THE UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER

CKD-MBD: Progress, or Just a Name Change?

Internal Medicine Grand Rounds

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This is to acknowledge that Dr. Cronin has disclosed that he does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Cronin will be discussing off-label uses in his presentation.

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Clinical interests include management of ESRD, radiocontrast nephrotoxicity, and management of acute renal failure. The purpose of this Grand Rounds is to provide a general review of the management of ESRD with a focus on the newly defined syndrome called CKD-MBD, or Chronic Kidney Disease-Mineral and Bone Disorder. Two case reports will be used to illustrate the complex problems confronting the practicing nephrologist.

Thirty years ago the treatment of renal osteodystrophy focused on lowering serum phosphorus and raising serum calcium in order to reduce parathyroid hormone (PTH) and its primary pathological manifestation in bone, osteitis fibrosa cystica. The other prevalent bone disease was osteomalacia, often the consequence of aluminum containing antacids. Adynamic bone disease occurred in a small group of patients. Controlling serum phosphate with aluminum hydroxide or calcium carbonate was the primary treatment to prevent osteitis fibrosa. In the intervening years, new discoveries have made this field more complicated. Receptors for vitamin D, calcium sensing, and FGF-23 and klotho have been identified on parathyroid tissue, the kidney, and other tissues, that affect bone and mineral metabolism along synergistic and counterregulatory pathways. Current drug therapies to control hyperparathyroidism include calcium and non-calcium based phosphate binders, activated vitamin D, and calcimimetics[1]. Despite these therapeutic advances, there is uncertainty among nephrologists about how best to use these therapies for our patients and a growing concern that in some cases the treatments may be causing harm.

It is not surprising that patients with ESRD have a high risk of dying from cardiovascular disease, since the underlying risk factors, hypertension, diabetes, hyperlipidemia, and atherosclerosis are highly prevalent in both group. But in the past several decades, a consensus has emerged that renal osteodystrophy and related mineral disorders of phosphorus, calcium, and parathyroid hormone are linked and even accelerate cardiovascular disease, the major morbid complication suffered by these patients. The term, CKD-MBD, or Chronic Kidney Disease-Mineral and Bone Disorder, describes the syndrome of uremic bone diseases and the mineral and hormonal disorders that are felt to be a central feature and possibly causal in the pathogenesis of the cardiovascular disorders characterized by vascular calcification[2].

CKD MBD. Definition[3].

1) A systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:
    a. Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism
    b. Abnormalities in bone turnover, mineralization, volume, linear growth, or strength
    c. Vascular or other soft-tissue calcification
2) Definition of Renal Osteodystrophy
    a. Renal osteodystrophy is an alteration of bone morphology in patients with CKD
    b. It is one measure of the skeletal component of the systemic disorder of CKD-MBD that is quantifiable by histomorphometry of bone biopsy

The following discussion will describe several aspects of this multifaceted disorder highlighting the following areas:

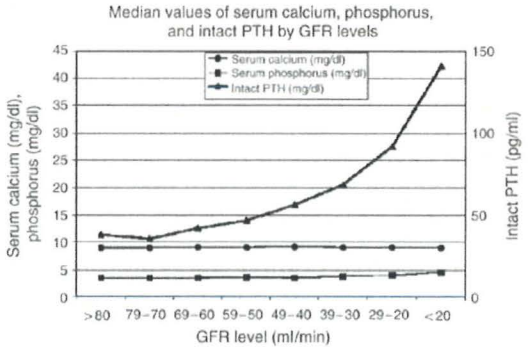
1. Development of secondary hyperparathyroidism (sHPT)
2. The changing spectrum of uremic bone disease
3. Current treatments for sHPT and their effects on vascular calcification and mortality

4. Current management strategies and guidelines

Development of secondary hyperparathyroidism

In early CKD, the reduction in glomerular filtration rate (GFR) brings disruptions to calcium, phosphate, vitamin D, and parathyroid hormone homeostasis. Serum phosphate remains within the normal range until the late stages of CKD (Fig 1). This occurs because rising levels of FGF 23 and its co-receptor klotho block reabsorption of phosphate in the proximal tubule of the nephron and reduce gastrointestinal absorption of both phosphorus and calcium through blockade of 1-alpha hydroxylase, the enzyme that converts 25 OH vitamin D to 1,25 (OH)2 D in the kidney (Fig 2)[4]. Reduction of active vitamin D, calcitriol, are detectable at GFR values of 40 ml/min[5-6] (Fig 3). With low VDR receptor occupancy, PTH transcription is

Fig. 1. Median values of serum Ca, P, and iPTH by eGFR levels



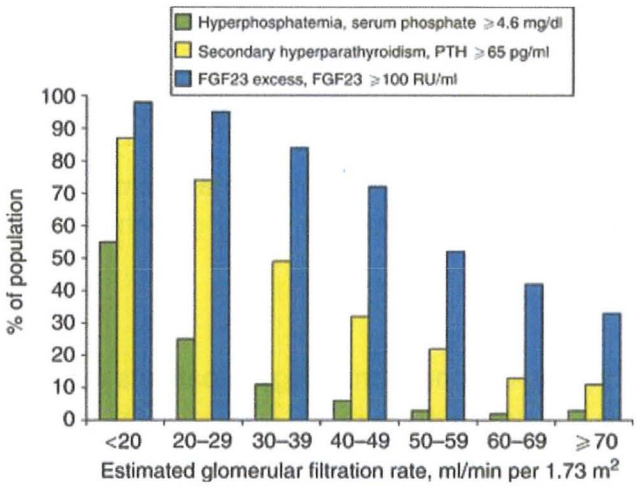


Fig. 2. Serum FGF-23 levels rise before PTH In early CKD.

Isakova. Kl. 79: 1370, 2011.

increased and PTH secretion is stimulated by hypocalcemia via the CaSR. Rising PTH levels also reduce urinary phosphate reabsorption. The CaSR is a more potent regulator

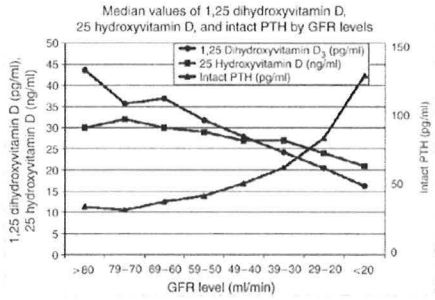


Fig. 3. Median values of 1,25 OH_2 D_3, 25(OH)D_3 and iPTH by GFR levels.

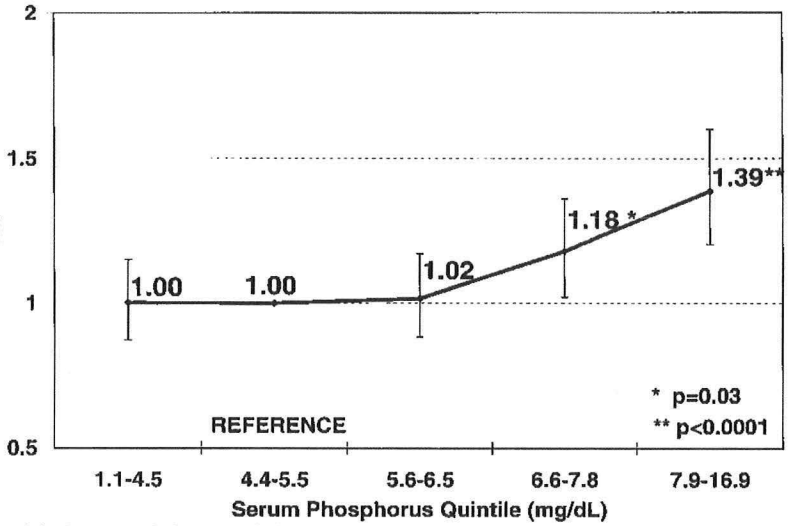
of parathyroid gland activity than the VDR, but both appear to have a role in the development of parathyroid hyperplasia[7-8]. Lower calcitriol levels also lead to a reduced number of VDRs on the parathyroid gland, an important factor in the development of parathyroid hyperplasia and nodule formation[9]. Hyperphosphatemia is both a cause and an effect of secondary hyperparathyroidism. A falling GFR in early CKD and reduced phosphate excretion begins the process that leads to parathyroid gland hyperfunctioning. However, in some patients with advanced CKD, autonomously functioning parathyroid tissue causes hyperphosphatemia of an endogenous origin due to PTH driven bone resorption.

Central Role of Phosphorus

Since conventional 3x/weekly dialysis removes only 40% of phosphate ingested each week by a average dialysis patient, preventing gastrointestinal absorption of the remaining phosphate with binders is required. Aluminum based binders provided excellent phosphate control for many years until their toxicity on a number of organ systems became apparent. They are now used only rarely and for short periods as a bridge to safer phosphate binders. Calcium based phosphate binders are still widely used, but calcium overload and frank hypercalcemia limits their use in some patients. Calcium overload is of special concern when calcium based binders are combined with activated vitamin D to control secondary hyperparathyroidism. Also, vitamin D therapy increases GI absorption of phosphorus, an action running counter to the primary goal of reducing serum phosphorus. Analogues of calcitriol provide good PTH

Fig 4. Relative mortality risk by serum phosphorus quintiles.

Block. AJKD. 1998



suppression with less effect to enhance intestinal calcium and phosphate absorption, but studies to show their superiority to the calcitriol are still lacking when evaluating meaningful end points[10]. Large cohort studies suggesting that hyperphosphatemia and a high calcium phosphate product were mortality risk factors for dialysis patients began to appear in the late nineties[11-12] (Fig. 4).

Renal Osteodystrophy. The spectrum of renal bone disease has changed remarkably over the past few decades. In a series reported in 1986 of 142 unselected bone biopsies, the distribution of lesions was low turnover bone disease (7%), mineralization defect, i.e. osteomalacia, (25%), and high turnover bone disease, or osteitis fibrosa, (68%)[13]. The high usage of aluminum containing phosphate binders and their known propensity to cause osteomalacia and sometimes low turnover bone disease were the likely explanation for this distribution. Bone biopsies showed Al^{+++} deposition at the mineralization front which inhibited mineralization of osteoid[14]. In the intervening years, use of aluminum binders has virtually disappeared, and osteomalacia is now uncommon. Currently, low bone turnover, also called adynamic bone disease, is the predominant lesion, noted in 58% of 630 bone biopsies obtained between 2003 and 2008 from patients involved in research protocols in both the US and Europe[15] (Fig. 5).

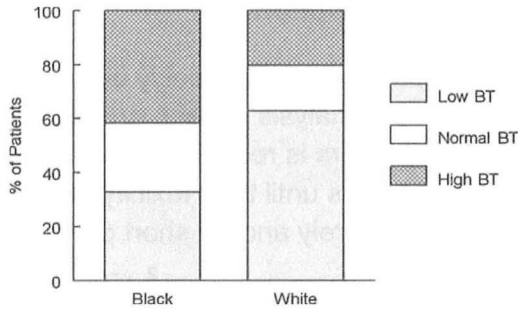


Fig 5. Prevalence of low, normal, and high bone turnover in black and white CKD stage 5 patients on maintenance dialysis.

Low bone turnover histology correlated inversely with PTH levels and was more common in whites. High turnover disease was more common in blacks who had higher PTH levels in each category of bone turnover compared with whites. A mineralization defect, osteomalacia, was infrequent, found in 3% of biopsies.

Low bone turnover and low PTH states are undesirable because they are associated with more bone fractures and with vascular calcification[16-18]. Patients at high risk for low bone turnover are more likely to be older, male, have diabetes, receiving peritoneal dialysis, and taking calcium containing phosphate binders or vitamin D[14, 19-20]. Low bone turnover disease is not limited to patients with ESRD as it is found in 25% of non-dialysis CKD patients and is associated with the lowest values for PTH[21].

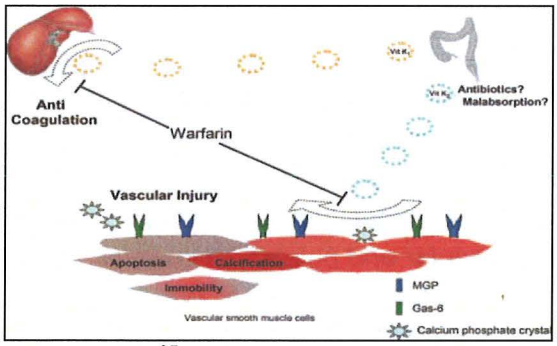
Calcific Uremic Arteriolopathy (CUA). Calcific uremic arteriolopathy, or calciphylaxis as it is commonly called, is a disorder with high morbidity and a 60-80% mortality[22]. Calcium plays a prominent role in pathologic specimens, but it is not clear whether calcium has a primary or secondary role. The syndrome develops in patients with renal failure, hypercalcemia,

hyperphosphatemia, and high parathyroid hormone levels and typically affects small rather than large vessels. Clinical efforts to prevent or control secondary hyperparathyroidism may have inadvertently lead to situations ripe for developing CUA, i.e. low bone turnover, a high calcium load, and vitamin D therapy. These are conditions associated with vascular calcification. Medial calcification occurs in the elastic layer of medium and small sized vessels and often is seen in digital vessels of the hands and feet when examined by xray. Medial calcification, unlike intimal calcification, is not associated with inflammation. Vascular stiffness is a more likely outcome than vascular occlusion that is seen with intimal calcification. Nevertheless, in pathologic specimen from patient with CUA, vascular thrombi may be a final common pathway leading to tissue ischemia and necrosis. The location of vascular lesions may be acral or pannicular, with acral lesions leading to amputation, e.g. digits, but overall less lethal than the pannicular lesions.

The demographics of CUA in dialysis patients are that it tends to occur in younger patients and patients longer on dialysis; it has an incidence of about 4%[23]. Serum calcium, phosphate, calcium x phosphate product, and PTH are high, and vascular calcification is seen by Xray in 100%. A non-ulcerating CUA, or "early disease," form has been reported characterized by non-ulcerating subcutaneous plaques, especially on the calves[24]. Mortality for these patient is still high, 36% at six months, and may just indicate earlier detection and not a unique variant of the disease.

Warfarin and vascular calcification. Exposure of patients with vascular calcification to warfarin may be a trigger for CUA[25]. Warfarin, through its action of depleting vitamin K, interferes with the carboxylation process required to activate several coagulant factors produced in the liver, the mechanism of action for its use as an anticoagulant. Less well known is the effect of warfarin on two vitamin K dependent proteins, matrix Gla protein (MGP) and Growth Arrest Specific gene 6 (Gas 6) protein, that are produced and carboxylated in the endothelium

Figure 6. Warfarin prevents vitamin K from participating in the carboxylation process, inhibiting both hepatic and peripheral production of VKDPs. In the periphery, warfarin inhibits activation of MGP and Gas-6, interrupting the protective mechanisms of these proteins against vascular calcification.



and protect the vasculature from injury and assist in repair[25]. Both MGP and Gas 6 inhibit vascular calcification. High phosphate levels also inhibits Gas-6 activity[26]. In the rat, warfarin induces calcification of medium sized arteries, particularly in the presence of vitamin D[27]. While these mechanisms are less well studied in man, there are numerous clinical reports of calciphylaxis developing after initiation of warfarin[28-29]. A case controlled study of 28 patients from Japan with pathologically confirmed calciphylaxis identified warfarin therapy (OR 11.4, CI 2.7-48) and hypoalbuminemia (OR 19.8, CI 4.4-89.5) as significant risk factors for calciphylaxis[30]. The dilemma for clinicians is whether the beneficial anticoagulant effects of

warfarin for treatment of atrial fibrillation and the other usual clinical indications outweigh the risk of blocking formation of vitamin K dependent proteins in the periphery that maintain a healthy vasculature and protect against vascular calcification.

Strategies to Prevent Secondary Hyperparathyroidism.

Restricting dietary intake of phosphate and phosphate binders continue to be the primary tools to prevent secondary hyperparathyroidism. Conventional hemodialysis, 3.5-4 hours three times weekly, removes approximately 900 mg of phosphorus. The average dialysis patient ingests 900 mg of phosphorus daily. Thus, without phosphate binders, this patient would have a net positive balance of 3600 mg of phosphorus after one week. Since aluminum binders are now rarely used because of their toxicity to bone, neural, and other tissues, the choice of agent is either calcium based or non-calcium based binders, or some combination. Calcium based binders for patients at risk for vascular calcification are an increasing concern, but several large studies have not shown a mortality benefit when sevelamer, a non-calcium based binder, was compared to calcium based binders[31-32]. A post-hoc analysis of a small study comparing sevelamer to calcium based binders did show higher mortality with calcium based binders[33]. Whether the choice of binder, calcium based or not, has an effect on vascular calcification is not settled, although some experts decidedly favor non-calcium based binders for ESRD patients[34]. Two large studies found less coronary calcium with sevelamer than calcium binders in dialysis patients[35-36]. Yet another large study found no difference in coronary calcium comparing sevelamer to calcium acetate in patients controlled for lipids[37]. Lanthanum carbonate is the most recent non-calcium binders to appear and fills a similar niche as sevelamer for use in patients where calcium binders are undesirable. Lanthanum accumulates in the livers of uremic rats, but there is no known toxicity in humans. Gastrointestinal sides effects may limits its use in some patients. A small pilot study suggests that lanthanum carbonate, compared to non-lanthanum phosphate binders, is capable of slowing the progression of coronary artery calcification[38].

The cost differential among binders is formidable. Using the Dallas VA formulary costs as a basis, the three times daily dollar cost for calcium carbonate, 500 mg tab, is $0.02, calcium acetate, 667 mg tab, is $0.81, sevelamer carbonate 800 mg, $2.94, and lanthanum carbonate 750 mg, $3.95. A systemic review of 40 randomized trials comparing non-calcium to calcium based phosphate binders in ESRD patients found no difference in mortality, hospitalization, or other cardiovascular end points[39]. However, various surrogate end points such as achieved serum calcium, serum phosphorus, and PTH levels differed among the agents. Rather than abandon calcium based binders, a reasonable approach would be to use non-calcium based binders in patients with hypercalcemia, low bone turnover or its surrogate, a low PTH value, and in patients with known vascular calcification.

Lowering serum phosphate levels with binders during early CKD with the hope of preventing secondary hyperparathyroidism has been studied. A small (212 patients) randomized, non-blinded study of pre-dialysis patients given sevelamer or calcium carbonate, reported less mortality and less coronary calcification in patients randomized to sevelamer[40]. The confounder in this study, and other studies evaluating sevelamer, is that it had effects not shared by the

other binders, i.e. lowered total cholesterol, LDL and CRP. Kovesdy et al, studied an historical cohort of men with non-dialysis CKD and also found a mortality benefit for taking any phosphate binder[41]. Another study, described as a pilot clinical trial in patients with moderate non-dialysis CKD, randomized subjects to calcium acetate, sevelamer, lanthanum, or placebo[42]. The binders caused a small, but significant, reduction in plasma phosphate, 4.2 to 3.9 mg/dl, and the PTH level was held stable. Serum phosphate in placebo patients fell slightly, 4.2 to 4.1 mg/dl, but PTH rose significantly. Unexpectedly there was a significant increase in coronary and aortic calcification in subjects exposed to all three binders compared to subjects receiving placebo. Subgroup analysis indicated that vascular calcification was most pronounced in patients receiving the calcium based binder. The finding that the phosphate binder arm, not the placebo arm, associated with vascular calcification is concerning. It is worth noting that prescribing phosphate binders in non-dialysis CKD is an off label use.

Most studies comparing the efficacy of different binders use surrogate end points, i.e. serum phosphate, calcium, or PTH. Whether phosphate binders lessens mortality in ESRD has not been studied directly in a randomized, placebo controlled trial, and remains an open question. Two large cohorts with multivariable adjustments examined this question and reported conflicting findings. Isakova et al, found an 18% one year risk reduction for death in a cohort of 10,004 patients, years 2004-2005, who were exposed to phosphate binders in their first 90 days of dialysis[43]. Winkelmayer et al, in a cohort of 3603 patient, years 1996-1997, found no survival benefit for patients assigned to a Ca++ based binder, hazard ratio of 0.89, ($p<0.28$)[44].

Vitamin D.

Activated vitamin D, and its analogues, are powerful agents for correcting vitamin D deficiency and for managing secondary hyperparathyroidism through suppression of formation of PTH via the vitamin D receptor (VDR). Replacement dose vitamin D is associated with a number of beneficial effects on a many tissues, including the health and protection of the heart and vascular endothelial tissues[45]. With the pharmacologic doses often used to suppress PTH in ESRD, hypercalcemia and hyperphosphatemia may occur and predispose to vascular calcification. Choosing the correct dose that achieves both physiologic replacement and pharmacologically desired effects on the parathyroid gland can be difficult. Parathyroid gland size appears to be a determinant of successful vitamin D therapy, with smaller glands being more responsive[46]. Active vitamin D therapy in pharmacologic doses may over suppress PTH, cause low bone turnover, and increase the risk for vascular calcification and is contraindicated in these situations.

Calcimimetics.

Calcimimetics are positive allosteric modulators of the CaSR. Cinacalcet suppresses PTH production and release from the principal cells of the parathyroid gland by enhancing the sensitivity of the CaSR to extracellular calcium. When cinacalcet is given to renal patients, PTH falls within a few hours and serum calcium falls within 4-8 hours[47]. In a clinical study of 59 ESRD patients, regular use of cinacalcet caused a prolonged, 100 week, sustained reduction in serum PTH to < or =300 pg/m in 55% of patients[48]. Nearly a third of patients had a 30%

reduction in serum PTH. Other agents, phosphate binder and vitamin D, were permitted in this study.

As an agent to reverse secondary hyperparathyroidism in ESRD, cinacalcet has an advantage over vitamin D in that it causes a decrease in both calcium and phosphorus, whereas vitamin D increases both through its effect on gastrointestinal absorption. However, cinacalcet is approved only for patients with ESRD; other agents like vitamin D must be used to prevent hyperparathyroidism in pre-dialysis patients. Since neither cinacalcet nor vitamin D alone is usually capable of achieving complete control of secondary hyperparathyroidism, a combined approach has gained favor. The OPTIMA trial showed that for patients with difficult to control hyperparathyroidism, the addition of cinacalcet to conventional treatment, i.e. binders and vitamin D, achieved better outcomes (PTH suppression, calcium and phosphate control) than those patient receiving only conventional therapy[49]. With addition of cinacalcet to the conventional regimen, the dose of vitamin D was reduced by 22%. Combination cinacalcet and vitamin D will likely be an effective dosing strategy for many patients. Calcimimetics like cinacalcet generally have a positive effect on surrogate measures such as serum PTH, serum calcium, and serum phosphate. Cinacalcet also reduces gland volume regardless of the size[50]. Whether the reduction in gland size is due to reduced cell volume or to apoptosis is unclear. Larger glands are more likely to have nodular hyperplasia, an abnormality characterized by reduced CaSR and VDRs[51-52].

What is yet unproven is whether calcimimetics will have a beneficial effect on a hard outcomes, such as cardiovascular mortality or morbidity. The EVOLVE trial is a multicentered trial comparing the effect of adding cinacalcet or placebo to standard therapies (phosphate binders and vitamin D) on death or non-fatal cardiovascular events (myocardial infarction, unstable angina, congestive heart failure, or peripheral arterial disease)in dialysis patients[53]. The results of this trial are expected before the end of 2012.

The cost of cinacalcet is considerable. At the low end of the daily dosing range, a 30 mg tablet costs $7.80; at the high end, a 180 mg tablet costs $47.00 (VA formulary costs).

Vascular Calcification.

Vascular calcification is far more prevalent in dialysis patients than in age-matched controls with normal kidney function and is detectable in young adults with ESRD[54-55]. Risk

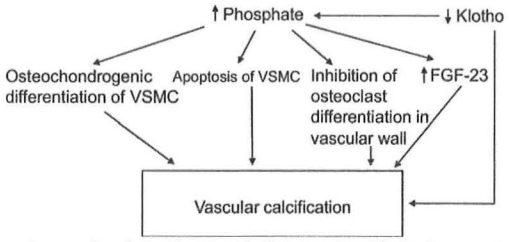


Fig 7. Mechanisms by which phosphate may contribute to the initiation and/or progression of vascular calcification; VSMC vascular smooth muscle cell.

factors for vascular calcification include hyperphosphatemia, calcium overload, and extremes of bone remodeling, either low bone turnover or hyperparathyroid bone disease[56]. Hyperphosphatemia induces vascular smooth muscle cells to undergo apoptosis and can induce them to undergo a change to an osteochondrogenic phenotype providing a framework to

explain the association of hyperphosphatemia and vascular calcification[57-58] (Fig 7.). With progressive CKD, FGF-23 levels rise and klotho levels fall. These changes are associated with vascular calcification, but whether they are markers or involved in pathogenesis is uncertain[59-60]. Since not all patients with CKD or ESRD develop vascular calcification, inhibitors of calcification like fetuin-A may be playing a role[61].

Parathyroidectomy is generally reserved for patient with tertiary hyperparathyroidism, i.e. hyperparathyroidism with hypercalcemia refractory to medical therapy including oral phosphate binders, calcitriol, and calcimimetics. Data from the late nineties indicate that the rate of parathyroidectomy had decreased by 30% from earlier figures[62]. The indications for parathyroidectomy are severe hypercalcemia, debilitating bone disease, intractable pruritus, progressive vascular calcification, and calcific uremic arteriolopathy. Laboratory indications for surgery usually include a PTH level >800 pg/ml and evidence that parathyroid size is large enough that histopathology will likely show nodular hyperplasia, a finding that correlates with decreased responsiveness to the suppressive effects of the CaSR and vitamin D[63-64]. If a patient has had prior exposure to aluminum containing binders, or low bone turnover disease is suspected, a bony biopsy should be performed prior to parathyroidectomy. In the absence of aluminum exposure, a bone biopsy is generally not required, particularly if PTH levels are very high. The normal parathyroid glands weigh 30-40 mg and four glands are typical. However, some patients have additional glands that can be scattered throughout the mediastinum and retroesophageal areas. Radionuclide scanning is helpful in detecting hyperplastic parathyroid glands. When technetium-99m-sestamibi and I-123 subtraction single photon emission computed tomography were used together, the sensitivity is 77% for pre-operatively identifying surgically recovered hyperplastic gland[65]. The surgical procedures of choice are subtotal parathyroidectomy and total parathyroidectomy with autotransplantation. Recurrence rates are about equal with either surgery, and range from 6-14 percent[66]. Autotransplantation of slivers of surgically removed gland to arm muscle or other accessible site has a surgical advantage to subtotal parathyroidectomy, as re-exploration of a previously operated neck is challenging. Parathyroidectomy may decrease vascular calcification. CT scanning of the coronary and carotid arteries of 10 patients after subtotal parathyroidectomy showed a reduction in calcification[67]. The effect was most prominent in patients with the highest coronary artery scores. Parathyroidectomy also reduces FGF-23 levels, a factor implicated in the pathogenesis of vascular calcification[68]. Parathyroidectomy improves long term survival compared to well match non-operated controls[69].

As noted above, administration of a cacimimetic agent can be viewed as a "medical parathyroidectomy," as it reduces PTH, serum calcium, and serum phosphorus and parathyroid gland mass reportedly decreases. However, evidence is lacking on which procedure offers the best long term benefit to patients with tertiary hyperparathyroidism.

What to do until the evidence arrives?

The KDIGO guidelines for managing patients with ESRD are almost exclusively rated at the "suggest" rather than "recommend" level, since the data for most important issues is still inconclusive. Rather than targeting specific values, treating to ranges and using trends is

stressed. Control of phosphate through diet, dialysis, and binders is recommended, taking into consideration the existing serum calcium in choosing the agent. Controlling PTH to 2-9 times the normal range (12-88 pg/ml) is more liberal than prior guidelines and acknowledges both the wide variability of PTH assays and the poor correlation between the PTH level and bone histology. Low or normal PTH levels should be avoided as they generally predict low bone turnover and both are associated with vascular calcification. For patients with a rising PTH level, activated vitamin D or an analogue can be used to lower the level. Calcimimetics may also be used to suppress PTH, with or without activated vitamin D, but hypocalcemia should be avoided. Parathyroidectomy remains a relatively low risk procedure for patients with tertiary hyperparathyroidism refractory to medical therapies.

Summary.

The umbrella term "CKD-MBD," which encompasses the uremic derangements in bone, minerals, and related hormones, and their effects on vascular calcification represents a fresh view of an old problem. Low bone turnover, hypercalcemia, and over suppression of PTH are associated with vascular calcification. These disturbances are often the result of well intentioned drug treatments aimed at preventing secondary hyperparathyroidism, i.e. calcium based phosphate binders and high dose vitamin D. The KDIGO CKD-MBD guidelines acknowledge these concerns and the gaps they create in our understanding and management of important clinical issues in ESRD. Research studies to answer such basic questions as whether phosphate provide more good than harm are essential.

Alternatives to phosphate binder therapy such as calcimimetics, with or without low dose vitamin D, may permit control or regression of secondary hyperparathyroidism with less harm to the vasculature. This question requires more study.

For patient with ESRD and widespread vascular calcification, calcific uremic arteriolopathy is a devastating complication. Warfarin use in at risk patients must weigh the benefits of anticoagulation with the risk of CUA.

Parathyroidectomy is reserved for patient with tertiary hyperparathyroidism or vascular complications like CUA that have failed all other interventions. Its effect is usually long-lasting with immediate reversal of the biochemical abnormalities and subsequent healing of bone.

References:

1. Cunningham J, Locatelli F, Rodriguez M. Secondary hyperparathyroidism: pathogenesis, disease progression, and therapeutic options. Clin J Am Soc Nephrol 2011;6:913-21.
2. Moe S, Drueke T, Cunningham J, et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2006;69:1945-53.

3. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl 2009:S1-130.
4. Isakova T, Wahl P, Vargas GS, et al. Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. Kidney Int 2011;79:1370-8.
5. Levin A, Bakris GL, Molitch M, et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. Kidney Int 2007;71:31-8.
6. Pitts TO, Piraino BH, Mitro R, et al. Hyperparathyroidism and 1,25-dihydroxyvitamin D deficiency in mild, moderate, and severe renal failure. J Clin Endocrinol Metab 1988;67:876-81.
7. Fukuda N, Tanaka H, Tominaga Y, Fukagawa M, Kurokawa K, Seino Y. Decreased 1,25-dihydroxyvitamin D3 receptor density is associated with a more severe form of parathyroid hyperplasia in chronic uremic patients. J Clin Invest 1993;92:1436-43.
8. Panda DK, Miao D, Bolivar I, et al. Inactivation of the 25-hydroxyvitamin D 1alpha-hydroxylase and vitamin D receptor demonstrates independent and interdependent effects of calcium and vitamin D on skeletal and mineral homeostasis. J Biol Chem 2004;279:16754-66.
9. Denda M, Finch J, Brown AJ, Nishii Y, Kubodera N, Slatopolsky E. 1,25-dihydroxyvitamin D3 and 22-oxacalcitriol prevent the decrease in vitamin D receptor content in the parathyroid glands of uremic rats. Kidney Int 1996;50:34-9.
10. Gravellone L, Rizzo MA, Martina V, Mezzina N, Regalia A, Gallieni M. Vitamin d receptor activators and clinical outcomes in chronic kidney disease. Int J Nephrol 2011;2011:419524.
11. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis 1998;31:607-17.
12. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol 2004;15:2208-18.
13. Llach F, Felsenfeld AJ, Coleman MD, Keveney JJ, Jr., Pederson JA, Medlock TR. The natural course of dialysis osteomalacia. Kidney Int Suppl 1986;18:S74-9.
14. Malluche HH. Aluminium and bone disease in chronic renal failure. Nephrol Dial Transplant 2002;17 Suppl 2:21-4.
15. Malluche HH, Mawad HW, Monier-Faugere MC. Renal osteodystrophy in the first decade of the new millennium: analysis of 630 bone biopsies in black and white patients. J Bone Miner Res 2011;26:1368-76.
16. Coco M, Rush H. Increased incidence of hip fractures in dialysis patients with low serum parathyroid hormone. Am J Kidney Dis 2000;36:1115-21.
17. Adragao T, Herberth J, Monier-Faugere MC, et al. Low bone volume--a risk factor for coronary calcifications in hemodialysis patients. Clin J Am Soc Nephrol 2009;4:450-5.
18. London GM, Marty C, Marchais SJ, Guerin AP, Metivier F, de Vernejoul MC. Arterial calcifications and bone histomorphometry in end-stage renal disease. J Am Soc Nephrol 2004;15:1943-51.
19. Miller PD. Is there a role for bisphosphonates in chronic kidney disease? Semin Dial 2007;20:186-90.
20. Haris A, Sherrard DJ, Hercz G. Reversal of adynamic bone disease by lowering of dialysate calcium. Kidney Int 2006;70:931-7.
21. Spasovski GB, Bervoets AR, Behets GJ, et al. Spectrum of renal bone disease in end-stage renal failure patients not yet on dialysis. Nephrol Dial Transplant 2003;18:1159-66.
22. Ross EA. Evolution of treatment strategies for calciphylaxis. Am J Nephrol 2011;34:460-7.
23. Angelis M, Wong LL, Myers SA, Wong LM. Calciphylaxis in patients on hemodialysis: a prevalence study. Surgery 1997;122:1083-9; discussion 9-90.

24. Fine A, Zacharias J. Calciphylaxis is usually non-ulcerating: risk factors, outcome and therapy. Kidney Int 2002;61:2210-7.
25. Danziger J. Vitamin K-dependent proteins, warfarin, and vascular calcification. Clin J Am Soc Nephrol 2008;3:1504-10.
26. Son BK, Kozaki K, Iijima K, et al. Statins protect human aortic smooth muscle cells from inorganic phosphate-induced calcification by restoring Gas6-Axl survival pathway. Circ Res 2006;98:1024-31.
27. Price PA, Faus SA, Williamson MK. Warfarin causes rapid calcification of the elastic lamellae in rat arteries and heart valves. Arterioscler Thromb Vasc Biol 1998;18:1400-7.
28. Beitz JM. Calciphylaxis: a case study with differential diagnosis. Ostomy Wound Manage 2003;49:28-38; quiz 9-40.
29. Block GA. Control of serum phosphorus: implications for coronary artery calcification and calcific uremic arteriolopathy (calciphylaxis). Curr Opin Nephrol Hypertens 2001;10:741-7.
30. Hayashi M, Takamatsu I, Kanno Y, Yoshida T, Abe T, Sato Y. A case-control study of calciphylaxis in Japanese end-stage renal disease patients. Nephrol Dial Transplant 2012;27:1580-4.
31. Suki WN, Zabaneh R, Cangiano JL, et al. Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. Kidney Int 2007;72:1130-7.
32. Tonelli M, Wiebe N, Culleton B, et al. Systematic review of the clinical efficacy and safety of sevelamer in dialysis patients. Nephrol Dial Transplant 2007;22:2856-66.
33. Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. Kidney Int 2007;71:438-41.
34. Moe SM, Chertow GM. The case against calcium-based phosphate binders. Clin J Am Soc Nephrol 2006;1:697-703.
35. Chertow GM, Burke SK, Raggi P. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney Int 2002;62:245-52.
36. Block GA, Spiegel DM, Ehrlich J, et al. Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. Kidney Int 2005;68:1815-24.
37. Qunibi W, Moustafa M, Muenz LR, et al. A 1-year randomized trial of calcium acetate versus sevelamer on progression of coronary artery calcification in hemodialysis patients with comparable lipid control: the Calcium Acetate Renagel Evaluation-2 (CARE-2) study. Am J Kidney Dis 2008;51:952-65.
38. Kalil RS, Flanigan M, Stanford W, Haynes WG. Dissociation between progression of coronary artery calcification and endothelial function in hemodialysis patients: a prospective pilot study. Clin Nephrol 2012;78:1-9.
39. Navaneethan SD, Palmer SC, Craig JC, Elder GJ, Strippoli GF. Benefits and harms of phosphate binders in CKD: a systematic review of randomized controlled trials. Am J Kidney Dis 2009;54:619-37.
40. Di Iorio B, Bellasi A, Russo D. Mortality in kidney disease patients treated with phosphate binders: a randomized study. Clin J Am Soc Nephrol 2012;7:487-93.
41. Kovesdy CP, Kuchmak O, Lu JL, Kalantar-Zadeh K. Outcomes associated with phosphorus binders in men with non-dialysis-dependent CKD. Am J Kidney Dis 2010;56:842-51.
42. Block GA, Wheeler DC, Persky MS, et al. Effects of phosphate binders in moderate CKD. J Am Soc Nephrol 2012;23:1407-15.
43. Isakova T, Gutierrez OM, Chang Y, et al. Phosphorus binders and survival on hemodialysis. J Am Soc Nephrol 2009;20:388-96.
44. Winkelmayer WC, Liu J, Kestenbaum B. Comparative effectiveness of calcium-containing phosphate binders in incident U.S. dialysis patients. Clin J Am Soc Nephrol 2011;6:175-83.
45. Heaf JG, Joffe P, Marckmann P. Vitamin d and stage 5 chronic kidney disease: a new paradigm? Semin Dial 2012;25:50-8.

46. Fukagawa M, Kitaoka M, Yi H, et al. Serial evaluation of parathyroid size by ultrasonography is another useful marker for the long-term prognosis of calcitriol pulse therapy in chronic dialysis patients. Nephron 1994;68:221-8.
47. Drueke TB, Ritz E. Treatment of secondary hyperparathyroidism in CKD patients with cinacalcet and/or vitamin D derivatives. Clin J Am Soc Nephrol 2009;4:234-41.
48. Moe SM, Cunningham J, Bommer J, et al. Long-term treatment of secondary hyperparathyroidism with the calcimimetic cinacalcet HCl. Nephrol Dial Transplant 2005;20:2186-93.
49. Messa P, Macario F, Yaqoob M, et al. The OPTIMA study: assessing a new cinacalcet (Sensipar/Mimpara) treatment algorithm for secondary hyperparathyroidism. Clin J Am Soc Nephrol 2008;3:36-45.
50. Komaba H, Nakanishi S, Fujimori A, et al. Cinacalcet effectively reduces parathyroid hormone secretion and gland volume regardless of pretreatment gland size in patients with secondary hyperparathyroidism. Clin J Am Soc Nephrol 2010;5:2305-14.
51. Yano S, Sugimoto T, Tsukamoto T, et al. Association of decreased calcium-sensing receptor expression with proliferation of parathyroid cells in secondary hyperparathyroidism. Kidney Int 2000;58:1980-6.
52. Tokumoto M, Tsuruya K, Fukuda K, Kanai H, Kuroki S, Hirakata H. Reduced p21, p27 and vitamin D receptor in the nodular hyperplasia in patients with advanced secondary hyperparathyroidism. Kidney Int 2002;62:1196-207.
53. Chertow GM, Correa-Rotter R, Block GA, et al. Baseline characteristics of subjects enrolled in the Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) trial. Nephrol Dial Transplant 2012;27:2872-9.
54. Goodman WG, Goldin J, Kuizon BD, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med 2000;342:1478-83.
55. Braun J, Oldendorf M, Moshage W, Heidler R, Zeitler E, Luft FC. Electron beam computed tomography in the evaluation of cardiac calcification in chronic dialysis patients. Am J Kidney Dis 1996;27:394-401.
56. Moe SM, Chen NX. Mechanisms of vascular calcification in chronic kidney disease. J Am Soc Nephrol 2008;19:213-6.
57. Mansfield K, Rajpurohit R, Shapiro IM. Extracellular phosphate ions cause apoptosis of terminally differentiated epiphyseal chondrocytes. J Cell Physiol 1999;179:276-86.
58. Proudfoot D, Skepper JN, Hegyi L, Bennett MR, Shanahan CM, Weissberg PL. Apoptosis regulates human vascular calcification in vitro: evidence for initiation of vascular calcification by apoptotic bodies. Circ Res 2000;87:1055-62.
59. Kendrick J, Cheung AK, Kaufman JS, et al. FGF-23 associates with death, cardiovascular events, and initiation of chronic dialysis. J Am Soc Nephrol 2011;22:1913-22.
60. Kuro OM. Phosphate and Klotho. Kidney Int Suppl 2011:S20-3.
61. Ketteler M. Fetuin-A and extraosseous calcification in uremia. Curr Opin Nephrol Hypertens 2005;14:337-42.
62. Kestenbaum B, Seliger SL, Gillen DL, et al. Parathyroidectomy rates among United States dialysis patients: 1990-1999. Kidney Int 2004;65:282-8.
63. Tominaga Y, Tanaka Y, Sato K, Nagasaka T, Takagi H. Histopathology, pathophysiology, and indications for surgical treatment of renal hyperparathyroidism. Semin Surg Oncol 1997;13:78-86.
64. Jofre R, Lopez Gomez JM, Menarguez J, et al. Parathyroidectomy: whom and when? Kidney Int Suppl 2003:S97-100.
65. Neumann DR, Esselstyn CB, Jr., Madera A, Wong CO, Lieber M. Parathyroid detection in secondary hyperparathyroidism with 123I/99mTc-sestamibi subtraction single photon emission computed tomography. J Clin Endocrinol Metab 1998;83:3867-71.

66. Llach F. Parathyroidectomy in chronic renal failure: indications, surgical approach and the use of calcitriol. Kidney Int Suppl 1990;29:S62-8.
67. Bleyer AJ, Burkart J, Piazza M, Russell G, Rohr M, Carr JJ. Changes in cardiovascular calcification after parathyroidectomy in patients with ESRD. Am J Kidney Dis 2005;46:464-9.
68. Sato T, Tominaga Y, Ueki T, et al. Total parathyroidectomy reduces elevated circulating fibroblast growth factor 23 in advanced secondary hyperparathyroidism. Am J Kidney Dis 2004;44:481-7.
69. Sharma J, Raggi P, Kutner N, et al. Improved long-term survival of dialysis patients after near-total parathyroidectomy. J Am Coll Surg 2012;214:400-7; discussion 7-8.