Interaction of Serum Phosphate with Age as Predictors of Cardiovascular Risk Scores in Stable Renal Transplant Recipients

Jillian Kerry¹ Holly Mansell, PharmD² Hamdi Elmoselhi³ Mike Moser, FRCS (C)^{1,3}
Ahmed Shoker, MD, FRCP(C)³

¹ College of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

² College of Pharmacy and and Nutrition, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

³ Saskatchewan Transplant Program, Saskatoon Health Region, Saskatoon, Saskatchewan, Canada

Address for correspondence Ahmed Shoker, MD, FRCP(C), Saskatoon Transplant Program, Saskatchewan Health Region, 1702 20th Street West, Saskatoon, SK S7M 0Z9, Canada
(e-mail: ahmed.shoker@usask.ca).

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Abstract

Keywords

- renal function
- cardiovascular risk factors
- cardiovascular disease
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- cardiovascular risk calculator for renal transplant recipients
- phosphorous

We calculated rate of changes in the cardiovascular risk calculator for renal transplant recipients (CRCRTR) major adverse cardiac events (MACE) in clinically stable renal transplant recipients (RTRs) to identify covariables that associate with fast cardiovascular (CV) risk progression. CRCRTR-MACE scores were calculated on 139 patients in 2011 and 2014. Score changes above and below median changes in scores were labeled fast or slow CV risk progression. Multivariate analysis (MVA) was performed to identify variables significant to percentage changes in scores. Receiver-operating characteristic (ROC) analysis was performed to define sensitivity and specificity of factors significant to fast score progression. Follow-up was 2.61 (2.02–4.47) years. Slow and fast progressions were present in 50.4 and 49.6% of patients, with a median change of 25.8% (– 92.1 to 1,444.7%). MVA showed percentage changes in age and serum phosphate were the only significant variables impacting fast progression in scores. ROC showed 2011 serum phosphate of 1.15 mmol/L to predict fast progression (area under the curve [AUC] of 0.628, $p > 0.0126$). Age older than 45 years combined with 2011 serum phosphate above 1.15 mmol/L had a significant AUC of 0.781, $p < 0.0010$ interleukin (IL)-1A and IL-28A were significant associates with serum phosphate above 1.1 mmol/L in the MVA. Changes in CV risk in RTR over time are highly variable. Serum phosphate, even within upper normal levels, predicts worsening of CV risk scores in stable RTR.

Cardiovascular (CV) disease (CVD) remains the leading cause of death in renal transplant recipients (RTR).^{1–3} As such, predicting the risk of developing a CV event (CVE) and understanding the relationship to individual risk factors remain highly relevant in this population. The cardiovascular risk calculator for renal transplant recipients (CRCRTR) major adverse cardiac events (MACE) was developed by Soveri et al⁴ to predict a 7-year risk of developing a CVE. In addition to including the traditional risk variables (diabetes mellitus [DM], low-density lipoprotein cholesterol, current or previ-

ous smoking, and coronary heart disease), this equation also includes creatinine (accounting for renal function), as well as the number of transplants.

In 2011, we identified CV risk factors in stable RTR and calculated predicted risk according to the Framingham risk score⁵ and the recently developed CRCRTR-MACE.⁴ We observed significant inter- and intraindividual variations in scores. This observation raised the question whether over time changes in risk scores vary significantly among patients, and if true, how can we identify patients at risk of fast

progression in CVD burden. With this in mind, the objective of this study was to search for CV risk factors in the same population almost 3 years later. We were particularly interested in examining the delta changes in risk scores over time, and identifying which variables contribute to either improvements or deterioration in CV risk and renal function.

Methods

Patients

The regional ethics board approved the protocol for this single-center retrospective cross-sectional study. CRCRTR-MACE scores were calculated from a dataset of 150 RTR followed by one transplant nephrologist, in Saskatoon in 2011. Of the original cohort of 150, 11 patients in total were excluded (7 because of allograft failure, while 4 moved from the province). The remaining 139 were available for the follow-up analysis at a planned set time for July 2014. These were stable patients who attended the transplant outpatient clinic between January 2011 and July 2014. Every 2 to 3 months, a medical history and physical examination was performed and documented by the transplant nephrologist at the clinic.

Clinical Evaluations

Demographics (age, height, weight, sex, and race), medical history (diabetes, CVD and CVEs, and causes of kidney failure), family history (premature CVD), smoking history, and immunosuppressive medications were recorded. Assessment of CV history was determined using the 2012 Canadian Cardiovascular guidelines.⁶ DM was defined as an elevated glycated hemoglobin $\geq 6.5\%$, or the use of oral hypoglycemic medications or insulin. Additional variables recorded include cholesterol, electrolytes (calcium, phosphate, and magnesium), blood pressure, creatinine, urea, albumin, parathyroid hormone, microalbuminuria, vitamin D level, hemoglobin, left ventricular ejective fraction (LVEF), and mode of dialysis pretransplant. A cutoff of $< 55\%$ for normal LVEF was measured using echocardiography. Estimated glomerular filtration rate (eGFR) was calculated according to the CKD-EPI (Chronic Kidney Disease-Epidemiology Collaboration) equation. The CRCRTR-MACE equation⁴ was used to calculate the 7-year probability of developing a CVE.

Patients were arbitrarily stratified according to CV risk: low risk ($< 10\%$), moderate risk ($10\text{--}19\%$), and high risk ($\geq 20\%$). On the contrary, we defined patients with fast progression in CVD risk as those who have a percentage change in CRCRTR-MACE score above the median change and those with percentage change below the median change as slow progressors.

Statistical Analysis

Data were collected and analyzed using SPSS version 22 (IBM Corp., Armonk, NY). Interval changes in demographics and biochemical values were presented in two ways: First, the 2011 values were subtracted from the 2014 values for each person and second the percentage change was calculated

from the simple equation: $2014 \text{ value} - 2011 \text{ value} \times 100$ divided by the 2011 value.

Normally distributed data were presented as mean $\pm$ standard deviation (SD) and nonnormalized data as median (minimum – maximum). Mann–Whitney *U*-test was used to test differences in group medians and Student *t*-test for group means. The McNemar test was used to compare patients on specific medications, covariables. Simple regression analysis was used to test correlation between percentage changes in CV risk scores and eGFR.

In addition, a detailed analysis of potential CV risk covariables was undertaken to determine factors that may contribute to improved or worsened CV risk scores. Multivariate analysis (MVA) after an initial univariate analysis (UVA) was performed incorporating many covariables presented in ►Table 1, while including the percentage change in over time score above or below the median change in total score as the exposure variable, in the MVA binary model. Patients with a percentage change above the mean or median change in score were referred to as fast progressors, while patients with a percentage change below the average or median change were labeled slow progressors. Receiver-operating curve (ROC) was performed to define sensitivity and specificity of significant factors to contributing to CRCRTR-MACE scores $\geq 20\%$.

Results

Descriptive Statistics

The total patient population eligible for analysis was 139, out of the original cohort of 150 RTR. Three patients passed away: two from CVEs with elevated phosphorus above 1.34 mmol/L and one from endocarditis. This equated to mortality rate of 1.3 patients/year. Seven patients returned to dialysis, equating to transplant failure rate of two patients/year. ►Table 1 shows the main patient characteristics.

Delta Changes in Cardiovascular Risk Variables

As expected there was a significant increase in patient age, the number of patients older than 60 years, and the transplant duration (►Table 1). In 2011, 17.3% of the RTR were categorized as having a history of smoking, while in 2014, this number decreased to 12.1%. The percentage of the population with systolic and diastolic hypertension (defined as values greater than 140 and 90 mm Hg⁷) increased to 23.0 and 12.2% from 16.5 and 11.3%, respectively, in 2011. Twenty-seven percent (27.3%) of RTR are now diabetic, and the mean hemoglobin A1c did not significantly change. The percentage of RTR with total cholesterol levels of > 5.5 significantly decreased from 23.7 to 15.8%. There was also a notable decrease in eGFR leading to a delta decrease in GFR of 10.6 mL/min (54.3–50.6), which translated to an annual decrement in eGFR of 4 mL/year. Similarly, the number of patients with eGFR below 60 and 45 mL/min increased substantially. The patients with eGFR less than 60 mL/min in 2011 witnessed a rapid decline in eGFR of 7 mL/min/year, $p < 0.05$ compared with those patients with eGFR above 60 mL/min at the outset of the study. Similarly, patients with eGFR < 45 mL/min in 2011 progressed at rate of

Table 1 Patient demographics

Parameter	2011	2014	Δ change in mean/median	Percentage change	p-Value*
Number	139	139			
Male (n) %	(77/150) 55.4%	(77/150) 55.4%			
Female (n) %	(62/150) 44.6%	(62/150) 44.6%			
Patient age	51.9 (22.4–83.9)	54.7 (25.1–87.1)	2.7 (2–4.4)	5.1% (2.9–15.3%)	0.000
BMI (kg/m ²)	27.4 (17.5–49.5)	27.6 (16.9–48.9)	0.2 (– 31.3 to 17.2)	1.3% (– 27.5 to 63.1%)	0.089
Transplant duration (y)	7.4 (0.02–24.9)	9.9 (2.4–27.2)	2.6 (2–4.5)	33.9% (9.1–9,480.5%)	0.000
Calcium (mmol/L)	2.4 $\pm$ 0.2	2.4 (0.8–93)	0 (– 2 to 90.7)	0.4% (– 67.9 to 3,996.9%)	0.62
Vitamin D (nmol/L)	66.9 (12.3–164.2)	68.4 $\pm$ 32	0 (– 51.2 to 19.3)	0.0% (– 41.9 to 39.6%)	0.962
Parathyroid (pmol/L)	8.1 (1.6–98.3)	7.9 (1.8–52.3)	0 (– 71.4 to 3.8)	0.0% (– 72.6 to 77.4%)	0.885
HbA1c (if diabetic)	7.5 $\pm$ 1.3	7.3 $\pm$ 1.4	1.5 $\pm$ 2.8	2.7 $\pm$ 13.2%	0.415
eGFR (CKD-EPI) mL/min	62.6 $\pm$ 24.9	51 (11.3–118.5)	– 10.6 (– 54.3 to 50.6)	– 17.5% (– 79.0 to 116.5%)	0.000
Diabetes	23.0%	27.3%			0.068 ^a
Smoking	17.3%	12.1%			0.164 ^a
CRCRTR-MACE 7-y risk	8.2 (1.5–82.4)	8.6 (1.2–92)	1.6 (– 72.4 to 84.2)	25.8% (– 92.1 to 1,444.7%)	0.228
CRCRTR-MACE 7-y risk $\geq$ 20% (% of patients)	19.6%	24%			0.551 ^a
Improved CRCRTR-MACE score (% of patients)			44.8%		
No change in CRCRTR-MACE score (% of patients)			0.0%		
Worsened CRCRTR-MACE score (% of patients)			55.2%		
% of patients above/below median CRCRTR-MACE				49.6/50.4%	
Phosphate (mmol/L)	1 (0.6–1.7)	0.9 (0.3–2.6)	0 (– 1 to 1.6)	– 1.0% (– 62.9 to 149.5%)	0.215
Phosphate $\geq$ 1.43 mmol/L (% of patients)	6.5%	6.6%			
Phosphate $\geq$ 1.1 mmol/L (% of patients)	33.1%	29.9%			
Phosphate $\leq$ 0.8 mmol/L (% of patients)	20.1%	27.7%			
Magnesium (mmol/L)	0.8 $\pm$ 0.1	0.7 (0.4–1.2)	0 $\pm$ 0.2	– 4.4% (– 46.2 to 72.2%)	0.095
Albumin (g/L)	38 (21–50)	37 (17–47.1)	– 1 (– 41 to 37)	– 2.5% (– 56.4 to 261.0%)	0.031
Microalbumin (mg/L)	13 (2–400)	20 (3–400)	2 (– 400 to 397)	18.8% (– 100.0 to 1,323.3%)	0.313

Abbreviations: BMI, Body mass index; CRCRTR, cardiovascular risk calculator for renal transplant recipients; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; MACE, major adverse cardiac events.

Note: Results presented as mean $\pm$ standard deviation for normality distributed variables and median (min–max) for nonnormality distributed variables. p-Value computed by paired-sample t-test.

^ap-Value computed by Mc-Nemar test and all the other p-values were computed by Mann–Whitney U-test, blood pressure, CRCRTR-MACE. We defined arbitrarily patients with worsened cardiovascular (CV) risk score above median change in total group score as fast CV risk progressors. Similarly, we defined patients with change in CV risk less than median change in the group as slow CV risk progressors.

*p-values less than 0.01 are in bold.

Table 2 Comparison between patient's subgroups with different GFRs and MACE according to GFR in 2011 and 2014

Subgroup	GFR $\geq$ 60 mL/min	GFR < 60 mL/min	GFR $\geq$ 45 mL/min	GFR < 45 mL/min
N	71	68	101	38
GFR in 2011	77.4 (60.6–131.8)	41.4 (12.8–59.9)	71.1 (47.7–131.8)	33.4 (12.8–43.4)
GFR in 2014	63.7 $\pm$ 17.7	34.9 (11.3–94)	57.8 $\pm$ 18.5	31.2 (11.3–94)
Δ change in GFR	– 18.5 $\pm$ 13.8	– 5.6 (– 37.2 to 50.6)	– 14.4 (– 53.3 to 15.5)	– 1.17 (– 11.7 to 50.6)
% change in GFR	– 22.2% (– 79 to 19%)	– 11% (– 67 to 117%)	– 20% (– 79 to 19%)	– 4.2% (– 41 to 117%)
p-Value	P1 = 0.002		P2 = 0.000	
MACE in 2011	6.4 (1.5–50.7)	12 (1.9–82.4)	6.9 (1.5–50.7)	15.3 (3.23–82.4)
MACE in 2014	8.7 (1.8–58.7)	7.9 (1.2–92.0)	8.7 (1.4–84.2)	7.5 (1.2–92.0)
Δ change in MACE score	4.0 $\pm$ 16.5	– 1.6 (– 72.4 to 84.2)	3.3 $\pm$ 15.3	– 8.5 (– 72.4 to 84.2)
% change in MACE score	93.5% (– 90 to 1,400.45%)	17.4 (– 92 to 1,000.77%)	57.1 (– 89.7 to 1,400.45%)	– 53.6% (– 92 to 1,000.77%)
p-Value	P3 = 0.003		P4 = 0.002	

Abbreviations: GFR, glomerular filtration rate; MACE, major adverse cardiac events; P1 = *p*-value between percentage change in GFR $\geq$ 60 mL/min and percentage change in GFR < 60 mL/min; P2 = *p*-value between percentage change in GFR $\geq$ 45 mL/min and percentage change in GFR < 45 mL/min; P3 = *p*-value between percentage change in MACE at GFR $\geq$ 60 and percentage change in MACE at GFR < 60 mL/min; P4 = *p*-value between percentage change in MACE at GFR $\geq$ 45 mL/min and percentage change in MACE at GFR < 45 mL/min.

Note: Results are represented as mean $\pm$ standard deviation or median (min–max) for normally and nonnormally distributed variables, respectively. *p*-Values were computed by Mann–Whitney *U*-test. Δ change was calculated from score in 2014 minus score in 2011, % change calculated as

$$\frac{\text{Score in 2014} - \text{Score in 2011}}{\text{Score in 2011}} \times 100.$$

4.6 mL/min/year. It was interesting that RTR with better baseline renal function exhibited a quicker decline in their function, compared with patients with existing poor function (**►Table 2**). For instance, patients with a GFR of < 45 showed a decline by mean of 4.2%, while RTR with a GFR of $\geq$ 45 declined by 20%, and RTR with a GFR of $\geq$ 60 mL/min diminished by 22.2%.

Regression analysis failed to show a significant correlation between delta change in the total group and scores by CRCRTR-MACE.

MVA of CVD Variables Contributing to Improved or Worsened Delta CVD Scores

UVA and MVA were performed to identify if percentage change in any demographic, clinical, or biochemical variables were correlated with percentage change in CV risk score (**►Table 3**). Only patient age and serum phosphate level remained significant in the MVA. In **►Fig. 1**, ROC analysis illustrates the effect of percentage change in serum phosphorous and age on CRCRTR-MACE score.

Discussion

Although the literature is replete with reports describing the prevalence of CV risk factors in RTR,^{8–11} we were unable to find information on interval changes in CVD scores in RTR. We will therefore focus our discussion on the two main findings of the study: (1) the rate of change in CV risk scores and (2) the role of phosphate on CV risk.

In this study, we stratified patients according to delta changes in CV risk scores. Fast progressors were arbitrarily defined as those with changes above the mean + SD (or above 90% confidence interval [CI] for nonnormalized data, as in CRCRTR-MACE scores). Conversely, RTR with delta changes < mean – 1 SD (or less than 10% CI values for CRCRTR-MACE) were labeled slow progressors. In CKD research, patients have been divided into fast and slow progressors based on arbitrary cutoff rates for changes in eGFR¹² or albumin excretion.¹³ The concept of identifying delta changes in total CV risk, however, appears to be novel as we could not find any other similar studies using this approach.

Fast progressors for CV risk were associated with worsening GFR. This makes sense, since GFR is a variable in the CRCRTR-MACE equation and decline in renal function is strongly associated with an increase in CVE.^{14,15} As eGFR is a potent CV risk factor, we undertook an additional analysis to determine the pace of interval changes in CV scores in subgroups with different GFRs from the beginning of the study in 2011. Patients with improved renal function exhibited a more rapid increase in CRCRTR-MACE, which was particularly surprising, since serum creatinine is a component of the CV risk equation. In the subgroup with the poorest renal function; however (eGFR < 45 mL/min), an improvement was in fact noted in the delta scores. Perhaps more attention was directed to managing these patients, knowing their diminished renal function. Likewise, less than optimal management may have been provided to the “healthier” group, given their apparent lack of CV risk. Supporting this theory, a bias toward sick patients has been noted in other aspects of health care as well.¹⁶

Table 3 Univariate, multivariate, and stepwise analyses of the relationship between percentage changes in patient's demographics and percentage change in MACE scores (above and below median)

Parameter	UVA	p-Value	MVA	p-Value	Stepwise Analysis	p-Value	95% CI	
							Lower	Upper
Intercept			– 0.030	0.771	– 0.085	0.410	– 0.288	0.118
Patient age	9.495	0.000	8.573	0.000	9.376	0.000	6.232	12.520
Weight	1.155	0.009	– 31.934	0.059				
BMI	1.177	0.008	28.741	0.110				
Body surface area	2.526	0.007	7.810	0.564				
Total cholesterol	1.03	0.001	0.535	0.317				
LDL cholesterol	0.532	0.013	0.024	0.948				
Phosphate	0.346	0.002	0.260	0.012	0.309	0.002	0.116	0.501
Magnesium	0.536	0.015	0.248	0.210				

Abbreviations: BMI, body mass index; CI, confidence interval; MACE, major adverse cardiac events; MVA, multivariate analysis; LDL, low-density lipoprotein; UVA, univariate analysis.

Notes: Changes above and below the median change in MACE score of 0.26 was used in a univariate and multivariate binary analyses. The following variables were not significant in univariate analysis: Transplant duration, triglycerides, high-density lipoprotein, high-sensitivity C-reactive protein, calcium, vitamin D, parathyroid hormone, HbA1c if diabetic, creatinine, urea, creatinine clearance (CKD-EPI), hemoglobin, ejection fraction, systolic blood pressure diastolic blood pressure, serum albumin, urine microalbumin, significant *p*-values were bolded.

Notably, MVA identified serum phosphate (other than age) as the only modifiable variable of significance contributing to worsening CRTRC-MACE. Phosphate homeostasis and disorders have been extensively reviewed elsewhere.¹⁷ In the renal patient, the focus on its role on metabolic disease has over-shadowed its well-documented role in CV pathology. It has been suggested that serum phosphorus is a nontraditional cardiac risk factor. Higher phosphate levels are associated with increased CVD and mortality in renal patients, patients with only mild to CKD as well as patients with normal renal function.^{18–20} This association is evident even at modestly elevated phosphate concentrations.^{21,22} In fact, serum phosphate has emerged as a potential factor that accelerates progression in renal dysfunction,^{21,23} and levels have been shown to directly correlate with atherosclerosis in humans²¹ and animal models.²⁴

The risks associated with high serum phosphate also seem to apply to general populations. For example, Foley showed that increased levels were significantly associated with coronary atherosclerosis in young adults with normal kidney function,²⁵ especially levels > 3.9 mg/dL. In the MVA models, high phosphate levels were associated with greater likelihood of higher calcification with adjusted odds ratio of 1.17 per 0.5 mg/dL with a *p*-value of 0.03. In a similar analysis of Framingham offspring cohort, serum phosphate levels above 3.5 mg/dL were also associated with an adjusted hazard ratio of 1.55 times levels < 2.9 mg/dL. On the contrary, in animal models reducing phosphate intake modestly has been associated with a reduction in atherosclerotic lesions and oxidative stress.²⁶

In addition to the increased risk of atherosclerosis, there is an impact on mortality. Sim et al²⁷ examined the relationship between phosphate and mortality in participants with eGFR > 60 mL/min, reporting an increased risk of 1.09 with every

mg/dL increase in serum phosphate. In a post hoc analysis from the Cholesterol and Recurrent Events (*n* = 4,127), a graded independent relationship was noted between higher levels of serum phosphate and the risk of death and CVDs in patients with prior myocardial infarction—even in patients with serum levels within the normal range.¹⁹

Postulated mechanisms of tissue injury by phosphate have been elucidated from animal experiments²⁶ and supported by clinical observation. These mechanisms as summarized by Nadkarni and Uribarri²⁸ include increased vascular calcification, promoting vascular inflammation and fibrosis, increasing fibroblast growth factor (FGF)-23 release, and oxidative stress.

Postrenal transplantation hypophosphatemia is a well-recognized condition.²⁹ Oral phosphorus replacement is commonly used to correct serum phosphorus level in these patients. Although there is no specific target serum level, most transplant physicians will deliberately aim to achieve good normal serum phosphorus level to prevent metabolic bone disease. These results and other similar observations lead us to question the wisdom of aggressive phosphate replacement in RTR with mild hypophosphatemia. First, studies have found little effect or no effect of dietary phosphorus restriction on fasting phosphate concentrations.^{17,30} A case in point is the fact that serum phosphate constitutes only 1% of phosphate body content.³⁰ Lower concentrations of serum phosphorus within the normal range could be associated with less coronary artery calcification.¹⁷ Further, oral phosphate intake increases FGF-23,³¹ which is reported to strongly associate with vascular injury. In fact, the presence of a more complex network of various hormonal and metabolic factors beyond oral intake in phosphate homeostasis has therefore been recognized.^{29,32} Oral phosphate may increase FGF-23 production which may worsen renal phosphate loss.³³

Fig. 1 Receiver-operating characteristic for percentage change in CRCRTR-MACE from 2011 to 2014. Depicts the AUC by ROC analysis of effect of age and serum phosphorus on percentage change in CRCRTR-MACE risk between 2011 and 2014. (A) Patient age cutoff at ≥ 45 years old. Criterion was a 15% change in MACE risk score. At this criterion level, sensitivity, specificity, positive predictive value, negative predictive value, positive negative likelihood ratio, and negative likelihood ratio were 86.08, 71.74, 84.0, 75.0, 3.05, and 0.19, respectively. (B) Serum phosphate cutoff at or equal to 1.1 mmol/L. Criterion was a 27% change in MACE risk score. At this criterion level, sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio were 71.43, 59.04, 46.9, 80.3, 1.74, and 0.48, respectively. (C) Cutoff of age ≥ 45 years and a simultaneous serum phosphate ≥ 1.1 mmol/L. Criterion was a 25% change in MACE risk score. At this criterion level, sensitivity, specificity, positive predictive value, negative predictive values, positive likelihood ratio, and negative likelihood ratio were 90, 63.16, 43.5, 95.2, 2.44, and 0.16, respectively. AUC, area under the curve; CRCRTR, cardiovascular risk calculator for renal transplant recipients; MACE, major adverse cardiac events; ROC, receiver-operating characteristic.

Further argument against generous oral phosphorus treatment is the fact that CKD patients with phosphate level above 4.3 mg/dL have an increased risk of progressive renal dysfunction and death.³⁴ One can then raise the intriguing possibility that aggressive correction of serum phosphate by oral replacement to prevent and/or treat transplant bone diseases may paradoxically increase CV injury.

Interestingly, serum phosphate interacted with age in this study. Age is usually associated with increased inflammation³⁵ and can contribute to vascular dysfunction.³⁶ Therefore, it is reasonable to suggest that increasing inflammation and possibly other biological function associated with increased serum phosphate may lead to further vascular dysfunction in the elderly transplant recipient.

There are limitations to this work. The finding that phosphate level was associated with risk progression was unexpected, and as such we did not measure FGF-23 as a potential mediator of high phosphate-induced tissue injury. Another important limitation of this study is that our outcome mea-

sure was CV risk, rather than cardiac events. Although studies using actual events as hard end points are preferable, they require larger populations and a longer duration of follow-up. We specifically used the CRCRTR-MACE as our tool to estimate CV risk. This equation, however, has not been widely used in clinical practice. It should be noted that this method of calculating CV risk appears to be the most promising in terms of accuracy in the kidney transplant population at this time.

In spite of these limitations, examining the delta change in CV risk over time in our RTR was a worthwhile endeavor. The results highlight (1) variability in progression of CV risk, (2) fast CV risk progression was associated with worsening GFR and it did start early in patients with the best function. The fact that the RTR with the renal best function exhibited the most increase in CV risk should serve as a reminder to manage modifiable risk factors in all RTR—even those patients who are considered healthy. (3) The finding that serum phosphate was the only clinical variable significantly associated with change in CV risk score after MVA (in addition to age) suggests

a pathogenic role of phosphorus in RTR, particularly in elderly patients. It leads us to conclude that more research is needed to elucidate the role of serum phosphate its role in CV pathology and CV risk reduction in transplant patients. This study questions the wisdom of generous oral phosphate treatment and proposes a need for a critical appraisal of oral phosphorus requirements in kidney transplant patients.

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