Article

Interaction of Time-Varying Albumin and Phosphorus on Mortality in Incident Dialysis Patients

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Summary

Background and objectives Hypoalbuminemia and hyperphosphatemia have been shown to be strong predictors of mortality in dialysis patients that might not be independent from each other. We prospectively investigated the relationship and interaction between serum albumin and phosphorus with all-cause mortality in an inception cohort of incident dialysis patients.

Design, setting, participants, & measurements We followed 235 incident dialysis patients in a prospective single-center cohort study (INVOR study) applying a time-dependent Cox proportional hazards model using all measured laboratory values (2887 albumin and 10306 phosphorus values).

Results Eighty-two patients (35%) died during a median follow-up of 35.1 months. Albumin was inversely associated with mortality (hazard ratio [95% confidence interval]: 0.23 [0.14 to 0.36]; $P < 0.001$), whereas higher phosphorus concentrations showed a trend to an increasing risk for mortality (hazard ratio 1.57 [95% confidence interval 0.97 to 2.54]; $P = 0.07$). Importantly, we observed a significant interaction between albumin and phosphorus ($P = 0.01$). The lowest risk was found with concurrent low phosphorus and high albumin values, whereas risk was increased with either concurrent low phosphorus and low albumin values or high phosphorus and high albumin values.

Conclusions In incident dialysis patients the associations of serum phosphorus and albumin concentrations with mortality are modified by each other over time. Phosphorus-lowering interventions that concomitantly can cause a fall in serum albumin level may be harmful and warrant additional studies. If confirmed, epidemiologic studies and therapeutic guidelines aiming for target values should consider this interplay.

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Introduction

Patients with ESRD are at significantly increased mortality risk compared with the age-adjusted general population (1,2). A variety of risk factors have been found to be associated with this increased risk. Although the traditional cardiovascular risk factors do not exclusively explain the excessively increased mortality (3,4), markers of mineral and bone disorders and measures of protein-energy wasting are associated with an increased risk (5–9). Among these, hypoalbuminemia (10,11) and hyperphosphatemia (12,13) are both well established predictors of all-cause mortality in dialysis patients.

Prevention and reduction of overt hyperphosphatemia by the restriction of dietary phosphorus intake and by administering oral phosphate binders are cornerstones in the management of ESRD patients (14,15). The recently published Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend that elevated serum phosphorus concentrations be lowered toward the normal range (16).

Restriction of dietary phosphorus intake, however, requires a reduction in oral protein intake, as protein-rich foods are the main source of dietary phosphorus (17). On the other hand, lowering protein intake can lead to malnutrition and protein-energy wasting and thereby increasing mortality in ESRD patients (6,9). Hypoalbuminemia is the most commonly used surrogate parameter for protein-energy wasting in daily clinical practice, although it has also been shown to be a marker for inflammation (18,19).

There are only limited prospective data concurrently evaluating the relationship between the two biomarkers albumin and phosphorus as time-varying parameters and survival outcomes over a long-term observation period in incident dialysis patients (20–22). Therefore, in this study we aimed to investigate the association of albumin and serum phosphorus as single parameters as well as their interaction with all-cause mortality in a well characterized inception cohort of incident dialysis patients who were followed for up to more than 7 years. We hypothesized

that albumin and phosphorus interact in their association with high mortality and thereby attenuate the single effects due to their seemingly opposing associations with survival. Most importantly, this investigation is not based on a single measurement of these parameters at baseline but makes use of all measured laboratory values during the entire observation period, providing a deep granularity of the data.

Materials and Methods
Patient Population
The INVOR Study (Study of Incident Dialysis Patients in Vorarlberg) is a single-center, prospective, observational cohort study of incident hemodialysis and peritoneal dialysis patients in Vorarlberg, the westernmost state of Austria with approximately 400,000 inhabitants. As described recently (23,24), all incident dialysis patients starting chronic dialysis treatment between May 1, 2000, and April 30, 2006, were enrolled. Patients having a malignant tumor at initiation of dialysis were excluded. A total of 235 patients were included in the study and followed for a maximum of almost 7.5 years until December 31, 2007, or until the patient died. Because mineral metabolism, cardiovascular risk, and overall survival considerably change after transplantation, the observations have been censored at transplantation. Four patients were lost to follow-up, three of them regained renal function and the other one moved away. The study was approved by the local ethics committees and all patients enrolled in the study provided written informed consent.

Data Description
As described recently (23,24), clinical, laboratory, and medication data were collected prospectively starting at the time of initiation of dialysis. Type of and change in dialysis therapy (hemodialysis [HD] or peritoneal dialysis [PD]) were recorded and considered as time-dependent treatment status for data analysis. All-cause mortality data including death causes (autopsy-proven in 33%) were evaluated. Laboratory parameters were measured in a central laboratory and recorded continuously during the study period. Blood for laboratory parameters was collected immediately before dialysis at different time intervals, most of them once to twice monthly (phosphorus, hemoglobin, creatinine, and calcium) and a few of them every 3 months (albumin, C-reactive protein [CRP], and immunoreactive parathyroid hormone [iPTH]). Patients had up to 52 measurements for albumin (median 11) and up to 188 phosphorus measurements (median 33) during the follow-up period. Overall, this resulted in 2887 albumin and 10,306 phosphorus measurements during the entire observation period, which were used in the time-dependent Cox regression model described below.

Statistical Analyses
The primary outcome of interest was all-cause mortality. To determine the effect of phosphorus and albumin concentrations and their interaction on mortality, a time-dependent Cox proportional hazards model (25) was used, allowing all variables to vary over different measurements during the entire observation period for each patient. That

is, each time span between two successive measurements enters the model independently. Each covariate that entered the model was updated at the time it was measured and modeled in a time-dependent fashion. If not all variables were measured at a particular date, the values measured at the last observation of this variable were substituted for the respective missing values ("last observation carried forward"). The proportional hazards assumption was tested for each model by testing for zero slopes of scaled Schoenfeld residuals. The assumption of linear effects was tested in models excluding the interaction terms via nonlinear P splines with three degrees of freedom (26), which is a linear combination of cubic functions.

The final Cox proportional hazards models included linearly modeled effects of albumin, phosphorus, and albumin-phosphorus interaction, adjusted for age, gender, and type of dialysis therapy (simple adjustment model) as well as extended adjustment models, which additionally included adjustment for CRP, hemoglobin, calcium, and iPTH. For this extended adjustment model, a significance region was calculated (27) to determine for which values of albumin the effect of phosphorus on mortality was significantly different from zero and *vice versa*. This time-dependent modeling of interaction effects reflects the assumed effect modification of albumin on phosphorus and *vice versa* during the complete observation period.

Because low albumin values apart from malnutrition might also reflect inflammation, additional interaction models were calculated to improve insight into the nature of effect modification (phosphorus*CRP and phosphorus*creatinine). Further subgroup analysis was performed stratifying for the type of dialysis treatment (HD, PD). The correlation of albumin and phosphorus was evaluated using Spearman's correlation coefficient as well as linear mixed effect models accounting for the repeated measures.

All analyses were conducted in R (28) using the package "survival."

Results
Patient Characteristics
Table 1 presents the baseline demographic, clinical, and laboratory characteristics of all 235 incident dialysis patients at the time dialysis treatment was started. Patients were followed for a median of 35.1 months ranging from 24 days to approximately 7.5 years. During this observation period 82 patients died (35%). Mortality rate was independent of gender (35% for both men and women). About 92% of all patients were treated with phosphate binders at least once during the observation period; 89% received calcium-based binders and 66% received calcitriol. The repeated measurements of albumin and phosphorus per patient were significantly but only weakly correlated (Spearman $r = 0.15$, $P < 0.001$).

Associations between Albumin, Phosphorus, and All-Cause Mortality
Since linearity and proportional hazards assumptions held in all models, linear effects were estimated in Cox proportional hazards models. The corresponding results for the simple model (adjusted for age, gender, type of

Table 1. Clinical characteristics of patients at baseline and during follow-up		
		All Patients ($n = 235$)
Characteristics at baseline		
age (years)		61.7 ± 14.0
gender (male/female), n (%)		146 (62.1)/89 (37.9)
body mass index[a]		26.1 ± 4.5
Start of dialysis with		
hemodialysis		197 (83.8)
peritoneal dialysis		38 (16.2)
Diabetes mellitus		82 (34.9)
Systolic BP (mmHg)		154.0 ± 22.7
Diastolic BP (mmHg)		83.0 ± 12.3
	Mean $\pm$ SD	25th; 50th; 75th Percentile
Laboratory parameters at baseline		
albumin (g/dl)	3.71 ± 0.65	3.30; 3.70; 4.20
phosphorus (mmol/L)	1.98 ± 0.61	1.57; 1.94; 2.30
calcium (mmol/L)	2.12 ± 0.27	1.98; 2.14; 2.30
iPTH (pg/ml)	350.5 ± 264.9	156.5; 287.2; 468.7
hemoglobin (g/dl)	11.17 ± 1.72	10.10; 11.30; 12.30
creatinine (mg/dl)	7.28 ± 2.64	5.50; 6.80; 8.60
C-reactive protein (mg/dl)	3.24 ± 5.34	0.30; 0.98; 3.00
bicarbonate (mmol/L)	21.0 ± 3.6	18.7; 21.0; 23.4
ferritin (ng/ml)	174.3 ± 206.5	44.0; 111.0; 234.0
total cholesterol (mg/dl)	189.8 ± 51.0	152.0; 184.0; 219.5
leukocytes (g/L)	8.18 ± 3.29	6.10; 7.40; 9.90
Kt/V	1.29 ± 0.41	1.10; 1.20; 1.43
Comorbidities at baseline		
CAD[b]		40 (17.0)
CVD[c]		70 (29.8)
PAD[d]		40 (17.0)
Follow-up		
follow-up time (months)[e]		38.9 ± 23.2
transplantation		58 (24.7)
all-cause mortality		82 (34.9)
Medications during follow-up		
phosphate binder		217 (92.3)
calcium-based		209 (88.9)
aluminum-based		22 (9.4)
sevelamer-HCl		125 (53.2)
erythropoietin		234 (99.6)
iron supplements		204 (86.8)
calcitriol		155 (66)

Values are mean $\pm$ SD or number with percentage in parentheses.
iPTH, immunoreactive parathyroid hormone.
[a] Calculated as weight in kilograms divided by height in meters squared (kg/m²).
[b] Coronary artery disease (CAD): myocardial infarction, percutaneous transluminal coronary angioplasty (PTCA), aortocoronary bypass (ACBP).
[c] Cardiovascular disease (CVD): myocardial infarction, percutaneous transluminal coronary angioplasty (PTCA), aortocoronary bypass (ACBP), coronary artery stenosis ≥50%, ischemic cerebral infarction, transient ischemic attack (TIA)/prolonged reversible ischemic neurological deficit (PRIND).
[d] PAD (peripheral arterial disease): arterial stenosis, percutaneous transluminal angioplasty (PTA), peripheral bypass, amputation.
[e] Follow-up time was calculated as the time from the start of dialysis until the patient died or the end of the observation period (December 31, 2007) was reached.

dialysis therapy) as well as the extended model (additionally adjusted for CRP, hemoglobin, calcium and iPTH) are shown in Table 2. Without the interaction term for albu-

min and phosphorus, phosphorus showed a positive trend toward increased overall mortality with higher values in the simple model (hazard ratio [HR] = 1.47, $P = 0.08$) and borderline significance in the extended model (HR 1.57; $P = 0.07$). In contrast, higher albumin concentrations were associated with a lower mortality risk in a highly significant manner in the simple adjustment model (HR = 0.19, $P < 0.001$). Adjusting for additional confounders in the extended model did not change the effect of albumin (HR = 0.23, $P < 0.001$).

Interaction between Albumin and Phosphorus and Their Association with All-Cause Mortality

Albumin and phosphorus showed a clear and significant interaction, in both the simple ($P = 0.004$) and the extended adjustment ($P = 0.01$) models. Because the effect estimates for the albumin and phosphorus main effects are not interpretable without taking into account the interaction effect, phosphorus effects are shown for specific fixed quantiles of albumin and *vice versa* (Figure 1). For albumin values higher than 3.5 g/dl (significance region), increasing phosphorus concentrations were significantly associated with an increased mortality risk, while this association was not found at concurrently lower albumin values. The analysis of varying albumin values at simultaneously fixed phosphorus quantiles yielded a linear inverse association between albumin and mortality risk with attenuation of this effect at very high phosphorus concentrations. For phosphorus concentrations higher than 2.7 mmol/L, greater albumin values were not associated with an additional decrease in mortality risk.

We could not find a significant interaction of phosphorus with CRP ($P = 0.36$ with log-transformed CRP) or creatinine ($P = 0.17$). However, the additional analyses suggest that the albumin effect was rather triggered by malnutrition than inflammation (Supplementary Material). Additional subgroup analysis revealed that the albumin-phosphorus interaction was only present in hemodialysis patients but could not be found in peritoneal dialysis patients.

Discussion

In the study at hand, we observed a significant interaction between time-varying albumin and phosphorus concentrations in their association with all-cause mortality in incident dialysis patients using a time-dependent multiple Cox proportional hazards analysis. Our data confirm earlier observations (20–22) that found an association between time-varying serum albumin and phosphorus and all-cause mortality and extend these findings by a new and important issue: the significant effect modification of one predictive variable on the other with regard to mortality.

Lower serum albumin has been shown to be independently associated with higher mortality in prevalent dialysis patients (10,29–32). Our data corroborate these studies, but in contrast to earlier reports in prevalent dialysis patients with a single measurement of albumin levels, we determined the mortality risk associated with serum albumin in incident dialysis patients using all available time-varying values. Thus, not only a single baseline measurement is used but the full spectrum of all measurements during the entire follow-up. This enables

Table 2. Cox regression analysis

	Univariate		Simple Adjustment[a]		Extended Adjustment[b]	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Including only main effects of phosphorus and albumin						
phosphorus (mmol/L)	1.09 (0.75 to 1.58)	0.67	1.47 (0.96 to 2.25)	0.08	1.57 (0.97 to 2.54)	0.07
albumin (g/dl)	0.21 (0.15 to 0.29)	<0.001	0.19 (0.13 to 0.28)	<0.001	0.23 (0.14 to 0.36)	<0.001
Including main effects of phosphorus and albumin + interaction effect						
phosphorus-albumin				0.004		0.01

Hazard ratios (HRs), 95% confidence intervals (CIs), and P-values of continuous and time-varying phosphorus and albumin concentrations as well as of their interaction term each in a univariate Cox model, in a simple adjustment model (adjusted for age, gender, and type of dialysis therapy) and an extended adjustment model (adjusted for age, gender, type of dialysis therapy, C-reactive protein, hemoglobin, calcium, and immunoreactive parathyroid hormone [iPTH]) on all-cause mortality risk.
[a] Adjusted for age, gender, type of dialysis therapy.
[b] Adjusted for age, gender, type of dialysis therapy, C-reactive protein, hemoglobin, calcium, and iPTH.

a better appraisal of the nutritional situation of each patient over time. In a large U.S. 2-year observational registry study, Kalantar-Zadeh *et al.* found a significantly increased all-cause and cardiovascular mortality with trimonthly varying serum albumin values <3.8 g/dl and estimated that hypothetically some 10,000 deaths could be prevented in the United States if serum albumin would be corrected to concentrations >3.8 g/dl (10). Although analyses were adjusted for several confounding factors related to the malnutrition-inflammation complex, serum phosphorus and its effect modification on albumin and *vice versa* have not been considered. We are not aware of other studies that have examined the effects of time-varying serum albumin and phosphorus and their interaction on all-cause mortality with multivariate adjustment.

Increasing oral protein intake may help increase serum albumin concentrations. KDOQI guidelines recommend 1.2 g protein/kg body weight per day (33). Because dietary phosphorus and protein content are closely related, one reasonable concern is that an increase in protein intake would entail an increased phosphorus intake. Noori *et al.* recently found a strong correlation between dietary protein and phosphorus intake and a significantly increased 5-year mortality risk with increasing dietary phosphorus intake and increasing dietary phosphorus/protein ratio (34). In our analyses a greater albumin concentration with concurrently higher phosphorus concentration was also associated with increased all-cause mortality. Above a phosphorus value of 2.7 mmol/L the beneficial mortality-lowering effect of higher albumin values was no longer obvious. Consequently, a fortified or even additional protein intake in this constellation to avoid malnutrition might not be useful for dialysis patients, considering the significant and clinically relevant albumin-phosphorus interaction. This latter association might illustrate the countervailing risks and benefits of high protein intake, probably caused by worsening hyperphosphatemia, and once again underscores the important interaction between serum albumin and phosphorus.

On the other hand, the highest mortality risk in our study was found for concurrently low albumin and phosphorus concentrations. Therefore, in patients with moderate hyperphosphatemia and decreased serum albumin, dietary phosphorus restriction via reduced protein intake may even be rather harmful than helpful to the patient. In support of our findings, a 3-year observational study among 30,000 prevalent hemodialysis patients showed a significant correlation between serum phosphorus and dietary protein intake as estimated by the normalized protein nitrogen appearance (nPNA). It furthermore found a decreased multivariable-adjusted death rate with increasing nPNA and concomitantly decreasing serum phosphorus, whereas decreasing nPNA with a concordant rise in serum phosphorus or decrease in both parameters was associated with increased mortality (17). In the same study similar results were observed when serum albumin was used as a surrogate for the nutritional status in multiple regression analysis. Moreover, in a recent *post hoc* analysis from the Hemodialysis (HEMO) study a more liberal phosphate prescription was associated with greater survival in prevalent hemodialysis patients (35). A decline in serum phosphorus observed over time should prompt a nutritional evaluation, and, if serum albumin has concurrently fallen, the patient might face a greater mortality risk.

One possibility for overcoming the problem of concordant overall protein restriction and the risk of malnutrition with reduced dietary phosphorus intake would be to avoid phosphorus-rich ingredients that are added to processed foods and beverages (36,37). Reducing the consumption of such phosphorus additives might help decrease phosphorus intake without the risk of protein-energy wasting. Besides, grain-based vegetarian sources of protein have been recently shown to allow a better phosphorus homeostasis compared with a meat-based diet (38). The lowest mortality risk in our study was found for simultaneously low phosphorus and high al-
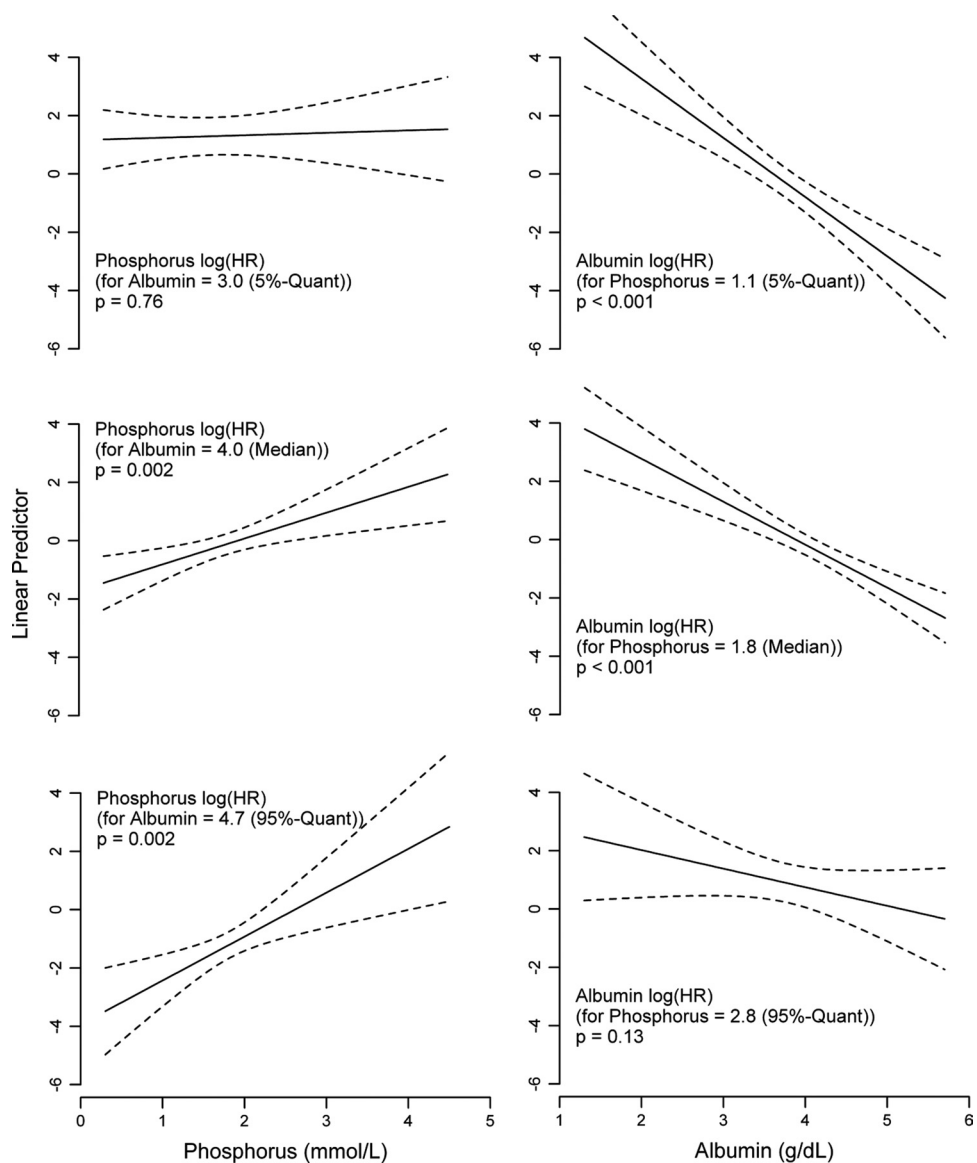
Figure 1. | **Cox regression results for the extended adjustment model.** The y-axis shows the log hazard ratios for varying values of phosphorus with their corresponding *P*-values, keeping the albumin values fixed at specific values (5%, 50%, and 95% quantiles [Quant]; left panels) as well as the log hazard ratios (HRs) with *P*-values for varying values of albumin, keeping the phosphorus values fixed at specific values (5%, 50%, and 95% quantiles; right panels).

bumin values. Therefore, careful use of phosphate binders might be appropriate in patients with normal serum albumin. Clearly, a potential benefit of a phosphorus-lowering strategy with phosphate binders and dietary phosphorus restriction based on the concomitant assessment of albumin and phosphorus has to be evaluated in a prospective trial to prove the hypothesis generated by our observational study.

Although interventional trial data demonstrating a survival benefit for lowering serum phosphorus are still missing, experimental data suggest possible causal mechanisms of adverse outcome. Elevated serum phosphorus has been shown to stimulate phenotypic transformation of vascular smooth muscle cells into osteoblast-like cells, promoting vascular calcification, causing endothelial cell dysfunction, increased arterial stiffness,

and cardiac fibrosis (7,39–41). Moreover, in large observational studies hyperphosphatemia has consistently been found to be an independent risk factor for all-cause mortality with the highest association of all markers of mineral and bone disorder (7). In our multiple-adjusted analyses of time-varying serum phosphorus we determined a borderline significant association between increasing phosphorus concentrations and all-cause mortality. These findings are well in line with the recently published results of the ARO (Analyzing Data, Recognizing Excellence, and Optimizing Outcomes) CKD Research Initiative investigating the association between markers of mineral and bone disease and mortality in 7970 prevalent European hemodialysis patients, which also found a trend to an increased all-cause mortality for elevated phosphorus concentrations (>1.78 mmol/L)

without reaching statistical significance when using an adjusted time-dependent analysis (42).

Hypoalbuminemia is not only caused by low protein intake and malnutrition, but also by chronic inflammation, which might explain part of the association between low serum albumin and increased all-cause mortality (19). Adjusting for CRP, we consistently found higher albumin values to have a risk-lowering effect. Investigation of albumin-phosphorus interaction and its association with all-cause mortality showed concordant low serum albumin and phosphorus to pose the highest risk in our incident dialysis cohort. This might be explained as follows: First, uremia-associated protein-energy malnutrition and inflammation, together also known as malnutrition-inflammation complex syndrome, are a strong indicator of increased mortality in dialysis patients (43). Therefore, low serum albumin might be the surrogate marker of malnutrition and inflammation, with concurrently low phosphorus as an additional marker of malnutrition due to low protein intake in this situation. Additional interaction models determining the effect modification of phosphorus by CRP and creatinine did not enable us to definitely specify whether the albumin effect was predominantly influenced by inflammation or nutritional status. However, these analyses rather suggest an alimentary effect, as the linear inverse association between creatinine values and mortality risk is attenuated at higher phosphorus concentrations and the mortality risk association with increasing phosphorus increases with higher creatinine values. Second, malnutrition and hypoalbuminemia have been shown to be associated with adynamic bone disease (44,45), and chronic inflammation has been found to decrease PTH (46,47) and bone turnover. Diminished release from bone may partially explain low phosphate levels in these situations.

Strengths and Limitations

There are limitations to this study. Because it is an observational study, no causal inference can be made from the study results. A further limitation is the relatively small sample size. Finally, no further nutritional parameters such as normalized PCR data or further inflammation markers were collected. Nevertheless, our study has several notable strengths. It is a single-center study with uniform laboratory measurements of high frequency and continuity collected over a long follow-up period. The prospective recruitment of all patients starting dialysis treatment over a period of 6 years in a clearly defined area allowed complete recruitment of all patients requiring renal replacement therapy with almost no loss to follow-up. We can therefore exclude the most important bias of cross-sectional studies with a mix of prevalent and incident cases and the resulting survival bias. All patients were treated by the same physicians during the whole observation period following current best practice guidelines. Moreover, our study characterizes the association between time-varying albumin and phosphorus concentrations and their interaction and all-cause mortality in an inception cohort of incident dialysis patients considering all measurements in this observation period in a time-dependent modeling.

Conclusions

Time-varying albumin and phosphorus values significantly interact in their association with all-cause mortality in incident dialysis patients. The lowest risk is found for simultaneously low phosphorus and high albumin values, whereas risk is increased for either concurrent low phosphorus and low albumin values or for high phosphorus and high albumin values. In patients with low serum albumin concentration therapeutic attempts should be aimed at hypoalbuminemia. The correction of serum phosphorus values seems to be less important in this situation. With albumin values within the normal range, reduction of hyperphosphatemia by the restriction of dietary phosphorus intake and by administering oral phosphate binders seems to be clinically meaningful. If confirmed in larger studies, decisions about phosphorus-lowering therapy should also take albumin values into account and epidemiologic studies and therapeutic guidelines aiming for target values should consider this interplay.

Disclosures

None.

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Supplementary Material to:

Interaction of time-varying albumin and phosphorus on mortality in incident dialysis patients

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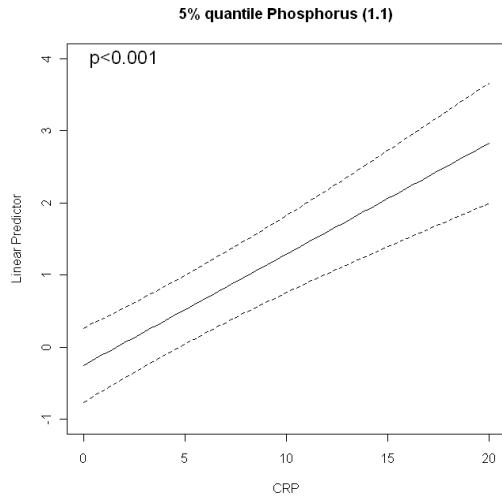Fax: (+43)512-9003-73560
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Results of additional analyses evaluating the interaction of phosphorus with CRP

Supplementary Table 1: Hazard Ratios (HR), 95% confidence intervals (CI) and p-values of continuous and time-varying phosphorus and log-trasformed CRP values as well as of their interaction term in a Cox model adjusted for age, sex and type of dialysis on all-cause mortality risk.
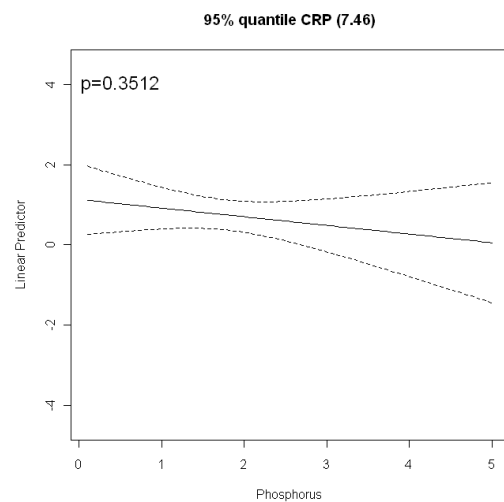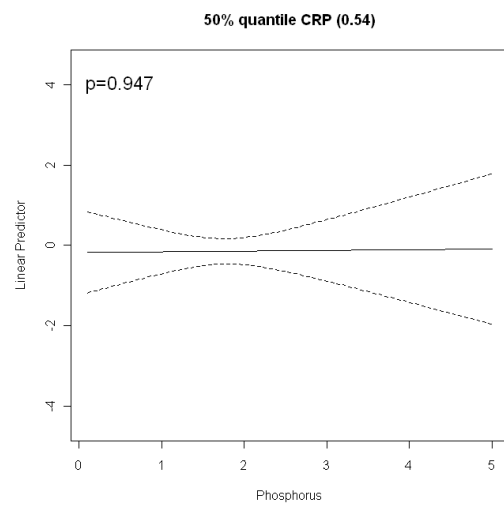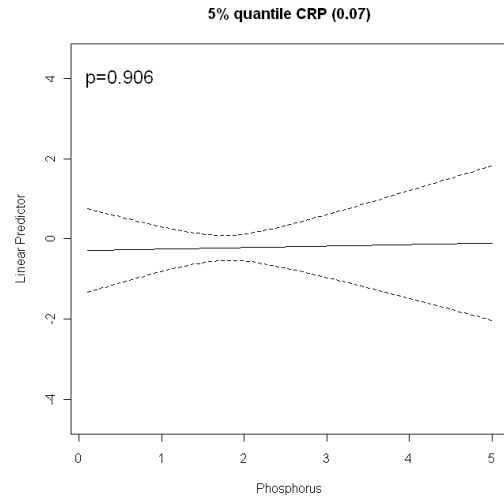
	HR (95% CI)	p
Including only main effects of Phosphorus and log(CRP)		
Phosphorus (mmol/L)	0.81 (0.52 - 1.27)	0.37
log(CRP (mg/dl))	2.14 (1.80 - 2.53)	<0.001
Including main effects of Phosphorus and log(CRP) + interaction effect		
Phosphorus*log(CRP)		0.36

Supplementary Figure 1: Cox regression results for the interaction between CRP and phosphorus and their association with all-cause mortality. The y-axis shows the log hazard ratios for varying values of CRP with their corresponding p-values, keeping the phosphorus values fixed at specific values (5%, 50% and 95% quantiles; left panel) as well as the log hazard ratios with p-values for varying values of phosphorus, keeping the CRP values fixed at specific values (5%, 50% and 95% quantiles; right panel). These plots are derived from a model on the original scale of CRP (not log-transformed, for CRP values < 20 mg/dl).

CRP log(HR) for varying Phosphorus levels

5% quantile Phosphorus (1.1)

p<0.001

50% quantile Phosphorus (1.8)

p<0.001

95% quantile Phosphorus (2.8)

p<0.001
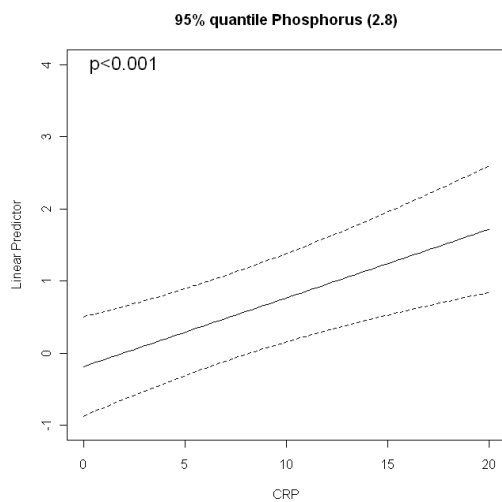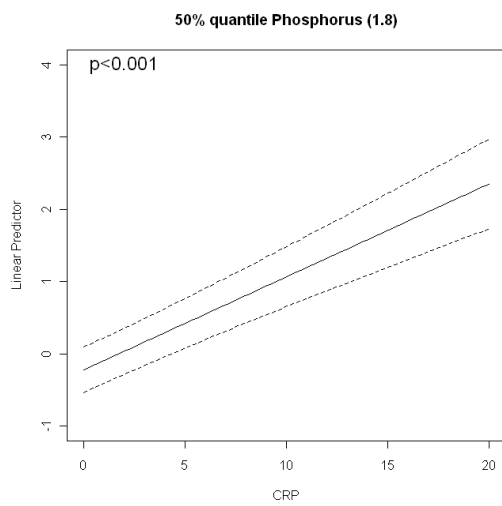
Phosphorus log(HR) for varying CRP levels

5% quantile CRP (0.07)

p=0.906

50% quantile CRP (0.54)

p=0.947

95% quantile CRP (7.46)

p=0.3512

Conclusion:
The HR for CRP is rather independent from phosphorus. The attenuation of HR with higher phosphorus values is only very slightly and not significant. CRP is significantly associated with mortality (with an HR>1) for all phosphorus values <3.43 mmol/L (=99%-quantile of phosphorus).

Conclusion:
With higher CRP values, the HR for phosphorus is slightly decreasing, but this association is not significant for any value of CRP.

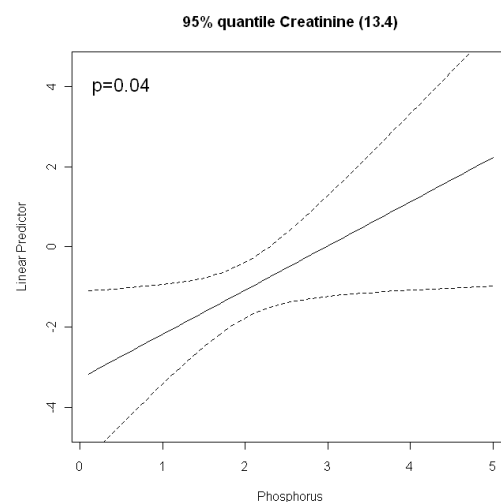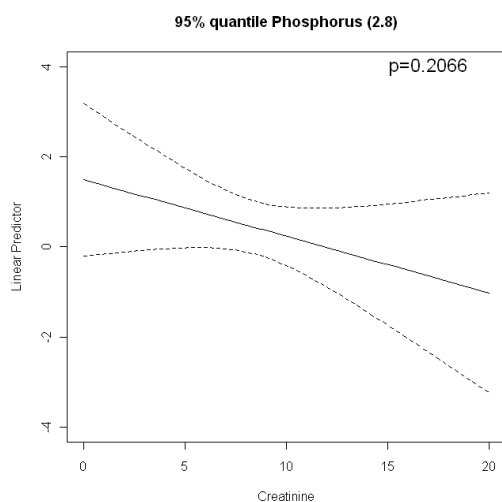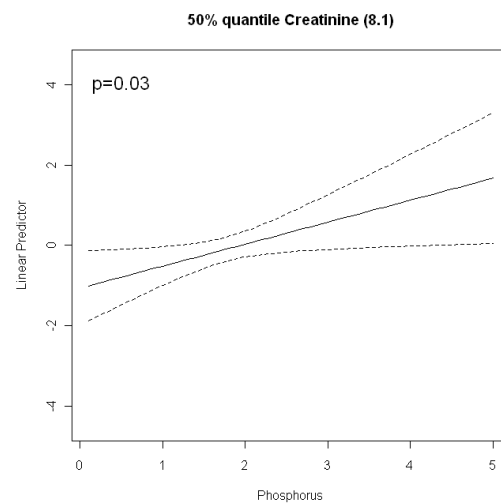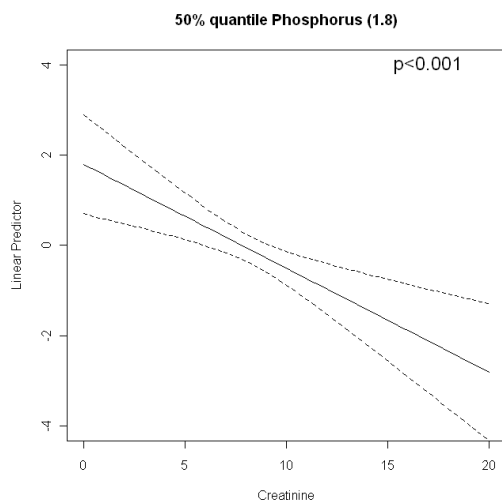# Results of additional analyses evaluating the interaction of phosphorus with creatinine
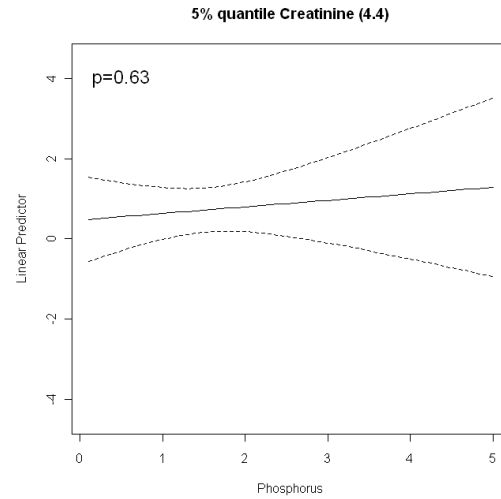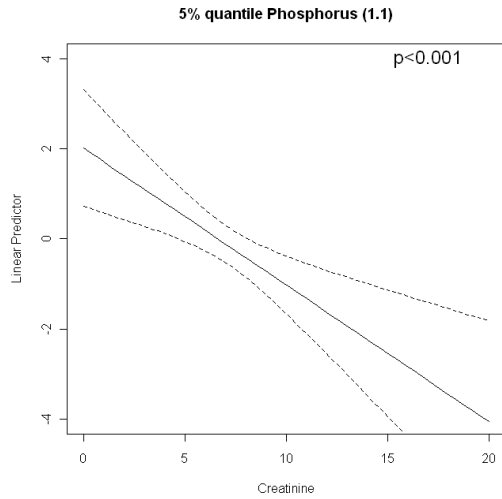
Supplementary Table 2: Hazard Ratios (HR), 95% confidence intervals (CI) and p-values of continuous and time-varying phosphorus and creatinine values as well as of their interaction term in a Cox model adjusted for age, sex and type of dialysis on all-cause mortality risk.

	HR (95% CI)	p
Including only main effects of Phosphorus and Creatinine		
Phosphorus (mmol/L)	1.54 (0.97 - 2.46)	0.07
Creatinine	0.80 (0.70 - 0.91)	<0.001
Including main effects of Phosphorus and Creatinine + interaction effect		
Phosphorus*Creatinine		0.17

Supplementary Figure 2: Cox regression results for the interaction between creatinine and phosphorus and their association with all-cause mortality. The y-axis shows the log hazard ratios for varying values of creatinine with their corresponding p-values, keeping the phosphorus values fixed at specific values (5%, 50% and 95% quantiles; left panel) as well as the log hazard ratios with p-values for varying values of phosphorus, keeping the creatinine values fixed at specific values (5%, 50% and 95% quantiles; right panel).

Creatinine log(HR) for varying Phosphorus levels

5% quantile Phosphorus (1.1)

p<0.001

50% quantile Phosphorus (1.8)

p<0.001

95% quantile Phosphorus (2.8)

p=0.2066

Conclusion:
There is a linear inverse association between creatinine values and mortality risk (HR) with an attenuation at higher phosphorus concentrations (not significant any more for phosphorus values >2.5 mmol/L; =88%-quantile).

Phosphorus log(HR) for varying creatinine levels

5% quantile Creatinine (4.4)

p=0.63

50% quantile Creatinine (8.1)

p=0.03

95% quantile Creatinine (13.4)

p=0.04

Conclusion:
The HR for phosphorus increases with higher creatinine. This association with mortality becomes significant for creatinine values >7.46 mg/dL (=40% quantile).