Metabolic Aspects of Phosphate Replacement Therapy for Hypophosphatemia After Renal Transplantation: Impact on Muscular Phosphate Content, Mineral Metabolism, and Acid/Base Homeostasis

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• **Hypophosphatemia caused by renal phosphate loss occurs frequently after kidney transplantation. In assumption of systemic phosphorus depletion, the presumed deficit commonly is replaced by oral phosphate supplements. However, such treatment is debatable, because intracellular phosphorus stores have not been assessed in this setting and may not be accurately reflected by serum phosphate concentrations. Moreover, disturbances in mineral metabolism from chronic renal failure, such as hypocalcemia and hyperparathyroidism, may be prolonged with oral phosphate supplements. Conversely, a neutral phosphate salt might improve renal acid excretion and systemic acid/base homeostasis for its properties as a urinary buffer and a poorly reabsorbable anion. Twenty-eight patients with mild early posttransplantation hypophosphatemia (0.3-0.75 mmol/L) were randomly assigned to receive either neutral sodium phosphate (Na_2HPO_4) or sodium chloride (NaCl) for 12 weeks and examined with regard to (1) correction of serum phosphate concentration and urinary phosphate handling; (2) muscular phosphate content; (3) serum calcium and parathyroid hormone (PTH); and, (4) renal acid handling and systemic acid/base homeostasis. Mean serum phosphate concentrations were similar and normal in both groups after 12 weeks of treatment; however, more patients in the NaCl group remained hypophosphatemic (93% versus 67%). Total muscular phosphorus content did not correlate with serum phosphate concentrations and was 25% below normophosphatemic controls but was completely restored after 12 weeks with and without phosphate supplementation. However, the percentage of the energy-rich phosphorus compound adenosine triphosphate (ATP) was significantly higher in the Na_2HPO_4 group, as was the relative content of phosphodiesters. Also, compensated metabolic acidosis (hypobicarbonatemia with respiratory stimulation) was detected in most patients, which was significantly improved by neutral phosphate supplements through increased urinary titratable acidity. These benefits of added phosphate intake were not associated with any adverse effects on serum calcium and PTH concentrations. In conclusion, oral supplementation with a neutral phosphate salt effectively corrects posttransplantation hypophosphatemia, increases muscular ATP and phosphodiester content without affecting mineral metabolism, and improves renal acid excretion and systemic acid/base status.**

INDEX WORDS: Hypophosphatemia; renal transplantation; renal phosphate handling; muscular phosphate content; parathyroid hormone; calcium; acid/base homeostasis.

HYPOPHOSPHATEMIA after renal transplantation is frequent and multifactorial in its origin, with renal phosphate wasting attributable to tubular dysfunction, immunosuppressive and diuretic drugs, and reduced intestinal absorption of phosphorus being the main causes.[1-4] It is common practice to supplement oral phosphate salts for severe hypophosphatemia, ie, serum phosphate (Pi) concentrations below 0.3 mmol/L, to prevent major acute complications such as hemolytic anemia, rhabdomyolysis, impaired cardiac contractility, respiratory insufficiency,[5] and long-term musculoskeletal complications.[6] However, we are not aware of any investigation that has examined phosphate replacement in the early posttransplantation period with regard to its associated effects on calcium, parathyroid hormone (PTH), and acid/base metabolism in moderate hypophosphatemia, ie, serum Pi concentrations between 0.3 and 0.75 mmol/L. Moreover, representing only a small fraction of total body phosphorus serum Pi may not be a good indicator of tissue phosphate stores (phosphate is approximately 40 times more abundant in cells than in serum). As a component of adenosine 5'-triphosphate (ATP), intracellular phosphorus is critical for tissues with a high-energy consumption, such as muscle. Similarly, phosphodiesters (PDEs) are

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important components of cellular membranes. So far, no study has comprehensively examined alterations in muscular phosphate content in posttransplantation hypophosphatemia and the impact of oral phosphate supplementation on muscular concentration of relevant Pi compounds.

Secondary hyperparathyroidism is prevalent in most patients with end-stage renal disease, and PTH activity has been shown to decrease very slowly after renal transplantation.[7] Oral phosphate supplementation might cause intermittent bursts of elevated serum Pi that triggers the release of PTH. Together with hypocalcemia attributable to intestinal as well as intravascular calcium binding by phosphate, prolongation of hyperparathyroidism may result. Conversely, phosphate promotes renal acid excretion through its properties as an intraluminal buffer and as a poorly reabsorbable anion.[8] Theoretically, this may improve systemic acid-base homeostasis in patients with renal metabolic acidosis. However, there is a lack of clinical studies that have examined renal acid/base regulation after kidney transplantation.

The aim of the current study was to evaluate the effect of oral neutral phosphate administration in renal posttransplantation hypophosphatemia with regard to (1) normalization of serum phosphate concentration and renal phosphate handling; (2) muscular phosphate content; (3) serum calcium and PTH metabolism; and (4) renal acid excretion and systemic acid/base homeostasis.

PATIENTS AND METHODS

All adult patients (older than 20 years) receiving a first kidney transplant at our institution after January 1, 1998, were evaluated for participation in the study. Inclusion criteria were hypophosphatemia (0.3 to 0.75 mmol/L) without prior phosphate supplementation on at least two consecutive occasions within 2 weeks before entry into the study and stable renal transplant function with a creatinine clearance greater than 30 mL/min. Patients were enrolled immediately when they met all of the inclusion criteria after transplantation and were randomly assigned to receive either neutral sodium phosphate (Na_2HPO_4) or sodium chloride (NaCl). Sodium phosphate was composed of Na_2HPO_4 and NaH_2PO_4 in a molar ratio of 4:1. This preparation is ''neutral,'' because it does not deliver or consume any protons (H^+) at a blood pH of 7.4. However, when excreted in the urine at a pH of less than 6.8, it promotes H^+ excretion (unlike the commercially available Neutra-Phos [Baltimore, MD] with a molar ratio for Na_2HPO_4:NaH_2PO_4 of 1:1). Both sodium phosphate and sodium chloride were provided in gelatin capsules containing 100 mg inorganic phosphate or 182 mg NaCl, respectively, with an identical sodium content per capsule (manufactured by Bichsel Laboratorien, Interlaken, Switzerland). The dosage of both treatments (in capsules per day) was adapted to the actual serum phosphate concentration: 3×3 for Pi between 0.3 and 0.49; 3×2 for Pi between 0.5 and 0.65; and 3×1 for Pi between 0.65 and 0.75 mmol/L. Treatment was stopped or temporarily interrupted, if serum phosphate was beyond 0.75 mmol/L on at least two consecutive occasions. Serum phosphate was checked twice a week during the first 2 weeks after discharge from the hospital, weekly during the next 4 weeks, and every other week thereafter. Except for study medication, immunosuppressive drugs, and diuretics, none of the patients received any treatment that interferes with phosphate or calcium metabolism. Diet was unrestricted during the study; however, all patients were encouraged to consume products rich in phosphorus content, such as meat and dairy.

Patient characteristics are summarized in Table 1. Groups were comparable for age, sex, body weight, underlying nephropathy, donor type, and renal transplant function. An identical number of patients had a PTH level beyond normal before transplantation ($n = 12$ in each group). Two patients in the control group had undergone parathyroidectomy previously. All patients received immunosuppressive treatment consisting of mycophenolate mofetil (CellCept, Roche, Switzerland) 1 g twice daily, and prednisone in a dose of 0.5 mg/kg body weight, tapered by 10 mg every month. Cyclosporine A (CsA) (Sandimmune Neoral, Novartis, Switzerland) was given to 13 of 14 patients in the control and to 12 of 14 patients in the phosphate treatment group, targeted to a serum trough level of 200 to 250 ng/mL. The remaining

Table 1. Patient Characteristics

	NaCl	Na_2HPO_4	*P*
Age (yr)	46.3 ± 3.6	43.9 ± 3.6	NS
Sex (M:F)	10:4	10:4	
Body weight (kg)	67.0 ± 3.2	69.2 ± 3.4	NS
Underlying nephropathy			
• Glomerulopathy	10	8	
• Interstitial nephropathy	1	0	
• Diabetic nephropathy	0	1	
• ADPKD	0	1	
• Analgesic nephropathy	0	1	
• Other	1 (M. Fabry)	0	
• Unknown	1	3	
Donor type			
• Brain death	10	13	
• Non–heart-beating	1	0	
• Living related/unrelated	2/1	1/0	
Baseline creatinine clearance (mL/min)	58.7 ± 5.0	69.1 ± 4.5	NS

Abbreviation: ADPKD, autosomal dominant polycystic kidney disease.

patients in both groups received FK506 (Prograf, Fujisawa, Japan) instead of CsA because of rejection or hirsutism. Two and three patients in the control and phosphate group, respectively, were treated for acute rejection before inclusion into the study. No further rejection episodes occurred during the study period.

Blood and Urine Measurements

Routine blood and urine analysis was performed at baseline and at 2, 6, and 12 weeks into the study. Urine was collected under oil and with thymol as a preservative over 24 hours before study examinations. Urinary ammonium and citrate were determined by an enzymatic assay,[9,10] on a Cobas Integra (Roche Diagnostics, Rotkreuz, Switzerland). Titratable acidity (TA) was calculated from urinary pH, pCO_2, and phosphate concentration according to the nomogram published by Kok et al.[11] Intact PTH was measured by radioimmunoassay (RIA; Nichols Institute Diagnostics, San Juan Capistrano, CA) at the beginning and at weeks 6 and 12 of the study. Blood gas analyses were performed on an AVL 945 (AVL Medical Instruments, Schaffhausen, Switzerland) from arterialized venous blood drawn from an arteriovenous (AV)-shunt fistula or after prewarming of the arm.[12] In only three patients of each group was the blood sample from a peripheral vein not adequately arterialized, but inclusion of these samples for group analysis did not affect the results. All blood sampling procedures were performed in the morning, after an overnight fast.

Measurements of Muscular Phosphate Concentration

Muscular phosphate concentrations were determined at baseline and after completion of the study by magnetic resonance (MR) spectroscopy. The MR experiments were performed on a Philips Gyroscan ACS-NT system (Philips Medical Systems, Best, The Netherlands) with 1.5-Tesla field strength and equipped with a second spectroscopy channel. In a first step, images of the lower left leg of the patient (in supine position with feet first) were acquired with the body coil. A circular phosphorus send–receive coil (diameter, 14 cm) was fixed under the lower leg. In the center of this spectroscopy coil, a reference substance (PAA, phosphono acetic acid) with peaks at 18.5 ppm relative to phosphocreatine (PCr), was filled in, which could also be identified in the MR images. Spectra of a volume of 50–70 mm^3 within the calf muscle were measured, using the ILOPS sequence. The complete procedure of absolute quantitative MR spectroscopy used within this study is described in detail by Buchli et al.[13] The image localized phosphorous spectroscopy (ILOPS) sequence with a repetition time of 14 seconds was repeated (for averaging) 64 times for the acquisition of 1,024 points with a sample frequency of 3,000 Hz. Because of a rather long repetition time, a correction of T_1 relaxation effects was not necessary. Data of all experiments were postprocessed identically: exponential filtering with 5 Hz, zero filling to 4,096 data points, fast fourier transformation (FFT) and (automatic) phase correction of zero order. The resulting spectrum of this procedure was fitted in the frequency domain with a least square algorithm, using a model of Lorentzian line shapes. For the selective muscle spectrum, the known splitting (shift and intensity relations) of the three ATP peaks were included in the model parameters. The fit results (peak area) were used for the final quantitative evaluation. The total accuracy of the concentration values, determined with the previously mentioned procedure, is approximately 90%.

The study protocol has been approved by the local ethics committee. All patients gave their written informed consent for participation.

Statistical Analyses

All results are expressed as means ± SEM. Differences between treatment groups were tested by ANOVA. Intraindividual differences within study groups were calculated by ANOVA for repeated measurements. Correlation between parameters was assessed by linear regression analysis. *P*-values < 0.05 were considered statistically significant.

RESULTS

Of 30 adult patients receiving a kidney transplant between January and May 1998, 28 (93%) developed posttransplantation hypophosphatemia according to study criteria. The mean time after transplantation to study entry was 32 ± 4 days in the control and 33 ± 4 days in the treatment group.

Normalization of Serum Phosphate Concentration

Figure 1 depicts the effect of (Na_2HPO_4) versus sodium chloride intake on serum phosphate

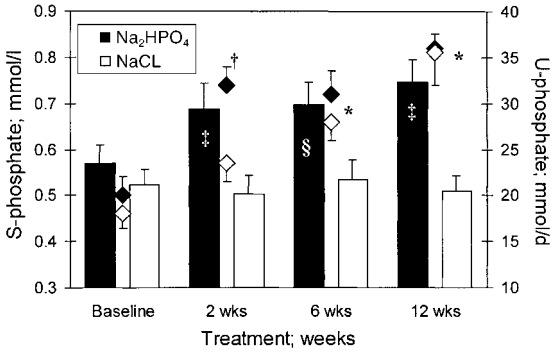

Fig 1. Serum phosphate concentration (S-phosphate) and 24-hour urinary phosphate excretion (U-phosphate). Mean serum phosphate concentration at 2 weeks was significantly higher with Na_2HPO_4 (◆) as compared with NaCl (◇) intake (†$P < 0.01$ versus baseline and NaCl). After 6 and 12 weeks, serum Pi was significantly different from baseline for both groups, but no longer between groups (*$P < 0.01$ versus baseline for both groups). Mean urinary phosphate excretion (bars) was increased significantly by neutral phosphate at all times (‡$P < 0.01$ versus baseline and NaCl; §$P < 0.01$ versus baseline), but not by NaCl.

levels. Posttransplantation patients treated with Na_2HPO_4 virtually corrected their hypophosphatemia within the first 2 weeks, from 0.50 ± 0.04 to 0.74 ± 0.04 mmol/L, and remained stable until completion of the study. Only six patients required more than 6 weeks to achieve normophosphatemia. In contrast, patients in the control group only gradually corrected their serum Pi concentration over 12 weeks, with 12 and 10 patients still being hypophosphatemic after 2 and 6 weeks, respectively. At the end of the study, both groups had virtually identical serum phosphate levels (0.81 ± 0.07 in the control versus 0.82 ± 0.03 mmol/L in the Na_2HPO_4-treated group; P = NS). Moreover, the number of days to reach a normal serum phosphate concentration did not significantly differ between groups (57.2 ± 9 in the Na_2HPO_4 versus 50.1 ± 9 days in the control group). However, by the end of the study, 13 of 14 patients (93%) in the Na_2HPO_4 group had a phosphate level greater than 0.75 mmol/L, compared with only 10 patients (67%) in the control group.

The increase in serum phosphate concentration from phosphate supplementation was accompanied by a significant increase in urinary phosphate excretion (Fig 1 and Table 2) from 23.5±2 mmol/d at baseline to 32.3±2.5 mmol/d after 12 weeks of treatment (P = 0.001). This increase was apparent within 14 days of neutral phosphate intake. In comparison, phosphaturia was stable in controls, with approximately 21 mmol/d throughout the study. In both groups, the fractional excretion of phosphate decreased over 12 weeks (Table 2), but this was significant only in the NaCl group (Na_2HPO_4 group: from 53 ± 6 to 40 ± 3%, P = NS; NaCl group: from 59 ± 6% to 35 ± 4%, $P < 0.0001$).

Muscular Phosphate Concentration

Muscular phosphate content was measured by nuclear magnetic resonance spectroscopy. Measurements were performed in posttransplantation study patients before and after 12 weeks of either neutral sodium phosphate (n = 10) or sodium chloride (n = 13) intake, and, for comparison, in normal volunteers (n = 8) and in patients with end-stage renal disease before and after a hemodialysis (HD) session (n = 6). Volunteers (five men, three women, aged 34 ± 3 years) had normal serum phosphate (1.09 ± 0.09 mmol/L), ionized calcium (1.13 ± 0.01), PTH (16 ± 3 pg/mL), and creatinine (87 ± 4 μmol/L) values. Their muscle phosphate concentration was 40.1 ± 1.1 mmol/L. In comparison, concentration in hyperphosphatemic HD patients was approximately 10% lower (P = NS) and did not significantly change after a HD session (34.2 ± 3.5 versus 36.8 ± 2.4 mmol/L before and after dialysis, respectively). Results of muscular phosphate measurements in posttransplantation patients are shown in Fig 2. The mean muscular phosphate concentration before supplementation with either Na_2HPO_4 or NaCl was similar (31.5 ± 2.2 and 31.3 ± 2.4 mmol/L; P = NS). However, as a combined group, the values were lower by approximately 25% compared with normal vol-

Table 2. Total and Fractional Excretion (FE) of Phosphate: Serum Calcium (S-Ca) and Parathyroid Hormone (PTH) Concentrations

	Baseline		2 Weeks		6 Weeks		12 Weeks	
	Na_2HPO_4	NaCl	Na_2HPO_4	NaCl	Na_2HPO_4	NaCl	Na_2HPO_4	NaCl
U-phosphate (mmol)	23.5 ± 2.0	21.1 ± 1.7	29.4 ± 2.8*	20.2 ± 2.0	29.8 ± 2.5†	21.7 ± 2.1	32.3 ± 2.5*†	20.5 ± 1.7
FE phosphate (%)	53 ± 6	59 ± 6	43 ± 4	40 ± 4†	46 ± 4	38 ± 3†	40 ± 3†	35 ± 4†
S-Ca^{++} (mmol/L) (1.28-1.42)	1.37 ± 0.03	1.33 ± 0.03	1.36 ± 0.03	1.34 ± 0.03	1.35 ± 0.03‡	1.35 ± 0.02	1.30 ± 0.02‡	1.30 ± 0.02
PTH (pg/mL) (10-65)	92 ± 17	91 ± 18	ND	ND	70 ± 12†	59 ± 9	53 ± 5‡	58 ± 7‡

*$P < 0.01$ *v* NaCl.
†$P < 0.02$ *v* baseline.
‡$P < 0.05$ *v* baseline.

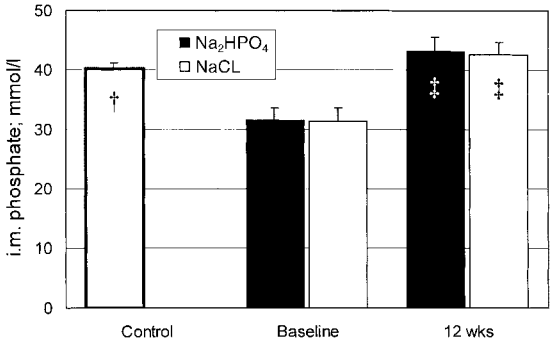

Fig 2. Muscular phosphate concentration in normal individuals (control) and in patients after renal transplantation before (baseline) and after (12 weeks) supplementation with either neutral sodium phosphate (Na_2HPO_4) or sodium chloride (NaCl). Total muscular phosphate content was significantly higher in normophosphatemic controls versus patients with hypophosphatemia (†$P < 0.01$ versus both baseline Na_2HPO_4 and NaCl). After 12 weeks, muscular phosphate content in both the Na_2HPO_4 and NaCl group was higher compared with baseline (‡$P < 0.01$).

unteers ($P < 0.01$) and by approximately 10% versus patients on chronic dialysis treatment ($P = 0.12$). Reassessment of posttransplantation patients after 3 months of supplementation with either Na_2HPO_4 or NaCl showed a significant increase in muscular phosphate content in both groups by 37% ($P < 0.01$) and 36% ($P < 0.01$), respectively, versus baseline. Absolute concentrations did not differ between treatment groups (43.1 ± 2.3 versus 42.6 ± 2.0 mmol/L; P = NS).

In contrast to total muscular phosphate concentration, a significant difference was detected in the relative content of different phosphate compounds among groups. As shown in Table 3 for normal volunteers, PCr is the main phosphate compound of muscle tissue, representing more than 50% of its total phosphorus content. However, the primary source of energy is ATP. ATP is hydrolyzed to adenosine diphosphate, from which it is regenerated through transfer of Pi from PCr, the energetically inactive carrier of phosphorus.[14] Table 3 shows the percentage of muscular ATP content to be lower in posttransplantation hypophosphatemic patients before supplementation with either Na_2HPO_4 or NaCl as compared with normal volunteers. After 12 weeks of neutral phosphate supplementation, the relative ATP content was significantly higher compared with NaCl intake. Likewise, relative PDE concentrations were clearly and significantly increased by phosphate supplementation (+38%). PDEs are part of many cellular structures, mainly nucleotides and cell membranes. Muscle tissue is rich in sarcoplasmic reticulum, which makes up approximately 90% of all cellular membranes.[15] Given its high abundance in muscle tissue, it is very likely that most of the PDEs detected in our experiments belong to sarcoplasmic reticulum.

Effect of Neutral Phosphate Intake on Changes in Systemic Calcium and PTH Concentrations

As shown in Table 2, mean serum ionized calcium concentrations at baseline were normal in both groups, whereas PTH levels were elevated to a comparable extent. Within the first 6 weeks of observation, ionized calcium concentration decreased to a slightly lower level in the Na_2HPO_4 group, whereas a small increase was noted in controls (without statistical significance for both changes between and within groups). After 12 weeks, ionized calcium was identical in

Table 3. Relative Distribution of Muscular Phosphate Compounds in Normal Controls and Patients With Posttransplantation Hypophosphatemia

	Normal Volunteers	Baseline		12 Weeks	
		Na_2HPO_4	NaCl	Na_2HPO_4	NaCl
PCr	52.7 ± 9.4	54.8 ± 1.8	57.2 ± 1.2	51.9 ± 0.6*	57.0 ± 1.3
ATP	28.6 ± 0.9	27.9 ± 1.2	26.5 ± 1.0	29.3 ± 0.7*	27.2 ± 0.6
PDE	6.4 ± 0.7	4.83 ± 0.6	5.36 ± 0.4	6.69 ± 0.4†	5.24 ± 0.7
PME	5.4 ± 0.8	5.77 ± 1.1	4.86 ± 0.5	5.61 ± 0.6	4.28 ± 0.7
Pi	6.9 ± 0.5	6.71 ± 0.3	6.31 ± 0.3	6.44 ± 0.4	6.28 ± 0.3

Abbreviations: PCr, phosphocreatine; ATP, adenosine 5′-triphosphate; PDE, phosphodiester; PME, phosphomonoester; Pi, inorganic phosphate.

*$P < 0.03$ *v* NaCl.

†$P < 0.05$ *v* baseline.

Table 4. Systemic Acid/Base Parameters

	Baseline		6 Weeks		12 weeks	
	Na_2HPO_4	NaCl	Na_2HPO_4	NaCl	Na_2HPO_4	NaCl
pH	7.39 ± 0.02	7.39 ± 0.02	7.36 ± 0.01	7.36 ± 0.02	7.36 ± 0.01	7.37 ± 0.01
pCO_2 (mm Hg)	36.6 ± 1.3	35.4 ± 2.0	41.1 ± 2.2	37.1 ± 2.6	39.9 ± 1.9	37.1 ± 1.9
HCO_3 (mmol/L)	21.6 ± 0.65	20.7 ± 0.77	22.0 ± 0.56	20.7 ± 0.62	22.2 ± 0.51*	21.2 ± 0.69

*$P < 0.05$ *v* baseline.

the two groups, with a significant difference versus baseline only in patients on phosphate supplements. PTH levels were significantly lowered to normal values after 12 weeks, regardless of treatment with neutral phosphate or sodium chloride. Of note, serum PTH concentrations were lower in both groups versus baseline already at 6 weeks. However, this difference was significant only for the phosphate group.

Effect of Neutral Phosphate Intake on Renal Acid/Base Handling and Systemic Acid/Base Homeostasis

As can be seen from Table 4, at an average 1 month after renal transplantation (=baseline), patients had hypobicarbonatemia, which was compensated for by increased respiration (expressed as low pCO_2). Figure 3 summarizes the results of posttransplantation renal acid excretion. At baseline, the renal acid/base excretion pattern was comparable between groups. Thereafter, TA increased significantly from 25.6 ± 2.2 at baseline to 31.9 ± 2.4 mmol/d at 12 weeks in patients with neutral phosphate intake (P = 0.007). Conversely, TA decreased slightly in controls, from 21.7 ± 1.9 at baseline to 19.7 ± 2.1 mmol/d after 12 weeks (P = 0.0007). TA was highly and significantly correlated with urine phosphate excretion in both groups (r = 0.76 and 0.72 for Na_2HPO_4 and NaCl, respectively, $P <$ 0.0001: calculated from combined time points). In contrast to TA, daily ammonium excretion decreased in the Na_2HPO_4 group from 26.8 ± 2.6 at baseline to 23.1 ± 3.1 mmol at 2 weeks, and increased in the NaCl group from 31.5 ± 3.3 to 33.6 ± 3.5 mmol over the same period (P = 0.033 for difference between groups at 2 weeks). Compatible with this trend toward lower net acid excretion (NAE), 24-hour urinary bicarbonate increased from 5.9 ± 0.9 at baseline to 10.1 ± 2.6 mmol at 2 weeks in the Na_2HPO_4 group, whereas a concomitant decrease from 6.2 ± 1.6 to 4.2 ± 0.8 mmol was noted in the NaCl group (P = 0.053 between groups at 2 weeks). Finally, urinary citrate excretion was higher by approximately 50% with neutral phosphate supplementation throughout the study; however, the difference did not reach statistical significance (baseline: 1.09 ± 0.24 versus 0.79 ± 0.17; after 12 weeks: 0.97 ± 0.25 versus 0.66 ± 0.14 mmol/d in the Na_2HPO_4 versus NaCl group, respectively). NAE denotes the product of urinary ammonium excretion and TA minus urinary bicarbonate loss. As shown in Fig 3, daily NAE was comparable between treatment groups at baseline (46.5 ± 5.1 in the Na_2HPO_4 versus 47.1 ± 5 mmol in the NaCl group) but became transiently lower in the Na_2HPO_4 group at 2 weeks (40.6 ± 5.8 versus 50.7 ± 4.8 mmol in controls) because of high bicarbonaturia and low ammonium excretion. Later on, patients with neutral phosphate intake had consistently higher

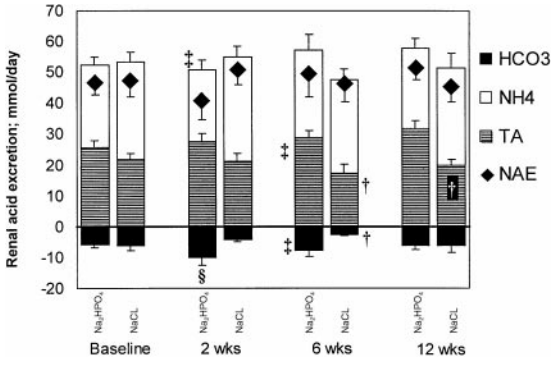

Fig 3. Daily renal acid and base excretion after renal transplantation in patients with neutral sodium phosphate (Na_2HPO_4) or sodium chloride (NaCl) intake. Stacked bar graph indicating acid excretion on the positive, and base excretion on the negative ordinate. Net acid excretion (NAE) is depicted as ◆, representing the difference of combined acid minus bicarbonate excretion. †$P < 0.05$ versus baseline; ‡$P < 0.05$ versus NaCl.

daily NAE compared with the NaCl group at 6 weeks (49.3 ± 7.4 versus 46.1 ± 5.7 mmol in controls) and 12 weeks (51.5 ± 3.9 versus 45.1 ± 4.6 mmol). Finally, urinary pH (baseline: 5.94 ± 0.02 versus 5.86 ± 0.06; after 12 weeks: 5.88 ± 0.01 versus 5.99 ± 0.01 in the Na_2HPO_4 versus NaCl group, respectively) and urinary volume (baseline: 2,936 ± 209 versus 2,243 ± 174; after 12 weeks: 2,418 ± 283 versus 2,036 ± 155 mL/d in the Na_2HPO_4 versus NaCl group, respectively) were comparable between groups.

In patients with added phosphate intake, serum bicarbonate increased steadily over 12 weeks (Table 4) and was significantly higher compared with baseline. Accordingly, pCO_2 increased as well. In contrast, patients in the NaCl control group had a more protracted and lesser increase in serum bicarbonate (NS). Consequently, their pCO_2 remained low at 37.1 mm Hg after 12 weeks of study observation.

DISCUSSION

The principal and unique findings of this study are fourfold: (1) normalization of serum phosphate concentration occurs usually within 2 weeks of oral phosphate supplementation and is accompanied by prolonged phosphaturia; (2) the early posttransplantation course is characterized by muscular phosphorus depletion, and oral phosphate replacement increases the percentage of phosphorous compounds relevant for energy delivery (ATP) and cytoplasmic membrane structures (PDE); (3) serum calcium and PTH metabolism is not affected by neutral phosphate supplements; and (4) sustained phosphaturia due to oral supplementation of neutral phosphate increases urinary TA, which modifies renal NAE and improves latent posttransplantation metabolic acidosis.

With an incidence of 93% in our study, hypophosphatemia has been confirmed to be a frequent sequel of renal transplantation.[1,2,4] Hypophosphatemia was paralleled by hyperphosphaturia of more than 20 mmol/d, and fractional phosphate excretion at baseline was beyond 50%, whereas in healthy individuals, less than 10% of filtered Pi usually escapes reabsorption in the proximal tubule.[16] Regardless of oral phosphate supplements, serum Pi concentrations were within normal limits after 12 weeks of observation. From our study, it is not possible to conclude whether this normalization is accounted for by the observed decrease in PTH, restoration of tubular reabsorptive capacity (Table 2), or a combination of both. With phosphate replacement, a faster and more complete recovery from hypophosphatemia was achieved. This shows that oral phosphate supplements are effective for correction of posttransplantation hypophosphatemia. It is debatable, however, whether hypophosphatemia per se is of any pathophysiologic relevance in the posttransplantation setting and whether administration of oral phosphate supplements is warranted.

Muscle is a major compartment for phosphate and might be affected by low serum Pi concentrations. We have examined muscular phosphate content by ^{31}P nuclear magnetic resonance technique. This method has successfully been used to investigate skeletal and heart muscle in normal and diseased states.[13,17-19] In comparison with normophosphatemic control subjects, total muscular phosphate concentration in our patients was lower by 25%. We cannot rule out that more severe hypophosphatemia in our study population may have resulted in more profound muscular phosphate depletion-causing symptoms (eg, weakness), which were virtually absent in our patients. However, muscular phosphate content was lower compared with chronic hemodialysis patients, who do not seem to accumulate phosphate from chronic renal failure. Considering the magnitude of phosphaturia, these findings suggest a negative total body phosphate balance after renal transplantation. Phosphatemia is a poor indicator of tissue phosphorus stores, because serum Pi did not correlate with muscular phosphate content. Such correlation occurs only in severe phosphate depletion.[20,21] Surprisingly, total muscular phosphate concentration did not differ between patients with and without additional phosphate intake. However, patients with phosphate supplements had a significantly higher percentage of muscular ATP and PDE at the end of the study (Table 3). ATP is an important energy carrier, and PDEs are a membrane component of sarcoplasmic reticulum, which regulates electromechanical coupling through calcium release. Therefore, phosphate supplementation may improve muscle contractility.

Successful renal transplantation increases phosphate excretion, restores the capacity to synthe-

size calcitriol, and leads to a gradual resolution of secondary hyperparathyroidism.[7] At the beginning of our study, approximately 1 month after transplantation, serum ionized calcium was within normal limits in both groups, but mean PTH values were still slightly elevated. Phosphate is known to be an independent trigger of PTH release,[22,23] and phosphate administration in hypophosphatemic patients has been shown to decrease 1,25 dihydroxycholecalciferol,[24] which, in turn, stimulates secretion of PTH.[25] In the current study, phosphate supplementation did not impair resolution of hyperparathyroidism. These findings are in contrast to a recent publication by Caravaca et al,[26] who found an increase in PTH after oral phosphate supplementation. However, their patients were studied at an average 41 months posttransplantation, with two thirds still being hyperparathyroid at that time (in contrast to only 25% of our patients after 4 months posttransplantation). Therefore, it is very likely that they have looked at a select population with failure to resolve hyperparathyroidism.

Metabolic acidosis attributable to renal insufficiency is associated with impaired protein turnover, osteomalacic and osteopenic bone disease, calcium nephrolithiasis, and β2-microglobulinemia.[27] After successful transplantation of a well-functioning graft, acid/base disorders should theoretically resolve. In our study, the mean pH of arterialized blood at an average of 32 days posttransplantation was 7.39, ie, formally within normal limits. However, with an arterial bicarbonate concentration of merely 21.1 mmol/L (combined groups), this was achievable only with a low pCO_2 tension (36 mm Hg, combined groups). Therefore, we postulate that early posttransplantation patients are in a state of compensated metabolic acidosis. Hypobicarbonatemia after renal transplantation can result from either decreased renal acid excretion, renal bicarbonate loss, or both. Baseline NAE was 47 mmol/d, which is too low in face of a serum bicarbonate of 21.1 mmol/L (expected amount: approximately 1 mmol/kg body weight on a Western diet). This is explained by low ammonium excretion and urinary bicarbonate loss. The third component of renal acid excretion is TA, which is made up mainly of phosphate. Metabolic acidosis stimulates renal phosphate excretion[28] because of reduced activity of the proximal tubular sodium-coupled phosphate transporter NaPi2.[29] Conversely, neutral phosphate administration generates and maintains renal metabolic alkalosis in healthy volunteers through renal and extrarenal mechanisms.[30] In rats, normal renal regulation of serum bicarbonate concentration during metabolic acidosis is critically dependent on sufficient Pi excretion rates for its properties as a urinary buffer, as well as that of a poorly reabsorbable anion.[8] However, these findings of potential clinical importance have not been verified so far under clinical conditions. Neutral phosphate intake in our patients resulted in a significant increase in TA, up to 25% from baseline and 65% versus controls, and was strongly correlated with phosphaturia. Nevertheless, a decrease rather than an increase in NAE was found in patients on phosphate supplements after 2 weeks of treatment as a result of pronounced bicarbonaturia and reduced ammonium excretion. Our experiments do not allow determination of the mechanisms for this phenomenon. During the second half of the study, urinary ammonium excretion remained lower in patients on phosphate supplements but approached that of controls. The fact that ammonium excretion after added phosphate intake did not exceed that in the control group is not unexpected, because increased ammonium secretion would mainly be caused by increased distal delivery of nonreabsorbable anions, which theoretically were provided in equimolar amounts from both sodium phosphate and sodium chloride. By the end of the study, a trend toward higher NAE was apparent in the Na_2HPO_4 group, which was entirely accounted for by profoundly and significantly more TA. In line with these findings was the significant improvement in systemic acid/base status, which was more pronounced in the Na_2HPO_4 group. Accordingly, the rise in serum bicarbonate was paralleled by an increase in pCO_2 , reflecting lesser respiratory activity. Conclusively, added phosphate intake as a neutral sodium salt modifies renal acid excretion and improves systemic acid/base status in hypophosphatemic patients after kidney transplantation.

In summary and conclusion, we have shown that oral supplementation with a neutral phosphate salt in patients with hypophosphatemia after renal transplantation improves the composition of muscular phosphate components, renal

acid excretion, and systemic acid/base homeostasis. Considering these favorable effects and the absence of any untoward results, oral supplementation with a neutral phosphate salt for mild posttransplantation hypophosphatemia is recommended.

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