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A comparison of renal phosphorus regulation in thermally-injured and multiple trauma patients receiving specialized nutrition support

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*Abstract*

To compare phosphorus intake and renal phosphorus regulation between thermally injured patients and multiple trauma patients, 40 consecutive critically ill patients, 20 with thermal injury and 20 with multiple trauma, who required enteral tube feeding were evaluated. Phosphorus intakes were recorded for 14 days from the initiation of tube feeding which was started 1 to 3 days post-injury. Serum for determination of phosphorus concentrations was collected at days 1, 3, 7, and 14 of the study period. A 24-hour urine collection was obtained during the first and second weeks of nutrition support for urinary phosphorus excretion, fractional excretion of phosphorus, renal threshold phosphate concentration, and phosphorus clearance. Average total daily phosphorus intake during the 14-day study for thermally injured patients and multiple trauma patients was  $0.99 \pm 0.26$  mmol/kg/d vs  $0.58 \pm 0.21$  mmol/kg/d, respectively,  $p < .001$ . Serum phosphorus concentration on the third day of observation was significantly lower in the thermally injured group than those with multiple trauma ( $1.9 \pm 0.8$  mg/dL vs  $3.0 \pm 0.8$  mg/dL,  $p \leq .01$ ). A trend toward hypophosphatemia in the thermally injured group persisted by the seventh day of feeding ( $2.7 \pm 1.2$  mg/dL vs  $3.3 \pm 0.6$  mg/dL,  $p \leq .04$ ). Differences in urinary phosphorus excretion was not statistically significant between the thermally injured and multiple trauma groups ( $271 \pm 213$  mg/d vs  $171 \pm 181$  mg/d for week 1, and  $320 \pm 289$  mg/d vs  $258 \pm 184$  mg/d for week 2, respectively). Urinary phosphorus clearance, fractional excretion of phosphorus, or renal threshold phosphate concentrations were also not significantly different between thermally injured and multiple trauma patients. During nutrition support, serum phosphorus concentrations are lower in thermally injured patients compared with multiple trauma patients despite receiving a significantly greater intake of phosphorus. Renal phosphorus regulation does not significantly contribute to the profound hypophosphatemia observed in thermally injured patients when compared with multiple trauma patients during nutrition support.

Hypophosphatemia is a problem in the hospitalized patient<sup>1</sup> and often occurs during the administration of specialized nutrition support.<sup>2-4</sup> Death coinciding with severe hypophosphatemia has been reported,<sup>5</sup> and phosphorus replacement is essential in the metabolic management of the critically ill patient.<sup>4,6,7</sup> Two populations of hospitalized patients noted to be particularly challenging in the attainment of phosphorus balance are thermally injured patients<sup>8-11</sup> and multiple trauma patients.<sup>12-14</sup> In the critically ill, hypophosphatemia often occurs within two to five days post-injury. The severity of hypophosphatemia has been reported to increase with the severity of illness<sup>15</sup> and the degree

of undernutrition.<sup>5</sup> Both thermally injured and multiple trauma patients have similar proposed etiologies of phosphorus loss including the metabolic response to stress,<sup>8</sup> nutrition administration,<sup>5,16</sup> alkalemia,<sup>17</sup> and medications.<sup>18-20</sup>

Although the presence of hypophosphatemia in thermally injured and multiple trauma patients is established, little work has been done in regards to examining renal regulatory response to alterations in phosphorus metabolism in critically ill, tube-fed patients. After years of clinical management of these two patient populations, through an active nutrition support service, a perception that thermally injured patients required more phosphorus to achieve normal serum phosphorus concentrations than their multiple trauma counterparts developed. This study was undertaken to compare severity of hypophosphatemia between thermally injured and multiple trauma patients and to ascertain whether a substantial difference in the renal regulatory response was the etiology for the presumed worsened hypophosphatemia in thermally injured tube-fed patients.

### *Clinical Relevancy*

This paper illustrates the significant hypophosphatemia that occurs with thermal injury when compared to other patients with serious injury such as multiple trauma. Profound hypophosphatemia occurred despite provision of substantially more phosphorus to the thermally injured patients than that given to multiple trauma patients. This phenomenon is not due to an apparent defect in renal phosphate regulation or exaggerated renal phosphorus excretion or differences in energy intake between the thermal injury and multiple trauma groups. Published literature suggests wound losses would also not account for the marked discrepancy between phosphorus intake and output as found in this study. Taken together, these data suggest other mechanisms outside of overt losses are responsible for the increased phosphorus requirements in thermally injured patients receiving specialized nutrition support.

### *Materials and Methods*

This was a prospective study conducted in a level I trauma center and a regional burn center from the Regional Medical Center at Memphis in Memphis, Tennessee. The study was approved by both the University of Tennessee Investigational Review Board and the medical center. The investigational review board waived the need for informed consent. A total of 40 consecutive patients requiring enteral feeding, 20 thermally injured patients and 20 multiple trauma patients, were studied. Only patients who were admitted into the burn or trauma intensive care centers were enrolled into the study. Patients had to be between 18 to 60 years of age, sustained either  $\geq 20\%$  total body surface area burn or multiple trauma, and required specialized nutrition support. Patients with significant renal impairment (serum creatinine  $> 1.6$  mg/dL), alkalemia (arterial pH  $> 7.50$ ), or history of diabetes mellitus were excluded. Patients were assessed for inclusion into the study at the initiation of specialized nutrition support, which was within one to three days of admission into the hospital. Patients could

receive either parenteral or enteral nutrition; however, the enteral route was used first in all patients.

The Tobiasen Burn Severity Index Score,<sup>21</sup> Trauma Score,<sup>22</sup> and Injury Severity Score<sup>23</sup> were calculated at the time of admission into the hospital. The Acute Physiology and Chronic Health Evaluation-II (APACHE-II) Score<sup>24</sup> was calculated for each patient within the first 24 hours of inclusion into the study. Serum phosphorus concentrations were collected at days 1, 3, 7, and 14 after the initiation of enteral nutrition. A 24-hour urine was collected within the first 48 hours of enteral nutrition (week 1) and repeated the following week (week 2) for determination of urinary phosphorus excretion, fractional excretion of phosphate (FEP), renal threshold phosphate concentration, and phosphorus clearance. Phosphorus clearance was calculated by dividing the urinary phosphorus excretion (mg/d) by the serum phosphorus excretion (mg/dl) and converted to ml/min. Fractional excretion of phosphate (%) was calculated from the ratio of urine phosphorus divided by serum phosphorus divided by the ratio of urine creatinine to serum creatinine and the overall product multiplied by 100. The renal threshold phosphate concentration was estimated using the nomogram of Walton and Bijvoet.<sup>25</sup> Daily phosphorus intake was recorded during the first 14 days of nutrition support. Phosphorus intake was divided into two separate categories: enteral (phosphorus received via tube feedings or by mouth) and IV (phosphorus received via IV bolus or by parenteral nutrition). Patients who were able to attempt an oral diet were offered meals consisting of 2000 kcal's (15% protein) and 37.5 mmol of phosphorus daily. Net total phosphorus intake was calculated from 60% absorption for the enteral route<sup>26,27</sup> and 100% availability by the IV route.

Medications reported to cause decreases in serum phosphorus concentrations were also recorded during the 14 days of the study. Arterial blood gases and serum electrolytes were monitored daily until the patients were weaned from mechanical ventilation. Thereafter, patients were started on a regular diet. In addition to the serum phosphorus concentrations collected via the established, restudy clinical protocol, additional serum phosphorus concentration measurements were obtained by the Nutrition Support Service or primary service as clinically indicated. Electrolyte replacement was managed by the Nutrition Support Service or the respective primary service. Patients with serum phosphorus concentrations below 3 mg/dL were given IV phosphorus boluses using guidelines developed at our institution.<sup>4</sup> Patients were determined to have mild (2.3mg/dL to 3.0 mg/dL), moderate (1.6 mg/dL to 2.2 mg/dL), or severe (<1.6 mg/dL) hypophosphatemia. Patients then received a one-time phosphorus bolus using a graduated dosing scheme: 0.16 mmol/kg, 0.32 mmol/kg, or 0.64 mmol/kg for mild, moderate, or severe hypophosphatemia, respectively. Serum phosphorus concentrations were done a least once daily with daily IV boluses given in addition to supplemental phosphorus added to the tube feeding as either sodium or potassium phosphate. The IV bolus infusions were given over 4 to 6 hours. Patients with serum phosphorus concentrations  $\leq 1.5$  mg/dL had repeat serum concentrations performed 2 to 4 hours after the bolus was given. If the serum concentrations was  $\leq 2.0$  mg/dL, a second IV bolus was given.

The Nutrition Support Service managed the patients' specialized nutrition support. The Toronto formula<sup>28</sup> was used to estimate caloric requirements of thermally injured patients. Multiple trauma patients' energy requirements were estimated at 30 to 35 kcal/kg/d. Estimated protein requirements were 2 to 2.5 g/kg/d for patients with thermal injury and 1.5 to 2 g/kg/d for multiple trauma patients. Mean daily caloric and protein intake was calculated for each group.

A 10 mL aliquot of urine was obtained from each week's 24-hour urine collection. The sample was immediately frozen at -20 degrees Celsius. Urine phosphorus assays were performed by quantitative colorimetric spectrophotometry (Sigma, St. Louis, MO). Urine samples were diluted to provide concentrations within the range of the lowest and highest concentration of the five point standard curve.

Statistical analyses were performed using SPSS version 6.1 for Windows (SPSS Inc, Chicago, IL). The *t* test for independent variables were used to compare the single measurements between the two groups. For comparison of two observations within the same group, the paired *t* test was used to measure the significance of these differences. These pairwise comparisons were confirmed by nonparametric analysis using the Mann-Whitney *U* test and Wilcoxon signed ranks test for independent and paired groups, respectively, to insure any observed differences were not attributable to differences in population distribution. For data expressing the same variable measured on multiple occasions over time, repeated measures analysis of variance (RMANOVA) was performed to detect differences in these measurements between the two populations. The populations were tested for sphericity and then the univariate RMANOVA was conducted if the assumption was correct. If the sphericity assumption was rejected, then the multivariate RMANOVA was performed. The Fisher Exact probability test was used to compare nominal data. All continuous data are expressed as mean  $\pm$  SD. Because of the large number of pairwise comparisons and the increased risk for error, these two-tailed comparisons were considered statistically significant at a lowered *p* value of  $\leq 0.01$ ; however, the *p* value was given for comparisons with a *p* value of  $< 1.0$ . Any *p* values  $\geq 1.0$  were expressed as N.S. (not significant).

### *Results*

Because the non-parametric statistical testing results did not conflict with the findings of the parametric tests, we chose to report the *p* values from the parametric tests. The baseline patient demographic characteristics and nutritional indices for the two groups appear in Table 1. Both groups were fairly well matched with similar age, gender distribution, height, weight, percent ideal body weight, serum albumin concentration, and serum pre albumin concentration. Significant differences between groups at baseline were a higher APACHE-II score in the thermally injured patients. All patients began enteral tube feedings within 1 to 3 days of injury and received either an immune-enhancing formula or a conventional high-

**Table 1.** Patient demographic data

Characteristic	Multiple trauma group (N = 20)	Thermal injury group (N = 20)	p ≤
<b>Demographics</b>			
Age (yrs)	35.3 ± 11.4	38.7 ± 11.7	NS
Gender (M/F)	15/5	15/5	NS
<b>Disease severity</b>			
Tobiasen BSI	—	7.4 ± 1.7	
Trauma Score	8.4 ± 2.6	—	
ISS	27.6 ± 7.2	—	
APACHE-II	9.2 ± 4.6	13.1 ± 4.7	0.01
<b>Admitting Diagnosis (N)</b>			
MVA	13	—	
CHI	9	—	
GSW	3	—	
Fall	3	—	
Assault	3	—	
Pedestrian Struck	1	—	
Thermal Injury	—	20	
Inhalation Burn Injury Involvement	—	5	
<b>Nutrition parameters</b>			
Height (cm)	173 ± 8	170 ± 12	NS
Weight (kg)	83.9 ± 15.0	79.7 ± 13.3	NS
IWB (kg)	69.4 ± 10	69.1 ± 9.6	NS
% IBW	124 ± 36	119 ± 28	NS
Albumin (g/dL)	2.2 ± 0.6	2.5 ± 0.9	NS
Prealbumin (mg/dL)	12 ± 5	13 ± 5	NS
Creatinine (mg/dL)	0.8 ± 0.2	1.0 ± 0.3	0.04
<b>Nutrition Formulas (N)</b>			
High protein	17	11	0.05
Immune-enhancing	3	9	

BSI, Burn Severity Index; ISS, Injury Severity Score; APACHE-II, Acute Physiology and Chronic Health Evaluation-II score; MVA, motor vehicle accident; CHI, closed head injury; GSW, gun shot wound; IBW, ideal body weight.

protein formula. Significantly more patients in the thermally injured group received an immune-enhancing formula than patients in the multiple trauma group (Table 1). However, urinary phosphorus excretion in the thermally injured patients who received an immune-enhancing formula vs those who received a conventional high-protein formula was not significantly different. Only two patients required the addition of short-term parenteral nutrition because of intolerance to tube feedings. Both patients were in the multiple trauma group and each received parenteral nutrition for 3 days during the entire 14 days of study. Four patients with multiple trauma and three patients with thermal injury were able to consume a regular diet near the end of the 14-day study period. The mean daily caloric and protein intake between the multiple trauma and thermal-injury patients over the 14-day observation period were not significantly different from each other ( $1259 \pm 392$  kcal/d and  $74 \pm 30$  g/d vs  $1668 \pm 271$  and  $92 \pm 21$  g/d, respectively,  $p = \text{N.S.}$ ). Medications received by the patients that may potentially alter phosphorus homeostasis were similar between groups except a greater number of thermally injured patients received furosemide (Table 2). However, furosemide and corticosteroid use was infrequent and not given on a consistent

**Table 2.** Medications influencing phosphorus homeostasis

Medications	Multiple trauma group	Thermal injury group	p ≤
Furosemide	0	11	0.01
Antacids (scheduled)	0	2	NS
Sucralfate	2	0	NS
Catecholamines			
Epinephrine	0	1	NS
Norepinephrine	0	1	NS
Glucocorticosteroids	1	8	0.02
Estrogen	1	0	NS

basis for any of the patients; there was no significant difference in urinary phosphorus excretion between those thermally injured patients who had received furosemide or glucocorticosteroids vs those not given these drugs.

Mean total daily phosphorus intake during the 14-day study was significantly higher in the thermally injured patients compared with those with multiple trauma ( $0.99 \pm 0.26$  mmol/kg/d vs  $0.58 \pm 0.21$  mmol/kg/d,  $p < .001$ ), as given in Table 3. The mean amount of daily phosphorus received in the thermally injured patient was greater each day of the study period when compared with multiple trauma patients. Multivariate repeated measures ANOVA demonstrated significant a difference in daily phosphorus intake over the 14 days of observation between the two groups (Fig. 1;  $p \leq .0001$ ). The net total amount of phosphorus received by the thermally injured patients was also significantly greater than the multiple trauma patients (Table 3). Multivariate repeated measures ANOVA did not demonstrate an overall difference in serum phosphorus serum concentrations between groups over the 4-sample, 14-day observation period (Fig. 2,  $p = .08$ ); however, serum phosphorus levels were significantly different ( $p \leq .01$ ) between both groups on the third day of feeding with a trend toward a difference ( $p = .04$ ) at day 7 [ $1.9 \pm 0.8$  vs  $3.0 \pm 0.8$  mg/dL (Day 3) and  $2.7 \pm 1.2$  vs  $3.3 \pm 0.6$  mg/dL (Day 7); Figure 2].

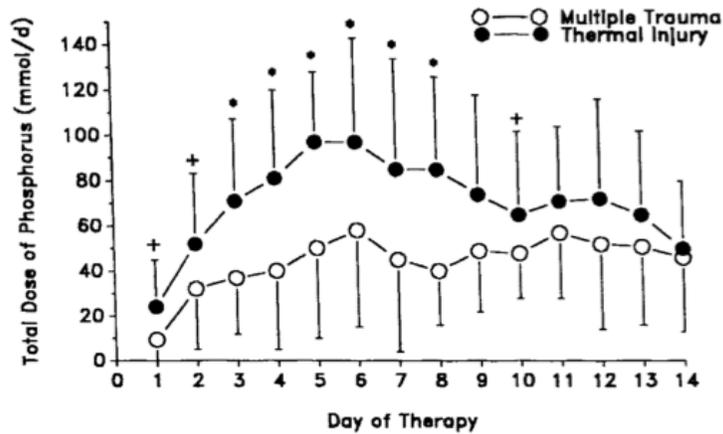
Table 4 contains the comparative data regarding variables to describe urinary phosphorus regulation. Mean urinary phosphorus excretion (mg/d) was 60% greater in the thermally injured patients than the multiple trauma patients during the first week, but this difference was not statistically significant due to substantial variability in phosphorus excretion between both groups. There was a trending increase in urinary phosphorus excretion by the second week for both groups; however these differences from week 1 to week 2 were not significant (Table 4). Mean urinary phosphorus excretion for the thermally injured patients was 24% greater than the multiple trauma group for week 2; however, these differences were not statistically significant. Fractional excretion of phosphorus (FEP) and urinary phosphorus clearance were not statistically different between groups the first week; however, during the second week, differences in the FEP and urinary phosphorus clearance between the groups approached statistical significance (Table 4;  $p \leq .05$  and  $p \leq .06$ , respectively). The renal threshold phosphate concentration was not significantly different between groups or different

**Table 3.** Average daily phosphorus intake

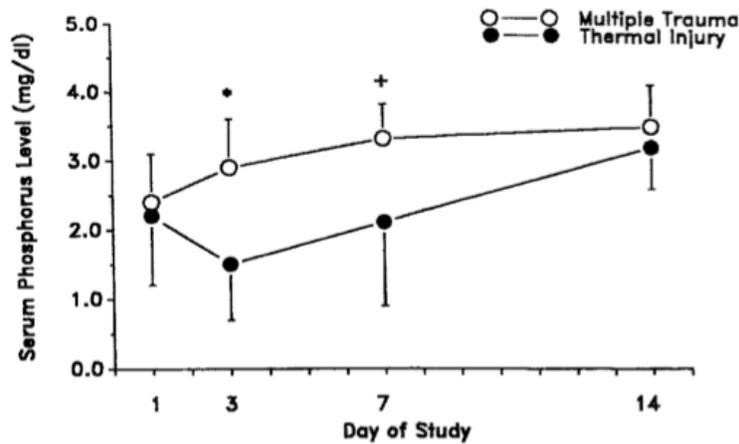
	Multiple trauma group	Thermal injury group	p ≤
<b>Week 1</b>			
Parenteral			
(mmol/d)	7 ± 0.1	21 ± 13	0.001
(mmol/kg/d)	0.08 ± 0.07	0.27 ± 0.16	0.001
Enteral			
(mmol/d)	32 ± 17	53 ± 17	0.001
(mmol/kg/d)	0.40 ± 0.23	0.69 ± 0.22	0.001
Total Intake			
(mmol/d)	39 ± 19	72 ± 27	0.001
(mmol/kg/d)	0.48 ± 0.23	0.95 ± 0.35	0.001
Total “Net” Intake*			
(mmol/d)	26 ± 12	53 ± 20	0.001
(mmol/kg/d)	0.31 ± 0.16	0.69 ± 0.25	0.001
<b>Week 2</b>			
Parenteral			
(mmol/d)	2.3 ± 0.0	5.5 ± 5.6	0.05
(mmol/kg/d)	0.03 ± 0.04	0.07 ± 0.06	0.02
Enteral			
(mmol/d)	51 ± 19	73 ± 23	0.001
(mmol/kg/d)	0.63 ± 0.25	0.95 ± 0.26	0.003
Total Intake			
(mmol/d)	53 ± 20	79 ± 27	0.001
(mmol/kg/d)	0.47 ± 0.26	1.01 ± 0.30	0.003
Total “Net” Intake*			
(mmol/d)	33 ± 13	49 ± 18	0.001
(mmol/kg/d)	0.40 ± 0.16	0.63 ± 0.19	0.001
<b>Both Weeks</b>			
<b>(Average)</b>			
Parenteral			
(mmol/d)	5 ± 5	13 ± 9	0.002
(mmol/kg/d)	0.06 ± 0.06	0.17 ± 0.12	0.001
Enteral			
(mmol/d)	42 ± 15	63 ± 18	0.001
(mmol/kg/d)	0.52 ± 0.21	0.82 ± 0.22	0.001
Total Intake			
(mmol/d)	47 ± 15	76 ± 20	0.001
(mmol/kg/d)	0.58 ± 0.21	0.82 ± 0.22	0.001
Total “Net” Intake*			
(mmol/d)	30 ± 10	51 ± 14	0.001
(mmol/kg/d)	0.37 ± 0.13	0.67 ± 0.19	0.001

\*Total “Net” Intake assumes 60% bioavailability of enteral phosphorus and 100% bioavailability from intravenous phosphorus

between weeks. No statistically significant correlation was observed between the Tobiasen Burn Severity Index score or Apache II score and urinary phosphorus excretion.



**Figure 1.** Mean daily phosphorus intakes in multiple trauma patients (open circles) compared with thermally injured patients (closed circles). Multivariate repeated measures ANOVA demonstrated a significant difference in daily phosphorus intake over the 14 days of observation between the two groups ( $p < .001$ ). Differences between groups by day are noted by: \* $p < .01$  + $p < .05$



**Figure 2.** Serial serum phosphorus concentrations in multiple trauma patients (open circles) and thermally injured patients (closed circles). Multivariate repeated measures ANOVA did not demonstrate an overall difference in serum phosphorus concentrations between both groups over the 14 day observation period ( $p = .08$ ); however, differences between groups by day are noted by: \* $p \leq .01$ ; + $p \leq .05$ .

**Table 4.** Renal phosphorus regulation

	Multiple trauma	Thermal injury	<i>p</i> ≤
Urinary Phosphorus Excretion (mg/d)			
Week 1	171 ± 181	271 ± 213	NS
Week 2	258 ± 184	320 ± 289	NS
Cl <sub>u</sub> -phos (ml/min)			
Week 1	4.6 ± 4.7	7.5 ± 6.7	NS
Week 2	5.3 ± 3.5	6.4 ± 5.2	0.06
FEP (%)			
Week 1	16 ± 15	22 ± 19	NS
Week 2	15 ± 13	32 ± 26	0.05
TmP/GFR (mmol/L)			
Week 1	1.07 ± 0.47	1.27 ± 0.43	NS
Week 2	0.99 ± 0.46	1.10 ± 0.62	NS

Cl<sub>u</sub>-phos, urinary phosphorus clearance; FEP, fractional excretion of phosphorus; TmP/GFR, renal threshold phosphate concentration; NS, not significant

### *Discussion*

Hypophosphatemia is a common problem in critically ill patients and even more prevalent in patients who are given specialized nutrition support.<sup>2-4</sup> Marik and coworkers found that 34% of tube-fed critically ill patients had significant hypophosphatemia (serum phosphorus < 0.65 mmol/L or < 2.1 mg/dL) as a result of the combination of refeeding, malnutrition, and critical illness.<sup>2</sup> Other data have suggested that hypophosphatemia may be particularly prevalent in thermally injured patients.<sup>8-12,28,29</sup> Human and experimental models have demonstrated the decrease in concentrations of high energy phosphorylated compounds after thermal injury in response to hypophosphatemia.<sup>10-12,30-35</sup> Our unpublished clinical observations from the Regional Medical Center's trauma and burn units suggested to us that the thermal injury patient receiving specialized nutrition support required more phosphorus in an effort to maintain a normal serum phosphorus concentration than a multiple trauma patient receiving specialized nutrition support. However, there were no published data to verify these observations. As a result, we sought to compare renal phosphorus excretion and other markers of renal phosphorus regulation between these two populations to ascertain if the apparent discrepancies in intake and serum phosphorus concentrations in thermally injured patients could be explained by differences in renal regulation of phosphorus. Our data confirmed our previous clinical observations that enterally fed, thermally injured patients have lower serum levels of phosphorus than enterally fed, multiple trauma patients despite receiving a substantially greater phosphorus intake. In addition, although urinary phosphorus excretion was modestly greater in thermally injured patients compared with multiple trauma patients, this difference was not statistically significant and does not explain the discrepancy between intake, output, and resultant serum concentrations of phosphorus in thermally injured patients.

Evidence of postburn hypophosphatemia within 2 to 10 days postinjury has been established for over two decades.<sup>8,9</sup> This decrease in serum phosphorus concentration also leads to decreases in high energy phosphorylated compounds in the muscle in burned patients.<sup>12</sup> Hypophosphatemia can no longer be disregarded, as a laboratory observation as the clinical consequences of even moderate hypophosphatemia such as impaired diaphragmatic contractility and myocardial depression are now well established.<sup>2,36,37</sup> Early investigations suggested that increased urinary excretion of phosphorus may be the etiology for postburn hypophosphatemia. These studies demonstrated mean daily urinary phosphorus excretion rates of approximately 15 to 35 mmol/d.<sup>8,9</sup> In contrast, thermally injured patients from our study had mean urinary phosphorus excretion rates of 9 to 12 mmol/d despite an average net combined parenteral and enteral combined intake of about 50 mmol/d (of which 30% of the total phosphorus intake was from the parenteral route). The thermally injured patients' urinary phosphorus excretion in our study was modestly greater than the comparative (multiple trauma) group, but due to considerable variability in the data, these differences were not statistically significant. In addition, the thermally injured group's urinary phosphorus excretion was much lower than expected, as they received an intake almost twice that of the multiple trauma control group during the first week of the study. These data appear to dispute the early findings of excessively high urinary phosphorus excretion rates. However, it is difficult to interpret these older studies and contrast it with our data due to a lack of pertinent information such as documentation of phosphorus intake, amount of nutrition given, and omission of a comparative group in those previous reports. In a recent study of mineral losses in the urine and wounds of burned patients fed enteral nutrition, Berger<sup>15</sup> suggested that the extent of urinary loss of phosphorus was the principal source of phosphorus depletion; however, the authors stated that the urinary phosphate excretion tended to be low between postburn days 4 to 7 with a mean loss of about 25 mmol/d, which was about twice the urinary excretion rate of our population. Also, their mean combined parenteral and enteral phosphorus intake was about 30 to 40 mmol/d for the first 10 days, which is lower than our mean total intakes of 72 mmol/d for the first week and 79 mmol/d for the second week ("net" intakes of 53 and 49 mmol/d, respectively). Reasons for this discrepancy between the data of Berger<sup>15</sup> and from our study are not clear, but it may be related to different patient populations. Severity of illness in the population may be an important difference between Berger's data and ours as the mean Tobiasen Burn Severity Index for their population was about 15 in contrast to a mean score of 7.4 for the burned patients in our study. The Burn Severity Index takes age, gender, extent and depth of burn injuries, presence or absence of inhalation injury, and burns to risk areas into account. Patients are considered to be severely burned when their index is greater than 7.<sup>21</sup> These data may suggest that our thermal injury population may have been less severely burned. Unfortunately, insufficient data were provided in the Berger study<sup>15</sup> to compare nutritional regimes with our data and may have been an additional contributing factor to these differences.

Previous literature suggested a renal tubular abnormality in phosphate reabsorption as an etiology for postburn hypophosphatemia as evidenced by an increased fractional excretion of

phosphorus.<sup>9</sup> Lenquist et al's data indicated that the fractional excretion of phosphorus was markedly elevated in thermally injured patients as the fractional excretion rates ranged from 8.5% to 50%.<sup>9</sup> We found the mean fractional excretion of phosphorus of thermally injured patients were similar to the multiple trauma patients during the first week (Table 4) at 22% and 16%, respectively. During the second week, thermally injured patients tended to have a greater fractional excretion rate of phosphorus compared with control; however, these differences were not statistically significant at the  $p \leq .01$  level of significance (32% vs 15%,  $p \leq .05$  respectively). However, this trending difference is mostly likely attributable to our persistence of aggressive phosphorus dosing in the thermally injured patients despite apparent recovery of phosphorus depletion as evidenced by rising serum phosphorus concentrations into the normal range. Unfortunately, these data may be confounded as the use of fractional excretion as a marker of increased tubular secretion or decreased reabsorption is limited, and some have suggested that its use may not be appropriate for phosphorus.<sup>27</sup> Renal threshold phosphate concentration (TmP/GFR ratio) using the Walton and Bijvoet nomogram<sup>25</sup> estimates the serum phosphorus concentration by which serum concentrations below suggest all phosphate is reabsorbed and above where phosphate excretion parallels that of inulin clearance. The mean renal threshold phosphate concentrations were similar between thermally injured and multiple trauma patients which is within the anticipated normal range of 2.5 mg/dL to 4.2 mg/dL.<sup>38</sup> When combined with the urinary excretion data, these data indicate that our thermally injured patients did not have a defect in renal tubular reabsorption. We also examined urinary phosphorus clearance, which describes the relationship between urinary phosphorus excretion and serum phosphorus concentration. The urinary phosphorus clearance arguably may be the best marker for assessing renal phosphorus compensatory response. Table 4 indicates that there was no significant change in urinary phosphorus clearance between weeks 1 and 2 for both groups; however the thermally injured patients had a greater urinary phosphorus clearance than the multiple trauma patients that nearly achieved statistical significance by the second week ( $p = .06$ , Table 3). These data support our fractional excretion data and may suggest a trend toward an increase in urinary clearance of phosphorus in the presence of aggressive phosphorus dosing when serum concentrations and, presumably, phosphorus stores approach normalization or equilibration by the second week of feeding. Because previously published studies lack detail regarding amount of phosphorus intake, it is impossible to evaluate our findings in perspective with other published literature.

Exudative losses are another consideration for source for phosphorus loss in burned patients. Berger and coworkers<sup>15</sup> suggested that exudative losses combined with urinary losses may explain the increased mineral requirements after thermal injury. In their analysis of 16 patients with 20% to 55% total body area surface burns, mean phosphorus losses were 5 to 22 mmol per day. However, individual daily exudative losses were highly variable ranging from 0 to 60 mmol. The investigators also found no significant correlation between exudative phosphorus loss and percent total body surface area burn; however, a modest linear correlation was found between exudative phosphorus loss and the Tobiasen Burn Severity Index ( $r = .55$ ). Exudative phosphorus losses were not measured in this study; however, our population had a mean Tobiasen index half of those patients described by Berger (7.4 vs 15,

respectively). Therefore, we would expect exudative phosphorus losses to be less in our patient population.

Certain medications used in the critical care setting have been shown to reduce serum phosphorus concentrations and cause negative phosphorus balance.<sup>18-20</sup> Some patients received these medications, as shown in Table 2. The most common medications known to induce hypophosphatemia used in our study populations included aluminum, magnesium, or combination-containing antacids and sucralfate. Some patients in either the trauma or burn intensive care unit received an “as needed” antacid order. The antacid was given based on the patient’s gastric pH. Only two patients, both in the TI group, were placed on a scheduled antacid dose each for 2 days. None received sucralfate. More thermally injured patients received furosemide than multiple trauma patients; however, the phosphaturic effects of furosemide are considered to be minimal.<sup>20</sup> Comparison of the renal phosphorus regulation markers in thermally injured patients showed no statistically significant difference between those who received furosemide vs those who did not receive furosemide. Similar findings were demonstrated when examining renal phosphorus markers in those thermally injured patients who received glucocorticosteroids. Therefore, medications were not likely to substantially influence phosphorus balance in our thermally injured and control multiple trauma populations during this study.

Patients received IV phosphorus via IV boluses or parenteral nutrition and enterally via tube feedings with or without supplemental phosphorus. Enteral phosphorus is approximately 60% to 70% bioavailable and may increase to 90% with low intakes.<sup>26,27</sup> The phosphorus content of the immune-enhancing formulas was either 500 mg/L or 864 mg/L depending on which formula was used. The high-protein enteral formulas contained 758 mg/L or 800 mg/L. More patients in the thermally injured group received immune-enhancing diets than in the multiple trauma group; however, it is unknown whether these formulas substantially influence phosphorus metabolism. Comparison of the data in those thermally injured patients who received immune-enhancing diets vs conventional high-protein feedings suggested no statistically significant influence by the type of enteral tube feeding upon these renal phosphorus markers. Additional enteral phosphorus supplementation was accomplished by adding either 5 to 10 ml of Phosphosoda (20 mmol sodium phosphate per 5 ml) or 15 or 30 mmol of potassium phosphate injection per liter of tube feeding. None of the patients in either group had significant diarrhea or evidence of malabsorption. It is unlikely that the type of enteral feeding formula or method of enteral phosphorus supplementation provided to the patients was a major confounding factor.

Thermal injury has been described in numerous studies as one of the most hypermetabolic conditions in critical illness.<sup>39-41</sup> Data from our burn center indicate measured resting energy expenditures ranging from approximately 110% to 200% of predicted energy expenditure by the Harris-Benedict equations.<sup>42</sup> Because their energy needs may be higher than other critically ill populations, it is anticipated that the demand for phosphorylated intermediary compounds of energy metabolism is also increased. Yu and coworkers<sup>39</sup> have estimated that

ATP-consuming reactions (that require additional phosphorus) explain approximately 57% of the increase in energy expenditure in thermal injury. In addition, patients may be rebuilding new tissues after skin grafting of their wounds. These data may provide a plausible explanation for the increased phosphorus requirements in our thermally injured patients given the lack of significant differences in urinary excretion compared with trauma patients.

Our target caloric goals were likely higher for the thermally injured patients than multiple trauma patients. However, due to episodic intolerance of enteral feeding and operative procedures, the thermally injured and multiple trauma patients received similar caloric intakes during this two week observation period. These data indicate hypophosphatemia could not be attributable to a greater caloric intake (increasing phosphorus requirements due to greater carbohydrate intake) in one group than another.

Other mechanisms may be responsible for the phenomenon of post-burn hypophosphatemia, including increased inflammatory cytokine production,<sup>43</sup> heterotopic bone formation,<sup>44</sup> increases in calcitonin production,<sup>9</sup> increased catecholamine secretion,<sup>9,10</sup> alkalemia,<sup>17</sup> insulin resistance, and decreased cellular uptake of phosphorus.<sup>12</sup> Patients with alkalemia were excluded from study entry, and unfortunately, we did not investigate these other potential mechanistic etiologies for hypophosphatemia.

An evaluation of phosphorus balance would provide some significant insight regarding phosphorus requirements in thermally injured patients. However, because of the difficulty in collecting exudative losses from all textiles surrounding the patient and determining the extent of phosphorus absorption from the tube feeding via stool losses, determination of phosphorus balance would be extremely difficult. Application of the knowledge learned regarding wound phosphorus losses in burned patients from a previously published study,<sup>15</sup> along with our own data, may provide some insight regarding estimated phosphorus balance in our patients. Using a conservative scenario, we could develop an estimation of phosphorus balance from the assumption of 60% phosphorus bioavailability from enteral sources, 100% availability from IV sources, and 22 mmol/d lost from cutaneous sources. Our data suggests that the thermally injured patients received an approximate mean “net” phosphorus intake of about 50 mmol/d and had a urinary loss of about 10 to 12 mmol/d. Adding cutaneous losses to the phosphorus balance equation would result in a positive balance of approximately 15 mmol/d despite a low serum phosphorus concentration. This “net” balance is remarkable as healthy adult subjects <40 to 50 years old are generally in phosphorus equilibrium; whereas during growth, in the first two decades of life, average phosphorus balance is only about 2 to 3 mmol/d.<sup>27</sup> Balance studies involving 24-hour urine collections are frequently fraught with error due to incomplete collection of the urine; however, all patients in our study were catheterized, located in an intensive care unit, and meticulous care was taken to ensure the accuracy of these collections. These data provide support to suggest a greater role for other non-renal factors leading to the development of post-burn hypophosphatemia.

### Conclusion

Despite a significantly greater intake of phosphorus, thermally injured patients had lower serum phosphorus concentrations during the first week of feeding than the multiple trauma patients. A trend toward an increase in urinary phosphorus excretion was noted for thermally injured patients when compared with multiple trauma patients; however, these differences were not statistically significant. Renal phosphorus regulation appears to contribute a lesser role in the pathogenesis for the profound hypophosphatemia observed in thermally injured patients receiving specialized nutrition support. Further research is necessary to characterize the metabolic aberrations of phosphate metabolism in thermally injured patients receiving specialized nutrition support.

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