of respiratory muscle weakness), cardiovascular complications such as impaired myocardial performance, hemolytic anemia, or even death[3]. Sequelae of patients with underlying malignancy such as nausea, vomiting and loss of appetite may result in HP from reduced dietary intake[4].

HP has been reported to be 0.2%-0.3% in all inpatients, 30% in intensive care unit (ICU) patients and 60-85% in sepsis[5-7]. Post-operative HP is also commonly reported following major abdominal surgery, including liver resection (hepatectomy)[8,9]. Post-hepatectomy HP (PHH) has been reported to be 55.5-100%[10-14]. Literature on the impact of PHH however, remains controversial. Immediately following hepatectomy, there is a drop in serum phosphate due to increased phosphate uptake in the regenerating injured liver, as well as increased urinary loss of phosphorous from activation of matrix extracellular phosphoglycoprotein in the injured liver[15,16]. Some studies have reported improved recovery of initial liver insufficiency in PHH, yet others reported increased major morbidity (cardiorespiratory, infections and haemorrhage)[10,11]. These studies were heterogenous in the extent of hepatectomy and PHH. In view of the lack of high quality evidence, this manuscript aims to review the pathophysiology, etiology, clinical significance and prognostic impact of PHH.

PATHOPHYSIOLOGY AND ETIOLOGY

The homeostasis of phosphate is a complex process. Phosphate regulation is maintained through intestinal phosphate absorption, renal phosphate excretion, and equilibrium of extracellular phosphate with that in bone or intracellular fluid[1]. Intracellular shift of phosphate is enhanced by respiratory alkalosis and insulin. Dietary sources of phosphate include eggs, milk, meat, soy-based products and foods with additives and preservatives[17]. Causes of HP include reduced dietary uptake, impaired intestinal absorption, increased phosphate excretion and intracellular shift of phosphate[2]. Metabolism of phosphate is closely linked to the calcium-parathyroid hormone (PTH)-vitamin D axis. Serum phosphate is mediated by PTH and 1,25 dihydroxyvitamin D (1,25$(OH)_2$D), which play critical roles in the regulation of phosphate homeostasis in the intestines, bone and kidneys; PTH is produced by the parathyroid glands and influence phosphate and calcium levels through the following: (1) Stimulation of bone resorption resulting in an increase in serum calcium and phosphate; (2) Inhibition of resorption of phosphate from tubular fluid in the kidneys resulting in decrease in serum phosphate; and (3) Stimulation of conversion of cholecalciferol to calcitriol in the kidney, whereby calcitriol is responsible for intestinal absorption of phosphate and calcium[18]. General causes of post-operative HP following major abdominal surgery has been postulated to be due to the result of hemodilution caused by bleeding or fluid administration during surgery[19]. Other contributory factors include diabetic ketoacidosis and refeeding syndrome especially in the context of malignancy and associated malnutrition[20]. Figure 1 summarizes the pathophysiology and etiology outlining HP.

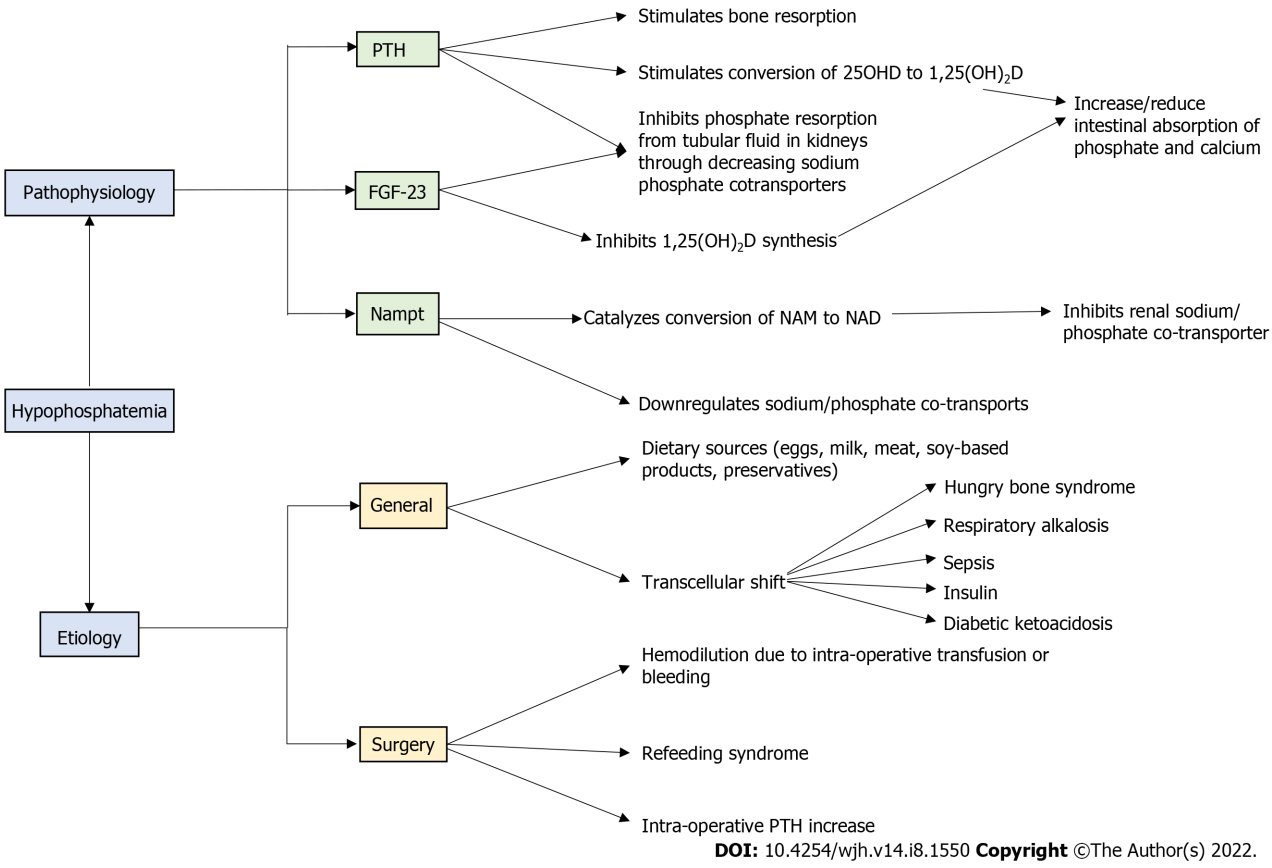

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Figure 1 Pathophysiology and etiology outlining hypophosphatemia. $1,25(OH)_2D$: 1,25 dihydroxyvitamin D; 25OHD: 25-hydroxyvitamin D; FGF-23: Fibroblast growth factor-23; NAD: Nicotinamide adenine dinucleotide; NAM: Nicotinamide; Nampt: Nicotinamide phosphoribosyltransferase; PTH: Parathyroid hormone.

Liver tissue contains 0.3% phosphate by weight[21]. PHH has been traditionally thought to be due to the increased metabolic demands by the regenerating liver[22]. Post-hepatectomy, there is rapid uptake of phosphate and increased mitotic counts in the regenerating residual liver, resulting in PHH[15]. However, it has been postulated that there are several pathophysiologic mechanisms behind HP following hepatectomy. Surgery has been shown to result in elevated PTH of up to 9 times intra-operatively[23]. PTH reduces renal proximal tubular phosphate uptake by decreasing the abundance of renal sodium phosphate cotransporters (Npt2a, Npt2c, and PiT-2) in the renal proximal tubule, resulting in increased fraction of excretion of phosphate (Fe-P) with resulting HP[24]. A study by Nafidi *et al* on 18 patients who underwent hepatectomy showed that intact-PTH (I-PTH) had significant increase on post-operative day (POD) 1 (from 4.5 ± 0.3 to 8.8 ± 0.9 pmol/L, $P < 0.01$)[25]. Phosphate levels was negatively correlated with I-PTH (r = -0.56: $P = 0.024$) on POD1, and Fe-P was positively correlated with I-PTH ($r = 0.52$: $P = 0.047$)[25]. An alternative explanation for PHH is secondary to increased urinary phosphorous loss due to the release of cathepsin B from activation of matrix extracellular phosphoglycoprotein in the injured liver[16,26]. This activation of matrix extracellular phosphoglycoprotein results in decreased concentration of phosphate influx into hepatocytes to sustain adenosine triphosphate (ATP) synthesis[16]. This is in contrary to the hypothesis that PHH is a result of influx of phosphate into liver for ATP synthesis which aids liver regeneration[22].

Phosphatonins, which are phosphaturic peptides that decrease renal sodium-dependent cotransport of phosphate, may also be responsible for PHH[27]. Fibroblast Growth Factor-23 (FGF-23) inhibits $1,25(OH)_2D$ synthesis and reduces the expression and activity of the sodium phosphate cotransporters in the renal proximal tubule, resulting in reduced intestinal and renal phosphate absorption[28]. FGF-23 is elevated in chronic kidney disease in view of higher phosphate and calcium concentrations[29]. Elevation in FGF-23 (which results in HP) has been demonstrated to be a strong predictor of mortality independent of renal function in patients with end-stage liver disease on transplant waiting list; this has been postulated to be due to the toxic effects of FGF-23 and increased risk of infections at above-physiological levels[30,31]. However, the effect of hepatectomy on FGF-23 levels has not been demonstrated[23].

Recently, translational studies have shown the role of nicotinamide (NAM) and nicotinamide phosphoribosyltransferase (Nampt) in the pathophysiology of PHH[32]. Nampt catalyzes rate-limiting step in conversion of NAM to nicotinamide adenine dinucleotide (NAD) which is essential for cellular

metabolism, energy production and deoxyribonucleic acid repair[33]. NAM inhibits intestinal and renal sodium-dependent inorganic phosphate (Na/Pi) transport system in rats[34]. Following hepatectomy, there is increase in Nampt and NAM. Excess Nampt and NAM influx in proximal tubular cells of the kidney results in downregulation of NaPi-IIa and NaPi-IIc protein levels[32]. In addition, Nampt catalyzes conversion of NAM to NAD, which inhibits renal Na/Pi transport in response to metabolic stimuli, resulting in PHH with hyperphosphaturia[35].

ADVANTAGES OF HYPOPHOSPHATEMIA

Search strategy

A literature review was performed on PubMed from inception till 11 January 2022 using a combination of search terms "hypophosphatemia" AND ("liver resection" OR "post-hepatectomy liver failure" OR "post-hepatectomy insufficiency"). The detailed search strategy is appended in Supplementary material (Supplementary Table 1). We obtained a total of 65 studies, of which 10 studies reported impact of HP on outcomes following hepatectomy; 2 studies did not have full-text available and had insufficient data in the abstract and hence were not included in our review[36,37]. We included 8 studies which reported on the impact of PHH on post-operative outcomes[10-14,38-40]. Table 1 summarizes the study characteristics of all included studies. Table 2 summarizes the median phosphate levels and difference in post-operative outcomes following liver resection for both healthy liver donors and diseased patients with PHH *vs* normophosphatemia (NP). Where applicable, overall mean and standard deviation values were combined from individual subgroups using methods described by Altman *et al*[41]. Figure 2 is a schematic representation of the advantages and disadvantages of PHH on post-operative outcomes with their respective proposed pathophysiology.

Summary of evidence on PHH

Literature has shown benefits of PHH with improvement in recovery from post-hepatectomy liver failure (PHLF). A retrospective study by Hallet *et al*[10] in 2016 investigated on the impact of PHH on post-operative liver function and recovery in 402 patients who underwent hepatectomy. They investigated on initial liver insufficiency (ILI), which was defined as serum bilirubin > 50 μmol/L and INR > 1.7 within 5 d post-operatively; patients who had PHH were also more likely to have ILI compared to NP (n = 44/223 (19.7%) *vs* n = 20/179 (11.2%), P = 0.02). However, they showed that of all patients with ILI, more patients with HP recovered from ILI compared to those with NP (90.9% *vs* 65.0%, P = 0.03).

Incidence of PHLF is reported to be 0.7%-35%, varying based on pre-operative liver function, underlying pathology and co-morbidities[42]. Definition of PHLF is controversial with lack of standardized definitions; the "50-50" criteria (serum bilirubin > 50μL/L and prothrombin time < 50% of normal on POD 5) was proposed by Balzan *et al*[43]. Consensus by the International Study Group of Liver Surgeries (ISGLS) in 2011 defined PHLF as post-operatively acquired deterioration in the ability of the liver (in patients with normal and abnormal liver function) to maintain its synthetic, excretory and detoxifying function, characterised by increase in the INR and hyperbilirubinemia on or after POD 5: Grade A (defined as abnormal laboratory values without change in clinical management), B (defined as requiring deviation from regular clinical management but without need for invasive treatment) and C (defined as requiring need for invasive treatment) has mortality of 0%, 12% and 54% respectively[44,45]. Intravenous phosphate replacement was given based on the serum phosphate levels in the study by Hallet *et al*[10] (Table 1). It is possible that more aggressive phosphate replacement in patients with PHH may have resulted in better improvement in ILI by creating influx of phosphate into hepatocytes to assist in liver regeneration[22]. Apart from liver (dys) function however, there was no difference in post-operative outcomes between PHH and NP in their study; there was no association between PHH and length of stay (PHH: median 7 (interquartile range (IQR) 6-10) d *vs* NP: median 7 (IQR 5-11) d, P = 0.55), morbidity (PHH: n = 13/223 (5.8%) *vs* NP: n = 12/179 (6.7%), P = 0.56) and mortality (PHH: n = 3/223 (1.3%) *vs* NP: n = 4/179 (2.2%), P = 0.50). It is important to note the definition of PHH defined in their study (PHH was defined as ≤ 0.65 mmol/L) correlates to moderate HP instead. Benefits of improved recovery from ILI in patients with PHH may only be seen in moderate or severe PHH, or due to more aggressive phosphate replacement in those subgroups.

Similar to the study by Hallet *et al*[10], Squires *et al*[13] demonstrated improved liver function with PHH. A retrospective study by Squires *et al* on 719 patients who underwent major hepatectomy showed that NP (defined as > 2.5 mg/dL or > 0.81 mmol/L) was associated with highest incidence of PHLF (12.3%), major complications (30.3%), 30 d mortality (6.5%) and 90 d mortality (7.1%), compared to moderate, severe or profound PHH[13]. Profound PHH had the lowest incidence of post-operative complications (PHLF: 3.4%, P = 0.008; major complications: 16.7%, P = 0.037; 30 d mortality: 0, P = 0.010; 90 d mortality: 3.4%, P = 0.166). Phosphate replacement was given based on surgeon discretion (n = 469/719, 69%). Multivariate analysis also showed that phosphate > 0.78 mmol/L on POD 2 is independently associated with significant risk of PHLF (Hazards ratio (HR) 1.78, 95% confidence interval (CI): 1.02-3.17, P = 0.048), major complications (HR 1.57, 95%CI: 1.02-2.47, P = 0.049), 30 d mortality (HR 2.70, 95%CI: 1.08-6.76, P = 0.031) and 90 d mortality (HR 2.51, 95%CI: 1.03-6.15, P = 0.044).

Table 1 Summary of study characteristics of all included studies in the literature review

No	Ref.	Definition of HP	PHH, *n* (%)	NP, *n* (%)	Type of liver resection (%)	Histopathology (%)	Post-operative phosphate replacement regime	Phosphate replacement, *n* (%)
1	Buell *et al* [14], 1998	< 2.5 mg/dL	21/35 (60)	14/35 (40)	Major hepatectomy (NR); Cryosurgery (NR)	CRLM: 8 (23) HCC: 4 (11) Others: 23 (66)	For phosphate < 3.0 mg/dL: sodium phosphate or potassium phosphate HP: mean of 15 mmol/d on POD1, to 25 mmol/d on POD3 NP: mean of 5 mmol/d	NR
2	George *et al* [11], 1992	NR	44/44 (100)	0	Right hepatectomy and extended right hepatectomy	NR	NR	NR
3	Giovannini *et al*[12], 2002	Normal: > 2.5 mg/dL; Mild-moderate: 1.6-2.5 mg/dL; Severe: < 1.5 mg/dL	38/59 (64.4)	21/59 (35.6)	Major hepatectomy (58); Minor hepatectomy (42)	CRLM: 10 (17) ICC: 7 (12) HCC: 16 (27) GBC: 2 (3) Others: 24 (41)	If > POD3 and oral feeding cannot be resumed: parenteral phosphate (fructose 1-6 diphosphate or potassium phosphate) at 20-50 mmol/d	NR
4	Hallet *et al* [10], 2016	≤ 0.65 mmol/L	223/402 (55.5)	179/402 (44.5)	Major hepatectomy (52) Minor (48) Hepatectomy	CRLM: 260 (65) ICC: 53 (13) HCC: 27 (7)Others: 62 (15)	Based on serum phosphate: Intravenous potassium phosphate or sodium phosphate	NR
5	Serrano *et al*[38], 2019	Normal: > 2.5 mg/dL; Mild: 1.6-2.5 mg/dL; Moderate: 1.0-1.5 mg/dL; Severe: < 1.0 mg/dL	161		Living donor hepatectomy	NA	Elemental phosphate based on phosphate levels: < 1.1 mg/dL: 25 mmol 1.1-1.9 mg/dL: 20 mmol 2.0-2.3 mg/dL: 15 mmol 2.4-2.7 mg/ dL: 10 mmol	NR
6	Squires *et al* [13], 2014	Normal: > 2.5 mg/dL; Mild: 1.6-2.5 mg/dL; Moderate: 1.0-1.5 mg/dL; Severe: < 1.0 mg/dL	488/719 (67.9)	231/719 (32.1)	Extended left hepatectomy (6) Extended right hepatectomy (20) Left hemihepatectomy (23) Right hemihep-atectomy (39) Central hepatectomy (2) Non-anatomical (10)	CRML: 229 (32) HCC: 69 (9) ICC: 88 (12) Metastatic NET: 34 (5) Other: 299 (42)	Discretion of surgeon Median replacement: 55 mmol (range 10-170 mmol)	469 (69)
7	Tan *et al* [39], 2003	Normal: > 2.5 mg/dL; Moderate: 1.5-2.5 mg/dL; Severe: 1.0-1.5 mg/dL; Profound: < 1.0 mg/dL	89/95 (93.7)	6/95 (6.3)	Right-lobe living donor hepatectomy: Right hepatectomy (94); Left lateral segmentectomy (5); Left lobectomy (11)	NA	Based on phosphate deficit: intravenous or oral phosphate	NR
8	Yuan *et al* [40], 2010	Normal: > 2.5 mg/dL; Mild: 1.5-2.5 mg/dL; Moderate: 1.0-1.5 mg/dL; Severe: < 1.0 mg/dL	Overall: 100/102 (98) Mild: 56/102 Moderate: 25/102 Severe: 19/102	2/102 (2)	Living donor hemi-hepatectomy	NA	Severe HP: Intravenous phosphate	7/19 (36.8)

All categorical variables are expressed as *n* (%). CRLM: Colorectal liver metastasis; GBC: Gallbladder carcinoma; HCC: Hepatocellular carcinoma; ICC: Intrahepatic cholangiocarcinoma; ILI: Initial liver insufficiency; INR: International normalized ratio; LOS: Length of stay; NA: NET: Neuroendocrine tumor; Not applicable; NP: Normophosphatemia; NR: Not reported; PHH: Post-hepatectomy hypophosphatemia; PHLF: Post-hepatectomy liver failure.

Following hepatectomy, liver regeneration with hepatocyte proliferation and deoxyribonucleic acid synthesis begins immediately and is mostly completed after 72 h[46,47]. Failure to reach PHH suggest the lack of phosphate uptake for ATP synthesis in the liver, resulting in higher incidence of PHLF. This was supported by increased PHLF and mortality in patients who had phosphate nadir after POD3[13].

Table 2 Summary of laboratory values and post-operative outcomes comparing patients with post-hepatectomy hypophosphatemia and normophosphatemia

		Mean nadir phosphate, mg/dL[a]			Mean INR[a]			Length of stay, d			Post-hepatectomy liver failure			Any morbidity			30 d mortality		
No	Ref.	PHH	NP	*P* value	PHH	NP	*P* value	PHH	NP	*P* value	PHH	NP	*P* value	PHH	NP	*P* value	PHH	NP	*P* value
1	Buell *et al* [14], 1998	2.1 ± 0.1[b]	3.0 ± 0.2[b]	< 0.05	NR			16.22 ± 12.09	11.22 ± 7.03	NR	NR			17/21 (81)	4/14 (29)	< 0.05	1/21 (5)	0/14 (0)	NR
2	George *et al* [11], 1992	NR			NR			NR			1/44 (2)	0/0	NA	11/44 (25)	0/0 (0)	NA	NR		
3	Giovannini *et al*[12], 2002	1.7 ± 0.8 (POD3)		NR	NR			NR			NR			Mild-moderate: 4/23 (17) Severe: 9/15 (60)	3/21 (14)	< 0.001[c]	Mild-moderate: 1/23 (4) Severe: 3/12 (20)	1/21 (5)	NR
4	Hallet *et al* [10], 2016	1.52 ± 0.31[d]	2.72 ± 0.74[d]	< 0.01	1.51 ± 0.37	1.53 ± 0.91	0.83	7 (6-10)	7 (5-11)	0.55	44/223 (19.7)	20/179 (11.2)	0.02	Major morbidity: 13/223 (5.8)	Major morbidity: 12/179 (6.7)	0.56	9/223 (4.0)	4/179 (2.2)	0.31
5	Serrano *et al* [38], 2019	2.00[e] (recorded at median 1.6 d post-operatively)			NR			7.2 ± 3.4[e]		NR	10/161 (6.2)		NR	Any morbidity > 30 d: 19/161 (11.8)		NR	NR		
6	Squires *et al* [13], 2014	2.2 [1.7-2.8]			NR			NR			Moderate: 8.0% Severe: 8.5% Profound: 3.4%[f]	12.3%[f]	0.008	Major morbidity: Moderate: 20.1% Severe: 19.5% Profound: 16.7%[f]	30.3%[f]	0.037	Moderate: 3.8% Severe: 2.8% Profound: 0%	6.5%	0.010
7	Tan *et al*[39], 2003	2.6 (range 1.3-5.0)		NR	NR			NR			NR			Any morbidity: 8/95 (8.4)		NR	NR		
8	Yuan *et al* [40], 2010	1.89 ± 0.72 (POD3)		NR	Mild: 1.51 ± 0.26 Moderate: 1.43 ± 0.19 Severe: 1.95 ± 0.40	NR	< 0.001[g]	NR			14/100 (14)	0/2 (0)	NR	NR			NR		

[a]Values are reported on post-operative day 2 unless otherwise specified.
[b]Values described here excluded patients who received cryosurgery; the study included cohort of patients who received both major hepatectomy and cryosurgery.
[c]Comparing severe PHH (< 1.5 mg/dL) with other range of phosphate values.
[d]Values were reported in mmol/L in the original study and subsequently converted to mmol/L for standardization.
[e]Overall mean and SD was calculated through the combination of mean and SD from patients who had liver insufficiency and those without using methods described by Michael *et al*[37].
[f]Exact values of patients with normal, moderate, severe and profound post-hepatectomy hypophosphatemia (PHH) were not provided in the study.
[g]Comparing between each subgroup of PHH. All categorical variables are expressed as *n* (%), and all continuous variables are expressed in median (range), median [IQR], or mean ± SD unless otherwise specified. NA: Not applicable; NP: Normophosphatemia; NR: Not reported; PHH: Post-hepatectomy hypophosphatemia; POD: Post-operative day; SD: Standard deviation.

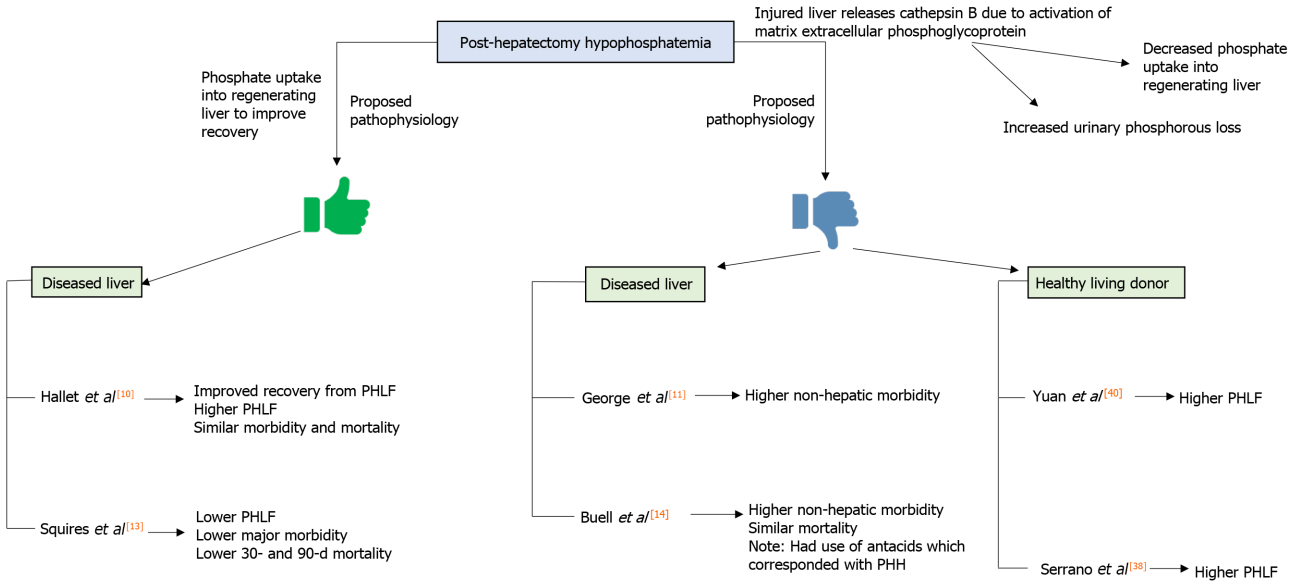

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Figure 2 Schematic diagram summarizing the postulated pathophysiology of the impact of post-hepatectomy hypophosphatemia on post-operative outcomes, as well as summary of the advantages (green) and disadvantages (blue) of post-hepatectomy hypophosphatemia in existing literature on post-operative outcomes. PHLF: Post-hepatectomy liver failure.

Unlike the study by Hallet *et al*[10] which showed increased PHLF, Squires *et al*[13] showed reduced PHLF with increased severity of PHH. This may be attributed to the patient selection in studies, where Squires *et al*[13] included patients with normal to profound PHH, whereas Hallet *et al*[10] only included patients with normal to moderate PHH. Severe and profound PHH may be more frequently seen in major hepatectomy in view of the extent of liver resection and burden on the regenerating liver. Failure to reach severe or profound PHH may indicate the liver's inability for adequate regeneration, and hence, worse outcome with higher PHLF during the initial post-operative day[10].

DISADVANTAGES OF HYPOPHOSPHATEMIA

Hepatectomy for liver pathology

The adverse effect of HP following hepatectomy was first shown by George and Shiu in 1992, where a retrospective study was conducted on 44 patients who underwent right or extended right hepatectomy [11]. They showed that severe HP (< 1.0 mg/dL, or < 0.32 mmol/L) was associated with increased major post-operative complications (cardiorespiratory $n = 5$, infections $n = 4$, haemorrhage $n = 1$, liver failure $n = 1$, $P < 0.001$). Protective effect of early phosphate replacement ($P < 0.05$) with fewer complications was also described, highlighting the importance of normalization of phosphate post-operatively. However, there is a lack of information on the extent of replacement and other outcome measures such as mortality.

Similarly, a retrospective study by Buell *et al*[14] in 1998 on 35 patients who underwent major hepatectomy and/or cryosurgery showed significantly higher post-operative complications (pancreatitis, pulmonary infections, gastrointestinal bleed, wound infection and ileus) in PHH compared to NP (HP: $n = 17/21$ (80%) *vs* NP: 4/14 (28%), $P < 0.05$)[14]. Length of hospital stay was 5 d longer (clinically but not statistically significant) in patients who had PHH compared to NP. Mortality was comparable between both PHH and NP. The authors defined PHH as phosphate < 0.81 mmol/L. Phosphate replacement was also initiated from POD 1 when phosphate < 0.97 mmol/L, with higher replacement in the PHH group compared to NP group. The authors noted a potential confounding factor responsible for HP in patients who underwent hepatectomy; use of antacid corresponded to PHH ($P < 0.05$). However, liver function (represented using aspartate aminotransferase as surrogate marker, HP: 462 U/L and NP: 440 U/L) was comparable. Cause of PHH may be due to the phosphate binding by antacids resulting in reduced phosphate absorption[48], rather than increased metabolic demands by regenerating liver, suggesting an improvement in liver function. While there is a correlation between PHH and increased morbidity and possibly length of stay, correlation does not equate to causation. Use of antacids may have resulted in PHH, and antacid use have been reported to result in post-operative ileus and predispose patients to pneumonia through airway colonisation[49,50]. Majority of patients who undergo hepatectomy are prescribed acid-suppressive therapy (H2 receptor antagonists or proton-

pump inhibitors) for stress ulcer prophylaxis[51]. The use of antacids following hepatectomy is however not routine. Hence the results by Buell *et al* should not be generalized to all patients who undergo hepatectomy[14].

Living donor hepatectomy

It is important to analyse this subgroup of healthy patients who underwent liver donor hepatectomy. The physiology of healthy patients with normal liver function differs from diseased patients with malignancy and/or liver dysfunction. A study by Yuan *et al* in 102 living donors who underwent hemi-hepatectomy showed a negative correlation between nadir phosphate level and peak total bilirubin (r=-0.337, P = 0.001) and international normalized ratio (INR) (r=-0.293; P = 0.004)[40]. Positive correlation was observed between severity of PHH and PHLF (r = 0.549, P = 0.023). The deleterious effects of PHH on liver function may be due to the activation of matrix extracellular phosphoglycoprotein in injured liver, resulting in decreased phosphate influx into hepatocytes to sustain ATP synthesis[16]. Hence, PHH may be associated with worse liver function and increased incidence of PHLF following hepatectomy. The authors additionally showed that in patients with severe HP (≤ 1.0 mg/dL, or ≤ 0.32 mmol/L), use of intravenous phosphate replacement resulted in better hepatic function (incidence of PHLF in severe PHH with replacement n = 0/7 (0%), without replacement n = 6/12 (50%)). However, it is important to note that while correlation was obtained for phosphate severity with PHLF, the R^2 value was 0.301 (not calculated in the study); only 30.1% of the variance may be explained by severity of HP on PHLF. In addition, unlike studies which examine the impact of PHH on hepatectomy in patients with underlying pathology (*e.g.*, HCC, cholangiocarcinoma), the study population by Yuan *et al*[40] was on healthy living donors. Healthy living donors have NP; in contrary, patients who undergo hepatectomy may have underlying chronic liver disease which commonly presents with HP due to malnutrition and vitamin D deficiency[52]. Pre-operatively, however, phosphate levels were reported to be normal[13,14]. This may be due to unreported pre-operative nutrition optimisation and phosphate replacement, and may have resulted in improvement in post-operative liver regeneration, compared to healthy living donors. Hence, results by Yuan *et al*[40] may not be applicable in majority of patients who undergo hepatectomy for underlying pathology. Similarly, Serrano *et al*[38] who investigated 161 patients who underwent living donor hepatectomy showed that intraoperative time and low postoperative phosphate levels through the first 38 h were good predictors of liver insufficiency (defined as serum bilirubin > 3 mg/dL and/or INR > 1.7 on POD 5 or more) (area under curve 0.731, sensitivity 60%, specificity 75.5%, positive predictive value 14%, negative predictive value 96.6%)[38].

In contrary, Tan *et al*[39] in 2003 retrospectively reviewed 95 living donors who underwent right hepatectomy showed NP with mean phosphate of 2.6 mg/dL (0.84 mmol/L), 2.7 mg/dL (0.87 mmol/L) and 2.9 mg/dL (0.94 mmol/L) on POD 1 to 2, POD 3 and POD 4 respectively[39]. Intravenous or oral phosphate replacement was given based on their existing deficits. The authors failed to demonstrate that PHH was more frequent in the subgroup of patients with morbidity. Of patients who had morbidity (n = 8/95 (8.4%)), incidence of PHH was however, not more frequent. A possible explanation behind this lack of statistical significance is that none of the patients included had profound PHH unlike the study by Yuan *et al*[40]. To add on, it is worth noting that the morbidity reported by Tan *et al*[39] were surgical complications such as pneumothorax, incisional hernia, intravenous line complications requiring occupational therapy and right pleural effusion and atelectasis. These complications are general surgical complications which should not be attributed to PHH. We caution to draw any conclusion from their study on the impact of PHH on post-operative outcomes.

MANAGEMENT OF HYPOPHOSPHATEMIA FOLLOWING HEPATECTOMY

Phosphate replacement regimes have been suggested by various studies and reviews but no international consensus statements have been put in place for recommended phosphate replacement[3,53,54]; Table 3 summarizes the list of example of phosphate replacement formulations, recommended doses and special considerations to note. While phosphate replacement is required for HP, it is also prudent to avoid over-aggressive replacement of phosphate. Phosphate replacement may result in hypocalcemia, metastatic calcification from HP, hypotension, hyperkalemia (in the event where potassium-containing phosphate replacement is used), dehydration and acute kidney injury[55]. These deleterious effects are more often seen in intravenous replacement; intravenous replacement may result in precipitation of calcium resulting in hypocalcemia and renal failure due to calcium phosphate precipitation in kidneys, resulting in cardiac arrhythmias. Hence, oral route is the preferred route of administration for mild-moderate HP and for patients who are able to tolerate orally. Should intravenous phosphate be used, its rate should be limited to maximum of 20mmol/hour[56]. The extent of increase in serum phosphate and potassium have been demonstrated using calculated sodium potassium phosphate ($Na_2K_5PO^4_6$) replacement, where infusion of $Na_2K_5PO^4_6$ with calculated phosphate dose (in mmol) of 0.5 x body weight x (1.25 -[serum phosphate]) resulted in mean rise in phosphate of 0.38 ± 0.04 mmol/L and mean rise in potassium of 0.3 mmol/L[57]. Repeat serum phosphate should be rechecked at 2-12 h following completion of phosphate replacement.

Table 3 Summary of phosphate replacement regimes for hypophosphatemia

Indications		Formulation	Route of administration	Composition	Recommended dosage	Special considerations
Mild hypophosphatemia (0.65-0.81 mmol/L)		Phospho-soda (C.B. Fleet Company, Virginia)	Oral	180mg $Na_2HPO^4 \cdot 7H_2O$ + 480 mg $NaH_2PO^4 \cdot H_2O$/mL Phosphate: 4.150 mmol/mL Sodium: 4.822 mEq/mL Potassium: 0	1000mg/d	Chronic renal failure / reduced glomerular filtration rate: to use half of recommended initial dose Causes diarrhoea
		Phospha 250 Neutral (Rising Pharmaceuticals, Inc., United States)	Oral	Elemental phosphorus 250 mg (8 mmol), Sodium 298 mg (13 mEq), and Potassium 45 mg (1.1 mEq)		
Moderate hypophosphatemia (0.32-0.65 mmol/L)	Not on ventilator	Phospho-soda (C.B. Fleet Company, Virginia)	(same as above)	(same as above)	If ≥1.5 mg/dL: 1 mmol/kg of elemental phosphorus (minimum of 40 mmol and a maximum of 80 mmol) in 3-4 doses over 24 h If < 1.5 mg/dL: 1.3 mmol/kg of elemental phosphorus (maximum of 100 mmol) in 3-4 doses over 24 h	(same as above)
	On ventilator	Sodium phosphate (Abbott Laboratories, North Chicago, Illinois)	Intravenous	142 mg Na_2HPO^4 + 276 mg $NaH_2PO^4 \cdot H_2O$/mL Phosphate: 3.0 mmol/mL Sodium: 4.0 mEq/mL	0.08 mg/kg over 2-6 h if recent and uncomplicated HP 0.16 mg/kg over 2-6 h if prolonged and has multiple causes Maximum of 20 mmol/h	Chronic renal failure / reduced glomerular filtration rate: to use half of recommended initial dose
		Potassium phosphate (Invenex Pharmaceuticals, Grand Island, New York)		236 mg K_2HPO^4 + 224 mg KH_2PO^4 /mL Phosphate: 3.003 mmol/mL 4.360 mEq/mL		Chronic renal failure / reduced glomerular filtration rate: to use half of recommended initial dose To avoid if potassium > 4mmol/L
Severe hypophosphatemia (< 0.32 mmol/L) / Critically ill patients, or with severe complications of hypophosphatemia		Sodium phosphate or potassium phospahte	(same as above)	(same as above)	0.08-0.16 mg/kg over 2-6 h	(same as above)

Similarly, for post-hepatectomy, there is no standardized regime for phosphate replacement. Table 1 summarizes the various phosphate replacement regimes and indications for replacement in existing studies for patients with PHH. Indications for phosphate replacement differed largely across the studies, with studies replacing phosphate only for severe PHH (< 1.0 mg/dL), *vs* studies which replace phosphate for < 3.0 mg/dL[14,40]. Nevertheless, the benefits of phosphate replacement has been described with reduced post-operative complications and improvement in liver function[11,40]. In view of the lack of standardized protocol for phosphate replacement in PHH, we suggest the use of the same regimen for phosphate replacement in HP (Table 3), with the use of oral replacement for mild-moderate PHH, and intravenous replacement for severe PHH or in critically ill patients.

PROGNOSTICATION OF POST-OPERATIVE COURSE FOLLOWING HEPATECTOMY

This summarized study and reviewed literature have shown equivocal evidence (Tables 1 and 2), with both benefits and disadvantages of PHH on incidence of PHLF and/or morbidity. However, exclusively for healthy patients with living donor hepatectomy, our literature review showed that these group of patients who had HP were more likely to have PHLF[13,40]. In contrary, patients with diseased liver (underlying malignancy and/or cirrhosis) who undergo hepatectomy may have improved liver regeneration and/or lower PHLF following hepatectomy, or have increase in post-operative morbidity [10,13,14]. This difference in outcome may be attributed to pre-operative nutritional optimisation and phosphate replacement in patients with diseased liver.

PHLF is a dreaded complication following hepatectomy with mortality risk; this is especially so in the context of patients with underlying cirrhosis and/or deranged liver function. Thus far, several studies have devised prognostic factors and prognostic scoring systems for the prediction of PHLF and

mortality following hepatectomy[58-61]. Established predictive factors of PHLF include Albumin-Bilirubin score, prothrombin time and Child-Pugh score[58,60,61].

NP has been shown to increase incidence of PHLF; multivariate analysis by Squires *et al*[13] on 719 patients who underwent major hepatectomy showed that POD 2 phosphate > 2.4 mg/dL (0.78 mmol/L) was associated with higher PHLF (HR 1.78, 95%CI: 1.02-3.17, P = 0.048), major complications (HR 1.57, 95%CI: 1.02-2.47, P = 0.049), 30 d mortality (HR 2.70, 95%CI: 1.08-6.76, P = 0.031) and 90 d mortality (HR 2.51, 95%CI: 1.03-6.15, P = 0.044)[13]. Nevertheless, the evidence on the use of phosphate as a prognostic marker of PHLF is scarce, and more studies are required to demonstrate any correlation between phosphate and PHLF.

CONCLUSION

The pathophysiology behind PHH remains poorly understood. This review summarized existing literature investigating the impact of phosphate on post-operative outcomes following hepatectomy. However, definition of PHH is variable and majority of studies are retrospective with small sample size. Phosphate replacement regimes were not standardized across the studies. The heterogeneity of the reviewed studies limits our understanding of PHH on post-operative outcomes following hepatectomy. Nevertheless, PHH is a common phenomenon and it is important for clinicians to ensure adequate replacement in view of deleterious effects of PHH. Well-designed randomized controlled trials should be conducted to fill in the knowledge gap on the impact of phosphate levels and phosphate replacement in patients undergoing hepatectomy.

FOOTNOTES

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Country/Territory of origin: Singapore

ORCID number: Kai Siang Chan 0000-0001-9533-801X; Swetha Mohan 0000-0001-8463-1579; Vishal G Shelat 0000-0003-3988-8142.

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REFERENCES

1 **Fukumoto S**. Phosphate metabolism and vitamin D. *Bonekey Rep* 2014; **3**: 497 [PMID: 24605214 DOI: 10.1038/bonekey.2013.231]
2 **Sharma S**, Hashmi MF, Castro D. Hypophosphatemia: StatPearls Publishing, Treasure Island (FL), 2021
3 **Amanzadeh J**, Reilly RF Jr. Hypophosphatemia: an evidence-based approach to its clinical consequences and management. *Nat Clin Pract Nephrol* 2006; **2**: 136-148 [PMID: 16932412 DOI: 10.1038/ncpneph0124]
4 **Adhikari S**, Mamlouk O, Rondon-Berrios H, Workeneh BT. Hypophosphatemia in cancer patients. *Clin Kidney J* 2021; **14**: 2304-2315 [PMID: 34754427 DOI: 10.1093/ckj/sfab078]
5 **Larsson L**, Rebel K, Sörbo B. Severe hypophosphatemia--a hospital survey. *Acta Med Scand* 1983; **214**: 221-223 [PMID: 6660029 DOI: 10.1111/j.0954-6820.1983.tb08598.x]
6 **Marik PE**, Bedigian MK. Refeeding hypophosphatemia in critically ill patients in an intensive care unit. A prospective study. *Arch Surg* 1996; **131**: 1043-1047 [PMID: 8857900 DOI: 10.1001/archsurg.1996.01430220037007]
7 **Barak V**, Schwartz A, Kalickman I, Nisman B, Gurman G, Shoenfeld Y. Prevalence of hypophosphatemia in sepsis and infection: the role of cytokines. *Am J Med* 1998; **104**: 40-47 [PMID: 9528718 DOI: 10.1016/s0002-9343(97)00275-1]
8 **Oh TK**, Jo J, Oh AY. Perioperative Serum Calcium and Phosphorus Levels are Associated with Hospital Costs and Length

of Stay after Major Abdominal Surgery. *J Clin Med* 2018; **7** [PMID: 30249011 DOI: 10.3390/jcm7100299]
9 **Zheng J**, Glezerman IG, Sadot E, McNeil A, Zarama C, Gönen M, Creasy J, Pak LM, Balachandran VP, D'Angelica MI, Allen PJ, DeMatteo RP, Kingham TP, Jarnagin WR, Jaimes EA. Hypophosphatemia after Hepatectomy or Pancreatectomy: Role of the Nicotinamide Phosphoribosyltransferase. *J Am Coll Surg* 2017; **225**: 488-497.e2 [PMID: 28690207 DOI: 10.1016/j.jamcollsurg.2017.06.012]
10 **Hallet J**, Karanicolas PJ, Zih FS, Cheng E, Wong J, Hanna S, Coburn NG, Law CH. Hypophosphatemia and recovery of post-hepatectomy liver insufficiency. *Hepatobiliary Surg Nutr* 2016; **5**: 217-224 [PMID: 27275463 DOI: 10.21037/hbsn.2015.12.13]
11 **George R**, Shiu MH. Hypophosphatemia after major hepatic resection. *Surgery* 1992; **111**: 281-286 [PMID: 1311873]
12 **Giovannini I**, Chiarla C, Nuzzo G. Pathophysiologic and clinical correlates of hypophosphatemia and the relationship with sepsis and outcome in postoperative patients after hepatectomy. *Shock* 2002; **18**: 111-115 [PMID: 12166771 DOI: 10.1097/00024382-200208000-00003]
13 **Squires MH 3rd**, Dann GC, Lad NL, Fisher SB, Martin BM, Kooby DA, Sarmiento JM, Russell MC, Cardona K, Staley CA 3rd, Maithel SK. Hypophosphataemia after major hepatectomy and the risk of post-operative hepatic insufficiency and mortality: an analysis of 719 patients. *HPB (Oxford)* 2014; **16**: 884-891 [PMID: 24830898 DOI: 10.1111/hpb.12276]
14 **Buell JF**, Berger AC, Plotkin JS, Kuo PC, Johnson LB. The clinical implications of hypophosphatemia following major hepatic resection or cryosurgery. *Arch Surg* 1998; **133**: 757-761 [PMID: 9688005 DOI: 10.1001/archsurg.133.7.757]
15 **ISLAMI AH**, PACK GT, SCHWARTZ MK, SMITH ER. Regenerative hyperplasia of the liver following major hepatectomy; chemical analysis of the regenerated liver and comparative nuclear counts. *Ann Surg* 1959; **150**: 85-89 [PMID: 13661834 DOI: 10.1097/00000658-195907000-00010]
16 **Usami M**, Furuchi K, Ogino M, Kasahara H, Kanamaru T, Saitoh Y, Yokoyama H, Kano S. The effect of a nucleotide-nucleoside solution on hepatic regeneration after partial hepatectomy in rats. *Nutrition* 1996; **12**: 797-803 [PMID: 8974107 DOI: 10.1016/s0899-9007(96)00292-4]
17 **Erem S**, Razzaque MS. Dietary phosphate toxicity: an emerging global health concern. *Histochem Cell Biol* 2018; **150**: 711-719 [PMID: 30159784 DOI: 10.1007/s00418-018-1711-8]
18 **Goltzman D**, Mannstadt M, Marcocci C. Physiology of the Calcium-Parathyroid Hormone-Vitamin D Axis. *Front Horm Res* 2018; **50**: 1-13 [PMID: 29597231 DOI: 10.1159/000486060]
19 **England PC**, Duari M, Tweedle DE, Jones RA, Gowland E. Postoperative hypophosphataemia. *Br J Surg* 1979; **66**: 340-343 [PMID: 444854 DOI: 10.1002/bjs.1800660513]
20 **Dwyer K**, Barone JE, Rogers JF. Severe hypophosphatemia in postoperative patients. *Nutr Clin Pract* 1992; **7**: 279-283 [PMID: 1289701 DOI: 10.1177/011542659200700627 9]
21 **Woodard HQ**, White DR. The composition of body tissues. *Br J Radiol* 1986; **59**: 1209-1218 [PMID: 3801800 DOI: 10.1259/0007-1285-59-708-1209]
22 **Datta HK**, Malik M, Neely RD. Hepatic surgery-related hypophosphatemia. *Clin Chim Acta* 2007; **380**: 13-23 [PMID: 17349987 DOI: 10.1016/j.cca.2007.01.027]
23 **Salem RR**, Tray K. Hepatic resection-related hypophosphatemia is of renal origin as manifested by isolated hyperphosphaturia. *Ann Surg* 2005; **241**: 343-348 [PMID: 15650646 DOI: 10.1097/01.sla.0000152093.43468.c0]
24 **Blaine J**, Chonchol M, Levi M. Renal control of calcium, phosphate, and magnesium homeostasis. *Clin J Am Soc Nephrol* 2015; **10**: 1257-1272 [PMID: 25287933 DOI: 10.2215/cjn.09750913]
25 **Nafidi O**, Lapointe RW, Lepage R, Kumar R, D'Amour P. Mechanisms of renal phosphate loss in liver resection-associated hypophosphatemia. *Ann Surg* 2009; **249**: 824-827 [PMID: 19387319 DOI: 10.1097/SLA.0b013e3181a3e562]
26 **Mann DV**, Lam WW, Hjelm NM, So NM, Yeung DK, Metreweli C, Lau WY. Human liver regeneration: hepatic energy economy is less efficient when the organ is diseased. *Hepatology* 2001; **34**: 557-565 [PMID: 11526542 DOI: 10.1053/jhep.2001.27012]
27 **Berndt T**, Kumar R. Phosphatonins and the regulation of phosphate homeostasis. *Annu Rev Physiol* 2007; **69**: 341-359 [PMID: 17002592 DOI: 10.1146/annurev.physiol.69.040705.141729]
28 **Perwad F**, Zhang MY, Tenenhouse HS, Portale AA. Fibroblast growth factor 23 impairs phosphorus and vitamin D metabolism in vivo and suppresses 25-hydroxyvitamin D-1alpha-hydroxylase expression in vitro. *Am J Physiol Renal Physiol* 2007; **293**: F1577-F1583 [PMID: 17699549 DOI: 10.1152/ajprenal.00463.2006]
29 **Gutierrez O**, Isakova T, Rhee E, Shah A, Holmes J, Collerone G, Jüppner H, Wolf M. Fibroblast growth factor-23 mitigates hyperphosphatemia but accentuates calcitriol deficiency in chronic kidney disease. *J Am Soc Nephrol* 2005; **16**: 2205-2215 [PMID: 15917335 DOI: 10.1681/asn.2005010052]
30 **Prié D**, Forand A, Francoz C, Elie C, Cohen I, Courbebaisse M, Eladari D, Lebrec D, Durand F, Friedlander G. Plasma fibroblast growth factor 23 concentration is increased and predicts mortality in patients on the liver-transplant waiting list. *PLoS One* 2013; **8**: e66182 [PMID: 23825530 DOI: 10.1371/journal.pone.0066182]
31 **Faul C**, Amaral AP, Oskouei B, Hu MC, Sloan A, Isakova T, Gutiérrez OM, Aguillon-Prada R, Lincoln J, Hare JM, Mundel P, Morales A, Scialla J, Fischer M, Soliman EZ, Chen J, Go AS, Rosas SE, Nessel L, Townsend RR, Feldman HI, St John Sutton M, Ojo A, Gadegbeku C, Di Marco GS, Reuter S, Kentrup D, Tiemann K, Brand M, Hill JA, Moe OW, Kuro-O M, Kusek JW, Keane MG, Wolf M. FGF23 induces left ventricular hypertrophy. *J Clin Invest* 2011; **121**: 4393-4408 [PMID: 21985788 DOI: 10.1172/jci46122]
32 **Nomura K**, Tatsumi S, Miyagawa A, Shiozaki Y, Sasaki S, Kaneko I, Ito M, Kido S, Segawa H, Sano M, Fukuwatari T, Shibata K, Miyamoto K. Hepatectomy-related hypophosphatemia: a novel phosphaturic factor in the liver-kidney axis. *J Am Soc Nephrol* 2014; **25**: 761-772 [PMID: 24262791 DOI: 10.1681/asn.2013060569]
33 **Revollo JR**, Grimm AA, Imai S. The NAD biosynthesis pathway mediated by nicotinamide phosphoribosyltransferase regulates Sir2 activity in mammalian cells. *J Biol Chem* 2004; **279**: 50754-50763 [PMID: 15381699 DOI: 10.1074/jbc.M408388200]
34 **Katai K**, Tanaka H, Tatsumi S, Fukunaga Y, Genjida K, Morita K, Kuboyama N, Suzuki T, Akiba T, Miyamoto K, Takeda E. Nicotinamide inhibits sodium-dependent phosphate cotransport activity in rat small intestine. *Nephrol Dial Transplant* 1999; **14**: 1195-1201 [PMID: 10344361 DOI: 10.1093/ndt/14.5.1195]

35 **Dousa TP**. Modulation of renal Na-Pi cotransport by hormones acting *via* genomic mechanism and by metabolic factors. *Kidney Int* 1996; **49**: 997-1004 [PMID: 8691752 DOI: 10.1038/ki.1996.143]

36 **Smyrniotis V**, Kostopanagiotou G, Katsarelias D, Theodoraki K, Hondros K, Kouskouni E. Changes of serum phosphorus levels in hepatic resections and implications on patients' outcomes. *Int Surg* 2003; **88**: 100-104 [PMID: 12872904]

37 **Keushkerian S**, Wade T. Hypophosphatemia after major hepatic resection. *Curr Surg* 1984; **41**: 12-14 [PMID: 6697756]

38 **Serrano OK**, Mongin SJ, Berglund D, Goduguchinta V, Reddy A, Vock DM, Kirchner V, Kandaswamy R, Pruett TL, Chinnakotla S. Clinical utility of postoperative phosphate recovery profiles to predict liver insufficiency after living donor hepatectomy. *Am J Surg* 2019; **218**: 374-379 [PMID: 30660322 DOI: 10.1016/j.amjsurg.2019.01.006]

39 **Tan HP**, Madeb R, Kovach SJ, Orloff M, Mieles L, Johnson LA, Bozorgzadeh A, Marcos A. Hypophosphatemia after 95 right-lobe living-donor hepatectomies for liver transplantation is not a significant source of morbidity. *Transplantation* 2003; **76**: 1085-1088 [PMID: 14557757 DOI: 10.1097/01.Tp.0000085652.47821.8a]

40 **Yuan D**, Wei YG, Chen K, Li B, Yan L, Wen T, Zhao J, Yang J. Hepatectomy-related hypophosphatemia may predict donor liver dysfunction in live-donor liver transplantation. *Transplant Proc* 2010; **42**: 4548-4551 [PMID: 21168734 DOI: 10.1016/j.transproceed.2010.09.166]

41 **Michael J**. Campbell, Gardner MJ. Medians and Their Differences. In: Douglas Altman, David Machin, Trevor Bryant, Gardner M, editors. Statistics with Confidence: Confidence Intervals and Statistical Guidelines, 2000: 36-44

42 **Schreckenbach T**, Liese J, Bechstein WO, Moench C. Posthepatectomy liver failure. *Dig Surg* 2012; **29**: 79-85 [PMID: 22441624 DOI: 10.1159/000335741]

43 **Balzan S**, Belghiti J, Farges O, Ogata S, Sauvanet A, Delefosse D, Durand F. The "50-50 criteria" on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. *Ann Surg* 2005; **242**: 824-828, discussion 828 [PMID: 16327492 DOI: 10.1097/01.sla.0000189131.90876.9e]

44 **Rahbari NN**, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, Koch M, Makuuchi M, Dematteo RP, Christophi C. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery* 2011; **149**: 713-724

45 **Bismuth H**, Houssin D, Mazmanian G. Postoperative liver insufficiency: prevention and management. *World J Surg* 1983; **7**: 505-510 [PMID: 6624126 DOI: 10.1007/bf01655941]

46 **Michalopoulos GK**, DeFrances MC. Liver regeneration. *Science* 1997; **276**: 60-66

47 **Michalopoulos GK**. Liver regeneration after partial hepatectomy: critical analysis of mechanistic dilemmas. *Am J Pathol* 2010; **176**: 2-13 [PMID: 20019184 DOI: 10.2353/ajpath.2010.090675]

48 **Maton PN**, Burton ME. Antacids revisited: a review of their clinical pharmacology and recommended therapeutic use. *Drugs* 1999; **57**: 855-870 [PMID: 10400401 DOI: 10.2165/00003495-199957060-00003]

49 **Nayak R**. Post-operative Ileus. In: Gandhi A, Malhotra N, Malhotra J, Gupta N, N B, editors. Principles of Critical Care in Obstetrics. New Delhi: Springer, 2016: 233-236

50 **du Moulin GC**, Paterson DG, Hedley-Whyte J, Lisbon A. Aspiration of gastric bacteria in antacid-treated patients: a frequent cause of postoperative colonisation of the airway. *Lancet* 1982; **1**: 242-245 [PMID: 6120273 DOI: 10.1016/s0140-6736(82)90974-6]

51 **Kadohisa M**, Sugawara Y, Shimata K, Kawabata S, Narita Y, Uto K, Yoshii D, Hayashida S, Oya Y, Yamamoto H, Inomata Y, Hibi T. Duodenal Ulcer as a Postoperative Complication in the Donor in Living-Donor Liver Transplantation. *Transplant Proc* 2018; **50**: 1129-1131 [PMID: 29731079 DOI: 10.1016/j.transproceed.2018.01.026]

52 **Long RG**, Meinhard E, Skinner RK, Varghese Z, Wills MR, Sherlock S. Clinical, biochemical, and histological studies of osteomalacia, osteoporosis, and parathyroid function in chronic liver disease. *Gut* 1978; **19**: 85-90 [PMID: 305386 DOI: 10.1136/gut.19.2.85]

53 **Lentz RD**, Brown DM, Kjellstrand CM. Treatment of severe hypophosphatemia. *Ann Intern Med* 1978; **89**: 941-944 [PMID: 102230 DOI: 10.7326/0003-4819-89-6-941]

54 **Kraft MD**, Btaiche IF, Sacks GS, Kudsk KA. Treatment of electrolyte disorders in adult patients in the intensive care unit. *Am J Health Syst Pharm* 2005; **62**: 1663-1682 [PMID: 16085929 DOI: 10.2146/ajhp040300]

55 **Shackney S**, Hasson J. Precipitous fall in serum calcium, hypotension, and acute renal failure after intravenous phosphate therapy for hypercalcemia. Report of two cases. *Ann Intern Med* 1967; **66**: 906-916 [PMID: 6025231 DOI: 10.7326/0003-4819-66-5-906]

56 **Rosen GH**, Boullata JI, O'Rangers EA, Enow NB, Shin B. Intravenous phosphate repletion regimen for critically ill patients with moderate hypophosphatemia. *Crit Care Med* 1995; **23**: 1204-1210 [PMID: 7600828 DOI: 10.1097/00003246-199507000-00009]

57 **Engwerda E**, van den Berg M, Blans M, Bech A, de Boer H. Efficacy and safety of a phosphate replacement strategy for severe hypophosphatemia in the ICU. *Neth J Med* 2018; **76**: 437-441 [PMID: 30569887]

58 **Wang YY**, Zhong JH, Su ZY, Huang JF, Lu SD, Xiang BD, Ma L, Qi LN, Ou BN, Li LQ. Albumin-bilirubin versus Child-Pugh score as a predictor of outcome after liver resection for hepatocellular carcinoma. *Br J Surg* 2016; **103**: 725-734 [PMID: 27005482 DOI: 10.1002/bjs.10095]

59 **Chin KM**, Allen JC, Teo JY, Kam JH, Tan EK, Koh Y, Goh KPB, Cheow PC, Raj P, Chow KHP, Chung YFA, Ooi LL, Chan CY, Lee SY. Predictors of post-hepatectomy liver failure in patients undergoing extensive liver resections for hepatocellular carcinoma. *Ann Hepatobiliary Pancreat Surg* 2018; **22**: 185-196 [PMID: 30215040 DOI: 10.14701/ahbps.2018.22.3.185]

60 **Chin KM**, Koh YX, Syn N, Teo JY, Goh BKP, Cheow PC, Chung YFA, Ooi LL, Chan CY, Lee SY. Early Prediction of Post-hepatectomy Liver Failure in Patients Undergoing Major Hepatectomy Using a PHLF Prognostic Nomogram. *World J Surg* 2020; **44**: 4197-4206 [PMID: 32860142 DOI: 10.1007/s00268-020-05713-w]

61 **Sposito C**, Monteleone M, Aldrighetti L, Cillo U, Dalla Valle R, Guglielmi A, Ettorre GM, Ferrero A, Di Benedetto F, Rossi GE, De Carlis L, Giuliante F, Mazzaferro V. Preoperative predictors of liver decompensation after mini-invasive liver resection. *Surg Endosc* 2021; **35**: 718-727 [PMID: 32124061 DOI: 10.1007/s00464-020-07438-2]

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