Calcium Phosphate Metabolism and Cardiovascular Disease in Patients with Chronic Kidney Disease

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ABSTRACT

Traditional risk factors for atherosclerotic cardiovascular disease (CVD) do not adequately explain the considerable increase in cardiovascular mortality observed among patients with end-stage renal disease (ESRD): these patients experience mortality rates 10–100 times those without ESRD. Disorders of mineral metabolism, including abnormalities in calcium, phosphorus, parathyroid hormone, and vitamin D, represent cardiovascular risk factors unique to the ESRD population. These disturbances manifest clinically through the promotion of extraskeletal calcification and disorders of bone remodeling, two processes which appear to share a common pathogenesis. This article presents evidence describing the impact of calcification-induced arterial stiffness on cardiovascular outcomes of patients with ESRD, along with data relating altered mineral metabolism to all-cause and cardiovascular mortality. Specific management recommendations include 1) early intervention to prevent the development of overt secondary hyperparathyroidism, 2) a more judicious strategy for vitamin D therapy, and 3) a thoughtful approach to the use of calcium-containing phosphate binders, taking into account the underlying bone remodeling disorder and the presence or absence of extraskeletal calcium accumulation.

Traditional risk factors for atherosclerotic cardiovascular disease (CVD) do not adequately explain the considerable increase in cardiovascular mortality observed among patients with end-stage renal disease (ESRD): these patients experience mortality rates 10–100 times those without ESRD (1,2). Speculation exists regarding uremia-specific atherogenic risk factors such as chronic inflammation, oxidant stress, hyperhomocysteinemia, and a unique dyslipidemic profile, yet there is no consensus that chronic kidney disease (CKD) by itself represents a state of accelerated atherogenesis (3). While short-term cardiovascular risk in the general population is estimated from diagnostic testing that detects "significant" intraluminal stenosis of large epicardial coronary arteries, this strategy fails to explain cardiovascular outcomes in patients with CKD. In a prospective evaluation of 433 incident ESRD patients, Foley et al. (4) found no association between known coronary artery disease (CAD) and subsequent mortality. A recent report found that patients with ESRD and CKD with normal coronary angiograms had 2-year hazard ratios of mortality of 2.64 and 5.19 relative to those with normal kidney function. These values were nearly identical to those found in patients with "significant" obstructive luminal coronary disease (4,5).

As depicted in Fig. 1, disorders of mineral metabolism (including abnormalities in calcium, phosphorus, parathyroid hormone [PTH], and vitamin D) represent cardiovascular risk factors unique to patients with CKD. The effects of disturbed mineral homeostasis are thought to be mediated by the promotion of vascular and visceral calcification, disorders of bone remodeling, and direct toxicity of PTH. These abnormalities affect the cushioning/capacitance function of the arterial system rather than the conduit function. While this consequence is less familiar to most nephrologists, evidence now implicates abnormalities in arterial stiffness as an important mediator of cardiovascular events in patients with CKD. The evolving discovery of a close relationship between bone remodeling disorders and arterial vascular disease provides a fundamental basis for the enhanced cardiovascular event rates seen in the CKD population, the majority of whom have skeletal abnormalities. Furthermore, there is accumulating evidence that the modern management of renal osteodystrophy (ROD) and mineral metabolism disorders may have a negative impact on overall vascular health. This brief review is limited primarily to disorders of calcium and phosphorus homeostasis; the reader is referred to a recent review by Rostand and Drueke (6) for a detailed discussion of the cardiovascular toxicity of PTH and vitamin D.

Mechanisms and Basic Principles

The development of vascular calcification (VC) is a complex, actively regulated process involving mechanisms

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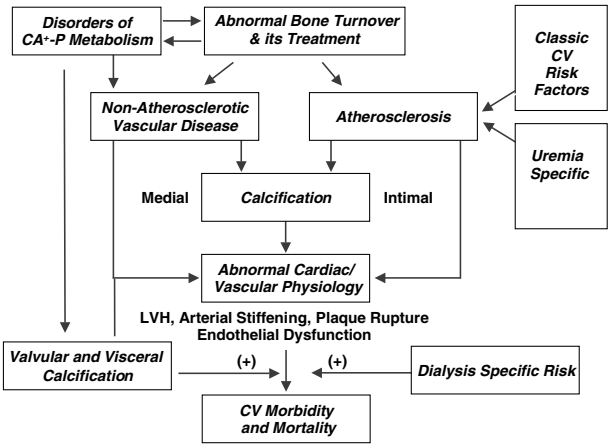

FIG. 1. Interactions of calcium phosphate metabolism with cardiovascular disease in patients with CKD.

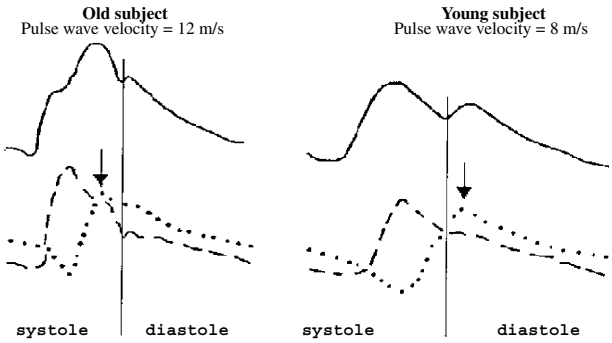

FIG. 2. Arterial stiffness, pulse wave velocity, and wave reflections. Pressure waves in young and old subjects. Pressure wave (——), backward wave (****), forward wave (- - - -).

similar to those of normal skeletal mineralization (7,8). Most importantly, serum phosphate concentration is a potent stimulator of the process of vascular calcification (9–11). Increasing phosphate concentration in vascular smooth muscle cell culture results in a dose-dependent increase in intracellular phosphate via a type III sodium-phosphate cotransporter. This ultimately increases bone-related protein expression of markers such as cbfa-1 and osteocalcin. Animal models confirm this phenotypic change in vascular smooth muscle cells and human pathologic studies in ESRD patients substantiate the expression of bone-related proteins in areas of VC (12,13).

Vascular calcification occurs either in the intimal or medial vascular space. Intimal calcification develops in concert with atherosclerotic plaque and it is now well accepted that increasing amounts of vascular calcium in nondiabetic, nonrenal failure patients is a surrogate for atherosclerotic plaque burden. Diabetic and CKD patients also accumulate calcium in the vascular media, an event which does not impact the conduit function of blood vessels and is not associated with plaque. Because there is no associated impairment of distal blood flow, the development of medial calcification has historically generated little interest; however, the hemodynamic consequences of medial calcification have been recognized more and more. Guerin et al. (14) have shown that for ESRD patients, the presence and extent of VC assessed by Doppler ultrasound predicts an increased arterial stiffness measured either by aortic pulse wave velocity (PWV) or carotid incremental elastic modulus (E_{inc}). This effect is independent of age and hypertension.

Both aortic PWV and E_{inc} are strong independent predictors of all-cause and cardiovascular mortality in patients with ESRD (15). In a cohort of 241 hemodialysis (HD) patients, for each 1 m/sec increase in aortic PWV, the all-cause mortality adjusted odds ratio was 1.39 (confidence interval [CI] 1.19–1.62) (16). The mechanism underlying this higher cardiovascular risk appears to be a direct effect of arterial stiffness in increasing systolic blood pressure, decreasing diastolic blood pressure, and thus widening pulse pressure (PP). This effectively increases left ventricular (LV) afterload and results in left ventricular hypertrophy (LVH) (17). By accelerating the aortic PWV, increased arterial stiffness also results in a reflected pressure wave that returns to the heart during systole rather than during early diastole as occurs in subjects with normal arterial structure. This phenomenon is well demonstrated from a study by Asmar et al. (18) on aging (Fig. 2). This early wave reflection further augments systolic blood pressure, lowers diastolic blood pressure, and increases PP. This second peak in the arterial waveform systolic blood pressure is expressed as the augmentation index and has been correlated with LV size in patients on HD (19–21). Ultimately these phenomena decrease coronary perfusion and result in diminished subendocardial blood flow, particularly in patients with coexisting classic atherosclerotic coronary disease.

Two large and recently reported studies confirm the adverse risk associated with high systolic blood pressure, low diastolic blood pressure, and widened PP. Each 10 mmHg increase in PP was associated with a 12% increase in the hazard for 1-year mortality in a study by Klassen et al. (22) involving 37,000 HD patients. Tozawa et al. (23) analyzed 1243 Japanese HD patients and found PP to be a more potent predictor of total mortality than systolic or diastolic blood pressure. This effect was not seen in diabetics; however, the PP in diabetics was significantly higher than in nondiabetics (82 versus 68, $p < 0.0001$) and likely confounded the relationship.

Interest in the detection of VC has increased with the advent of electron beam computed tomography (EBCT). Using a beam of electrons deflected onto a tungsten ring with real-time gating to the electrocardiogram (EKG), this technique is able to image coronary arteries with limited motion artifact. Areas of more than 2–3 pixels consistent with calcium are counted, multiplied by a density coefficient, and an Agatston total calcium score is generated for the area of interest. A complete cardiac scan takes one to two breath holds and is complete in 1–2 minutes.

Data from the non-CKD general population confirms the ability of EBCT calcium score percentile to predict hard coronary events (myocardial infarction [MI] or death) with improved ROC characteristics beyond Framingham risk factors (24). Regardless of whether localized calcium accumulation stabilizes or destabilizes plaque (a controversial issue), increasing total calcium

scores reflect an increased plaque burden, which translates into increased cardiovascular risk.

This technique cannot discriminate intimal from medial calcium accumulation, so direct extrapolation of EBCT results from the general population to patients with ESRD is not possible. It is known that patients with ESRD are more likely to have calcified atherosclerotic plaques compared to controls; however, the EBCT calcium score may also reflect increased medial calcium (25). Blacher et al. (15) confirmed the significance of arterial calcification and arterial stiffness in HD patients by showing a striking correlation between the number of calcified vessels and all-cause and cardiovascular mortality. In this multivariate analysis, increases in common carotid artery E_{inc} conferred additional risk of mortality. It is biologically plausible that increased coronary artery medial calcification may augment the risk of atherosclerotic disease by limiting the normal coronary remodeling process. This could partially explain the phenomenon of ischemic events in patients with non-"significant" coronary artery disease.

We investigated the presence of VC at the initiation of HD using EBCT, and found that 17% of patients have severe coronary calcification, 30% have severe aortic calcification, and 40% have no evidence of coronary calcification (26). Furthermore, we have shown in this study a median coronary calcium score of 31 in new dialysis patients. This is in stark contrast to the median score of 595 reported by Raggi et al. (27) in patients prevalent on dialysis for 37 months, in whom only 17% of patients had zero coronary scores. These investigators report a strong correlation between the baseline coronary calcium score and the presence of atherosclerotic vascular disease events.

Together these data suggest that the presence of VC reflects a pathologic state of altered vascular structure that has profound effects on vascular function—and ultimately on survival. This information provides the basis upon which it is possible to interpret clinical trials relating abnormalities in mineral metabolism to adverse cardiovascular events. Increased arterial stiffness, as manifest by aortic PWV or E_{inc}, and the presence and extent of coronary and extracoronary vascular calcium accumulation appear to be excellent surrogate markers of cardiovascular outcome.

Prevalence of Disordered Mineral Metabolism

The development of increased arterial stiffness occurs as glomerular filtration rate (GFR) diminishes and the rate at which VC progresses is remarkably high after the initiation of renal replacement therapy. These arterial structural abnormalities appear to begin before patients with CKD develop ESRD. An inverse correlation exists between aortic PWV and estimated creatinine clearance for patients in the lower tertile of creatinine clearance in the general population independent of gender, mean blood pressure, and classic cardiovascular risk factors (28). Konings et al. (29) found a significant increase in arterial stiffness in patients with CKD by assessing carotid artery distensibility. These structural changes parallel the evolution of abnormalities in mineral metabolism as GFR declines.

Early in the course of CKD, a diminution of 1,25-vitamin D_3 formation occurs and results in a compensatory increase in PTH. Serum phosphorus concentration begins to increase, and even small increases within the normal range may further increase PTH. Kates et al. (30) reported that 45% of patients with a serum creatinine of 1.2–3.0 mg/dl had PTH levels of 150–380 pg/ml, which was directly correlated with a phosphorus concentration of 3.7–5.0 mg/dl. A compensated state of mildly increased phosphorus concentration, normal serum calcium concentration, low-normal vitamin D_3, and mild to moderately increased PTH exists until GFR declines more substantially. Despite the "normal" phosphate values, Felsenfeld and Rodriquez (31) suggested that the insufficient phosphate lowering effect of increased PTH in CKD contributes to the PTH resistance and diminishes the calcemic response of bone to PTH.

As GFR approaches stage 5 CKD, increases in phosphorus concentration and decreases in vitamin D_3 ultimately result in overt secondary hyperparathyroidism in the majority of patients. Contrary to conventional teaching, it is rare for clinically significant decreases in albumin-adjusted serum calcium below 8.5 mg/dl to occur. In an evaluation of 157 CKD patients, Martinez et al. (32) found no decline in serum calcium as GFR decreases, though only 18 patients had a GFR less than 30 cc/min. The Kidney Disease Outcomes and Quality Initiative (KDOQI) guidelines (33) on CKD summarize the literature regarding the prevalence of disordered mineral metabolism in CKD (Table 1). An analysis of practice patterns of nephrologists in patients with CKD in the northeastern United States reveals that 55% of patients with CKD had evidence of disturbed mineral metabolism (phosphorus > 4.5 mg/dl or PTH > 100 pg/ml) (34).

Data from the U.S. Renal Data System (USRDS) Dialysis Morbidity and Mortality Wave II Study of incident HD patients in 1996 and 1997 show a mean calcium of 8.7 mg/dl and phosphate of 5.5 mg/dl (29). In an earlier cohort of prevalent HD patients (1990 and 1993) (30), we found mean serum calcium and phosphate values of 9.4 and 6.2 mg/dl, respectively. In our analysis, 39% of patients had a mean phosphorus concentration

TABLE 1. KDOQI Guidelines: Abnormal Mineral Metabolism in CKD

- Onset and severity of bone disease and abnormal mineral metabolism are related to level of GFR with a threshold of ~60 ml/min/1.73m^2
- PTH levels are earliest marker of abnormal bone mineral metabolism
- Serum calcium is frequently but not consistently abnormal with decreased GFR
- Serum phosphorus is increased in patients with decreased GFR
- Bone histology is abnormal in the majority of patients with kidney failure

greater than 6.5 mg/dl, while a recent report from ESRD Network 11 found 32% of HD patients with a mean serum phosphorus greater than 6.0 mg/dl during a 3-month period (35). Vitamin D use was associated with a 14% incidence of calcium × phosphate product greater than 70, driven mainly by hyperphosphatemia, which was found in nearly one-third of vitamin D-treated patients. Disturbingly, patients were as likely to have their vitamin D increased in the setting of hyperphosphatemia as they were to have the dose reduced or held. Of those prescribed vitamin D, 29% had PTH values within a target of 130–260; 33% were above this value and 40% had PTH values below the target range. These "iatrogenic" disorders of mineral metabolism are likely to have important cardiovascular consequences in addition to the induction of low-turnover bone disease.

The complex relationship that exists between disorders of bone remodeling, abnormal mineral metabolism, vascular calcification, and the current treatment paradigm involving phosphorus binders and vitamin D use is shown in Fig. 3. It has become clear that the consequences of ROD involve more than an impact on skeletal structure and function. In fact, the most significant consequence of ROD may be the key role that bone integrity plays in modulating vascular health. Both high- and low-turnover bone diseases have been associated with elevated calcium and phosphorus and are associated with the presence of vascular calcification and increased mortality (36). As a result, relying solely on serum intact PTH as a guide in decisions regarding the provision or withholding of vitamin D may augment cardiovascular risk, given the reported poor ability of this test to precisely predict bone histopathology (37). New 1-84-specific PTH assays are now available, which may improve the ability to predict bone turnover; however, until prospective studies are completed, the role of these new assays in clinical practice remains unclear.

Disorders of bone remodeling do not only reflect the relative status of PTH homeostasis. Systemic and local factors such as growth factors and local cytokine production clearly impact bone turnover independent of PTH and thus may influence cardiovascular risk (38,39). Indeed, even in nonuremic patients, a strong correlation exists between osteoporosis and vascular calcification. Several HMG-CoA reductase inhibitors and all bisphosphonates appear to modulate both bone resorption and the propensity toward arterial calcification (40). Ibandronate appears to be the most potent inhibitor of bone resorption and arterial calcification (41). These data suggest that the link between bone remodeling disorders and arterial calcification is more than biochemical, but rather is a result of a common pathogenesis. Furthermore, it would appear reasonable to evaluate the impact of these inhibitors of bone resorption on renal osteodystrophy and cardiovascular events in the CKD population (42).

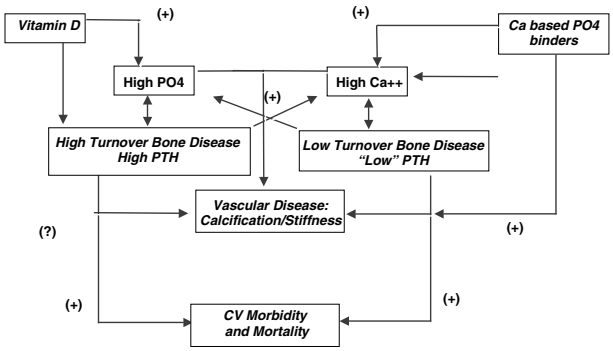

FIG. 3. Cardiovascular risks associated with vitamin D and calcium-based phosphate binder therapy.

Phosphorus

Phosphorus is directly involved in the pathogenesis of VC, as described above, and is likely to be the single most important modifiable risk factor in mineral metabolism disorder-induced cardiovascular disease. Three large, independent studies show phosphorus concentration to be an independent predictor of mortality in ESRD. In 1998 we reported a 6% increase in mortality per 1 mg/dl increase in serum phosphorus concentration (43). Similarly Klassen et al. (22) recently found that phosphorus concentration was directly associated with PP and that 1-year mortality was 8% higher per 1 mg/dl increase in phosphorus concentration. In the latter analysis of 37,000 patients on HD, phosphorus concentration was directly associated with pulse pressure, which was a strong predictor of 1-year mortality. PP and increased phosphorus concentration were also associated with the development of LVH and LV dilatation in an analysis of 433 incident dialysis patients, both of which were predictive of increased 2-year mortality (4). Preliminary analysis of data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) shows a 5% increase in the adjusted risk of mortality per 1 mg/dl increase in phosphorus concentration. Thus numerous data sources confirm that as phosphorus concentration rises above normal limits, mortality is increased.

The effect of phosphorus concentration on vascular calcification is supported by Raggi et al. (27), who found that the extent of EBCT-detected coronary artery calcification in adult HD patients was associated with age, male sex, white race, diabetes, dialysis therapy, higher serum calcium, and higher serum phosphorus concentration. Each 1 mg/dl increase in phosphorus concentration conferred a risk for increased calcification equal to 2.5 years of dialysis therapy. Serum phosphorus concentration was also strongly correlated with aortic calcification, as were age, race, dialysis therapy, and PTH. Serum phosphorus concentration was higher in young HD patients with coronary calcification than in those without calcification, and was positively correlated with changes in coronary calcium scores with serial EBCT (44). A 41% increase in relative risk of death resulting from coronary artery disease has been reported in patients with serum phosphate greater than 6.5 mg/dl, as has a 20% increase in mortality from sudden death (45). In a recent examination of 12,000 ESRD patients, control of serum phosphate was one of only four modifiable factors significantly associated with long-term survival, the others being dialysis dose, hematocrit, and not missing treatments (46). These data support the

cardiovascular nature of phosphorus-induced mortality risk.

Calcium and Calcium Load

A direct association of serum calcium concentration with CVD is less evident than that of phosphorus concentration and is confounded by the frequent but transient elevations in calcium concentration so common among patients with ESRD. Foley et al. (47) reported an increase in mortality associated with hypocalcemia less than 8.8 mg/dl; however, no data on PTH were available to eliminate the possibility that the risk seen reflected underlying PTH status. Chertow et al. (48) found the opposite result in a very large cross-sectional analysis of HD patients in whom serum calcium concentration less than 8.0 was associated with improved survival. We were unable to show any significant relationship between serum calcium and survival in an analysis of 2600 prevalent HD patients (30), while Klassen et al. (22) report a 16% increase in 1-year mortality with each 1 mg/dl percentage increase in serum calcium in an analysis of 37,000 HD patients. Furthermore, serum calcium, like serum phosphorus concentration, was associated with an increased PP, albeit weakly. Goodman (44) reported no difference in serum calcium between young dialysis patients with or without coronary calcification; however, Raggi et al. (27) found that serum calcium was strongly associated with baseline coronary but not aortic calcium scores in adult HD patients. Each 1 mg/dl increase in serum calcium was associated with a risk for coronary calcification equivalent to 5 years of dialysis therapy.

It is important to consider that serum calcium values do not necessarily reflect calcium balance and it is apparent that many patients with ESRD will be in markedly positive calcium balance with the administration of calcium-containing phosphate binders, particularly when given in combination with exogenous vitamin D. This calcium load may itself suppress PTH, thereby increasing the risk of low bone turnover; it has also been clearly associated with an increased risk of episodic hypercalcemia when compared to noncalcium-containing phosphate binders (49). The administration and the prescribed dose level of calcium-containing phosphate binders has also been associated with the presence of coronary and extracoronary vascular calcification (14,44). In addition, a recent randomized prospective trial in 200 prevalent HD patients demonstrated that calcium binder administration was associated with significant progression of both coronary and aortic calcium scores in a 1-year period, while the use of the noncalcium binder, sevelamer hydrochloride, was found to arrest the progression of vascular calcification (50). This report is of interest in that serum phosphorus and calcium concentrations and calcium × phosphate product were aggressively controlled to an equivalent degree with both study groups; however, patients in the calcium arm were more likely to have oversuppressed PTH and had a marked increase in the incidence of hypercalcemia (43% versus 17% in the sevelamer arm).

Calcium × Phosphate Product

It has long been accepted that an increased calcium × phosphate product augments the risk of visceral and vascular calcification. The more clinically relevant question is at what product level does the risk increase and whether the risk is independent of calcium and phosphorus concentrations. With a new appreciation for the molecular basis for extraskeletal calcification, the risk of an elevated calcium × phosphate product value may vary by the specific component, though this hypothesis has not been specifically investigated. Further confounding the role of calcium × phosphate product is the question of whether transient elevations are more or less predictive of risk compared to sustained values above a threshold. Many reports that find no relationship between calcium × phosphate product and cardiovascular events are limited by the short window of observation regarding control of divalent ion concentrations.

We have reported an increased relative risk (RR) of death associated with an elevated calcium × phosphate product that reached statistical significance in the top quintile (calcium × phosphate product greater than 72, RR 1.34), and this was independent of PTH. A strong relationship between calcium × phosphate product and the RR of death from coronary artery disease (RR 1.06) and sudden death (RR 1.07) per each 10 mg^2/dl^2 increase was recently described; however, this seemed to be primarily related to phosphorus concentration since adjustment for serum phosphorus concentration made these risks statistically insignificant (45). In a study of young HD patients, a higher calcium × phosphate product (mean 65 mg^2/dl^2) was associated with coronary calcification and also was positively correlated with increases in coronary artery calcium score on follow-up EBCT scans (44).

Progression of aortic calcification may also be associated with an elevated calcium × phosphate product, with as few as four episodes of a calcium × phosphate product level greater than 60 mg^2/dl^2 in 1 year being associated with an increased degree of aortosclerosis, particularly in diabetic HD patients (51). This aortic calcification is related to arterial stiffness as measured by aortic PWV (52).

Management

Initial management of incipient secondary hyperparathyroidism should attempt to prevent parathyroid hyperplasia by controlling serum phosphorus concentration through dietary phosphate restriction and the use of calcium-containing binders. The provision of calcium binders is unlikely to be of any harm in patients with preserved skeletal integrity and early stages of CKD, and may ameliorate hypocalcemia in those patients in whom it exists. The goal phosphorus concentration in this stage should be less than 4.5 mg/dl. If control of phosphorus concentration through calcium binder therapy is inadequate to maintain PTH within normal limits, oral vitamin D_3 in doses less than 0.5 μg/day has been shown to be safe and

effective, with no observed impact on residual renal function (53,54). However, serum calcium and phosphorus values must be closely followed if vitamin D compounds are prescribed.

As patients develop stage 5 CKD, control of calcium, phosphorus, and PTH becomes more difficult. Dietary restriction of phosphorus has limited effectiveness and is undesirable if it decreases protein intake as it may result in protein malnutrition. Indeed, serum phosphorus concentration and PTH are directly related to the nutritional status of elderly HD patients (55). KDOQI guidelines, which recommend 1.2 g/kg/day protein intake in patients with ESRD, obligate typically more than 1000 mg/day of phosphorus. In this setting, available data demand that calcium-based phosphate binders must be limited in order to lessen the risks of calcium loading, hypercalcemia, elevated calcium × phosphate product, oversuppression of PTH, and progression of vascular calcification. It is unclear what the "safe" dose of calcium may be and it almost certainly varies with the underlying bone disorder and whether or not vascular calcification already exists. In the setting of low-turnover bone disease or known calcification, calcium should be severely limited in favor of nonaluminum, noncalcium phosphate binders.

The goal of binder therapy should be a normal serum phosphorus concentration less than 5.5 mg/dl without hypercalcemia (less than 10 mg/dl) or excessive calcium loading. Previously accepted standards of care (phosphorus concentration less than 6 mg/dl, calcium concentration less than 11 mg/dl, calcium × phosphate product less than 70 mg^2/dl^2) must be abandoned in view of the effect on vascular calcification and survival.

Clinical management of secondary hyperparathyroidism remains quite difficult for nephrologists today. Both excessive or inadequate PTH must be avoided; however, given the limitations of the current assay and its modest correlation with bone histology, one can only say with confidence that PTH less than 100 pg/ml or greater than 450 pg/ml are likely to be undesirable. A major shift must occur in practice when PTH values are between these extremes, with recognition of the serious toxicity associated with the ability of vitamin D therapy to produce elevations in calcium and phosphorus. Although calcium supplementation alone may effectively control mild to moderate secondary hyperparathyroidism, the doses required to do so have been reported to be as high as 7000 mg of elemental calcium/day (56). Vitamin D analogues, which have less of an effect on gastrointestinal calcium and phosphate absorption, are preferred if vitamin D is to be administered. The future management of secondary hyperparathyroidism will involve the use of calcimimetic agents, which are agonists of the calcium-sensing receptor and have the ability to suppress PTH secretion and parathyroid gland hyperplasia while avoiding the adverse effects on calcium and phosphorus homeostasis (57,58). Furthermore, the conceptual basis for achieving a target PTH may change with the recognition that cyclic PTH levels increase bone formation and bone mass (59).

We advocate a "do no harm" approach to PTH management within the range stated above, which acts to balance the potential toxicity of PTH with the clear risk associated with phosphorus and calcium elevations. Despite the popular movement away from bone biopsies, biopsy data may be needed to appropriately balance these risks until definitive data are available with the newer PTH assays.

Specific therapy targeting arterial stiffness may be a therapeutic strategy in the future. There is some evidence that HMG-CoA reductase inhibitors and calcium channel blockers may reduce the accumulation of calcium in atherosclerotic plaques and recently both of these classes of drugs have been associated with increased survival in patients with ESRD (60–62). Calcium channel blocker use was associated with a 32% lower RR of cardiovascular mortality among a cohort of 4065 incident ESRD patients, an effect which may be related to its ability to prevent PTH-induced increases in intracellular calcium accumulation. The renin-angiotensin-aldosterone system may also be important in the development of arterial stiffness. In a cohort of 150 HD patients, Guerin et al. (63) have shown that patients who had both blood pressure lowering and a decrease in their aortic PWV had a survival advantage, particularly with the use of the ACE inhibitor perindopril. In addition, there is accumulating evidence that bisphosphonates not only have a beneficial impact on bone resorption in osteoporosis, but that they may inhibit arterial calcification and lipid accumulation (64). Though they continue to be dismissed in the management of renal osteodystrophy, this important class of drugs may prove to be quite beneficial for both skeletal and vascular integrity.

Conclusion

Disturbances in mineral metabolism affect the cardiovascular outcomes of patients with CKD, likely mediated by their ability to alter the cushioning/capacitance function of arteries and to promote coronary, extracoronary, and visceral calcification. Interventions to ameliorate these effects must begin early in the course of CKD when the underlying abnormalities begin. The prevention of hyperphosphatemia and hypercalcemia should be paramount when developing strategies to manage renal osteodystrophy. An expanding understanding of the mechanisms of bone remodeling and arterial calcification suggest that these processes are closely linked. It may be that the almost universal disturbances in normal bone remodeling underlie the greatly increased cardiovascular risk seen in patients with ESRD. Thus mineral metabolism disorders should be considered as important and unique cardiovascular risk factors in patients with CKD.

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Why ''Nephrology''?

Have you ever wondered how the specialty of Nephrology got its name, and when? Why are we called ''nephrologists'' and not (for example) ''renologists''? Back in 1940 there was no Nephrology – only a scarerted group of physicians and scientists in interested in studying the kidney and its diseases world-wide. There was no dialysis, and no renal biopsies. As these techniques were introduced into clinical medicine around 1950, and investigation of renal physiology flowered, so Nephrology emerged at that time – but as yet had no name....

The introduction of this term is often attributed to either Gabriel Richet or Jean Hamburger, in Paris or Kenzo Oshima in Japan in 1960. In fact, the term is much, much older. Hamburger himself (1) found it in the French dictionaries of Boiste (1803) and Morin (1809), and most famously in Littré's widely used dictionary of 1862 – but only in the sense of renal anatomy. Carl Gottshalk also identified it in an American dictionary of 1842 (Dunglison's). The earliest use I can find of this term *outside* of a dictionary, however, and in its modern sense is by the English nephrologist Arnold Osman (1893–1972) (2). On several occasions from 1945 (3) onwards he referred to nephrology and nephrologists, and described himself as ''Honorary Nephrologist, Children's hospital, Hampstead''. A 10,000 word document from 1948 in his unpublished papers is called ''*The science and practice of nephrology* '' in which the terms ''Nephrology'' and ''Nephrologist'' are used throughout. In 1950, in an obituary of Franz Volhard (*BMJ* I: 1376, 1950) he *wrote* ''*Volhard made many contributions to the practice of nephrology* ... no-one has made more contributions to this important branch of medicine '', and in 1952, in a review of Homer Smith's great classic *The kidney: structure and function* '' he added ''*the nephrologist and the research worker will find it indispensable* ''. (*Br Med J* ii: 376, 1952). Why, when he and other British nephrologists formed the first nephrological society in 1950 (with Osman as president) it was called the ''Renal Association'' (4) is unclear! In addition in 1954 the Italians founded the *Minerva Nefrologica*, and in 1957 the *Società Italiana di Nefrologia*. Thus it is certain that the word was current in the 1950s and even the 1940s, and is much older than usually believed, even if it did not receive wide currency until it was used in the title of the first ISN meeting in Evian in 1960. The French Société de Néphrologie was registered by Marcel Legrain, its then president in May 1960, a few months before the ISN meeting; it had been preceded by the Société de Pathologie Rénale, founded in 1949, the oldest body of nephrologists in the world.

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