

SECTION SIX:

Hyperphosphatemia

Traditional dialysis is challenged to remove the phosphate ingested even in a protein-restricted diet. The resulting hyperphosphatemia increases the risk of cardiac calcification and cardiac events. Daily dialysis, and particularly nocturnal dialysis, can improve phosphate control, which could allow reduced dependence on binders and/or reduced dietary restrictions.

OVERVIEW

Hyperphosphatemia is difficult to manage in dialysis patients. Even with a restricted diet, the recommended dietary protein intake of 1.0-1.2 g protein/kg/day brings with it 800-1,400 mg phosphorus/day.⁹² Phosphate binders inhibit intestinal absorption of dietary phosphate, but significant amounts are still absorbed. Because phosphate does not rapidly exchange between body compartments, conventional dialysis sessions do not clear all of the excess phosphorous from the body. Serum phosphorous levels may decrease during dialysis, but rise significantly following the treatment as the body compartments equilibrate.

Thus, many patients are in net positive phosphorus balance. Current recommendations for dialysis patients suggest target serum phosphorous levels of 2.5 to 5.5 mg/dL and Ca x P products $<55 \text{ mg}^2/\text{dL}^2$, respectively.⁹² Mean serum phosphorous levels of a group of nearly 7,000 dialysis patients were 6.2 mg/dL; 60% of the patients had serum phosphorus levels above 5.5 mg/dL, the upper limit of the acceptable range.⁹³

In addition, phosphate binders commonly contain calcium (which can lead to calcium overload, hypercalcemia, and metastatic calcification). Some newer alternatives without calcium, such as sevelamer chloride and lanthanum carbonate, may be unavailable to some patients.

High serum phosphorous and Ca x P products are associated with cardiovascular calcification, which makes the heart and coronary arteries less flexible and efficient and more prone to cardiac events and death. Relative risk of death is 1.27 for hemodialysis patients with serum P $>6.5 \text{ mg/dL}$ as compared to patients with serum P $<6.5 \text{ mg/dL}$. Even after correcting for comorbid conditions; relative risk for death from coronary artery disease at these serum phosphorous levels was

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1.57.⁹³ Elevated serum phosphorous levels and Ca x P products are also associated with the development of secondary hyperparathyroidism, renal osteodystrophy, and visceral and vascular calcification. These conditions substantially increase morbidity, and the risk of cardiovascular death in hemodialysis patients.^{92,94}

POTENTIAL BENEFITS OF MORE FREQUENT THERAPY

By increasing therapy frequency and/or duration, post-treatment serum phosphorus rebound, which is detrimental to overall phosphate removal, is reduced, as compared to conventional dialysis. This may result in lower sustained phosphorous levels with lower requirements for calcium containing phosphate binders. This may also allow for a liberalized diet. Improved phosphorous control could also reduce the substantial morbidities and risk of cardiovascular death associated with elevated phosphorous levels and Ca x P products.

SUMMARY OF PUBLISHED RESULTS

Both short daily and long nocturnal hemodialysis have been reported to clear phosphorous more effectively than conventional thrice-weekly hemodialysis; however, longer treatments appear to have some advantage.

	Short Daily	Long Nightly
Change in Serum phosphorous levels	Reductions from 17% to 31% 95-97	Reductions from 22% to 48% ^{8, 56, 98-100}
Change in Ca x P	Reductions of 15% ⁹⁵	Reductions of 27.2% ⁹
Change in binder requirements	Reductions from 24% to 75% 5, 20-22, 51, 96	Reductions from 30% ⁵ to 100% (none required) ^{2, 6, 8, 9, 58, 69, 98-100}

Bone biopsies from some patients revealed a decrease in percent surface area of resorption and amount of osteoid while on daily dialysis as compared to a previous period on conventional dialysis.⁷⁷ Improvements in bone density on daily dialysis were also reported in other studies.^{95, 101}

TABULATED STUDY RESULTS ON HYPERPHOSPHATEMIA

Study & Design	Supporting Points
<p>Lockridge Jr, RS. Hemodial Int. 2004; 8:61⁹</p> <p>Nocturnal HD 25 pts; 1-5 yr Prospective</p>	<ul style="list-style-type: none"> • Calcium-phosphate decreased from 47.1 to 34.3 (p<0.001) • All phosphate binders were discontinued
<p>Galland, R. Sem Dial. 2004; 17:104⁹⁶</p> <p>Daily HD 17 pts; 3.25 yr Prospective</p>	<ul style="list-style-type: none"> • Mean serum phosphate levels were significantly reduced from 1.99 ± 0.53 mmol/L at baseline to 1.64 ± 0.43 mmol/L (p<0.01) • Phosphate binder dose was decreased significantly from 40.1±37 to 24.9±21.9 g/patient/week (p<0.05)
<p>Al-Hejali, F. J Am Soc Nephrol. 2003; 14:2322⁹⁸</p> <p>Lindsay, RM. Am J Kid Dis. 2003; 42:S24⁹⁹</p> <p>Daily HD 11 pts Nocturnal HD 12 pts; 1.5 yr Prospective</p>	<ul style="list-style-type: none"> • There was no significant change in serum phosphate levels or in intake of phosphate binders with daily hemodialysis • Serum phosphate levels decreased on nocturnal HD from 5.0 ± 1.5 mg/dL to 3.9 ± 1.1 mg/dL (not significant) • All patients on nocturnal hemodialysis discontinued phosphate binders
<p>Rocco, MV. Rocco, MV. J Am So Nephrol.2003; 14:502A¹⁰²</p> <p>Daily HD 18 pts; 8 mo Case control</p>	<ul style="list-style-type: none"> • At baseline there was no difference between conventional and daily HD groups in serum phosphate and Ca x P or in intake of phosphate binders • At 8 months, all of these measures were significantly lower in daily group
<p>Agar, JWM. Hemodial Int. 2003; 7:278⁸</p> <p>Nocturnal HD 10 pts; 3 mo Prospective</p>	<ul style="list-style-type: none"> • Serum phosphate levels decreased from 1.61±0.11 mM to 0.84±0.07 mM (p=0.04) • All phosphate binders were discontinued

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<p>Kim, SJ. Am J Kid Dis . 2003; 41:E12 ¹⁰³</p> <p>Nocturnal HD 1pt; 9 mo Prospective</p>	<ul style="list-style-type: none"> • Patient had extraosseous tumoral calcinosis, which was nearly completely dissolved after 9 months of nocturnal HD • Ca x P product decreased from 85 mg²/dL² to <55 mg²/dL²
<p>Maduell, F. Kidney Int. 2003; 64:305 ²⁰</p> <p>Daily HDF 8 pts; 6 mo Prospective</p>	<ul style="list-style-type: none"> • Serum phosphate levels did not change significantly • Intake of phosphate binders was reduced from 7.3±3 tablets per day at baseline to 2.85 ± 4 tablets/day at 6 months (p<0.001)
<p>Traeger, J. Dial Transplant. 2001;30:76 ²²</p> <p>Daily HD 15 pts; ≥1 yr Prospective</p>	<ul style="list-style-type: none"> • During short daily HD, intake of phosphate binders decreased by 75%
<p>Lugon, JR. Sao Paulo Med J. 2001;119:105 ⁹⁵</p> <p>Daily HD 5 pts; 2 yr Prospective</p>	<ul style="list-style-type: none"> • Mean serum phosphate levels were significantly lower (6.0 ± 1.8 mg/dL vs. 7.2 ± 2.7 mg/dL) on daily HD compared to conventional HD (p<0.05) • Mean calcium X phosphate products were also significantly lower (58.3 ± 20.9 mg/dL vs.68.6 ± 27.3 mg/dL) (p<0.05) • Bone biopsies showed that patients with low turnover bone disease improved on daily HD • One patient with aluminum (Al) deposits in bone at the start of daily HD was found to have no significant Al in bone after 2 years on daily HD
<p>Chan, CT. J Am Soc Nephrol. 2001;12:262A ⁹⁷</p> <p>Daily HD 32 pts; 1 yr Prospective</p>	<ul style="list-style-type: none"> • Significant reduction in serum phosphate concentrations during 1st 6 months on daily HD from 1.99 ± 0.55 mM to 1.37 ± 0.64 mM (p=0.006) • There were no significant changes in prescribed phosphate binders
<p>Galland,R. Am J Kid Dis. 2001;37Suppl 2:S95 ²¹</p> <p>Daily HD 10 pts; 13-38 mo Prospective</p>	<ul style="list-style-type: none"> • During short daily HD, intake of phosphate binders decreased by 75%

<p>Lindsay, RM. <i>ASAIO J.</i> 2001;47:449⁵</p> <p>Daily HD 9 pts Nocturnal HD 10 pts; 1-18 mo Prospective/ Case-control</p>	<ul style="list-style-type: none"> • Both short daily and long nocturnal HD patients significantly reduced intake of phosphate binders as compared to previous doses on conventional HD (Daily HD: 2.96 ± 1.56 g/day to 1.68 ± 0.45 g/day) (nocturnal HD: 2.17 ± 1.63 g/day to 1.52 ± 0.54 g/day) ($p < 0.004$) • Controls on conventional HD did not decrease phosphate binders
<p>Cacho, C. <i>Nephrol News Issues.</i> 2000;14:36²</p> <p>Nocturnal HD 6 pts; 6 mo Prospective</p>	<ul style="list-style-type: none"> • Serum phosphate levels decreased in all patients and none required phosphate binders
<p>Pierratos, A. <i>Nephrol Dial Transplant.</i> 1999;14:2835⁶</p> <p>Nocturnal HD 37 pts; 5 yr Prospective</p>	<ul style="list-style-type: none"> • Patients discontinued phosphate binders within 1 week of starting nocturnal HD
<p>Kooistra, MP. <i>Nephrol Dial Transplant.</i> 1998;13:2853⁵¹</p> <p>Daily HD 13 pts; 1 yr Retrospective</p>	<ul style="list-style-type: none"> • Doses of aluminum-containing phosphate binders decreased from 2.5 ± 0.9 g/day (conventional HD) to 1.9 ± 0.6 g/day (daily HD)
<p>Bonomini, V. <i>Nephrol Dial Transplant.</i> 1998;13:2774⁷⁷</p> <p>Daily HD 6 pts; 6-12 mo Prospective</p>	<ul style="list-style-type: none"> • From bone biopsies: % surface area of resorption decreased from $4.2\% \pm 1.4\%$ to $3.7\% \pm 2.1\%$ (conventional HD compared to daily HD) • Percentage surface area of osteoid decreased from $6.8\% \pm 1.8\%$ (conventional HD) to $5.4\% \pm 1.35\%$ (daily HD)
<p>Mucsi, I. <i>Kidney Int.</i> 1998;53:1399¹⁰⁰</p> <p>Nocturnal HD 8 pts; 5 mo Prospective</p>	<ul style="list-style-type: none"> • Serum phosphate levels fell during nocturnal HD from 2.1 ± 0.5 mM at the beginning to 1.3 ± 0.2 mM ($p < 0.001$) • Dietary phosphate increased by 50% on nocturnal HD • After 4 months on nocturnal therapy no patient was taking phosphate binders (compared to a median of 2.4 g/day prior to nocturnal HD)

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<p>O'Sullivan, DA. Mayo Clin Proc. 1998;73:1035 ⁵⁶</p> <p>Nocturnal HD 5 pts; 8 wk Prospective</p>	<ul style="list-style-type: none">• Serum phosphate levels decreased after 2 months on nocturnal HD from 7.47 ± 1.02 mg/dL to 4.55 ± 1.16 mg/dL ($p < 0.04$)
<p>Pierratos, A. J Am Soc Nephrol. 1998;9:859 ⁶⁹</p> <p>Nocturnal HD 11 pts; 3 yr Prospective</p>	<ul style="list-style-type: none">• All patients discontinued calcium carbonate used as a phosphate binder within 1 - 4 weeks of starting nocturnal HD
<p>Uldall, R. Adv Ren Repl Therap. 1996;3:133 ⁵⁸</p> <p>Nocturnal HD 5 pts; 6-16 mo Prospective</p>	<ul style="list-style-type: none">• All patients discontinued phosphate binders• Phosphate removal was 2,709 mg/week with conventional HD and 5,638 mg/week for nocturnal HD