Serum Phosphate: A Novel Cardiovascular Risk Factor Even in Nonrenal Patients

Relation between Serum Phosphate Level and Cardiovascular Event Rate in People with Coronary Disease. *Circulation* 112: 2627–2633, 2005

Tonelli M., Sacks F., Pfeffer M., Gao Z.H., Curhan G.; for the Cholesterol and Recurrent Events (CARE) Trial Investigators

It has been known for decades that hyperphosphatemia is a feature of ESRD that may cause secondary hyperparathyroidism and soft tissue calcification (1), including vascular calcification (2). The latter comprises mainly calcification of intimal plaques (3) and of the media (4,5) of central arteries (Mönckeberg sclerosis), less frequently calcification of muscular arteries (the only type of vascular calcification that potentially disappears after reversal of hyperparathyroidism [6]) and calcific uremic arteriolopathy (calciphylaxis) (7,8).

Because calcification of the intima and media seemed not to pose an immediate threat to the dialysis patient’s life, it was in the past treated to some extent with “benign neglect”, until in 1998 the renal community was rudely made aware of the clinical relevance of serum phosphate by the communication of Block et al. (9); he found that in dialysis patients, survival was 27% less when predialysis serum phosphate concentration exceeded 6.5 mg/dl. Remarkably, there was no indiscriminate increase of mortality from all different causes across the board; the increase mainly concerned death from coronary heart disease (10). This finding is not implausible, because in patients with ESRD and coronary heart disease, coronary plaque calcification is four times more frequent than in nonrenal patients with coronary heart disease (3).

Obviously, vascular calcification is a much more complex process (11–14) than originally was thought (15). It certainly can not be explained fully by hyperphosphatemia alone, but phosphate, more specifically intracellular phosphate (12), plays a major role in the genesis of vascular calcification, particularly in the presence of ionized calcium (16).

Myocardial infarction accounts only for a relatively small proportion of deaths in dialysis patients; the most frequent causes are sudden death and heart failure (www.usrds.org). For this and other reasons, I suspect that the role of hyperphosphatemia presumably extends beyond its role to promote calcification of coronary (3) and central (5) arteries. For instance, recently, more advanced thickening of the intima and media of the carotid artery was found in hyperphosphatemic hemodialysis patients (17). Furthermore, in an experimental study, we showed in subtotally nephrectomized rats that myocardial fibrosis and microvessel disease of the heart developed only in the presence of hyperphosphatemia (18), illustrating that in uremia phosphate also plays a more general role in the genesis of the excessive cardiovascular risk profile beyond causing vascular calcification. Phosphate has numerous roles in cellular metabolism and presumably also is an important intracellular signaling substance.

Is the adverse role of high serum phosphate concentrations in renal patients restricted to end-stage renal failure? Kestenbaum et al. (19) recently reported that in patients with chronic kidney disease, serum phosphate concentrations >3.5 mg/dl were associated with higher mortality, and the risk increased stepwise with each 0.5-mg/dl higher serum phosphate concentration. Even the target of 5.5 mg/dl serum phosphate in dialysis patients, proposed by Block and Port (20) and the phosphate recommendations of current guidelines (21), which are extremely difficult to achieve to begin with, may not provide optimal cardiovascular protection.

In the past, a paper by the Hammersmith hospital group (22), which failed to receive the attention that it deserved, had provided documentation in a small series of nonrenal patients with coronary heart disease that serum phosphate concentrations were positively and significantly ($P < 0.003$) correlated with the severity of coronary artery disease and were correlated with the severity of stenoses and presence of occlusions (22).

The above paper of Tonelli et al., a prespecified *post hoc* analysis of the Cardiac Arrhythmia Suppression Trial (CAST), extends this observation. In 4127 fasting patients, the authors documented that higher levels of serum phosphate within the normal range are associated with
more adverse outcomes. In the CAST study, patients with a history of myocardial infarction had been randomly assigned to receive either Pravastatin 40 mg/d or placebo. They were followed for approximately 60 mo, during which time 375 patients died. The median serum phosphate concentration was 3.3 mg/dl, and only 5.8% had fasting serum phosphate concentrations outside the normal range (2.5 to 4.5 mg/dl).

There was a direct association between GFR and serum phosphate concentrations: The relation was inverse when GFR was <60 ml/min and positive when GFR was >60 ml/min. The observed relationship between serum phosphate and outcome was not an artifact of low GFR, however, because the GFR was similar in all quartiles of serum phosphate, and the relation between phosphate and outcome persisted when individuals with a GFR <60 ml/min were excluded.

The serum phosphate concentration at baseline was significantly associated with all-cause death even when adjusted for numerous confounders. The calcium × phosphate product was not independently associated with adverse outcome. If the serum phosphate concentration was higher by 1 mg/dl, then the hazard ratio was higher by 27% (hazard ratio 1.27; 95% confidence interval 1.02 to 1.58), comparable to the increase of risk that Block et al. (9) had found in dialyzed patients! Furthermore, a graded independent relation existed between serum phosphate and death across the entire spectrum of serum phosphate concentrations (P = 0.03 for trend). Apart from all-cause mortality, high serum phosphate concentrations (> 3.5 mg/dl) also were associated with a higher risk for de novo heart failure and myocardial infarction but not a higher risk for stroke. Residual confounding always is a concern in such post hoc analyses of patients who are not randomly assigned according to the question asked in the analysis, but the consistency of the results is remarkable. As a cautionary note, one must be aware that the results in this population with high cardiovascular risk cannot be extrapolated to the general population.

Fasting serum phosphate measurements are confounded easily by a number of factors, such as circadian rhythm, causing intraday differences of up to 30% (with a nadir in the late forenoon); habitual phosphate intake; phosphate leak from blood cells unless serum is separated within 2 h (I suspect that this also is the explanation for the highest serum phosphate value of 9.3 mg/dl in the CAST study); hemolysis; increase in P concentration in serum relative to plasma because of release from platelets; artifacts by clouding from hyperlipemia, and so forth. It well may be that the above relationship has been missed in past studies for such reasons. In the above study, blood was obtained under standardized conditions and measured in a central laboratory.

The finding raises the issue of the underlying mechanism. The authors speculate that because of the known role of phosphate in the control of vitamin D concentrations (23) and the effect of active vitamin D on renin activity (24) and cardiac function (25,26), changes in vitamin D metabolites well may explain the finding. This hypothesis is not unreasonable but is unproved in the absence of vitamin D measurements and does not exclude other explanations. For instance, as early as 1925, the effect of glucose on phosphate had been documented as well as the effect of insulin on phosphaturia and serum phosphate (27). In view of the roles of hyperinsulinemia and insulin resistance in the cardiovascular risk profile, this (and other) alternatives justify detailed pathomechanistic studies.

Finally, as a nephrologist, one is saddened by the reflection that even serum phosphate concentrations in the normal range are injurious to the nonrenal patient with coronary heart disease. How can we ever achieve “optimal” phosphate concentrations in the renal patient!

References
Intravenous calcitriol regresses myocardial hypertrophy in hemodialysis patients with secondary hyperparathyroidism. *Am J Kidney Dis* 33: 73–81, 1999


**Estimated GFR: Are There Limits to Its Utility?**

**Monitoring Kidney Function in Type 2 Diabetic Patients with Incipient and Overt Diabetic Nephropathy.** *Diabetes Care* 29: 1024–1030, 2006

Rossing P., Rossing K., Gaede P., Pedersen O., Parving H.-H.

There is no doubt that it is highly desirable to detect and monitor renal function of patients with diabetic nephropathy early in the course of the disease, because the benefit from early intervention is much superior to that of late intervention, as illustrated by the reduction of the relative risks in intervention studies on patients with early (1,2) as compared with late stages of diabetic nephropathy (3,4). The usefulness of albuminuria to detect patients who are at high risk for progression to overt diabetic nephropathy has been known for decades (5), but an important turning point in the evolution of diabetic nephropathy is onset of GFR loss that progresses to ESRD. Relying only on albuminuria also may miss the substantial proportion of patients who have type 2 diabetes and have low GFR despite the absence of albuminuria (6). Information on GFR and its evolution therefore is of considerable clinical interest.

Recently, algorithms have been widely introduced to estimate GFR (estimated GFR [eGFR]) by using the Cockcroft-Gault (7) or, better, the Modification of Diet in Renal Disease (MDRD) equations (8,9). The National Kidney Foundation advises regular monitoring of GFR in patients with renal disease, including diabetic renal disease, using this algorithm (10).

Rossing et al. (11) addressed the important issue of whether the precision and accuracy of eGFR is sufficient to permit clinically useful monitoring of the evolution of diabetic nephropathy in patients with type 2 diabetes. This comparison of methods is clinically relevant, because measurements of true GFR using the $^{51}$Cr-EDTA (12), $^{99m}$Tc-DTPA (13), $^{125}$I-iothalamate (14), or iohexol (15) technique as the gold standard is complex, time-consuming, laborious, and expensive; they involve repeated blood or urine sampling or even exposure to radiation.

To clarify this issue, the authors followed two cohorts of patients:

1. A cohort of 156 microalbuminuric patients who had type 2 diabetes and were followed for 8 yr with four measurements of GFR, using the well-validated $^{51}$Cr-EDTA clearance technique as described by the authors previously (16).
2. A cohort of 227 patients who had type 2 diabetes with overt diabetic nephropathy and were followed for a median of 6.5 yr (range 3 to 17) with a median of seven measurements of GFR (range 3 to 22).

The ability of eGFR, estimated using Cockcroft-Gault or the MDRD equation, to predict GFR at baseline or the change of GFR with time was definitely sobering: In the cohort of microalbuminuric patients, the mean GFR at baseline was 117 ± 24 ml/min per 1.73 m² by $^{51}$Cr-EDTA clearance as compared with 92 ± 20 with the MDRD and 103 ± 24 with the Cockcroft-Gault algorithm; the difference between both estimates of GFR and true GFR was highly significant ($P < 0.001$). More important is the issue of how well eGFR corresponded to true GFR: The 95% limits of agreement varied from −66.1 to 20.3 for the MDRD estimate and from −58.7 to 30.7 for the Cockcroft-Gault estimate.

How well did the GFR estimates reflect the rate of decline of GFR? The annual loss of true GFR was 4.1 ± 4.2 ml/min per 1.73 m² as compared with 2.9 ± 2.8 with MDRD and 3.4 ± 3.2 with Cockcroft-Gault algorithm. Both estimates differed significantly ($P < 0.001$) from loss of true GFR, and the differences between the methods increased with increasing rates of decline in GFR.

In the cohort with overt diabetic nephropathy, the mean GFR at baseline was 84 ± 30 ml/min
per 1.73 m² by ⁵¹Cr-EDTA clearance as compared with 73 ± 24 with the MDRD and 73 ± 24 with the Cockcroft-Gault algorithm; the difference between both estimates of GFR and true GFR again was highly significant (P < 0.001). The 95% limits of agreement were from −47 to 25 for the MDRD and from −39 to 33 for the Cockcroft-Gault estimate. The annual loss of true GFR was 5.2 ± 4.1 ml/min per 1.73 m², and both the MDRD estimate with 4.2 ± 3.8 and the Cockcroft-Gault estimate with 4.6 ± 4.1 were off the mark (both P < 0.001).

A GFR of 60 ml/min indicates transition from chronic kidney disease (CKD) stage 2 to stage 3 and is a sensible clinical boundary marker. The predictive value that a patient with an eGFR <60 has a true (measured) GFR <60 was only 51% for the MDRD and 66% for the Cockcroft-Gault estimate. The relevance of accurately assessing this boundary marker of GFR is underlined by the observation that a measured GFR <60 was a significant predictor of death (hazard ratio 1.7, P < 0.02), although this was “explained” by known risk factors and was no longer statistically significant after appropriate adjustment. In contrast both GFR estimates failed to predict death.

Which conclusions did the authors draw? Both estimates of GFR underestimated true GFR at baseline as well as the rate of loss of GFR in microalbuminuric and macroalbuminuric patients with diabetes. In addition they had a low sensitivity to detect impaired renal function in patients with GFR <60 ml/min per 1.73 m². Therefore, the authors concluded that eGFR according to MDRD or Cockcroft Gault is unacceptable for monitoring kidney function in patients with type 2 diabetes and incipient and overt diabetic nephropathy. This conclusion certainly is supported by their findings.

Are there potential explanations for the poor performance of GFR estimates? One notorious crux is the measurement of creatinine. More than 50 substances were shown to react as noncreatinine chromogens in the alkaline picrate Jaffe reaction, causing substantial overestimation of serum creatinine by approximately 20% (17,18). The contribution of noncreatinine chromogens to measured serum creatinine values diminishes with progressive renal failure, because, in contrast to creatinine, they do not cumulate. In end point methods, nonspecific chromogens can be reduced by adsorption to Lloyds reagent or in continuous flow systems (autoanalyzer) via removal of proteins by dialysis. (The ideal approach to measure true creatinine obviously would be the absolutely specific enzymatic methods, which generally are not available, however, and are relatively expensive.)

The authors of the above paper selected the kinetic Jaffe method, which is based on the differences in time course of color development by noncreatinine chromogen and by creatinine in the alkaline picrate reaction. The values were not calibrated to the MDRD reference laboratory (19), which is a definite limitation of the study of Rossing et al. It is not certain, however, whether the calibration issue alone, important although it is, explains the gross deviations that were found by Rossing et al. Another potential confounder, the known higher variability of GFR in individuals with normal GFR, also is excluded by the protocol, which included simultaneous measurement of “gold standard” GFR using the ⁵¹Cr-EDTA clearance.

The importance of calibration is illustrated by the recent controversy (20) in JASN about the true prevalence of chronic kidney disease (CKD) in the general population, based on Third National Health and Nutrition Examination Survey data (21). The argument of whether insufficient standardization of the creatinine measurement explained major differences of GFR estimates and different results concerning the prevalence of CKD in population screening studies had been raised. This argument is plausible, because even laboratories that use the same technique may differ systematically (17,22–24). The abbreviated MDRD equation is based on serum creatinine values that are determined using the Beckman Astra 8 method, as used in the Cleveland clinic. Most laboratories use technologies with incomplete correction for the presence of noncreatinine chromogens, thus obtaining artificially elevated serum creatinine values. Because the correction for the presence of noncreatinine chromogens is different in the different methods (17,25), correction formulas have been evaluated (22) and proposed (26,27). Kidney Disease Outcomes Quality Initiative guidelines advise the use of only corrected serum creatinine values in the abbreviated MDRD equation. The importance of standardization of creatinine
measurements has been strongly emphasized recently (www.nkdep.nih.gov) (17,28). Obviously, one cannot obtain reliable results when imprecise data are fed into the eGFR equation (for according to a famous slogan in informatics, “One cannot feed in garbage and get out fruit juice”). The input of potentially imprecise serum creatinine values is a major limitation of predictive equations that are developed to predict measured creatinine clearance (Ccr), as in the Cockcroft-Gault equation (7), or other equations (29–31). Because of tubular secretion of creatinine, the use of Ccr as a GFR estimate in the Cockcroft-Gault equation is problematic to begin with, because Ccr is not a faithful index of GFR. Less problematic but fraught with the same problem of accuracy of serum creatinine measurements are equations that had been developed to predict true GFR measured with one of the above “gold standard” methods (8).

Several studies in healthy individuals (kidney donors) as well as in patients with CKD found that the MDRD equation underestimated GFR in outpatients with moderate to advanced CKD but was particularly problematic in healthy individuals (28,32,33). This is not surprising because the equation was derived from a study of patients with impaired renal function and extrapolations tend to become more inaccurate the farther they are away from the original database.

Rossing et al. (11) emphasized that although the guidelines of the National Kidney Foundation (10) recommend regular monitoring of renal patients, including patients with diabetes and eGFR, the sensitivity to detect impaired renal function in their patients with type 2 diabetes and a true GFR <60 ml/min per 1.73 m² was completely unsatisfactory: 72% with the MDRD and 66% with the Cockcroft-Gault equation. This argument certainly is valid.

How do these results compare with other studies in patients with diabetes? Rigalleau et al. (34) compared the values of the ⁵¹Cr-EDTA clearance with estimates of GFR on the basis of the MDRD or the Cockcroft-Gault equation and found that the MDRD equation had better maximal accuracy for recognizing moderate and severe renal failure. In a cross-sectional study, Vervoort et al. (35) compared relatively small cohorts of healthy individuals with patients with type 1 diabetes and came to the conclusion that the MDRD equation gave inaccurate results in patients with normal or increased renal function. In this study, it was even inferior to the Cockcroft-Gault equation. In the Diabetes Control and Complications Trial (DCCT), Ibrahim et al. (36) compared MDRD- and Cockcroft-Gault–based GFR estimates with the measured iothalamate clearance. In these patients with normal serum creatinine, the MDRD equation underestimated the iothalamate GFR and thus was likely to flag early declines in kidney function, thereby limiting the clinical usefulness to recognize early loss of renal function. In a study with 4 yr of follow-up, the Joslin clinic (37) evaluated the loss of GFR in 30 patients with type 2 diabetes, measuring GFR by iothalamate clearance; creatinine-based eGFR compared poorly with trends in iothalamate clearance, so the results generally are in line with the unsatisfactory performance of creatinine-based estimates of GFR in the study of Rossing et al. (11).

Is it all doom and gloom? Four years ago, Mussap et al. (38) reported the results of a study in 52 albuminuric patients with type 2 diabetes. The loss of GFR measured as ⁵¹Cr-EDTA clearance was strongly correlated (r = 0.84) with the reciprocal of cystatin C. This was confirmed in the study of Perkins et al. (37). Furthermore, a recent cross-sectional study in 251 patients with diabetes and a measured GFR of 89.2 ± 3.0 showed that GFR by ⁹⁹mTc-DTPA was strongly correlated with cystatin C–based estimates of GFR. For this purpose, they used a formula that was obtained in a test population (39). Cystatin C also was shown recently to be a more powerful predictor of all-cause mortality and cardiovascular events than serum creatinine concentrations and creatinine-based estimates of GFR (40), so this procedure might kill two birds with one stone. Serum cystatin C has been validated as a good indicator of GFR (41–44). Cystatin C, a nonglycosylated 13-kD microprotein, does not share most of the problems of creatinine (e.g., measurement artifacts from noncreatinine chromogens, tubular secretion, dependence on diet and muscle mass), but there nevertheless are several factors that have an impact on its serum levels independent of GFR (44,45). Currently, there also is the delicate issue of cost (up to 10 Euro per measurement), although this may go down if the parameter is measured more widely.
It is too early to state that cystatin C is a way out of the dilemma or to make definite statements on its clinical usefulness, but the study of Rossing et al. (11), the largest prospective study in type 2 diabetes so far, certainly has the merit to have proved definitely the inadequacy of creatinine-based estimates to monitor the evolution of GFR in the critical early stages of diabetic nephropathy, thereby exposing the need to develop better but clinically applicable methods to assess GFR.

References


