Coronary Heart Disease

Relation Between Serum Phosphate Level and Cardiovascular Event Rate in People With Coronary Disease

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Background—Higher levels of serum phosphate are associated with adverse cardiovascular outcomes, especially in the setting of overt hyperphosphatemia. Given the biological importance of phosphorus, it is plausible that higher levels of serum phosphate within the normal range may also be associated with adverse outcomes.

Methods and Results—We performed a post hoc analysis of data from the Cholesterol And Recurrent Events (CARE) study. Baseline serum phosphate levels were measured in 4127 fasting participants who were randomized to receive pravastatin 40 mg daily or placebo and followed up for a median of 59.7 months. We used Cox proportional-hazards models to examine the association between serum phosphate and adverse clinical outcomes after adjustment for potential confounders. During nearly 60 months of follow-up, 375 participants died. A significant association was noted between baseline serum phosphate level and the age-, race-, and sex-adjusted risk of all-cause death (hazard ratio per 1 mg/dL, 1.27; 95% confidence interval, 1.02 to 1.58). After categorization based on baseline phosphate level (<2.5, 2.5 to 3.4, 3.5 to 3.9, and ≥4 mg/dL) and further adjustment, a graded independent relation between phosphate and death was observed (P for trend=0.03). For instance, participants with serum phosphate ≥3.5 mg/dL had an adjusted hazard ratio for death of 1.27 (95% confidence interval, 1.02 to 1.59) compared with those with serum phosphate of <3.5 mg/dL. Higher levels of serum phosphate were also associated with increased risk of new heart failure, myocardial infarction, and the composite of coronary death or nonfatal myocardial infarction, but not the risk of stroke.

Conclusions—We found a graded independent relation between higher levels of serum phosphate and the risk of death and cardiovascular events in people with prior myocardial infarction, most of whom had serum phosphate levels within the normal range. Given the ready availability and low cost of serum phosphate assays, this finding may prove clinically useful. (Circulation. 2005;112:2627-2633.)

Key Words: cardiovascular diseases • kidney failure • myocardial infarction • phosphates

Phosphorus is essential for multiple and diverse biological functions, including cellular signal transduction, mineral metabolism, and energy exchange. Although >80% of total body phosphorus is stored in bone and teeth, intracellular phosphorus exists in the form of organic compounds such as adenosine triphosphate and as free anions like H2PO4−, which are commonly referred to as phosphate. Serum phosphorus primarily occurs in the form of inorganic phosphate, which is maintained within the physiological range by regulation of dietary absorption, bone formation, and renal excretion, as well as equilibration with intracellular stores.1–4

There has been considerable interest recently in the relation between increasing serum phosphate levels and adverse cardiovascular outcomes.5 However, available studies have examined the relation between phosphate and cardiovascular outcomes in prevalent subjects with impaired kidney function, many of whom had overt hyperphosphatemia and abnormal serum calcium levels resulting from secondary hyperparathyroidism.5–9 Given the biological importance of phosphorus, it is plausible that higher levels of serum phosphate may also be associated with adverse outcomes even in the absence of kidney disease and hyperphosphatemia.

We tested the hypothesis that higher serum phosphate levels were associated with risk of all-cause mortality and adverse cardiovascular outcomes in a population of participants with coronary disease, the vast majority of whom did not have overt hyperphosphatemia.

Methods

Study Design and Patients

This post hoc analysis of data from a previously conducted randomized trial was approved by the institutional review board at the
Measurement of Serum Phosphate and Kidney Function

Baseline phosphate levels were measured in fasting participants with an ammonium molybdate assay on the Olympus AU1000 auto-analyzer (normal range, 2.5 to 4.5 mg/dL). Baseline serum phosphate was considered a continuous variable and in categories (<2.5, 2.5 to 3.4, 3.5 to 3.9, and ≥4 mg/dL). We estimated glomerular filtration rate (GFR) using the following equation: 186×SCr^{1.154}×age (in years)^{-0.203}×1.210 (if black)×0.742 (if female), where SCr is serum creatinine (in mg/dL). This formula has been shown to have good agreement with iothalamate measurements of GFR. Participants with GFR <60 mL/min/1.73 m² body surface area were considered to have chronic kidney disease as per recent guidelines. In sensitivity analyses, we used the Cockcroft-Gault equation or serum creatinine as alternative estimates of kidney function. Proteinuria was defined by trace or greater protein on dipstick urinalysis.

Statistical Analysis
We used χ² tests or 1-way ANOVA to test for differences in categorical or continuous factors, respectively, between different categories of serum phosphate. Multivariate linear regression was used to determine factors associated with baseline serum phosphate levels. We used Cox proportional-hazards models to examine the relation between serum phosphate levels and clinical outcomes. Backward and forward stepwise selection techniques obtained similar results, and variables that were significant at the P <0.2 level during backward stepwise selection were included in the final model for the relation between phosphate and all-cause death. In addition to age, race, and sex, baseline variables considered for inclusion in the multivariate model were smoking status; alcohol use; diabetic status; age, race, and sex, baseline variables considered for inclusion in the multivariate model; baseline serum cholesterol; systolic and diastolic blood pressures; hemoglobin; serum calcium; serum albumin; waist-to-hip circumference ratio; body mass index; left ventricular ejection fraction; fasting serum glucose; fasting serum triglyceride; low-density lipoprotein cholesterol; high-density lipoprotein cholesterol; total cholesterol; and country of treatment (the United States or Canada). The same covariates for the all-cause death model were used to adjust models examining the relation between phosphate and the other clinical outcomes. Adjusted survival curves were produced for these final models using the mean of covariates method. In sensitivity analyses, additional variables that were independently associated with serum phosphate levels in the current data set or were likely to be associated with the risk of clinical outcomes were forced into the models. We determined that the proportional-hazard assumption was satisfied by examining plots of the log-negative-log of the within-group survival functions versus log-time and by comparing Kaplan-Meier (observed) with Cox (expected) survival curves. Values are reported as mean±SD or percentages; 95% confidence intervals (CIs) are provided when appropriate, and all probability values are 2 sided. Analyses were performed with Stata 8 SE software.

Results

Baseline Characteristics
Of 4159 CARE participants, 4127 had serum phosphate measured at baseline and were eligible for this analysis. The demographic characteristics of these remaining participants are shown in Table 1. Serum phosphate ranged from 1.6 to 9.3 mg/dL (median, 3.3; interquartile range, 3.0 to 3.6; mean, 3.3±0.5 mg/dL), and 5.8% had serum phosphate levels outside the normal range of 2.5 to 4.5 mg/dL (hyperphosphatemia in 24 of 4127, hypophosphatemia in 215 of 4127). The median duration of follow-up was 59.7 months.

Factors Associated With Higher Serum Phosphate Levels
Baseline characteristics of study participants are shown in Table 1. Factors that were independently associated with serum phosphate level are shown in Table 2. Overall, there was a direct association between GFR and serum phosphate levels, but stratified analyses showed that serum phosphate was inversely correlated with kidney function when baseline GFR was <60 mL/min/1.73 m² and directly correlated with kidney function when baseline GFR was ≥60 mL/min/1.73 m². However, mean kidney function was qualitatively similar in all 4 categories of baseline serum phosphate. For example, mean GFR was 68.2 mL/min/1.73 m² in subjects with serum phosphate <2.5 mg/dL and 72.8 mL/min/1.73 m² in those with serum phosphate ≥4 mg/dL. In addition, mean serum phosphate levels were similar in people with and without baseline GFR <60 mL/min/1.73 m² (3.3±0.5 versus 3.3±0.5 mg/dL; P>0.9).

Association Between Serum Phosphate Level and All-Cause Death
A significant association was noted between baseline serum phosphate level and the age-, race-, and sex-adjusted risk of all-cause death (hazard ratio [HR] per 1 mg/dL, 1.27; 95% CI, 1.02 to 1.58; P=0.03; Table 3). When participants were divided into 4 categories based on their baseline phosphate level (<2.5, 2.5 to 3.4, 3.5 to 3.9, and ≥4 mg/dL), a graded relation between phosphate and death was observed after adjustment for age, race, and sex (P for trend=0.01; Table 3). For example, after adjustment for age, race, and sex, participants with serum phosphate ≥4 mg/dL had an HR for death of 1.42 (95% CI, 0.97 to 2.07) compared with those with serum phosphate of 2.5 to 3.4 mg/dL. Further adjustment for factors independently associated with mortality using stepwise multivariate analysis did not substantially affect the
graded relation between phosphate and the risk of death (P for trend=0.03). The fully adjusted risk of mortality in the highest category of phosphate was 1.32 (95% CI, 0.90 to 1.94) compared with the referent group (Table 3 and Figure 1). Results were similar when individuals with baseline GFR <60 mL/min/1.73 m² were excluded and when serum creatinine or the Cockcroft-Gault equation was used to estimate kidney function (data not shown). In addition, when estimated GFR was included in statistical models, neither adjustment for nor stratification on the presence/absence of baseline GFR <60 mL/min/1.73 m² influenced our results (data not shown).

**Association Between Serum Phosphate Level and New Congestive Heart Failure**

Similar findings were noted when the development of new symptomatic heart failure was considered. Higher levels of serum phosphate were associated with an increased risk of new heart failure after adjustment for age, sex, and race (P for trend=0.02; Table 3) and in the model (P for trend=0.03; Table 3). Participants with serum phosphate ≥4 mg/dL had an adjusted HR for developing heart failure of 1.43 (95% CI, 0.95 to 2.14) compared with those with serum phosphate of 2.5 to 3.4 mg/dL.
Association Between Serum Phosphate Level and Cardiovascular Events

After full adjustment, higher levels of baseline serum phosphate were significantly associated with the composite outcome of fatal or nonfatal myocardial infarction (P for trend=0.03). Participants with serum phosphate ≥4 mg/dL had a fully adjusted HR for experiencing myocardial infarction of 1.50 (95% CI, 1.05 to 2.16) compared with those with serum phosphate of 2.5 to 3.4 mg/dL. Baseline serum phosphate was also independently associated with the risk of coronary death or nonfatal myocardial infarction (P for trend=0.03; Table 3). Participants with serum phosphate ≥4 mg/dL had a fully adjusted HR for experiencing the composite outcome of coronary death or nonfatal myocardial infarction of 1.32 (95% CI, 0.95 to 1.84) compared with those with serum phosphate of 2.5 to 3.4 mg/dL. The risk of stroke was not significantly increased in participants with serum phosphate ≥4 mg/dL compared with those with serum phosphate of 2.5 to 3.4 mg/dL (adjusted HR, 0.93; 95% CI, 0.46 to 1.85).

A graded association was noted between baseline level of serum phosphate and the adjusted risk of all-cause mortality, development of heart failure or fatal or nonfatal myocardial infarction, and the composite outcome of fatal coronary disease or nonfatal myocardial infarction (all P for trend=0.03; Figure 1 and Figure 2). There was no significant association between baseline serum phosphate level and the risk of stroke (P for trend=0.27).

The relation between the baseline calcium-phosphate ion product and adverse clinical outcomes was tested by inserting a cross-product interaction term into the Cox models. The interaction term was nonsignificant in all models, suggesting that the calcium-phosphate product was not independently associated with any of the adverse outcomes.

Sensitivity Analyses

In sensitivity analyses, we adjusted for additional baseline factors found to be associated with serum phosphate levels in the current data set (alcohol use, country of treatment, use of β-adrenergic blockers, systolic blood pressure). These characteristics were forced into the adjusted model presented above but did not appreciably affect the association between higher levels of serum phosphate and the increased risk of death (P for trend=0.047), new heart failure (P for trend=0.02), fatal or nonfatal myocardial infarction (P for trend=0.04), the composite of fatal coronary disease or nonfatal myocardial infarction (P for trend=0.04), or stroke (P for trend=0.33).

Finally, we forced additional variables that could conceivably be associated with either exposure or outcome (baseline diuretic use, pravastatin use, serum calcium, and proteinuria) into the adjusted model; they did not appreciably affect results (data not shown).

Discussion

We found a graded, independent association between baseline fasting serum phosphate level and the risk of all-cause death, development of new heart failure, and coronary events in this population of individuals with previous myocardial infarction, most of whom had serum phosphate levels within the normal range. Compared with models with adjustment only for age, race, and sex, additional adjustment for potential confounders (including medication use and left ventricular ejection fraction) slightly attenuated but did not abolish the association between serum phosphate and adverse outcomes.

We identified several characteristics that were significantly associated with higher serum phosphate levels, including female sex, black race, diabetic status, higher levels of serum albumin, lower levels of hemoglobin, and current smoking. Use of β-adrenergic blockers and higher levels of alcohol consumption were also associated with higher serum phosphate levels, although the magnitude of the increase was small. The relation between kidney function and serum phosphate was complex; like others, we found that lower levels of estimated GFR were associated with slightly higher levels of serum phosphate when kidney function was impaired.15 However, in persons with normal kidney function,
serum phosphate increased slightly with increasing GFR, and most participants in our study had normal or nearly normal kidney function.

Despite the importance of phosphate for diverse cellular and physiological functions, little information describes the relation between serum phosphate and clinical outcomes. Several recent studies demonstrate that higher levels of phosphate are associated with an increased risk of all-cause and cardiovascular death when kidney function is impaired, especially in people with end-stage renal disease.\(^6\)–\(^9\) Vascular calcification has been postulated as the link between hyperphosphatemia and adverse outcomes in the setting of kidney disease, perhaps accelerated by abnormal calcium levels and hyperparathyroidism.\(^5\),\(^16\) However, unlike participants in the present trial (only 5.2% of whom had hyperphosphatemia at baseline), many of the subjects in these previous studies had overt hyperphosphatemia or were receiving medications that may have influenced the association between serum phosphate and outcome. To our knowledge, the present study is the first to examine the relation between serum phosphate and clinical outcomes in participants with generally normal kidney function.

The potential mechanism for the association between serum phosphate levels and adverse outcomes in the present study is unclear. Higher levels of serum phosphate might identify subjects with secondary hyperparathyroidism, which has been associated with adverse cardiovascular outcomes, especially when kidney function is impaired.\(^7\),\(^17\) However, secondary hyperparathyroidism would have been unusual in CARE participants, given their relatively preserved kidney function, and primary hyperparathyroidism would be expected to reduce serum phosphate levels. Although we did not have data on parathyroid hormone levels, we controlled for estimated GFR and for other factors that might be associated with hyperparathyroidism such as serum calcium and albumin.

Levels of 25-hydroxyvitamin D and calcitriol are reduced in heart failure, in association with increased serum phosphate but apparently normal serum calcium, after correction for serum albumin.\(^18\)–\(^20\) This low vitamin D status is hypothesized to influence cardiac contractility through effects on intracellular calcium and phosphate levels\(^20\) and has been linked to a modest increase in the risk of myocardial infarction in the general population.\(^21\) Although CARE participants were free of symptomatic heart failure at baseline, we speculate that higher serum levels of phosphate might be a marker for low vitamin D status and subclinical myocardial

### Table 3. Adjusted Association Between Serum Phosphate Level and Clinical Outcomes

<table>
<thead>
<tr>
<th>Event Category</th>
<th>Unadjusted</th>
<th>Age-, Race-, and Sex-Adjusted</th>
<th>Fully Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events, n (%)</td>
<td>Unadjusted HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>All-cause death</td>
<td>&lt;2.5 mg/dL</td>
<td>9 (6.9)</td>
<td>0.78 (0.40–1.52)</td>
</tr>
<tr>
<td></td>
<td>2.5–3.4 mg/dL</td>
<td>229 (16.7)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>3.5–3.9 mg/dL</td>
<td>104 (10.0)</td>
<td>1.25</td>
</tr>
<tr>
<td></td>
<td>≥4.0 mg/dL</td>
<td>33 (10.3)</td>
<td>1.42</td>
</tr>
<tr>
<td></td>
<td>per 1 mg/dL</td>
<td>1.27</td>
<td>1.02–1.58</td>
</tr>
<tr>
<td>Fatal coronary disease or nonfatal myocardial infarction</td>
<td>&lt;2.5 mg/dL</td>
<td>13 (9.9)</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td>2.5–3.4 mg/dL</td>
<td>289 (11.0)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>3.5–3.9 mg/dL</td>
<td>137 (13.1)</td>
<td>1.24</td>
</tr>
<tr>
<td></td>
<td>≥4.0 mg/dL</td>
<td>45 (14.1)</td>
<td>1.36</td>
</tr>
<tr>
<td></td>
<td>per 1 mg/dL</td>
<td>1.21</td>
<td>1.00–1.46</td>
</tr>
<tr>
<td>Fatal or nonfatal myocardial infarction</td>
<td>&lt;2.5 mg/dL</td>
<td>9 (6.9)</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>2.5–3.4 mg/dL</td>
<td>217 (8.2)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>3.5–3.9 mg/dL</td>
<td>98 (9.4)</td>
<td>1.17</td>
</tr>
<tr>
<td></td>
<td>≥4.0 mg/dL</td>
<td>39 (12.2)</td>
<td>1.52</td>
</tr>
<tr>
<td></td>
<td>per 1 mg/dL</td>
<td>1.24</td>
<td>1.00–1.53</td>
</tr>
<tr>
<td>Symptomatic heart failure</td>
<td>&lt;2.5 mg/dL</td>
<td>8 (6.1)</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>2.5–3.4 mg/dL</td>
<td>174 (6.6)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>3.5–3.9 mg/dL</td>
<td>88 (8.4)</td>
<td>1.27</td>
</tr>
<tr>
<td></td>
<td>≥4.0 mg/dL</td>
<td>33 (10.3)</td>
<td>1.54</td>
</tr>
<tr>
<td></td>
<td>per 1 mg/dL</td>
<td>1.22</td>
<td>0.95–1.57</td>
</tr>
</tbody>
</table>

In the fully adjusted models, HRs have been adjusted for age, sex, race, baseline smoking status, diabetic status, waist-to-hip circumference ratio, baseline fasting glucose, baseline GFR, baseline hemoglobin, baseline serum albumin, baseline aspirin use, and left ventricular ejection fraction.

*Probability value for linear trend.
dysfunction. This hypothesis is supported by data indicating that diet-induced reductions in serum phosphate levels lead to increased calcitriol levels in healthy men.22,23 Because no information on 25-hydroxyvitamin D or calcitriol levels was available to us, however, this hypothesis requires further study. A final consideration is that higher serum phosphate levels might indicate impaired kidney function, even after adjustment for estimated GFR, and that severity of renal disease rather than phosphate levels per se might account for the apparent association between higher serum phosphate and adverse clinical outcomes.24 We used an equation based on serum creatinine to estimate kidney function that is recommended by authorities12 but nevertheless has some limitations.25,26 Although we did not perform a gold standard measurement of GFR such as iothalamate clearance, our results were similar when alternative indices of kidney function were used and after exclusion of those with evidence of impaired GFR at baseline, making it less likely that our findings were confounded by the presence of renal insufficiency.

Strengths of our study include its relatively large size and the use of a central laboratory for all biochemical measurements. In addition, laboratory measurements were made in subjects in the fasting state, which likely reduced the variability of serum phosphate levels between participants.27 Finally, outcomes were ascertained according to prespecified criteria by individuals who were unaware of serum phosphate levels. However, our study also has some limitations that should be considered. First, because this was a post hoc observational analysis, we cannot rule out the possibility of residual confounding. However, the hypothesis that serum phosphate levels would be associated with adverse outcomes was formulated before the analyses were started, reducing the risk of spurious conclusions. In addition, we adjusted for multiple potential confounders, including characteristics as-

Figure 1. Fully adjusted risk of clinical outcomes by baseline serum phosphate. Probability values for trend are as follows: All-cause death, \( P = 0.03 \); new symptomatic heart failure (CHF), \( P = 0.03 \); fatal or nonfatal myocardial infarction (MI), \( P = 0.03 \); and coronary death or nonfatal myocardial infarction, \( P = 0.03 \). HRs have been adjusted for age, sex, race, smoking status, diabetic status, waist-to-hip circumference ratio, fasting glucose, GFR, hemoglobin, serum albumin, aspirin use, and left ventricular ejection fraction (all at baseline).

Figure 2. Fully adjusted time to clinical outcomes by baseline serum phosphate. Curves show the survivor function for each stratum of baseline serum phosphate using the mean of covariates method. Probability values for trend are as follows: All-cause death, \( P = 0.03 \); new congestive heart failure, \( P = 0.03 \); fatal or nonfatal myocardial infarction, \( P = 0.03 \); and coronary death or nonfatal myocardial infarction, \( P = 0.03 \). HRs have been adjusted for age, sex, race, smoking status, diabetic status, waist-to-hip circumference ratio, fasting glucose, GFR, hemoglobin, serum albumin, aspirin use, and left ventricular ejection fraction (all at baseline).
associated with serum phosphate levels in the current data set. Second, this analysis concerns a select population of individuals with prior myocardial infarction who were eligible for a randomized trial and therefore may not be representative of the general population. Additional studies should be done to confirm that the association between phosphate and adverse outcomes exists in other populations. Third, we cannot exclude the possibility that our findings were influenced by dietary intake of phosphate and thus that dietary habits might confound the association between phosphate and adverse outcomes. Fourth, the number of participants and outcomes in some strata (especially those with serum phosphate <2.5 mg/dL) was small, and some probability values were of marginal statistical significance. The small numbers of subjects with levels of serum phosphate in the lowest and highest categories probably contributed to the nonsignificant relation between serum phosphate (as a continuous variable) and outcome, because tests for trend were significant when phosphate was treated as a categorical variable. Finally, although we did not have ionized calcium levels, simultaneous adjustment for serum calcium and albumin did not affect our results, suggesting that levels of ionized calcium are unlikely to be an important confounder of the relation between serum phosphate and clinical outcomes.

In conclusion, we found a graded independent relation between higher levels of serum phosphate and the risk of heart failure, cardiovascular events, and all-cause death in people with prior myocardial infarction, most of whom had serum phosphate levels and kidney function within the normal range. Given the ready availability and low cost of serum phosphate assays, this finding may prove clinically useful. Further studies are required to determine the explanation for the association between phosphate and adverse clinical outcomes and to confirm that this relation is present in other populations.

Acknowledgments

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References


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