Phosphate problem in PD

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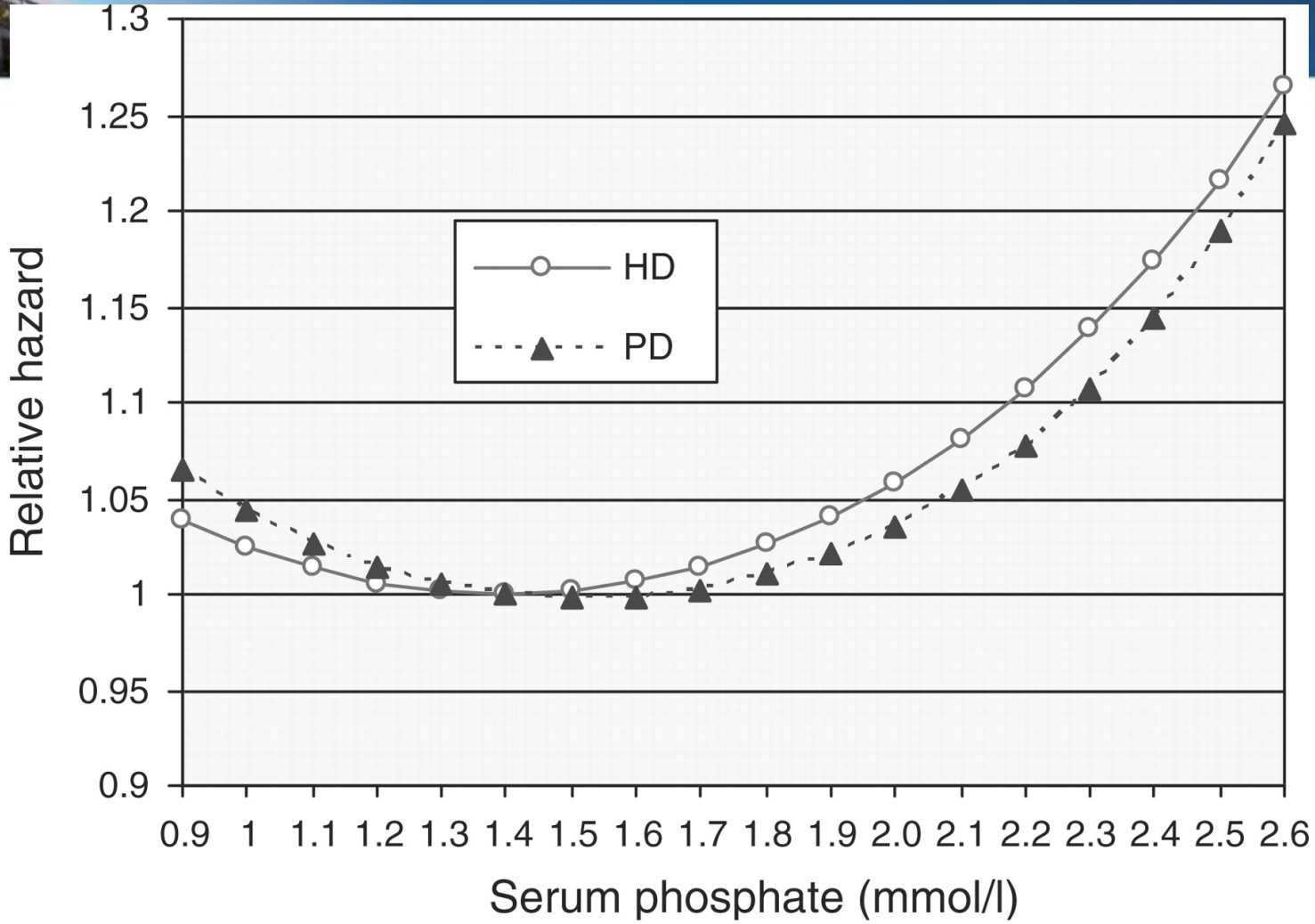
Hyperphosphatemia is an

independent predictor of mortality

in ESRD patients.

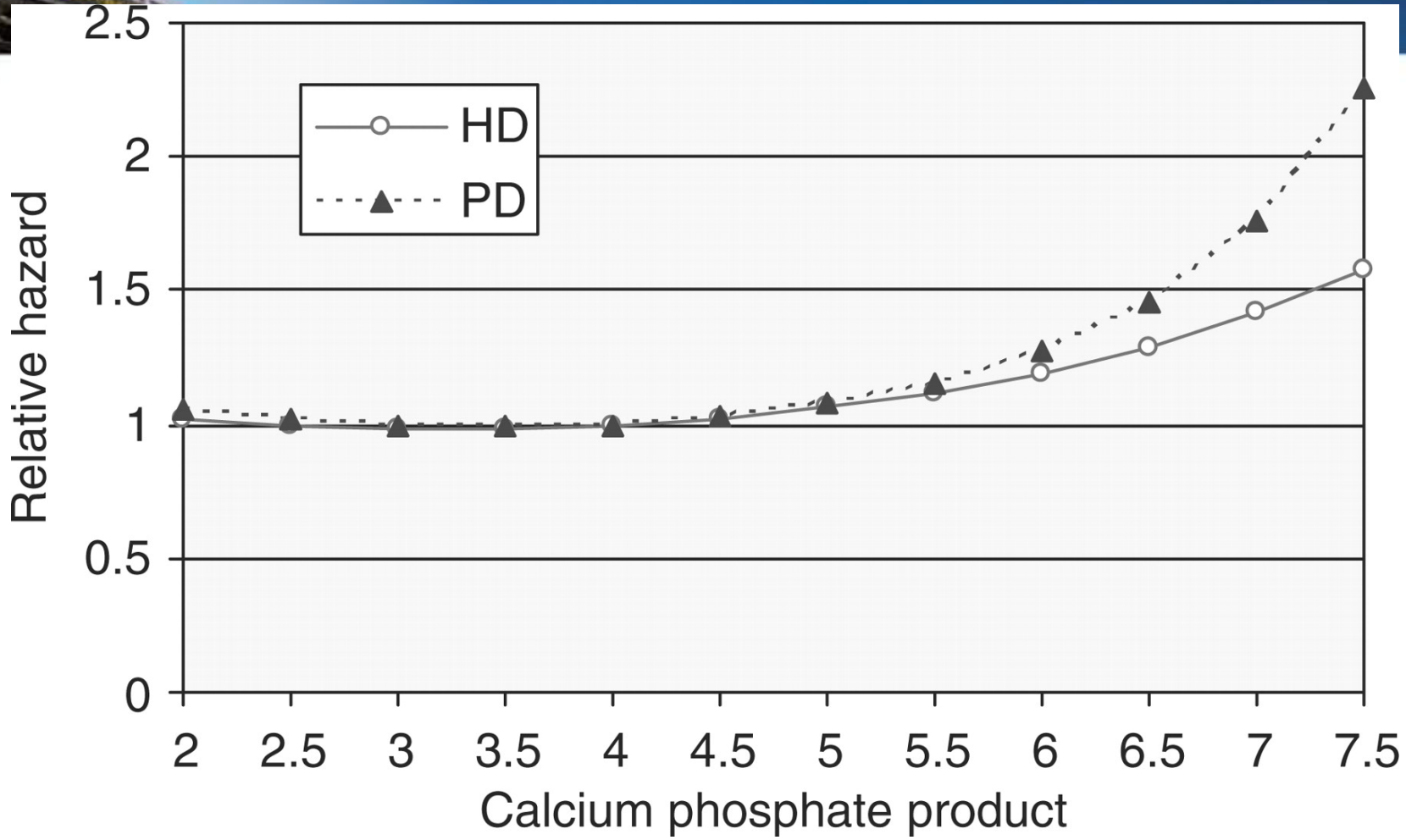
Nephrol Dial Transplant 2007; 22:667–8

Serum phosphate and relative hazard of death by dialysis modality.



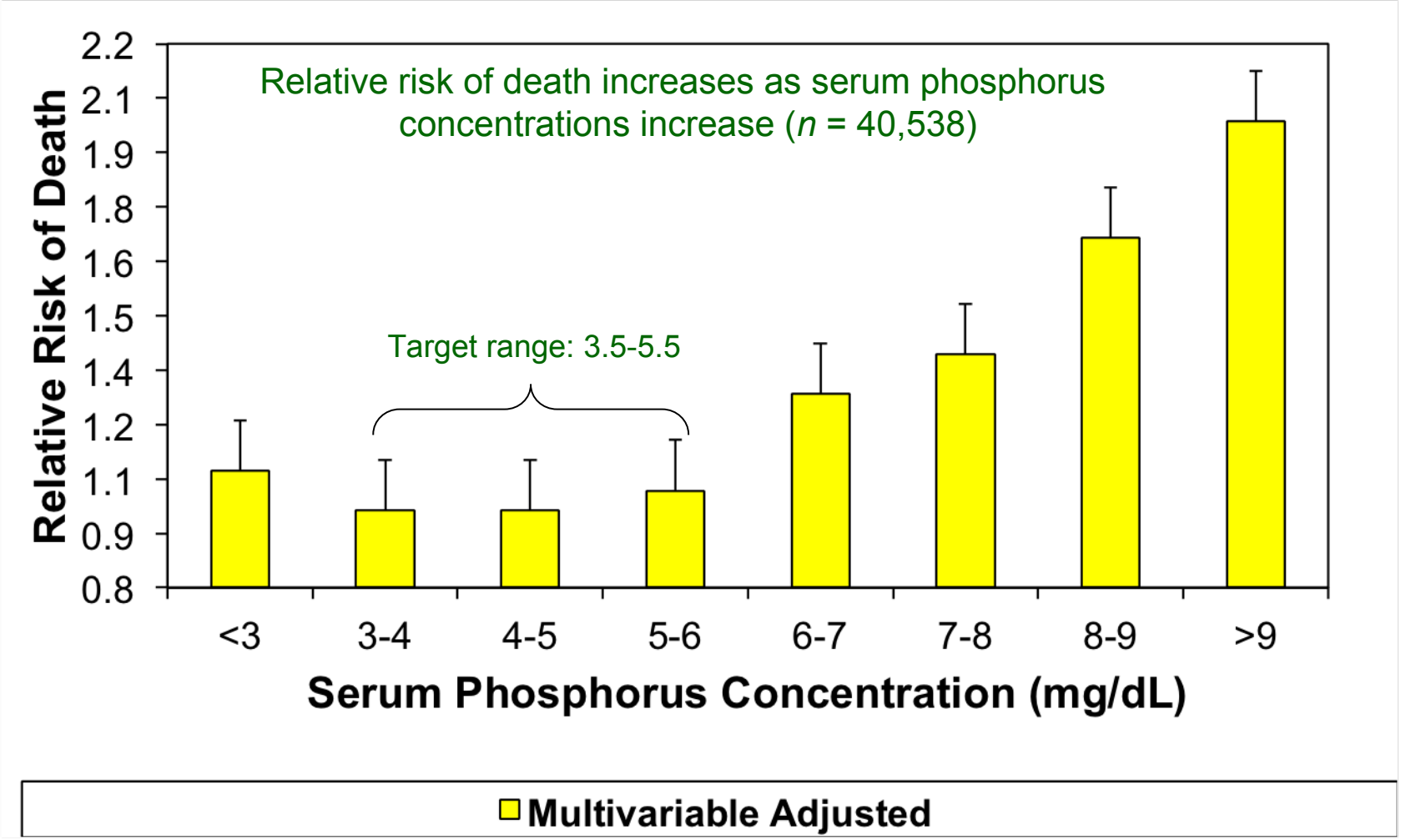
David Ansell Nephrol. Dial. Transplant. 2007;22:667-668

Serum calcium [adjusted for albumin measured by bromocresol green (BCG)] and phosphate product and relative hazard of death by dialysis modality.



David Ansell Nephrol. Dial. Transplant. 2007;22:667-668

血磷值越高 死亡率越高



Adapted from Block GA, et al. *J Am Soc Nephrol*. 2004; 15:2208-2218.

Hyperphosphatemia in dialysis patients is also associated with hemodynamic disturbances, ventricular hypertrophy, and systolic dysfunction.

J Intern Med 2005; 258: 378–84.

Left ventricular function and calcium phosphate plasma levels in uraemic patients.

Galetta F[1], Cupisti A, Franzoni F, Femia FR, Rossi M, Barsotti G, Santoro G.

Author information

Abstract

BACKGROUND. Recent investigations have focused on the pathogenetic role of disturbances of calcium phosphate metabolism in causing cardiovascular morbidity and mortality in haemodialysis patients. The aim of the present study was to assess left ventricular function and its relationship to phosphate and calcium plasma levels in stable uraemic patients on haemodialysis treatment.

METHODS: Twenty uraemic patients (mean age 51+/-13 years) on maintenance haemodialysis and free from overt cardiac dysfunction, and 20 healthy volunteers underwent standard echocardiography, tissue Doppler-derived early (E(m)) and late (A(m)) diastolic velocities, tissue characterization with cyclic variations of integrated backscatter (CV-IBS), and serum biochemistry.

RESULTS: With respect to tissue Doppler imaging (TDI), uraemic patients showed a lower E(m) peak, a higher A(m) peak, and a reduced E(m)/A(m) ratio of both interventricular septum and lateral wall ($0.01>P<0.001$) than controls. CV-IBS of both septum and posterior wall was significantly smaller in uraemic patients than in the control subjects ($P<0.001$). Moreover, the E(m)/A(m) ratio of septum and lateral wall were negatively related to serum phosphorus and to calcium phosphate product ($P<0.001$ for all). Accordingly, an inverse relationship was also found between CV-IBS of septum and lateral wall and calcium phosphate product and phosphorus ($P<0.05$ for all).

CONCLUSIONS: These results showed early cardiac impairment of diastolic myocardial function evaluated by TDI and IBS analysis, and a close relationship between these changes and the calcium-phosphate plasma levels. These findings are well in keeping with the important role of hyperphosphataemia as a risk factor for cardiovascular damage, and justify the effort for optimal control of calcium phosphate metabolism in uraemic patients.

PMID: 16164578 [PubMed - indexed for MEDLINE]

Serum phosphate concentration and quantitative coronary artery calcification exhibit a linear correlation

in both PD and HD patients.

Nephron Clin Pract 2006; 104:c33–40.

Nephrol Dial Transplant 2004; 19:3205–6.

Coronary artery calcification, systemic inflammation markers and mineral metabolism in a peritoneal dialysis population.

Ammirati AL[1], Dalboni MA, Cendoroglo M, Draibe SA, Fernandes Canziani ME.

Author information

Abstract

AIMS: To assess the prevalence of coronary artery calcification (CAC) in peritoneal dialysis (PD) patients and to determine whether comorbidities such as inflammation, dyslipidemia and mineral metabolism disorders correlate with its development.

METHODS: Forty-nine PD patients (45% male; median age, 52 years) were submitted to multislice computed tomography. Inflammatory markers, anti-oxidized LDL antibody, calcium-phosphate balance and lipid profiles were assessed.

RESULTS: Twenty-nine patients (59.2%) presented CAC (median calcium score, 234.7 Agatston units). Patients with CAC were older than those without, more frequently presented a history of coronary artery disease or hypertension and had lower HDL cholesterol levels, as well as presenting higher levels of osteoprotegerin and LDL oxidation. The logistic regression revealed that the independent determinants of CAC were age (odds ratio = 1.12; p = 0.006) and number of prescribed anti-hypertensive drugs (odds ratio = 2.38; p = 0.048). When the population was stratified by calcium score quartile, soluble Fas levels were significantly higher in patients with severe calcification. In patients younger than 45, CAC correlated positively with phosphorus levels (r = 0.52; p = 0.04).

CONCLUSION: In PD patients, CAC is highly prevalent. Our results indicate that conditions such as inflammation and mineral disturbances are associated with its development.

Coronary artery calcification

in hemodialysis patients is significantly

associated with ischemic heart disease and

mortality.

Kidney Int 2007; 71:438–41.

Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients.

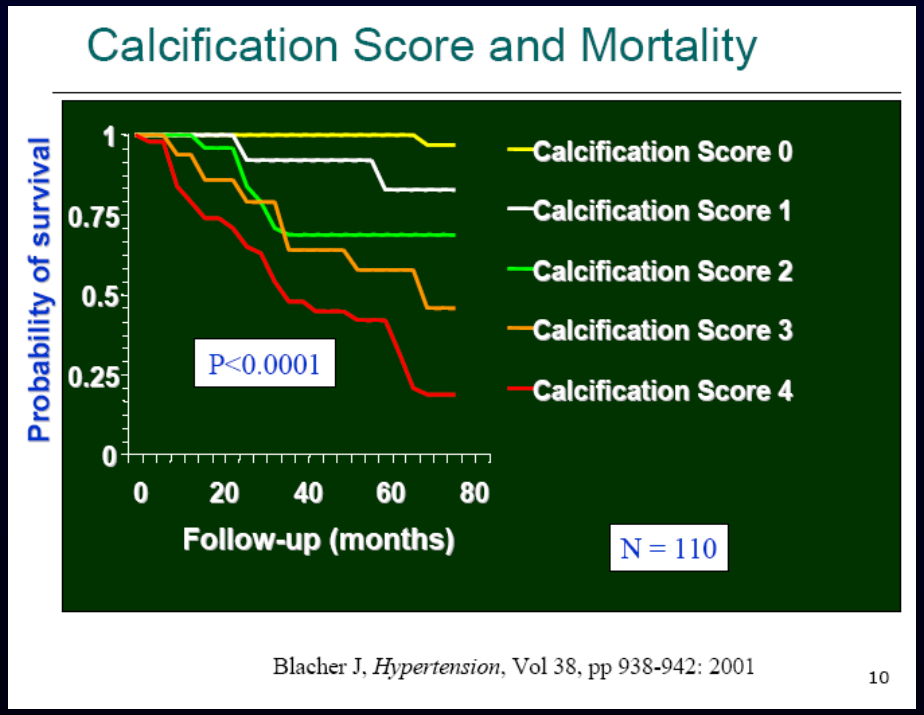
Block GA[1], Raggi P, Bellasi A, Kooienga L, Spiegel DM.

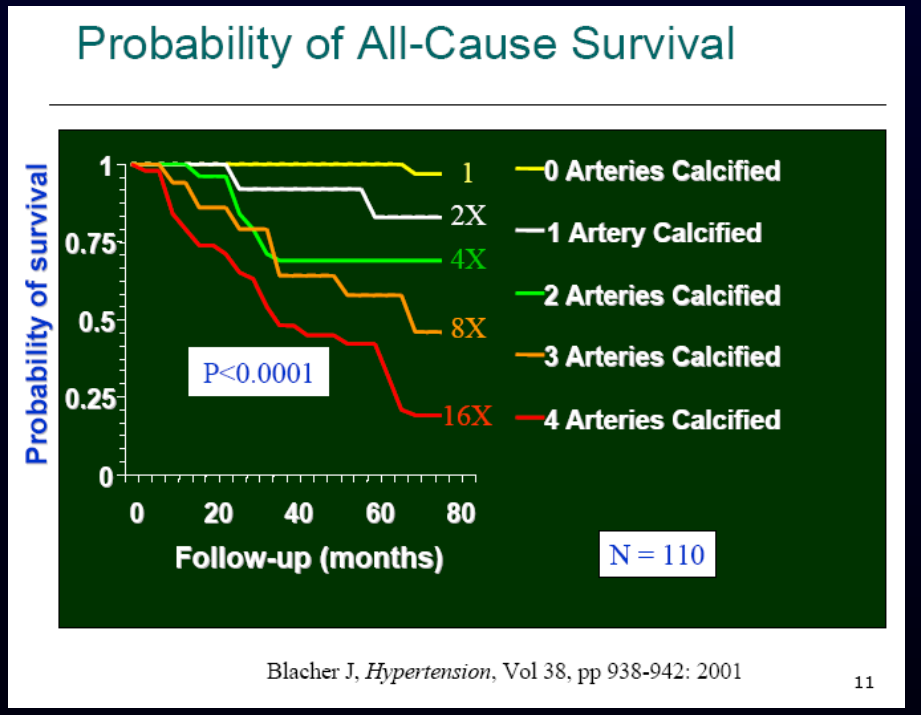
Author information

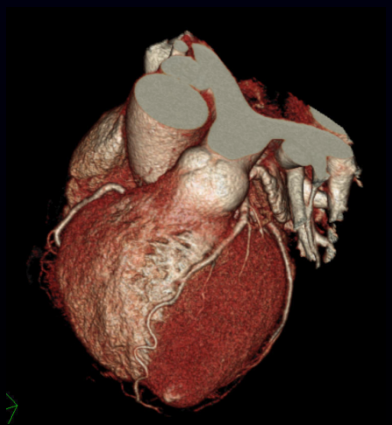
Abstract

The risk of death in hemodialysis patients treated with calcium-containing phosphate binders or sevelamer is not known. We assessed all-cause mortality in 127 patients new to hemodialysis assigned to calcium-containing binders or sevelamer after a median follow-up of 44 months from randomization. This was a predetermined secondary end point of a randomized clinical trial designed to assess progression of coronary artery calcium (CAC) scores in the two treatment arms. Thirty-four deaths occurred during the follow-up period: 23 in subjects randomized to calcium-containing phosphate binders and 11 in subjects randomized to sevelamer. Baseline CAC score was a significant predictor of mortality after adjustment for age, race, gender, and diabetes with increased mortality proportional to baseline score (P=0.002). Mortality was borderline significantly lower in subjects randomized to sevelamer (5.3/100 patient years, confidence interval (CI) (2.2-8.5) compared to those randomized to calcium-containing binders (10.6/100 patient years, CI 6.3-14.9) (P=0.05). The greater risk of death for patients treated with calcium-containing phosphate binders persisted after full multivariable adjustment (P=0.016, hazard ratio 3.1, CI 1.23-7.61). In subjects new to hemodialysis baseline CAC score was a significant predictor of all-cause mortality. Treatment with sevelamer was associated with a significant survival benefit as compared to the use of calcium-containing phosphate binders.

血管鈣化越厲害 死亡率越高







The ability to quantify vascular calcification with "electron-beam CT" or "helical CT"

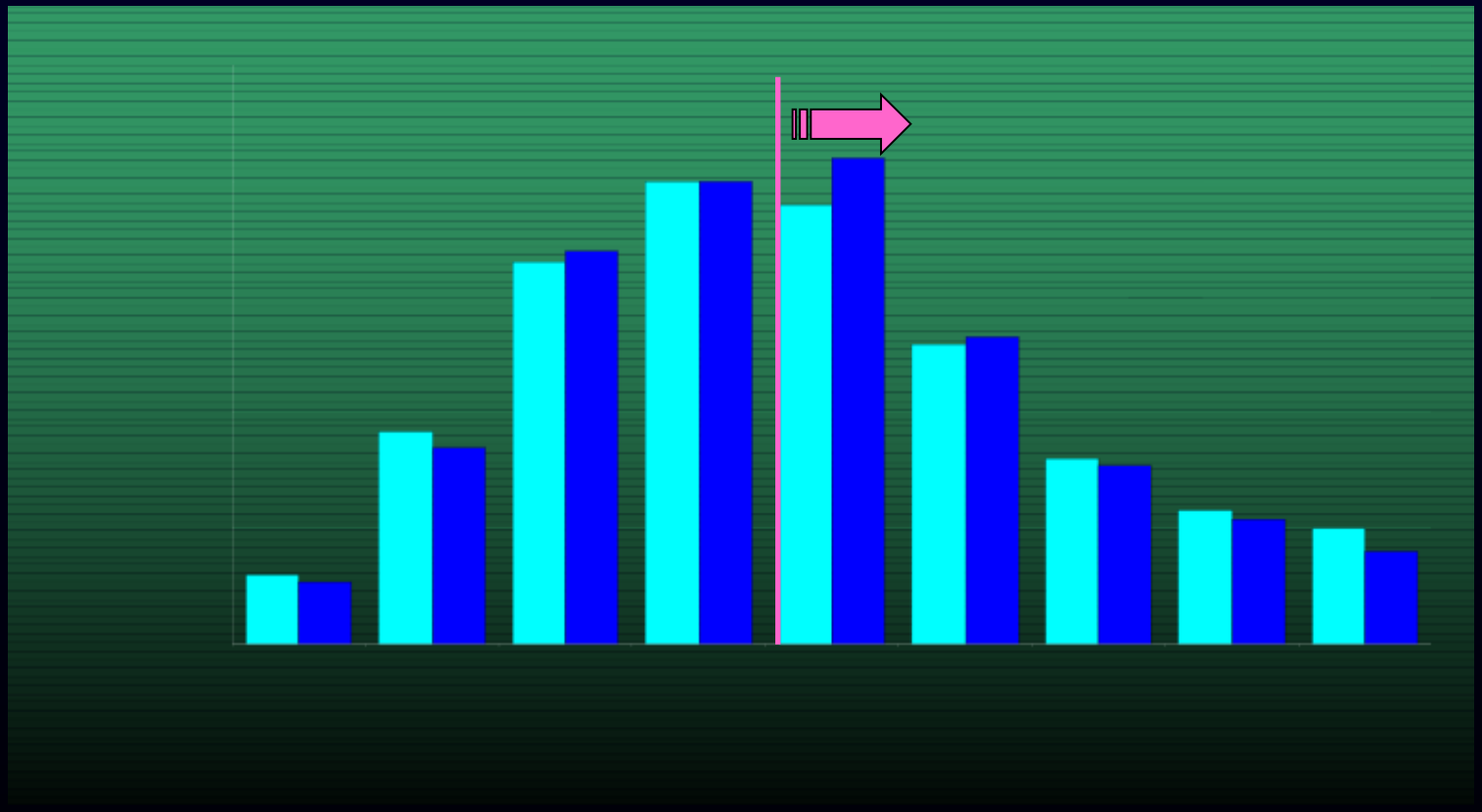
All available evidence suggests a similar risk for adverse vascular outcomes among PD patients with poorly controlled serum phosphate (5,6).

Nephrol Dial Transplant 2007; 22:667–8.

In vitro, hyperphosphatemia not only increased mineral deposition in human aortic smooth muscle cell culture in a dose-dependent manner, but also stimulated those cells to undergo phenotype changes predisposing to calcification at a concentration greater than 4.3 mg/dL.

Circ Res 2000; 87:E10–17.

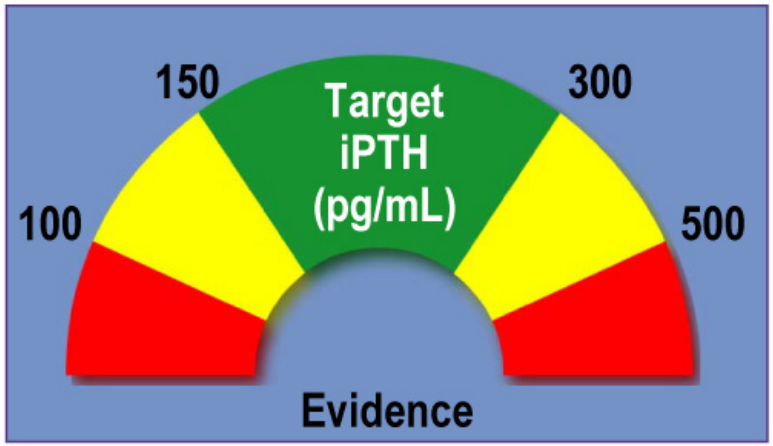
Hyperphosphatemia in HD patients

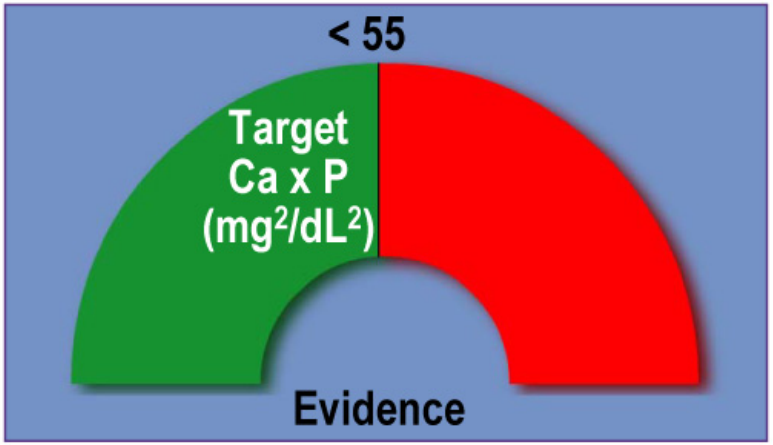


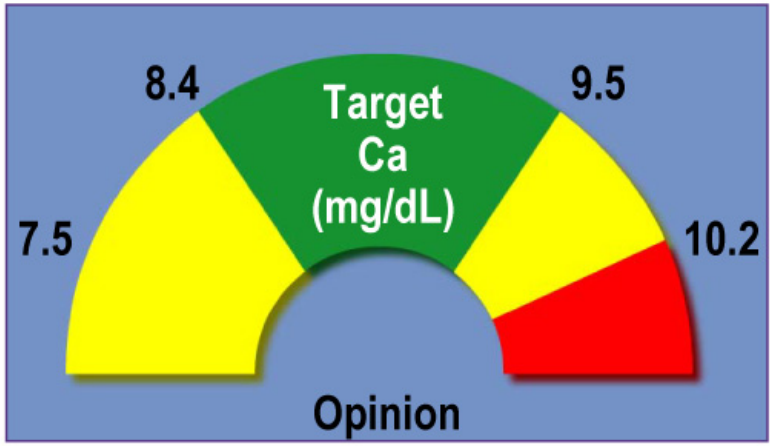
Serum phosphate > 5 mg/dL in 70% of dialysis patients
Serum phosphate > 6 mg/dL in 50% of dialysis patients

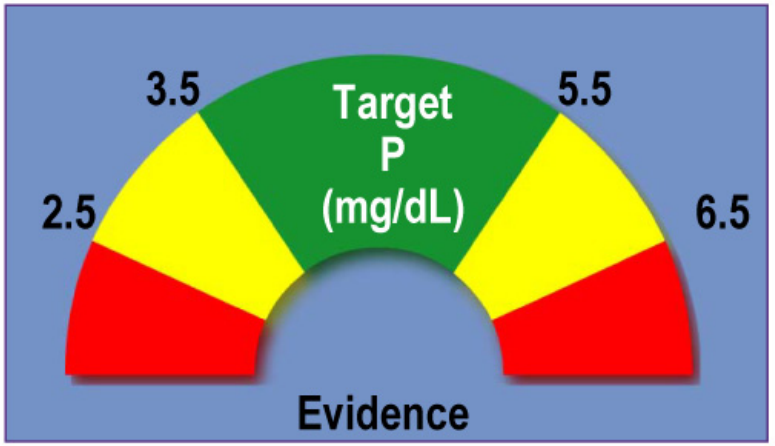
Block GA et al. Am J Kidney Dis. 1998;31:607-617

K/DOQI™ Bone Metabolism and Disease Guidelines in Stage 5 CKD





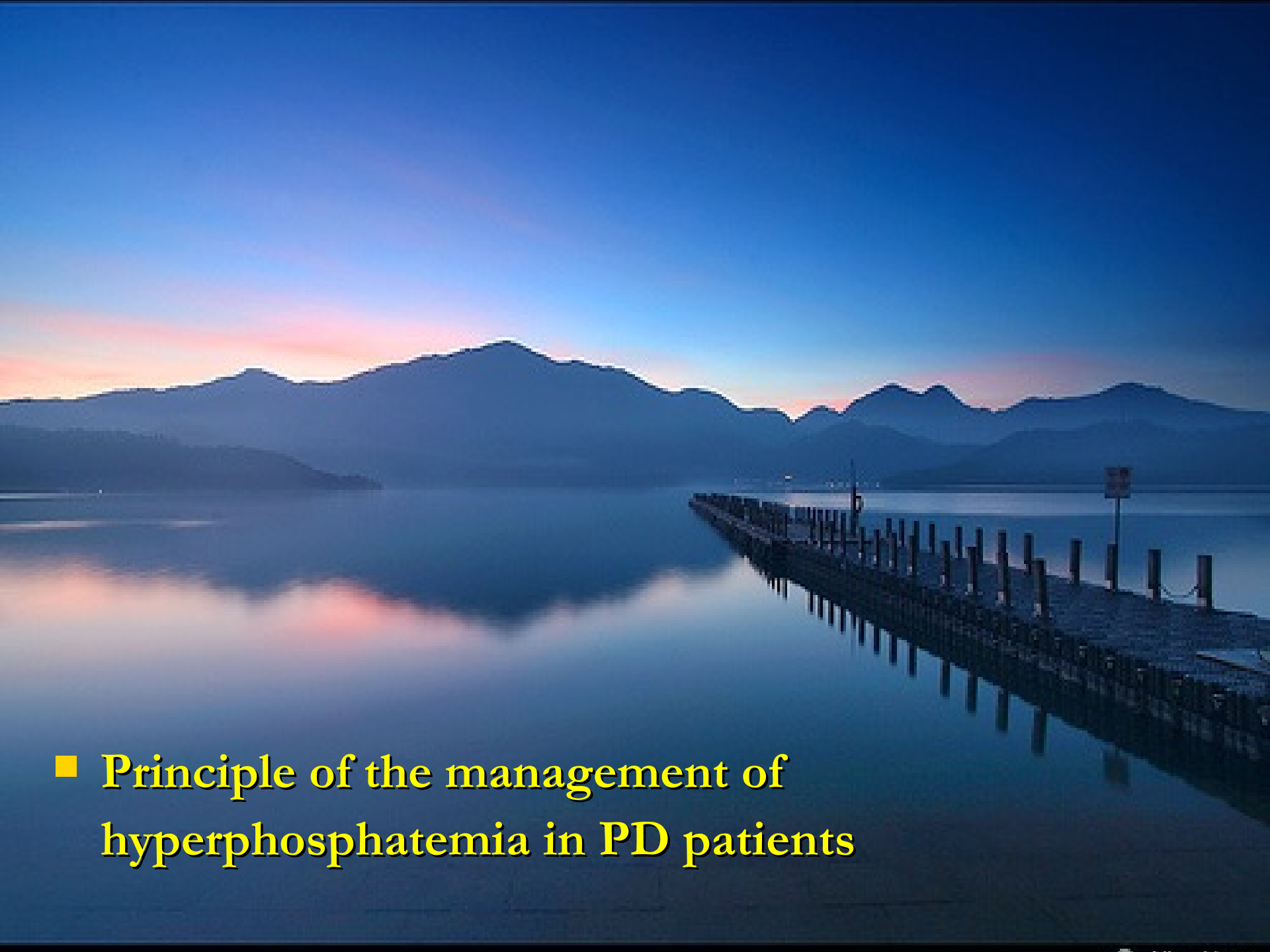




iPTH = intact parathyroid hormone
Ca x P = calcium-phosphorus product
National Kidney Foundation. *Am J Kidney Dis*. 2003;42(suppl 3):S1-S201.

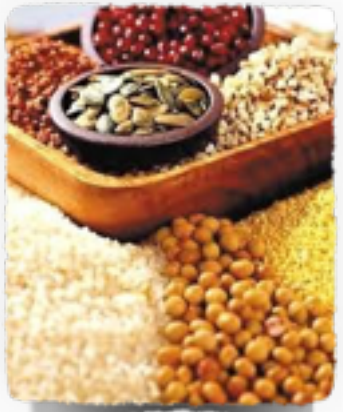
Despite the well-known risks associated with hyperphosphatemia, more than 40% of PD patients have serum phosphate concentrations above the 2003 K/DOQI target of 5.5 mg/dL.

Am J Kidney Dis 2003; 42(Suppl 3):S1–201.



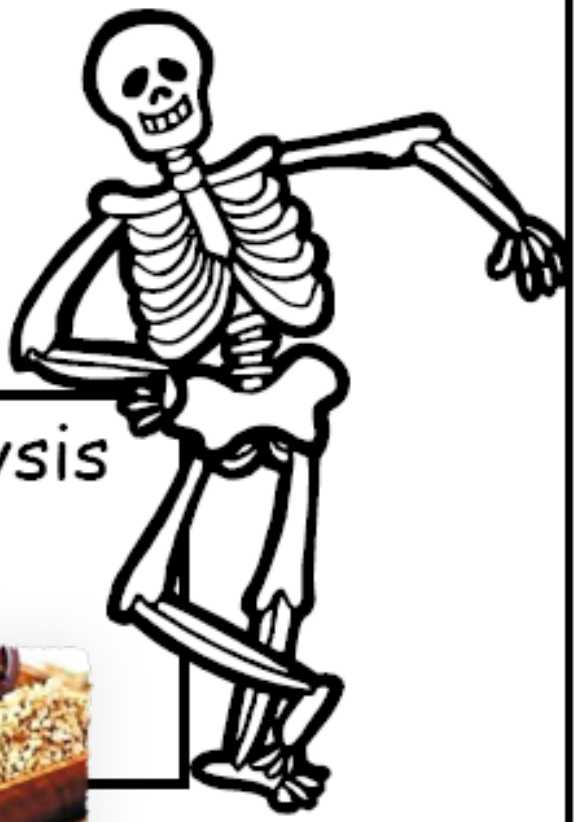
- Principle of the management of hyperphosphatemia in PD patients

Among PD patients, Management of hyperphosphatemia involves three principles:

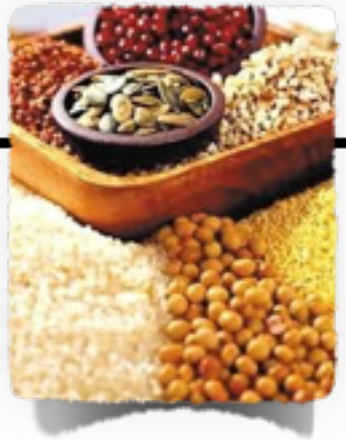


- **Dietary phosphate restriction**
- **Administration of phosphate binder**
- **Removal of phosphate by dialysis and residual renal function**

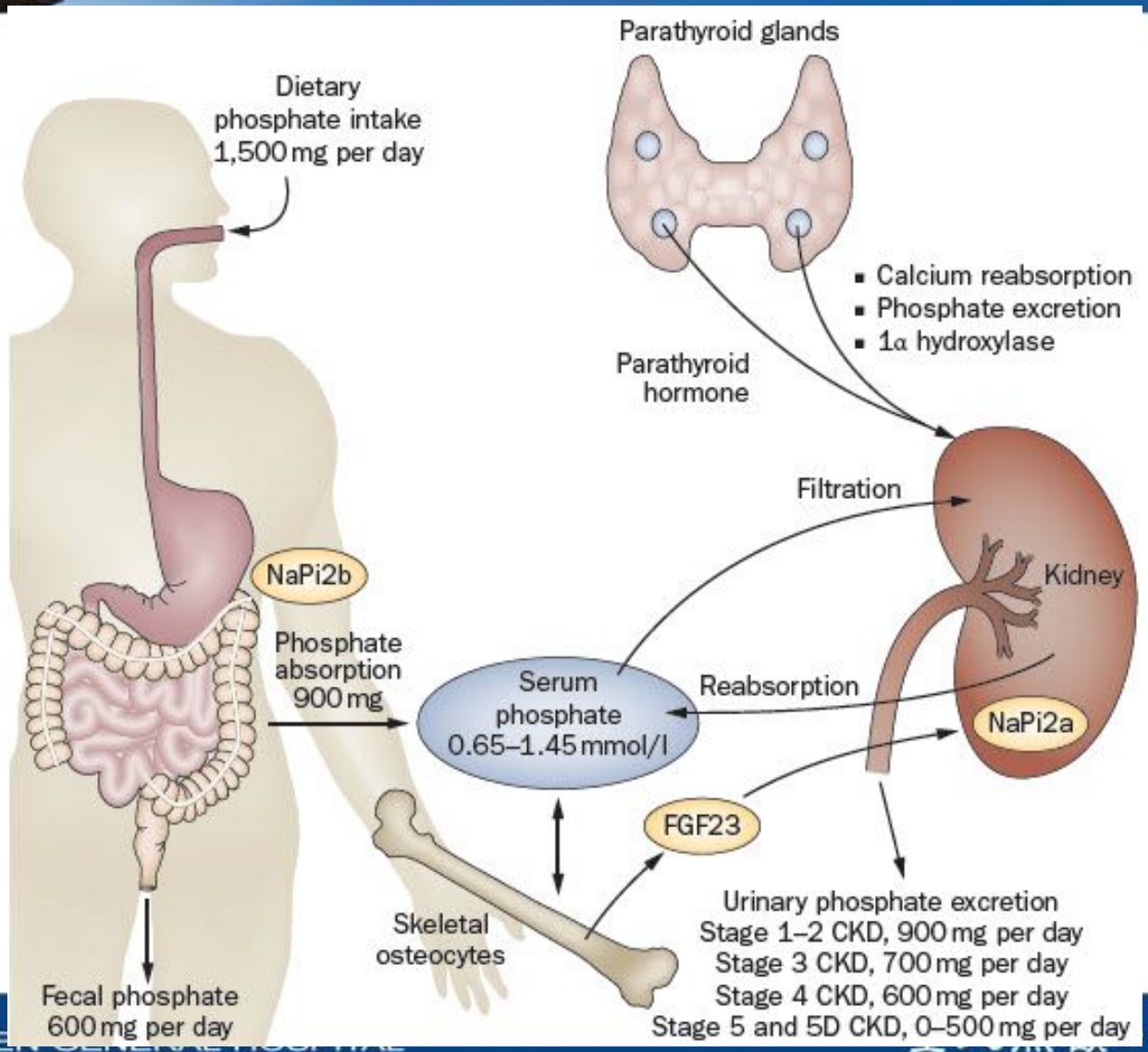
Treatment for Hyperphosphatemia



- Phosphorus removal by dialysis
- Dietary restriction
- Phosphate binders

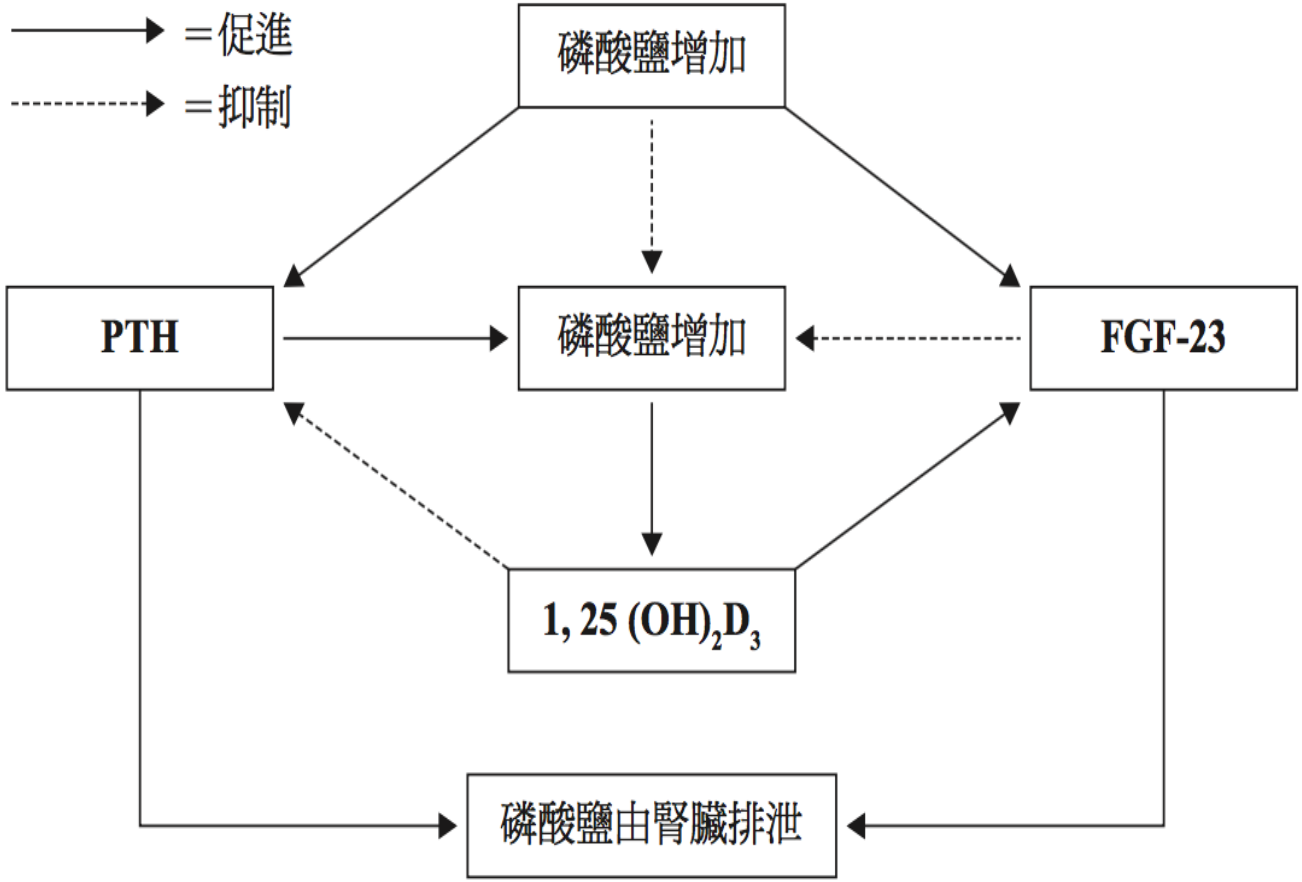


PHOSPHATE BALANCE



表一：FGF-23的生理作用

作用	機轉
血磷濃度下降	抑制近端腎小管的Na-Pi cotransporter，降低磷酸鹽的再吸收，使磷酸鹽由尿液中排泄出去
活性維生素D_3血中濃度下降	抑制近端腎小管的1α hydroxylase活性、促進24α hydroxylase活性
副甲狀腺荷爾蒙血中濃度上升	FGF-23會抑制副甲狀腺荷爾蒙的製造及分泌，但是由於它也會抑制活性維生素D_3的產生，因此會促進副甲狀腺荷爾蒙的產生



圖一：副甲狀腺荷爾蒙與FGF-23對於血磷濃度的調節

當血磷濃度上升時，副甲狀腺荷爾蒙(parathyroid hormone, PTH)及Fibroblast growth factor 23 (FGF-23)會上升，促進磷酸鹽從尿液排出。此外副甲狀腺荷爾蒙會促進1-α hydroxylase活性，使得$1,25(OH)_2D_3$製造增加，逆回饋抑制副甲狀腺，使副甲狀腺荷爾蒙分泌下降。FGF-23會抑制1-α hydroxylase活性，使得$1,25(OH)_2D_3$製造降低。

PHOSPHATE BALANCE IN PD

- Total-body phosphate content is approximately 700 g. Of that total, approximately 85% is found in bone and teeth as hydroxyapatite; 14% is in the intracellular fluid, mainly as organic phosphate; and less than 1% is in ECF as inorganic phosphate.
- Dietary phosphate intake is the main source of new inorganic phosphate — although in hyperparathyroidism, net efflux from bone may occur.

PHOSPHATE BALANCE IN PD

- Phosphate content in a typical Western diet is 800~2000 mg/day, and most dialysis patients are prescribed a diet with a phosphate content of between 550 mg and 1100 mg daily.
- The amount of dietary phosphorus absorbed has been reported to vary between 44% and 80% among patients treated with calcium- or aluminum-based phosphate binders or sevelamer.

PHOSPHATE BALANCE IN PD

In a population of 53 patients on CAPD and CCPD, mean phosphate intake was 906 mg/day by dietary history, mean dose of calcium-based binders was 3.7 g/day.

Mean total phosphate excretion in dialysate and urine was 423 mg daily, mean serum phosphorus was 5.2 mg/dL.

Mean intestinal phosphorus absorption was 47%.

PHOSPHATE BALANCE IN PD

- Total weekly phosphate clearance of ~57 L/1.73 m2, equal to about 3135 mg of phosphorus can be absorbed weekly.
- Assuming intestinal phosphate absorption of 50%, a weekly dietary intake in excess of 6270 mg will result in suboptimal phosphate control.
- Assuming that the usual phosphate content per gram of protein varies in the range 14 – 15 mg/g, the foregoing amount of phosphorus is provided by a daily protein intake of 60 – 64 g.
- That protein intake is lower than the recommended daily intake of 1.2 g/kg for most patients.

IMPORTANCE OF RESIDUAL RENAL FUNCTION IN MAINTENANCE OF PHOSPHATE BALANCE

- **RRF contributes significantly** to the maintenance of phosphate balance.
- **Urinary phosphate excretion** is **highly correlated with residual GFR** among PD patients.
- Strong correlation between **RRF** and **serum phosphate** concentration has been reported.
- Interpolating the reported time profile for phosphate clearance, **renal phosphate clearance** accounted for **63%** of the total phosphate clearance **at initiation of PD**, and it accounted for **49%** of clearance **at 7 months**.

IMPORTANCE OF RESIDUAL RENAL FUNCTION IN MAINTENANCE OF PHOSPHATE BALANCE

In a cross sectional study of 252 prevalent PD patients

only 29% of patients with preserved RRF had a serum phosphate concentration >5.6 mg/dL, as compared with 44% of the anuric patients.

rGFR was also a significant predictor of serum phosphate concentration.

Renal phosphate clearance declines with decreasing rGFR, and that decline may be associated with deteriorating phosphate control.

IMPORTANCE OF RESIDUAL RENAL FUNCTION IN MAINTENANCE OF PHOSPHATE BALANCE

In the short term, the declining renal clearance may be mitigated by an increase in peritoneal clearance, but in anuric patients, increased peritoneal clearance may not be able to compensate because of the limited numeric variability in peritoneal clearance.

Am J Kidney Dis 2005; 46:512–19.

Peritoneal membrane transport characteristic is an important,

but non-modifiable, determinant of peritoneal phosphate clearance.

Mechanism of Peritoneal Phosphate Removal

- Dialysate-to-plasma (D/P) ratios of most small solutes do not substantially increase after 3 hours, but that the D/P ratios of larger solutes continue to rise with time.
- The D/P phosphate continues to rise with time; after an 8-hour dwell with 1.5% dextrose solution, the corresponding D/P creatinine and D/P phosphate ratios were 0.9 and 0.55 respectively.

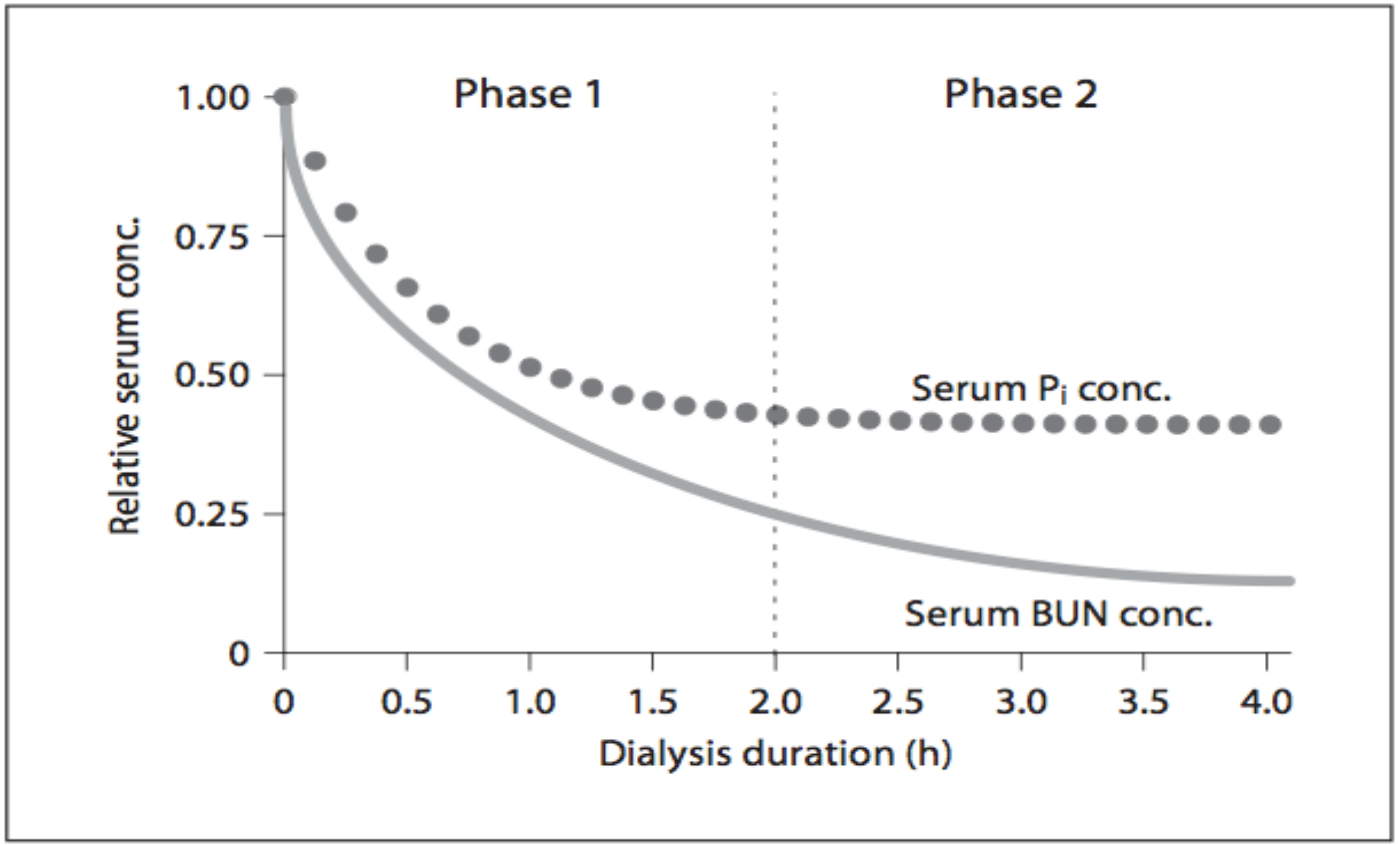


Fig. 1. Comparison of intradialytic phosphate and blood urea nitrogen (BUN) kinetics. Serum P_i concentration sharply drops during the first phase of dialysis (phase 1) and, after reduction of serum P_i to about 40% of predialysis levels, stabilizes throughout the rest of the treatment (phase 2). In contrast, BUN levels steadily decline during dialysis without reaching a plateau.

Table 1 Ranges of phosphate removal (grams per week) by different dialysis strategies

Conventional diffusive hemodialysis, 4 hours	2.3–2.6 g
Extended diffusive hemodialysis, ≥5 hours	3.0–3.6 g
Nocturnal hemodialysis, ~8 hours	4.5–4.9 g
Endogenous hemofiltration with reinfusion, 4 hours	1.8–2.4 g
Postdilution hemodiafiltration, 4 hours	3.0–3.3 g
Predilution hemofiltration (exchange volumes 1.2 × body weight)	0.9–1.5 g
Peritoneal dialysis (CAPD, 2 L × 4/day)	2.0–2.2 g

International Journal of Nephrology and Renovascular Disease 2013:6

Table 1. Weekly P_i mass removal with various HD and PD treatment modalities

Modality and ref.	P_i mass removal mg/week	Dialysis schedule	Flow rates ml/min	Treatment specifications
Hemodialysis				
HD high-flux [8]	2,356 ± 864	3 × 230 min	Q_B: 323 ± 22 Q_D: 500	UFV 1.8 ± 0.8 liters
HD + passive muscle activity [9]	PCM: 3,515 ± 945 TEMS: 3,591 ± 795	3 × 195–240 min	Q_B: 300–400 Q_D: 600	S-P_i 5.1 ± 0.9 mg/dl
HD – double dialyzer [10]	2,970 mg	3 × 4 h	Q_B: 350–400 Q_D: 800	F80A or F160 dialyzers S-P_i 5.3 mg/dl
Postdilution HDF [11]	3,570 ± 270 mg	3 × 4 h	Q_B: 315–345 Q_D: 500	F8 dialyzer, MSA 1.8 m^2 Q_{UF} 25–35 ml/min
Mixed-dilution HDF [12]	975 ± 272 mg/Tx (2,975 mg/week)	231 ± 18 min	Q_B: 385 ± 20 Q_D: 625 ± 16	Q_{UF} 181 ± 12 ml/min MSA 1.8 m^2
SDHD [13]	2,452 ± 720 mg	6 × 3 h	Q_B: 400 Q_D: 800	high-flux dialyzer S-P_i 4.2 mg/dl
NHD [14]	8,000 ± 2,800	6 × 6–8 h	Q_B: 150–300 Q_D: 300	high-flux dialyzer F80
	P_i mass removal mg/week	Dwell time h	Flow rates ml/min	Treatment specifications
Peritoneal dialysis				
APD, CCPD [8]	2,739 ± 1,042	18.5 ± 7.3	–	DV 13.2 ± 3.5 liters ex. 5.5 ± 1.1 S-P_i 5.0 ± 1.4 mg/dl
CAPD [8]	2,790 ± 1,022	24.0	–	DV 10.5 ± 2.1 liters ex. 4.2 ± 0.5 S-P_i 4.2 ± 0.9 mg/dl

HDF = Hemodiafiltration; APD = automated PD; CCPD = continuous cycling PD; CAPD = continuous ambulatory PD; Tx = treatment; PCM = passive cycling movements; TEMS = transcutaneous electrical muscle stimulation; Q_B = blood flow rate; Q_D = dialysate flow rate; S-P_i = serum P_i concentration; Q_{UF} = ultrafiltrate flow rate; MSA = membrane surface area; DV = peritoneal fluid drainage volume; UFV = ultrafiltration volume; ex. = number of PD fluid exchanges.

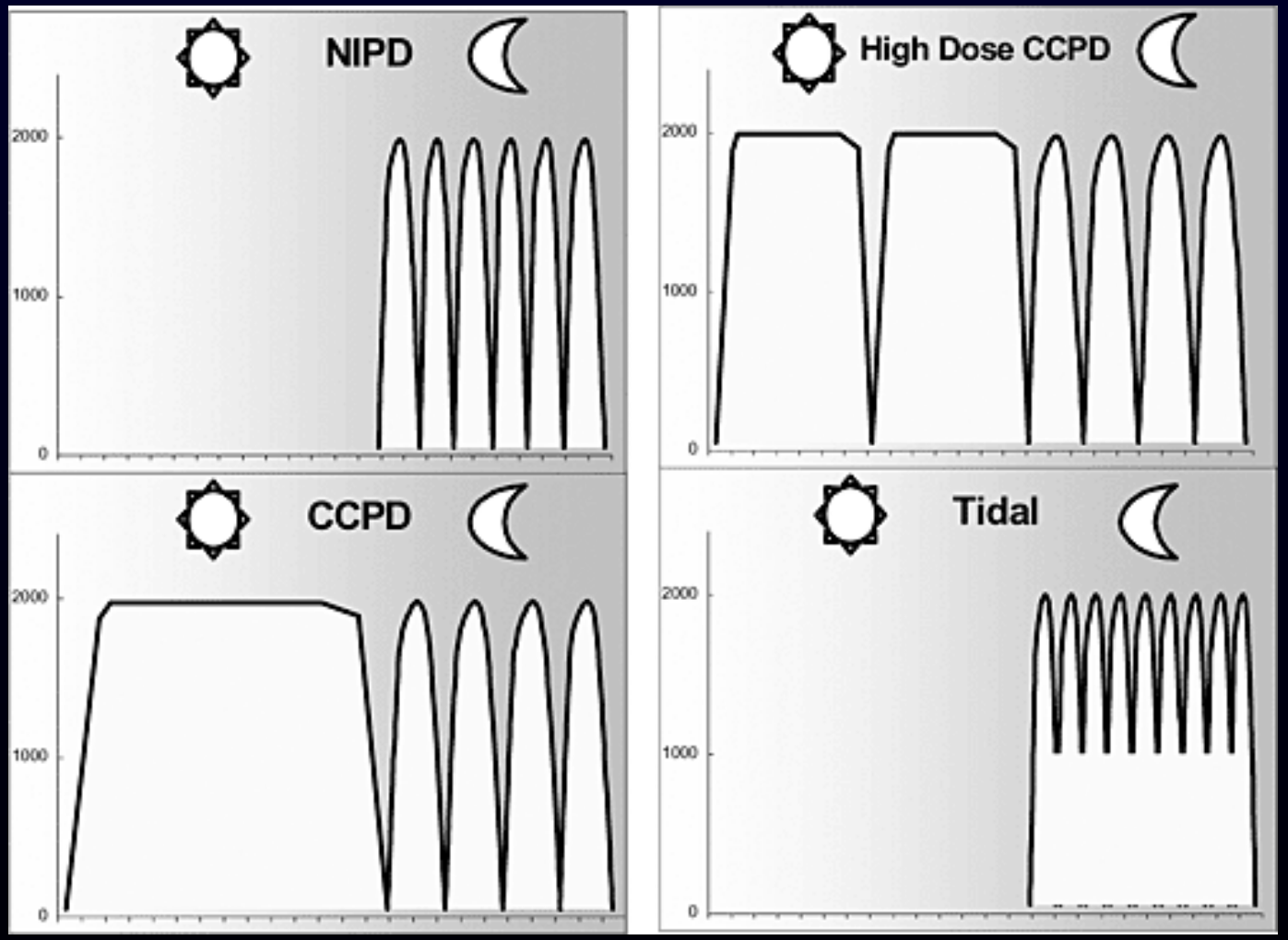
Mechanism of Peritoneal Phosphate Removal

- The correlation between D/P phosphate and D/P creatinine is known to be linear.
- Peritoneal phosphate removal is the result of both diffusive and convective clearance.
- Phosphate removal on PD was 66 mg with 1.5% dextrose solution and 111 mg with 4.25% dextrose solution.
- Dialysate glucose concentration was one of the predictors of phosphate removal.
- Removal of phosphate was independent of UF volume.

PERITONEAL PHOSPHATE CLEARANCE

Peritoneal phosphate clearance would be predicted to be better in the continuous PD modalities such as CAPD and CCPD than in the intermittent NIPD modality.

Even significant increases in the dialysate volume and number of cycles results in only a marginal increase in peritoneal phosphate clearance.


NIPD
2000
1000
0
High Dose CCPD
2000
1000
0
CCPD
2000
1000
0
Tidal
2000
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