

Left Ventricular Hypertrophy: Is Hyperphosphatemia among Dialysis Patients a Risk Factor?

Steven G. Achinger and Juan Carlos Ayus

Texas Diabetes Institute, Bexar County Hospital District, San Antonio, Texas

Cardiovascular disease occurs in ESRD patients at rates that are far higher than is seen in the general population, and cardiovascular deaths account for the majority of deaths among dialysis patients. Abnormal mineral metabolism is a novel cardiovascular risk factor among dialysis patients. Recently published results demonstrated that even with good control of BP and anemia, conventional hemodialysis is associated with significant left ventricular hypertrophy (LVH); however, daily hemodialysis was associated with a significant reduction in LV mass index (LVMI). Furthermore, it was shown that control of serum phosphorus correlates with the reduction in LVMI. These data suggest a novel mechanism for the deleterious effect of elevated serum phosphorus on cardiovascular outcomes among hemodialysis patients: LVH. Other investigators have noted an association of hyperphosphatemia and LVH; however, this study was the first to demonstrate that improvement in serum phosphorus is associated with reduction in LVM. In addition, it is shown that daily hemodialysis is an effective modality in improving serum phosphorus through significantly improved phosphorus removal. Elevated serum phosphorus leads to vascular calcification, which can lead to LVH by decreasing vascular compliance. However, our study showed an improvement in LVMI during a 12-mo period. Because vascular calcification is unlikely to remit over this time period, it is proposed that serum phosphorus has a reversible, cardiotoxic effect that leads to LVH that can be reversed successfully with good control of serum phosphorus.

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Mortality among hemodialysis patients remains unacceptably high with the prognosis of patients with newly diagnosed ESRD in the United States approximating that of lung cancer patients (1). Cardiovascular disease is present in patients with ESRD at rates that far exceed the general population and accounts for the majority of deaths among patients with ESRD (2). However, cardiovascular disease in the ESRD population has unique aspects. This is exemplified best by the results of the 4-D trial, in which control of hypercholesterolemia failed to improve mortality among dialysis patients (3). Approaches to preventing cardiovascular death among dialysis patients requires an approach that is tailored to the particular aspects of cardiac disease in uremia. There is a high prevalence of echocardiographic abnormalities among dialysis patients (Figure 1); only 16% of prevalent dialysis patients have normal anatomic and functional findings (4), and these abnormalities predict mortality among dialysis patients (5,6). Hyperphosphatemia is a widely recognized risk factor for cardiovascular mortality in the ESRD population (7,8). Currently, the mechanistic link between hyperphosphatemia and cardiovascular mortality in dialysis patients is not known; however, recent data suggest that the deleterious effects of hyperphosphatemia may be related to left ventricular hypertrophy (LVH) (9–11). Furthermore, our group recently published data that suggest that correction of hyperphos-

phatemia is associated with reduction in left ventricular mass index (LVMI) (11). This review focuses on the new evidence that suggests that hyperphosphatemia leads to LVH and highlights effective treatment options.

Physiologic Consequences of Hyperphosphatemia

Hyperphosphatemia is a consequence of altered divalent ion balance that is caused by the decline in GFR in renal failure. Unlike serum calcium, which is not a good indicator of total body calcium stores (12), elevations in serum phosphorus in ESRD are indicative of total body phosphorus excess. Hyperphosphatemia is the underlying abnormality that leads to many of the mineral metabolism complications of ESRD, such as secondary hyperparathyroidism and resultant bone disease (13) and vascular calcification (14). It now is recognized that the metabolic complications of ESRD have a significant impact on mortality through increases in cardiovascular disease; therefore, understanding of these complications and efficacious therapies is critical to improving outcomes.

The best known cardiovascular consequence of hyperphosphatemia is vascular calcification, which is a common complication of ESRD and diabetes (15–17). Vascular calcification, at the cellular level, is an active process that can be induced by hyperphosphatemia (14). *In vitro* studies have demonstrated that uremic serum induces vascular smooth muscle cells to increase production of osteopontin and alkaline phosphatase and subsequently increase calcification (18). High levels of phosphate in cell culture can induce phenotypic changes in vascular smooth muscle cells, upregulating genes that are as-

Address correspondence to: Dr. Juan Carlos Ayus, Medical Director, Dialysis Service, Texas Diabetes Institute, University Dialysis West, 701 S. Zarzamora, San Antonio, TX 78201. Phone: 713-795-9333; Fax: 713-942-9342; E-mail: carlosayus@yahoo.com

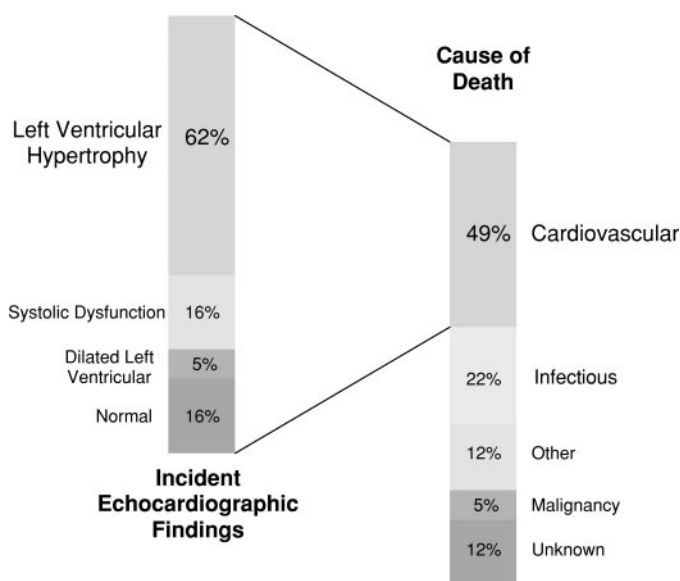


Figure 1. Burden of echocardiographic cardiac disease and cardiac mortality among dialysis patients.

sociated with bone formation (osteocalcin, osteopontin, and Runx2) and leading to apatite deposition in the matrix surrounding the cells (14,19,20). Elevated extracellular phosphate levels leads to increased cellular uptake of phosphate *via* pit-1, a type III sodium-phosphate co-transporter (14). The ensuing elevated intracellular phosphate levels induce the cellular transformation that ultimately leads to the release of pro-calcifying factors (including calcium-binding proteins and alkaline phosphatase) (19). In human studies, increased expression of *Osf2/Cbfa1* (a transcription factor that is involved in osteoblast differentiation and bone formation) has been demonstrated in the epigastric arteries of uremic patients (21). These findings show that vascular calcification that is induced by hyperphosphatemia is a regulated process with similarities to bone mineralization and not a passive phenomenon.

Other factors that play a role in vascular calcification include age, dialysis vintage, and the use of calcium-containing phosphorus binders (15) as well as the presence of diabetes (22). These other factors create a substrate on which vascular calcification can occur, and poor mineral metabolism (especially elevated serum phosphorus) over time accelerates this underlying process. Therefore, poor metabolic control (once ESRD is established) as well as calcium loading through calcium-containing phosphate binders are major modifiable risk factors for this condition (Figure 2). The goal of therapy is to prevent the progression of vascular calcification in those with established manifestations and to prevent the development in those who do not have established calcification.

Hyperphosphatemia and LVH

LVH is a powerful predictor of cardiovascular outcomes in hemodialysis patients and is a multifactorial process with many causes in ESRD, such as anemia, pressure loading through hypertension, and reduced vascular compliance (5,23). Our

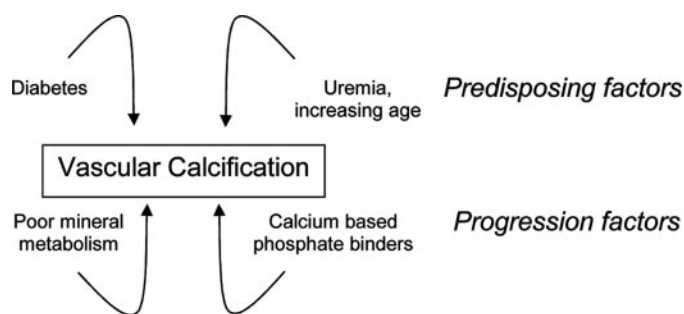


Figure 2. Development of vascular calcification among dialysis patients.

group recently published results that demonstrate that even with aggressive therapy for BP control (average systolic BP of 145 mmHg) and anemia, conventional hemodialysis is associated with significant LVH (mean LVMI of 155 g/m²) (11), whereas short daily dialysis is associated with a significant reduction in LVMI (154 to 108 g/m²) and control of serum phosphorus (mean serum phosphorus of 4.2 mg/dl) correlates with this reduction in LVMI. These findings suggest a novel mechanism for the deleterious effect of hyperphosphatemia on cardiovascular outcomes among hemodialysis patients (11). Previous investigators have noted the association of hyperphosphatemia and LVH (9,10), although our study is the first that we are aware of to show that improvement in serum phosphorus is associated with improvement in LVH. Several studies now have noted an association of altered mineral metabolism and LVH and cardiac dysfunction. Marchais *et al.* (24) noted increased diastolic and mean arterial pressures, higher cardiac index, higher heart rate, and increased stroke index in hyperphosphatemic *versus* normophosphatemic patients. Strozec *et al.* (9) showed that poor control of serum phosphorus and calcium-phosphorus product is associated with increased LVM. A recent report by Galetta *et al.* (10), using echocardiography and tissue Doppler imaging, showed that higher plasma phosphate and calcium-phosphate products are associated with signs of diastolic dysfunction in a cross-sectional study. Hayashi *et al.* (25) performed echocardiography before and after hemodialysis in 13 conventional hemodialysis patients and demonstrated that elevated serum phosphorus and calcium-phosphorus product are associated with decreased isovolumetric contraction velocity and peak systolic velocities, suggesting that poor mineral metabolism can affect systolic function. Furthermore, they showed that after a single hemodialysis session, these indices improved. These recent studies suggest that poor mineral metabolism has adverse consequences on LV geometry and function and that dialysis improves LV function, particularly in those with poor control of mineral metabolism. In support of these findings, a recent animal study showed that isolated hyperphosphatemia (induced by five-sixths nephrectomy, parathyroidectomy, parathyroid hormone replacement, and high-phosphorus diet) (26), in a model of chronic renal failure, leads to increased LVM. It is interesting that, in this study, vascular calcification was not demonstrated in the experimental animals (26). These studies suggest that poor con-

trol of mineral metabolism plays a role in the pathogenesis of LVH among dialysis patients.

Our findings show that in patients in whom phosphorus is improved, LVH improves (11). Decreased vascular compliance through vascular calcification that is induced by poor mineral metabolism is a very likely mechanism for the association of poor mineral metabolism and cardiovascular disease. However, our study suggests that other mechanisms may contribute. Vascular calcification is a long-term process that is not likely to be reversed in a 12-mo study of daily hemodialysis, such as ours (11), especially because the most efficacious dialytic intervention at achieving phosphorus control, nocturnal hemodialysis, does not induce a remission of vascular calcification (27). Therefore, it would be unlikely that control of serum phosphorus would contribute to improvement in LVMI if vascular calcification is necessary for hyperphosphatemia to induce LVH. If reduction in serum phosphorus can contribute to reduction in LVM, then a different mechanism is likely. Previous *in vitro* studies showed that elevated phosphorus can induce cellular changes and cellular phenotype (14,19). This leaves open the possibility that hyperphosphatemia can facilitate LVH through changes in systemic vascular resistance by altering vascular reactivity or endothelial function by inducing endothelial or vascular smooth muscle phenotype. Therefore, our results, for the first time, suggest that the effects of hyperphosphatemia on LVM, noted by several other groups independent from us (9,10), is a reversible process (Figure 3). We propose that there is a pathway, independent of overt vascular calcification, that mediates the development of LVH in dialysis patients. Whether this is an effect on vascular reactivity or a direct myocardial effect is purely speculative at this point, and future study in this area is needed.

Elusive Target: Ideal Serum Phosphorus

Given the known associations of elevated serum phosphorus and mortality on dialysis, control of serum phosphorus is one of the key elements in risk factor reduction and is recognized by

the Kidney Disease Outcomes Quality Initiative (K/DOQI) as an important area of intervention (28). K/DOQI goals are based on observational studies that showed higher mortality associated with hyperphosphatemia (7,8). However, these and other, more recently published studies challenge the current K/DOQI goal for serum phosphorus. Block *et al.* (8) reported that the lowest multivariable adjusted relative risk for death occurred for serum phosphorus of 4.0 to 5.0 mg/dl with an adjusted 10% relative increase for 5.0 to 5.5 mg/dl. In Dialysis Outcomes and Practice Patterns Study (DOPPS), a serum phosphorus of 4.5 to 5.0 mg/dl had the lowest multivariable adjusted relative risk for death, with a 12% relative increase for 5.0 to 5.5 mg/dl (29). These and other findings from a European dialysis population (30) suggest that current K/DOQI goals may be too permissive of hyperphosphatemia >5.0 mg/dl (8,29,30).

As currently written, the K/DOQI guidelines do not mandate reducing phosphorus to the levels that are known to be associated with the lowest risk for mortality (Figure 4). Daily hemodialysis with session length of 3 h is a modality that has been shown to reduce effectively serum phosphorus levels (11,31); increasing dialysis frequency currently is recommended only when the relative risk for death is increased by 43% (28). In addition, these guidelines suggest changing only the variable of dialysis frequency, without explicitly stating that total dialysis time also must be increased, because just altering frequency has not been shown to reduce effectively serum phosphorus levels (32–34). We believe that the best interpretation of the available literature suggests that to mitigate the effects of hyperphosphatemia, serum phosphorus goals should be <5.0 mg/dl and that the most efficacious approach to achieving this is to use either nocturnal hemodialysis (which is the modality with the greatest phosphorus removal) or daily hemodialysis six times a week with a session length of 3 h. Some patients may be able to achieve control of serum phosphorus with more modest increases in total time, but it must be emphasized that simply changing dialysis frequency while keeping total time constant will not improve metabolic control.

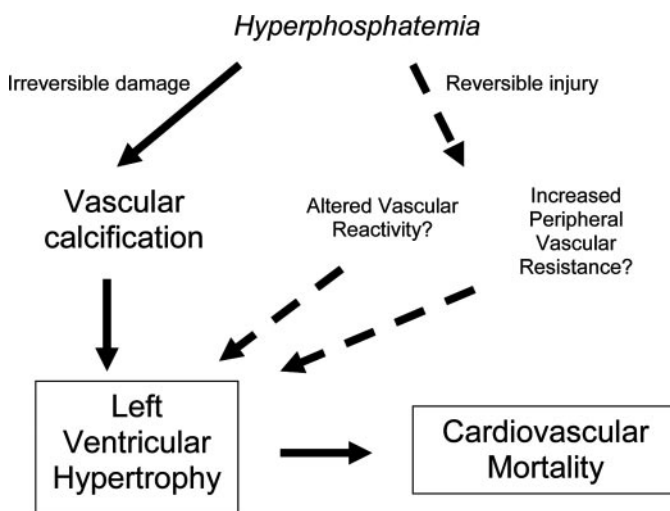


Figure 3. Proposed model for the deleterious effects of hyperphosphatemia on cardiovascular mortality.

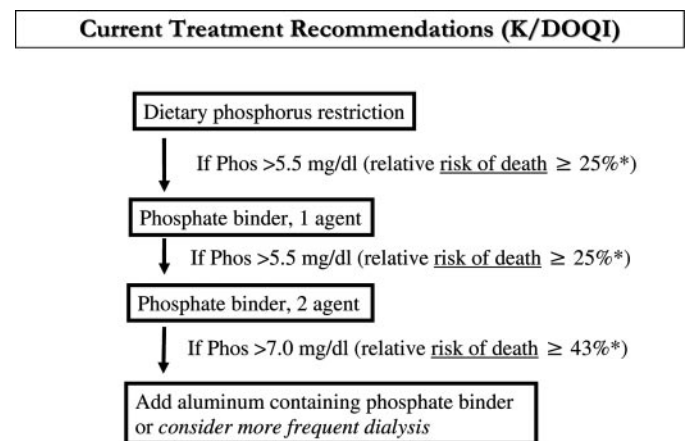


Figure 4. Algorithm for treatment of hyperphosphatemia according to the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines (28). *Relative risk for death reported by Block *et al.* (8).

Phosphorus Removal with Hemodialysis Is Limited

Hemodialysis does not remove significant amounts of phosphorus, mainly because of the pooling of phosphate in the intracellular compartment, which causes much of the phosphorus not to be readily accessible during a treatment. During either high-flux or low-flux hemodialysis, serum phosphorus rapidly decreases, reaching a hypophosphatemic nadir at approximately 120 min (35,36). After this, there is an immediate postdialysis phosphate rebound in which the serum phosphorus level rises and even can surpass the predialysis level (35–38). Therefore, a point at which redistribution is complete is not clearly identified. It is interesting that this rebound in serum phosphorus levels has been noted to begin even before the end of hemodialysis. Therefore, phosphate kinetics in dialysis patients is complicated and not completely understood at this point.

Phosphate efflux into the dialysate is greatest during the first hour of the treatment, corresponding to the time during which serum phosphorus levels are highest (35). Phosphate efflux then falls off, but remains at roughly half the initial value at the end of the treatment despite stable serum phosphorus levels. Recently, we directly measured serum phosphorus removal in a group of conventional and short daily hemodialysis patients with good control of serum phosphorus (predialysis phosphorus 4.2 to 4.5 mg/dl), and we found that daily dialysis removes significantly more phosphorus than conventional and that conventional dialysis removes only 1573 mg of phosphorus, when predialysis phosphorus levels are well controlled (39). What is clear is that conventional dialysis does not remove sufficient phosphorus to achieve good control of serum phosphorus in the majority of dialysis patients.

Mineral Metabolism: How to Get Control?

The National Kidney Foundation's K/DOQI provides for the nephrology community a set of standardized target ranges for metabolic control. Recent data, however, suggest that these goals often are not met (29,40) with conventional hemodialysis. Newer vitamin D analogues (41), calcimimetics (42), and non-calcium-based phosphate binders (43–45) all are welcome developments in the effort to improve metabolic control; however, failure to achieve mineral metabolism goals remains a significant problem (46). A consensus on how best to improve achievement of K/DOQI goals for mineral metabolism has not yet been reached in the context of conventional hemodialysis.

Recently, intensive hemodialysis therapies (nocturnal and daily hemodialysis) have shown some promise in the area of mineral metabolism. Nocturnal hemodialysis, which increases both dialysis frequency and total weekly dialysis time, will induce negative phosphorus balance, to the point that phosphorus supplementation becomes necessary. This modality has been shown to achieve excellent control of serum phosphorus without the use of phosphate-binding medications (47). However, daily hemodialysis had mixed effects on serum phosphorus in previous studies (32–34). Our group was the first to report good control of serum phosphorus in a controlled study

of daily in-center hemodialysis with reduction in use of phosphate binders (11). The prescription of more frequent dialysis sessions, using the same weekly total time, would be predicted to enhance phosphorus removal by maximizing the first-hour removal, which is greatest during the first hour of hemodialysis (48). What this does not account for is the increased protein intake that also is seen in the setting of short daily hemodialysis (31,49–51), so the net effect is no major change in phosphorus balance, which has been shown consistently with short daily hemodialysis. In a single small study, Lugon *et al.* (33) reported improvement of serum phosphorus; however, this occurred with predialysis phosphorus of 7 mg/dl, because dialytic phosphorus removal is much more efficient at this high of a predialysis phosphorus (Figure 5, Table 1). Yuen *et al.* (31) also showed that frequent hemodialysis, prescribed for longer weekly durations, is associated with improved control of hyperphosphatemia. Therefore, the current literature does not support the use of "short" (1.5 to 2.5 h) daily hemodialysis as a modality to improve control of mineral metabolism; however, daily hemodialysis (six times per week, 3 h per session) has been shown to be effective.

To our knowledge, conventional hemodialysis with currently accepted phosphate-binding therapy has never achieved mean serum phosphorus of <5.0 mg/dl in a large, controlled study. There is no question of the efficacy of phosphate-binding medications when the predialysis serum phosphorus is poorly controlled; however, as serum phosphorus levels begin to decline, the efficacy of conventional hemodialysis at removing serum phosphorus decreases significantly (Figure 5, Table 1). This occurs because removal of phosphorus with hemodialysis is much more effective when predialysis phosphorus levels are high (36–38,52–57). Dietary phosphorus restriction and phosphate-binding efficiency that maintains phosphorus balance when the serum phosphorus is 6.5 mg/dl will not be enough if the serum phosphorus drops to 5.5 mg/dl. Stated another way, the more effectively one reduces phosphorus levels by decreas-

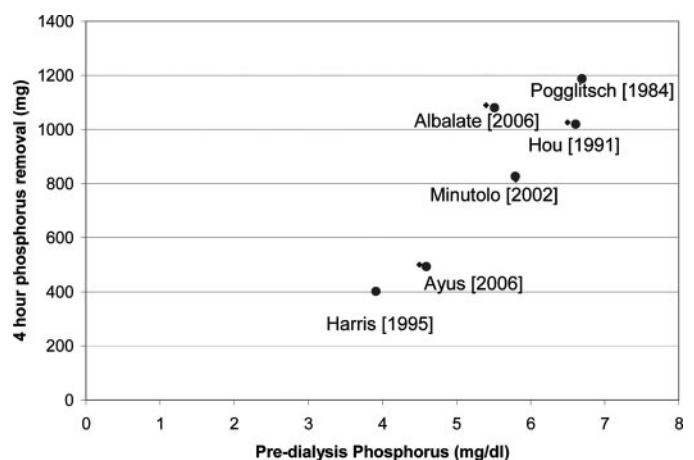


Figure 5. Four-hour dialytic phosphorus removal *versus* predialysis phosphorus. Studies from Table 1 were included in Figure 5 when treatment times were reported as 4 h and predialysis phosphorus levels were stated.

Table 1. Previous studies that quantified dialysis phosphorus removal

Author (Reference)	Treatment Time (h)	Blood Flow/ Dialysate Flow (ml/min)	Phosphate Binder	Predialysis Phosphorus (mg/dl)	Phosphorus Removal per Treatment (mg)
Desoi and Umans (54)	2.5 to 4.0	400 to 450/550 to 640	Calcium based	4.6	254
Harris <i>et al.</i> (55)	4	225 to 250/NS	NS	3.9	404
Mastrangelo (58)	3	NS	NS	3.8	447
Ayus <i>et al.</i> (39)	4	400/800	Sevelamer	4.5	524
Carney and Gillies (52)	5	NS	Aluminum based	4.43	533
Lindsay <i>et al.</i> (34)	1.5 to 2.5 (6× per wk)	450/500	Calcium carbonate	4.3 to 5.6	743
Minutolo <i>et al.</i> (36)	4	315 to 345/500	Calcium carbonate	5.8	814
Chauveau <i>et al.</i> (37)	4	300/500	Calcium carbonate	NS	929
Hou <i>et al.</i> (53)	4	300/500	None	6.5	1026
Lindsay (56)	3.5 to 4.5 (3× per wk)	450/500	Calcium carbonate	4.9 to 6.2	1053
Albalade <i>et al.</i> (57)	4	350/500	Any	5.4	1089
Poggliusch <i>et al.</i> (38)	4	NS	NS	6.7	1190

ing intake, the less effective dialysis is at removing phosphorus. Therefore, a veritable wall is erected, below which the phosphorus level cannot drop without increasing dialytic removal, unless the patient risks malnutrition. We provide evidence that conventional hemodialysis removes only 1572 mg/wk when the serum phosphorus is well controlled, whereas with similar predialysis phosphorus levels, short daily hemodialysis removes approximately 2452 mg of phosphorus in a week (39). Therefore, at lower levels of predialysis serum phosphorus, conventional hemodialysis has very limited phosphorus removal. For this reason, phosphorus binders alone, in the presence of adequate protein intake, will not be able to achieve excellent control of serum phosphorus (4.0 to 4.5 mg/dl) in the majority of patients.

In this context, we propose the following algorithm in the approach to hyperphosphatemia (Figure 6). It is important first to achieve good control with the use of either phosphate binders or phosphate binders in conjunction with daily dialysis. Once serum phosphorus goal is reached, we believe that it is prudent to attempt to withdraw phosphate-binding medications, slowly, while maintaining serum phosphorus below 5.0 mg/dl to limit exposure to potential adverse effects.

Conclusion

Epidemiologic studies have shown clear associations of increased serum phosphorus and mortality among dialysis patients (7,8). Poor control of mineral metabolism also has been associated with functional and structural cardiac abnormalities (9,10,24). We recently provided evidence, for the first time, that improvement of serum phosphorus during the period of 1 yr is associated with reduction in LVMI in hemodialysis patients (11). Hyperphosphatemia has been linked to vascular calcification, and it currently is hypothesized that this is the mechanism of cardiac damage with hyperphosphatemia. Our data suggest a reversible nature of the cardiotoxic insult of hyperphos-

Treatment Algorithm for Hyperphosphatemia

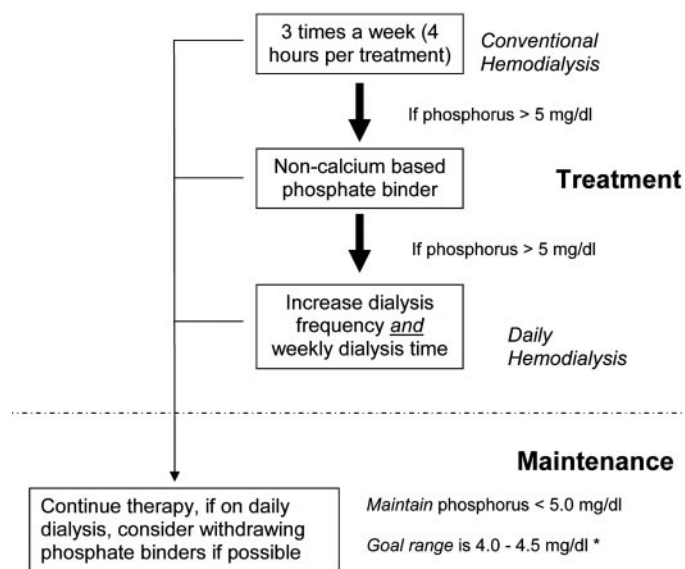


Figure 6. Proposed algorithm for treatment of hyperphosphatemia. *Authors' opinion.

phatemia, and cardiovascular calcification would not explain these findings because it is doubtful that established vascular calcification could be reversed through daily hemodialysis. We therefore hypothesize that an independent pathway leads to a reversible insult that leads to LVH. Our data, however, cannot tell us whether phosphorus *per se* or another covariate (e.g., another uremic toxin) leads to the cardiotoxicity. Further study in this area is needed. However, current practices do not lead to adequate control of serum phosphorus, and we propose a treatment algorithm that calls for increasing dialysis frequency and total weekly dialysis time to achieve adequate control of

serum phosphorus (Figure 6). We encourage the nephrology community to support increased dialysis treatments as an effective tool to achieve optimal control of serum phosphorus to improve cardiovascular risk among dialysis patients.

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