Association of Pretransplant Serum Phosphorus with Posttransplant Outcomes

Marcelo S. Sampaio, † Miklos Z. Molnar,‡§ Csaba P. Kovesdy,■ Rajnish Mehrotra,¶ Istvan Mucsi,¶ John J. Sim,¶¶ Mahesh Krishnan,‡ Allen R. Nissenson,§§ and Kamyar Kalantar-Zadeh§§§

Summary
Background and objectives Serum phosphorus levels are associated with mortality, cardiovascular disease, and renal function loss in individuals with and without chronic kidney disease. The association of pretransplant serum phosphorus levels with transplant outcomes is not clear.

Design, setting, participants, & measurements Data of the Scientific Registry of Transplant Recipients (SRTR) up to June 2007 were linked to the database (2001 through 2006) of one of the U.S.-based large dialysis organizations (DaVita). The selected 9384 primary kidney recipients were divided into five groups according to pretransplant serum phosphorus levels (mg/dl): <3.5, 3.5 to <5.5 (reference group), 5.5 to <7.5, 7.5 to <9.5, and ≥9.5. Unadjusted and multivariate adjusted risks for transplant outcomes were compared.

Results Patients were 48 ± 14 years old and included 37% women and 27% African Americans. After multivariate adjustment, all-cause and cardiovascular death hazard ratios were 2.44 (95% confidence interval: 1.28 to 4.65) and 3.63 (1.13 to 11.64), respectively, in recipients in the ≥9.5 group; allograft loss hazard ratios were 1.42 (1.04 to 1.95) and 2.36 (1.33 to 4.17) in recipients with 7.5 to >9.5 and ≥9.5, respectively. No significant association with delayed graft function was found.

Conclusions Pretransplant phosphorus levels 7.5 to <9.5 mg/dl and ≥9.5 mg/dl were associated with increased risk of functional graft failure and increased risk of all-cause and cardiovascular deaths, respectively, when compared with 3.5 to <5.5 mg/dl. Additional studies are needed to examine whether more aggressive control of pretransplant serum phosphorus may improve posttransplant outcomes.


Introduction
Serum levels of phosphorus are associated with mortality (1,2), cardiovascular disease (CVD) (3), and renal function loss in chronic kidney disease (CKD) patients (4–6). Both low and high serum phosphorus levels are associated with an increased risk of death (7,8), whereas risks of a cardiovascular event and kidney dysfunction increase linearly with serum phosphorus levels (4,7). In CKD patients on dialysis (dialysis-CKD), phosphorus levels over 6.5 to 7.0 mg/dl are significantly associated with increased mortality (1,9,10), and therapeutic guidelines recommend maintaining serum phosphorus in the 3.5 to 5.5 mg/dl range (11). Despite this, 50 to 60% of the U.S. dialysis-CKD patients who are potential kidney transplant candidates have serum phosphorus over 5.5 mg/dl.

The reasons for an inferior survival among low and high phosphorus dialysis-CKD patients are different. Hypophosphatemia, in the majority of the cases, is a marker of a poor nutritional status, whereas hyperphosphatemia can induce vascular calcification. High phosphorus levels can stimulate differentiation of vascular smooth muscle cells into osteoblastic-like cells, with bone matrix production and mineralization (12,13). As a consequence of stiffer arteries, pulse wave velocity, arterial sheer stress, and cardiac output resistance increase and may cause vascular intima damage and left ventricular hypertrophy (14–16). Coronary artery calcification may also contribute to coronary insufficiency and myocardial ischemia (17). Therefore, hyperphosphatemia is considered a non-traditional risk factor for CVD in CKD patients, and for many kidney recipients vascular disease is an undesired heritage from the dialysis period (18,19).

Increased phosphorus wasting and hypophosphatemia are described in the posttransplant period (20,21). In native kidneys phosphaturia can cause calcium-phosphorus deposition in the tubules, which may trigger a local inflammatory response and lead to tubular obstruction, and ultimately to kidney failure (22). These mechanisms may be reproducible in the renal allograft and may contribute to graft dysfunction (23).

The effect of pretransplant recipients’ serum phosphorus level on transplant outcomes is un-
clear; however, a recent study showed in living kidney
donor transplants that a higher donor phosphorus level
was an independent risk factor for early allograft dys-
function (24). We sought to examine the association of
pretransplant serum phosphorus levels with all-cause
and CVD mortality, graft failure, and delayed graft func-
tion (DGF) in a U.S.-based renal transplant population
and we hypothesized that higher phosphorus levels are in-
crementally associated with poor graft and patient outcomes.

Materials and Methods

Patients

We linked data on all kidney transplant recipients listed
in the Scientific Registry of Transplant Recipients (SRTR)
up to June 2007 to a list of individuals with CKD who
underwent maintenance hemodialysis treatment from July
2001 to June 2006 in one of the outpatient dialysis facilities
of a U.S.-based large dialysis organization (DaVita Inc.,
before its acquisition of former Gambro dialysis facilities)
using patients' social security numbers. The study was
approved by the Institutional Review Boards of both Los
Angeles Biomedical Research Institute at Harbor-UCLA
and DaVita Clinical Research.

Clinical and Demographic Measures

The creation of the national DaVita dialysis patient co-
hort has been described previously (25–31). To minimize
measurement variability, all repeated measures for each
patient during any given calendar quarter (i.e., over a
13-week interval) were averaged and the summary esti-
mate was used in all models. Average values were ob-
tained from up to 20 calendar quarters (q1 through q20) for
each laboratory and clinical measure for each patient for
up to 6 years of follow-up. The first (baseline) studied
quarter for each patient was the calendar quarter in which
the patient’s dialysis vintage was >90 days. Demographic
data and details of medical history were collected, with
information on age, gender, race, type of insurance, marital
status, presence of diabetes, height, posthemodialysis dry
weight (to calculate averaged body mass index [BMI]), and
dialysis vintage. Dialysis vintage was defined as the dura-
tion of time between the first day of dialysis treatment and
the day of kidney transplantation.

Laboratory Measures

Blood samples were drawn using uniform techniques in
all of the DaVita dialysis clinics and were transported to
the DaVita Laboratory in Deland, Florida, typically within
24 hours. All laboratory values were measured by auto-
mated and standardized methods in the DaVita Labora-
tory. Most laboratory values were measured monthly,
including serum urea, creatinine, albumin, calcium,
phosphorus, bicarbonate, and total iron binding capacity
(TIBC). Serum ferritin and intact parathyroid hormone
(PTH) were measured at least quarterly. Hemoglobin
was measured at least monthly in essentially all patients
and weekly to biweekly in most patients. Most blood
samples were collected predialysis with the exception of
postdialysis serum urea nitrogen to calculate urea kinet-
ics. Kt/V (single pool) was calculated using urea kinetic
modeling equations as described elsewhere (27). To ex-
amine the “dose-response” association between pretrans-
plant serum phosphorus categories and outcomes risk, we
divided patients into five a priori defined categories based
on pretransplant serum phosphorus level: <3.5, 3.5 to
<5.5, 5.5 to <7.5, 7.5 to <9.5, and ≥9.5 mg/dl values.

Statistical Analyses

Data were summarized using proportions, means
(±SD). We examined P values for trends across pretrans-
plant serum phosphorus categories. Time-to-event sur-
vival analyses were done to determine association of se-
rum phosphorus with all-cause and cardiovascular
mortality and graft failure (defined as reintinitiation of
dialysis treatment or retransplantation). For delayed graft
function (DGF), defined as the need for any dialysis ther-
apy in the first week after transplantation (32), time to
event was not accounted for. Survival analyses to calculate
hazard ratios (HRs) and 95% confidence intervals (95%
CIs) of death or graft failure employed Cox proportional
hazards regression. In mortality analyses patients were
followed until event (death) or censoring (graft failure or
end of follow-up period), whichever happened first. In
graft failure analyses patients were followed until event
(graft failure) or censoring (death or end of follow-up
period), whichever happened first. In the combined out-
come analyses patients were followed until event (death or
graft failure) or censoring (end of follow-up period),
whichever happened first. Proportional hazard assump-
tion was tested using log(–log) against survival plots.

For each regression analysis, four levels of multivariate
adjustment were examined: (1) an unadjusted model that
included pretransplant serum phosphorus categories (3.5
to <5.5 mg/dl as reference) as the predictor; (2) case-mix
adjusted models that included the above plus age, gender,
recipient race-ethnicity (African Americans and other self-
categorized blacks, non-Hispanic whites, Asians, Hispan-
ics, and others), diabetes mellitus, dialysis vintage (<6
months, 6 months to 2 years, 2 to <5 years, and ≥5 years),
primary insurance (Medicare, Medicaid, private, and oth-
ers), marital status (married, single, divorced, widowed,
and other or unknown), standardized mortality ratio of the
dialysis clinic during entry quarter, dialysis dose as indi-
cated by Kt/V (single pool), presence or absence of a
hemodialysis catheter, and residual renal function during
the entry quarter and eight comorbidities (atherosclerotic
heart disease, congestive heart failure, cancer, chronic ob-
structive pulmonary disease, CVD, hypertension, periph-
eral vascular disease, and tobacco use); (3) malnutrition-
inflammation-complex syndrome (MICS) adjusted models
which included all of the above covariates plus nine sur-
rogates of nutritional status and inflammation measured
during the last calendar quarter before transplantation in-
cluding BMI and eight laboratory variables (i.e., normal-
ized PCR [nPCR] as an indicator of daily protein intake,
also known as the normalized protein nitrogen appearance
[nPNA]) [33], and serum or blood concentrations of TIBC,
ferritin, calcium, bicarbonate, peripheral white blood cell
count, lymphocyte percentage, and albumin); and (4) case-
mix, MICS, and transplant data adjusted models included

all of the above plus eight transplant-related variables: (1) donor type (deceased or living), (2) donor age, (3) donor gender, (4) panel reactive antibody (PRA) titer (last value before transplant), (5) number of HLA mismatches, (6) cold ischemia time, (7) DGF (except when DGF was a dependent variable in logistic regression models), and (8) extended donor criteria using standard definition (donor history of hypertension and/or serum creatinine of donor >1.5 mg/dl and/or cause of death in donor is cerebrovascular event). All analyses were carried out with SAS version 9.1 (SAS Institute Inc., Cary, NC) and STATA version 11.1 (STATA Corporation, College Station, TX).

Results

The original 5-year (July 2001 through June 2006) national database of all DaVita patients included 164,789 adult patients. Out of 65,386 DaVita patients who were identified in the SRTR database, 17,629 had undergone one kidney transplantation during their lifetime, but only 14,508 dialysis patients had undergone kidney transplantation for the first time. From these 14,508 dialyzed patients we excluded patients on chronic peritoneal dialysis (n = 2092) and patients who did not have serum phosphorus measurements (n = 3032). The analytic cohort consisted of the remaining 9384 patients who underwent first kidney transplantation during the observation period and who were followed until death, graft failure, loss of follow-up, or survival until June 30, 2007 (Supplemental Figure S1). There were 737 deaths (7.9%) and 811 graft failures (8.6%) irrespective of subsequent deaths. The median cohort time was 803 days (interquartile range was 384 to 1330 days). The basic characteristics of waitlisted, but nontransplanted, patients have been described elsewhere (34). Tables 1 and 2 show the clinical, demographic, and laboratory data of the 9384 transplanted patients across five pretransplant serum phosphorus categories.

The crude all-cause mortality rate was 32.3/1000 patient-years (95% CI: 30.1 to 34.8). The associations of pretransplant phosphorus categories with the posttransplant risk of death, cardiovascular death, graft failure, or the composite of graft failure or death and delayed graft function are shown in Table 3. Compared with recipients with pretransplant phosphorus 3.5 to <5.5 mg/dl, recipients with pretransplant phosphorus of <3.5 and ≥9.5 mg/dl phosphorus had 66% (HR: 1.66, 95% CI: 1.18 to 2.33) and 32% (HR: 1.32, 95% CI: 0.85 to 2.03) higher all-cause mortality; and recipients with pretransplant phosphorus of 7.5 to <9.5 had 27% (HR: 0.73, 95% CI: 0.57 to 0.93) lower unadjusted death risk. After additional adjustment for case-mix and MICS and transplant-related variables, recipients with pretransplant phosphorus of ≥9.5 mg/dl phosphorus had 2.4-fold (HR: 2.44, 95% CI: 1.28 to 4.65) higher death risk compared with recipients with pretransplant phosphorus 3.5 to <5.5 mg/dl (Table 3A). Figures 1, 2, 3, and 4 show the cubic spline models for the association of the entire range of pretransplant serum phosphorus level with posttransplant outcomes. The association of pretransplant serum phosphorus level (Figure 1) with all-cause mortality was U-shaped; both very low and very high phosphorus levels were associated with higher mortality risk. However, in the low range the association was not statistically significant. A similar association pattern was found for cardiovascular death (Figure 2). After adjustment for case-mix and MICS and transplant-related variables recipients with pretransplant phosphorus levels of ≥9.5 mg/dl had 3.6-fold (HR: 3.63, 95% CI: 1.13 to 11.64) higher cardiovascular death risk compared with recipients with pretransplant phosphorus 3.5 to <5.5 mg/dl (Table 3B).

The crude graft loss rate was 35.6/1000 patient-years (95% CI: 33.2 to 38.1). Pretransplant phosphorus levels and graft loss risk (Figure 3) became more closely associated starting at the level of 5 mg/dl and continuing up to extremely high levels. In our fully adjusted model, recipients with pretransplant phosphorus levels of 7.5 to >9.5 and ≥9.5 mg/dl phosphorus had 1.4-fold (HR: 1.42, 95% CI: 1.04 to 1.95) and 2.4-fold (HR: 2.36, 95% CI: 1.33 to 4.17) higher risk of graft loss compared with recipients with pretransplant phosphorus 3.5 to <5.5 mg/dl (Table 3C).

The association of pretransplant serum phosphorus level (Figure 4) with the combined outcome was U-shaped. Both very low and very high phosphorus levels were associated with higher mortality risk; however, in the low range the association was not statistically significant.

We did not find significant associations between pretransplant phosphorus level and delayed graft function (Table 3E).

Discussion

In this retrospective analysis of 9384 primary kidney transplant recipients we describe an association between pretransplant serum phosphorus levels higher than 7.5 and 9.5 mg/dl with an increased risk of death-censored graft failure and death, respectively.

Our findings are noteworthy for a number of reasons. First, the association of phosphorus levels with all-cause mortality and with cardiovascular mortality was not entirely comparable to findings in dialysis-CKD patients. Pretransplant serum phosphorus was only significantly associated with mortality in renal transplant recipients at very high levels (>9.5 mg/dl), whereas in dialysis-CKD patients this association has been demonstrated at relatively lower phosphorus levels (>6.5 or 7.0 mg/dl) (1,10). This difference may in part be explained by the transplant selection process. Only the healthiest recipients among those with multiple dialysis-related complications, including severe hyperphosphatemia are eligible to receive a transplant. As an example, in our study, recipients in the 7.5 to <9.5 and >9.5 group were younger and had fewer cases of diabetes mellitus, and fewer pretransplant comorbidities when compared with the other groups. Moreover, the higher phosphorus levels in our population may represent a better nutritional status. When comparing baseline characteristics, those in the 7.5 to <9.5 and >9.5 mg/dl group had higher BMI (with fewer recipients with diabetes mellitus), higher nPCR, higher creatinine, and similar serum albumin compared with the other groups. These characteristics may have attenuated the association of moderately increased phosphorus levels with mortality.

Hyperphosphatemia (<3.5 mg/dl) was associated with mortality in the unadjusted and case-mix models, but not in the fully adjusted model (case-mix, MICS, and trans-
have been identified. Therefore, it is hard to assume that outcomes of fewer recipients, which could result in loss of plant characteristics). However, this last model examined outcomes of fewer recipients, which could result in loss of statistical power, and hence small associations may not have been identified. Therefore, it is hard to assume that phosphorus <3.5 mg/dl is not associated with mortality based only on the fully adjusted model results, as cubic spline curves showed a crescent risk of death with decrease of phosphorus to this level. However, in this low range the association was not statistically significant. This particular group of recipients should be further analyzed.

A second noteworthy finding was the association of phosphorus levels >7.5 mg/dl with death censored graft failure, while not showing associations with mortality. It seems that relatively lower levels of pretransplant phosphorus may be more closely associated with graft function than with survival. In the majority of kidney transplant recipients both serum phosphorus and PTH are expected to normalize after transplant, abrogating the effect of phosphorus as a vascular toxin. This does not immediately correct pre-established vascular lesions, although some cal-

Table 1. Baseline characteristics of 9384 dialysis patients who underwent renal transplantation between July 2001 and June 2006

<table>
<thead>
<tr>
<th>Pretransplant Serum Phosphorus Level (mg/dl)</th>
<th>&lt;3.5</th>
<th>3.5 to &lt;5.5</th>
<th>5.5 to &lt;7.5</th>
<th>7.5 to &lt;9.5</th>
<th>≥9.5</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53 ± 14</td>
<td>51 ± 13</td>
<td>47 ± 13</td>
<td>42 ± 13</td>
<td>37 ± 12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender (% women)</td>
<td>34</td>
<td>40</td>
<td>36</td>
<td>35</td>
<td>37</td>
<td>0.003</td>
</tr>
<tr>
<td>Race (% African American)</td>
<td>32</td>
<td>28</td>
<td>28</td>
<td>24</td>
<td>16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>35</td>
<td>39</td>
<td>35</td>
<td>30</td>
<td>22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.3 ± 5.3</td>
<td>26.2 ± 5.8</td>
<td>26.8 ± 5.8</td>
<td>27.0 ± 5.7</td>
<td>27.0 ± 6.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence of ischemic heart disease (%)</td>
<td>12</td>
<td>10</td>
<td>8</td>
<td>6</td>
<td>7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence of congestive heart failure (%)</td>
<td>14</td>
<td>10</td>
<td>10</td>
<td>9</td>
<td>8</td>
<td>0.02</td>
</tr>
<tr>
<td>Presence of hypertension (%)</td>
<td>76</td>
<td>77</td>
<td>77</td>
<td>74</td>
<td>71</td>
<td>0.03</td>
</tr>
<tr>
<td>Presence of cerebrovascular events (%)</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0.005</td>
</tr>
<tr>
<td>Presence of peripheral vascular disease (%)</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>0.002</td>
</tr>
<tr>
<td>Presence of chronic obstructive pulmonary disease (%)</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0.10</td>
</tr>
<tr>
<td>Presence of cancer (%)</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>0.05</td>
</tr>
<tr>
<td>Tobacco use (%)</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>0.01</td>
</tr>
<tr>
<td>Dialysis vintage (%)</td>
<td>0 to 6 months</td>
<td>9</td>
<td>11</td>
<td>12</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>6 to 24 months</td>
<td>25</td>
<td>29</td>
<td>26</td>
<td>23</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>2 to 5 years</td>
<td>33</td>
<td>37</td>
<td>36</td>
<td>39</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>&gt;5 years</td>
<td>32</td>
<td>22</td>
<td>25</td>
<td>28</td>
<td>25</td>
</tr>
<tr>
<td>Kt/V</td>
<td>1.71 ± 0.38</td>
<td>1.65 ± 0.36</td>
<td>1.59 ± 0.35</td>
<td>1.53 ± 0.33</td>
<td>1.46 ± 0.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>nPCR (g/kg per day)</td>
<td>0.98 ± 0.29</td>
<td>1.01 ± 0.26</td>
<td>1.06 ± 0.25</td>
<td>1.12 ± 0.25</td>
<td>1.15 ± 0.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>8.9 ± 3.5</td>
<td>9.6 ± 3.1</td>
<td>10.9 ± 3.0</td>
<td>12.1 ± 3.0</td>
<td>12.9 ± 3.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum albumin (mg/dl)</td>
<td>3.9 ± 0.5</td>
<td>4.0 ± 0.4</td>
<td>4.0 ± 0.4</td>
<td>4.0 ± 0.4</td>
<td>4.0 ± 0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum calcium (mg/dl)</td>
<td>19.4 ± 0.7</td>
<td>19.5 ± 0.7</td>
<td>19.5 ± 0.8</td>
<td>19.3 ± 0.9</td>
<td>9.0 ± 0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood hemoglobin (g/dl)</td>
<td>11.8 ± 1.5</td>
<td>12.1 ± 1.3</td>
<td>12.2 ± 1.3</td>
<td>12.3 ± 1.3</td>
<td>12.3 ± 1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>iPTH (pg/ml)</td>
<td>293 ± 277</td>
<td>305 ± 314</td>
<td>411 ± 394</td>
<td>552 ± 549</td>
<td>425 ± 303</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WBC (× 10³/L)</td>
<td>6.9 ± 2.3</td>
<td>6.8 ± 2.1</td>
<td>6.8 ± 2.0</td>
<td>7.2 ± 2.1</td>
<td>7.5 ± 2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of HLA mismatch</td>
<td>3.9 ± 1.8</td>
<td>3.6 ± 1.9</td>
<td>3.6 ± 1.8</td>
<td>3.5 ± 1.8</td>
<td>3.2 ± 1.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Number of HLA-DR mismatch</td>
<td>1.16 ± 0.74</td>
<td>1.06 ± 0.74</td>
<td>1.06 ± 0.74</td>
<td>1.07 ± 0.74</td>
<td>0.96 ± 0.71</td>
<td>0.14</td>
</tr>
<tr>
<td>PRA (%)</td>
<td>10 ± 24</td>
<td>9 ± 22</td>
<td>10 ± 24</td>
<td>12 ± 27</td>
<td>13 ± 28</td>
<td>0.01</td>
</tr>
<tr>
<td>PRA &gt;20% (%)</td>
<td>14</td>
<td>13</td>
<td>14</td>
<td>18</td>
<td>17</td>
<td>0.002</td>
</tr>
<tr>
<td>Donor age (years)</td>
<td>39 ± 15</td>
<td>40 ± 15</td>
<td>39 ± 15</td>
<td>37 ± 15</td>
<td>38 ± 13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Donor gender (% women)</td>
<td>49</td>
<td>46</td>
<td>48</td>
<td>47</td>
<td>51</td>
<td>0.30</td>
</tr>
<tr>
<td>Donor type (% living)</td>
<td>26</td>
<td>32</td>
<td>34</td>
<td>34</td>
<td>47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EDC kidney (%)a</td>
<td>23</td>
<td>21</td>
<td>18</td>
<td>14</td>
<td>9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cold ischemia time (hours)a</td>
<td>17.8 ± 8.3</td>
<td>18.1 ± 8.3</td>
<td>17.9 ± 8.3</td>
<td>17.6 ± 7.7</td>
<td>17.6 ± 8.3</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Data are presented mean ± SD. N/A, not applicable. BMI, body mass index; nPCR, normalized protein catabolic rate; iPTH, intact parathyroid hormone; WBC, white blood cell count; RA, panel reactive antibody (last value prior to transplant). EDC, extended donor criteria.

*aIn recipients who received a kidney from deceased donors.
Table 2. Posttransplant outcomes of 9384 dialysis patients who underwent renal transplantation between July 2001 and June 2006

<table>
<thead>
<tr>
<th>Pretransplant Serum Phosphorus (mg/dl)</th>
<th>&lt;3.5</th>
<th>3.5 to &lt;5.5</th>
<th>5.5 to &lt;7.5</th>
<th>7.5 to &lt;9.5</th>
<th>≥9.5</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude all-cause mortality rate (/1000 patient-years) [95% CI]</td>
<td>57.5 [41.7 to 79.4]</td>
<td>34.9 [31.2 to 39.0]</td>
<td>30.1 [26.9 to 33.8]</td>
<td>25.0 [20.1 to 31.1]</td>
<td>46.1 [30.4 to 70.0]</td>
<td>N/A</td>
</tr>
<tr>
<td>Crude CV mortality rate (/1000 patient-years) [95% CI]</td>
<td>18.6 [10.6 to 32.8]</td>
<td>79 [6.2 to 10.0]</td>
<td>7.6 [6.1 to 9.6]</td>
<td>7.1 [4.7 to 10.7]</td>
<td>16.8 [8.4 to 33.5]</td>
<td>N/A</td>
</tr>
<tr>
<td>Crude graft failure rate (/1000 patient-years) [95% CI]</td>
<td>43.5 [30.0 to 63.0]</td>
<td>329 [29.3 to 36.9]</td>
<td>33.4 [30.0 to 37.3]</td>
<td>42.3 [35.8 to 50.4]</td>
<td>71.2 [50.9 to 99.7]</td>
<td>N/A</td>
</tr>
<tr>
<td>History of acute rejection (%)</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>7</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Values in brackets indicate the crude death and cardiovascular death rate, crude graft failure rate, and crude DGF rate in the indicated group during the 6 years of observation. Abbreviations: CI, confidence interval; CV, cardiovascular; DGF, delayed graft function.
cificed lesions may be gradually reabsorbed after successful transplantation (35). As a result, it is possible that the mortality risk in those with moderate increases in serum phosphorus (>7.5 to 9.0 mg/dl) may be reduced after transplant. Elevated pretransplant phosphorus levels may represent the presence of large phosphorus reserves in the bones, which will usually be mobilized after transplantation. Increased renal phosphorus wasting with associated hypophosphatemia is often observed after transplantation (21). This is related to side effects of immunosuppressive drugs (calcineurin inhibitors [36], sirolimus [37], and steroids [20]) and to increased levels of PTH and fibroblast growth factor 23 (FGF-23) that persist at least in the first few months after transplantation (38). The presence of

### Table 3. Hazard ratio (95% confidence intervals) of posttransplant death (all-cause or cardiovascular) or graft failure or delayed graft function comparing pretransplant serum phosphorus categories (3.5 to <5.5 mg/dl the reference) using Cox regression and logistic regression analyses in 9384 dialysis patients who underwent renal transplantation and were observed for up to 6 years (July 2001 through June 2007)

<table>
<thead>
<tr>
<th>Pretransplant Serum Phosphorus Level (mg/dl)</th>
<th>Unadjusted (n = 9384)</th>
<th>+Case-mix Adjusteda (n = 8469)</th>
<th>+MICS Adjustedb (n = 8073)</th>
<th>+Transplant Data Adjustedc (n = 4830)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>A. Graft failure censored all-cause death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3.5</td>
<td>1.00</td>
<td>N/A</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>3.5 to &lt;5.5</td>
<td>0.98 (0.70 to 1.36)</td>
<td>0.89</td>
<td>1.00 (0.71 to 1.42)</td>
<td>0.81</td>
</tr>
<tr>
<td>5.5 to &lt;7.5</td>
<td>0.93 (0.58 to 1.49)</td>
<td>0.75</td>
<td>1.04 (0.67 to 1.48)</td>
<td>0.79</td>
</tr>
<tr>
<td>≥9.5</td>
<td>2.12 (1.02 to 4.41)</td>
<td>0.04</td>
<td>2.66 (1.18 to 6.01)</td>
<td>0.03</td>
</tr>
<tr>
<td>B. Graft failure censored cardiovascular death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3.5</td>
<td>2.39 (1.30 to 4.42)</td>
<td>0.005</td>
<td>2.40 (1.22 to 4.71)</td>
<td>0.01</td>
</tr>
<tr>
<td>3.5 to &lt;5.5</td>
<td>1.00</td>
<td>N/A</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>5.5 to &lt;7.5</td>
<td>0.98 (0.70 to 1.36)</td>
<td>0.89</td>
<td>1.00 (0.71 to 1.42)</td>
<td>0.81</td>
</tr>
<tr>
<td>7.5 to &lt;9.5</td>
<td>0.93 (0.58 to 1.49)</td>
<td>0.75</td>
<td>1.04 (0.67 to 1.48)</td>
<td>0.79</td>
</tr>
<tr>
<td>≥9.5</td>
<td>2.12 (1.02 to 4.41)</td>
<td>0.04</td>
<td>2.66 (1.18 to 6.01)</td>
<td>0.03</td>
</tr>
<tr>
<td>C. All-cause death censored graft failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3.5</td>
<td>1.33 (0.90 to 1.96)</td>
<td>0.15</td>
<td>1.19 (0.77 to 1.84)</td>
<td>0.45</td>
</tr>
<tr>
<td>3.5 to &lt;5.5</td>
<td>1.02 (0.87 to 1.20)</td>
<td>0.79</td>
<td>0.94 (0.79 to 1.11)</td>
<td>0.46</td>
</tr>
<tr>
<td>5.5 to &lt;7.5</td>
<td>1.32 (1.07 to 1.61)</td>
<td>0.01</td>
<td>1.10 (0.88 to 1.37)</td>
<td>0.43</td>
</tr>
<tr>
<td>≥9.5</td>
<td>2.16 (1.51 to 3.08)</td>
<td>&lt;0.001</td>
<td>2.06 (1.42 to 2.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>D. Combined all-cause death or graft failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3.5</td>
<td>1.46 (1.11 to 1.92)</td>
<td>0.01</td>
<td>1.42 (1.05 to 1.93)</td>
<td>0.02</td>
</tr>
<tr>
<td>3.5 to &lt;5.5</td>
<td>0.95 (0.84 to 1.07)</td>
<td>0.42</td>
<td>0.94 (0.83 to 1.07)</td>
<td>0.35</td>
</tr>
<tr>
<td>5.5 to &lt;7.5</td>
<td>1.04 (0.89 to 1.23)</td>
<td>0.61</td>
<td>1.03 (0.86 to 1.23)</td>
<td>0.77</td>
</tr>
<tr>
<td>≥9.5</td>
<td>1.71 (1.28 to 2.29)</td>
<td>&lt;0.001</td>
<td>2.08 (1.52 to 2.83)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Unadjusted (n = 8924)</th>
<th>+Case-mix Adjusteda (n = 8069)</th>
<th>+MICS Adjustedb (n = 7692)</th>
<th>+Transplant Data Adjustedc (n = 4830)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR (95% CI)</td>
<td>P</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>≥3.5</td>
<td>1.05 (0.77 to 1.43)</td>
<td>0.76</td>
<td>0.85 (0.59 to 1.21)</td>
</tr>
<tr>
<td>3.5 to &lt;5.5</td>
<td>1.00 (N/A)</td>
<td>1.00</td>
<td>0.85 (0.59 to 1.23)</td>
</tr>
<tr>
<td>5.5 to &lt;7.5</td>
<td>1.04 (0.92 to 1.16)</td>
<td>0.55</td>
<td>1.06 (0.93 to 1.19)</td>
</tr>
<tr>
<td>≥9.5</td>
<td>1.15 (0.98 to 1.35)</td>
<td>0.09</td>
<td>1.21 (1.01 to 1.44)</td>
</tr>
<tr>
<td></td>
<td>0.73 (0.69 to 1.42)</td>
<td>0.95</td>
<td>1.23 (0.83 to 1.82)</td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; CI, confidence interval; N/A, not applicable; OR, odds ratio.

*a*Adjusted for age, gender, recipient race-ethnicity, diabetes mellitus, dialysis vintage, primary insurance, marital status, standardized mortality ratio of the dialysis clinic during entry quarter, dialysis dose as indicated by Kt/V (single pool), presence or absence of a hemodialysis catheter, and residual renal function during the entry quarter and eight comorbidities.

*b*Adjusted for all of the covariates plus body mass index, normalized protein nitrogen appearance, serum or blood concentrations of total iron binding capacity, ferritin, calcium, bicarbonate, peripheral white blood cell count, lymphocyte percentage, and albumin.

*c*Adjusted for all of the above plus donor type, donor age, donor gender, panel reactive antibody titer (last value prior to transplant), number of HLA mismatches, cold ischemia time, delayed graft function (except when delayed graft function was a dependent variable in our logistic regression models), and extended donor criteria.
higher phosphorus concentrations in the tubules may lead to deposition of calcium-phosphorus crystals in the tubular epithelium, and contribute to the risk of graft failure (23). Molecules that facilitate crystal adhesion may be expressed in transplant tubular cells (22), which may potentiate crystal deposition in the allograft. The crystal deposition may create a focus of inflammation that may progress to fibrosis and nephron loss (39). Calcium oxalate, uric acid, and to a lesser extent calcium-phosphorus crystals increase production of monocyte-chemoattractant protein-1 and many other profibrotic and proinflammatory pathways (39,40). Therefore, a plausible hypothesis is that crystal deposition may contribute to graft loss either by triggering rejection episodes or by facilitating fibrosis.

The mechanism of increased graft loss in recipients with higher pretransplant phosphorus seems not to involve delayed graft function. In our population associations with DGF could be mitigated by the higher frequency of living donor recipients and we did not find a significant association (data not shown).

Two previous studies examined the relationship of pretransplant abnormalities in serum phosphorus, calcium, and PTH levels with transplant outcomes. Roodnat et al. (41) reported an association of elevated PTH but not phosphorus with increased graft failure, and Calabia et al. (42) showed that pretransplant calcium, PTH, and phosphorus levels were not associated with DGF. Other studies reported associations of serum phosphorus concentration during the transplant follow-up period with outcomes. Schaeffner et al. (43) reported that higher phosphorus or calcium-phosphorus product levels during the transplant follow-up period were associated with increased risk of graft dysfunction. Connolly et al. (44) and Stevens et al. (45) showed that posttransplant hyperphosphatemia was associated with increased mortality. Interestingly, in pediatric and adult populations, elevated FGF-23 levels during the transplant follow-up period were associated with increased risk for deterioration of kidney function and mortality, more so than phosphorus or PTH levels (46,47). Also, in pediatric recipients increased FGF-23 was associated with a higher number of rejection episodes (46).

Our study has several limitations related to its retrospective nature. Data on induction and maintenance immunosuppression, cardiovascular medications (statins, β-blockers, etc.), and coronary artery calcification were not available. Pretransplant use of phosphorus binders and other dietary treatments (48–51), vitamin D analogs, or calcimimetics was not taken into consideration, and it is
Conclusions

Individuals with pretransplant phosphorus levels >7.5 mg/dl have increased risk of functional graft failure across the entire range of pretransplant serum phosphorus levels and those with levels over 9.5 mg/dl are also at increased risk for all-cause and cardiovascular mortality. Recommendations to keep phosphorus levels below 3.5 and 5.5 mg/dl during the dialysis period are important not only to reduce dialysis-related mortality but also possibly for the success of kidney transplantation.

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Disclosures

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M.S.S. and M.Z.M. contributed equally to this work.

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