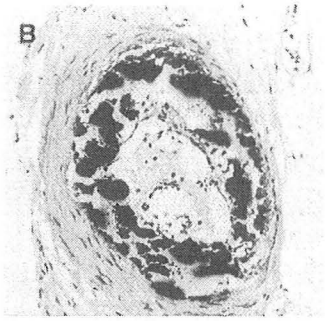
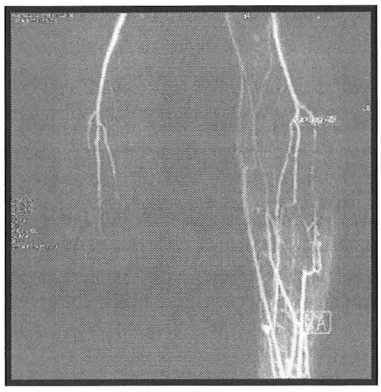
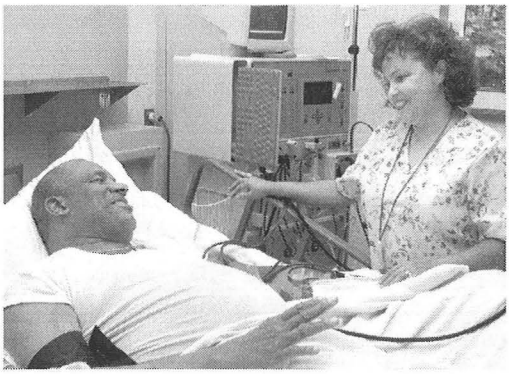
Calcifying Vasculature: Does Uremia Add Insult to Injury?







"An ossification, and not mere calcification; the plates which pervade the inner wall of the vessel are real plates of bone…following the same course of development."

Virchow 1863

INTERNAL MEDICINE GRAND ROUNDS

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March 14, 2002

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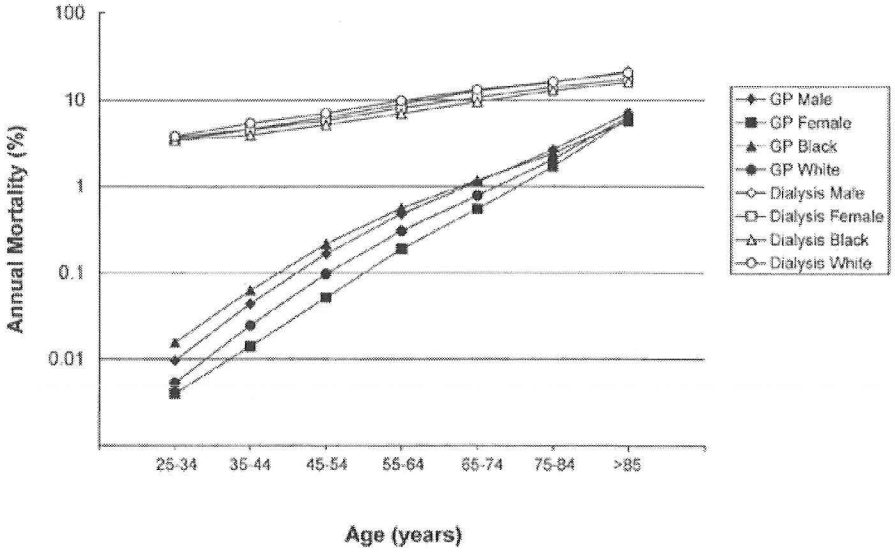
Introduction

Vascular calcification is associated with significant morbidity and mortality. Vascular calcification positively correlates with increased risk of myocardial infarction, and increased risk of dissection and plaque rupture after angioplasty. (1) Coronary calcification increases the risk of cardiovascular events or revascularization approximately three fold in asymptomatic patients (2,3). The presence of calcified vessels is associated with increased risk of ischemic episodes in patients with peripheral vascular disease (4). Furthermore calcification of native and bioprosthetic valves is a major cause of valve failure (5). Commonly associated risk factors for vascular disease include diabetes, hypertension, hyperlipidemia, smoking, and elevated homocysteine levels with additive effects of each risk increasing morbidity and mortality. Recent epidemiologic evidence suggests that perhaps renal disease be added to this list. The reason for this becomes clear as we explore the pathophysiology of vascular calcification. While many of the common risk factors for cardiovascular disease already may plague the renal patient, the uremic environment may be adding to the burden of rapidly calcifying the vasculature. How, why and what we need to do to decrease this uremic burden is what I would like to focus on today.

Cardiovascular Disease in Renal Failure

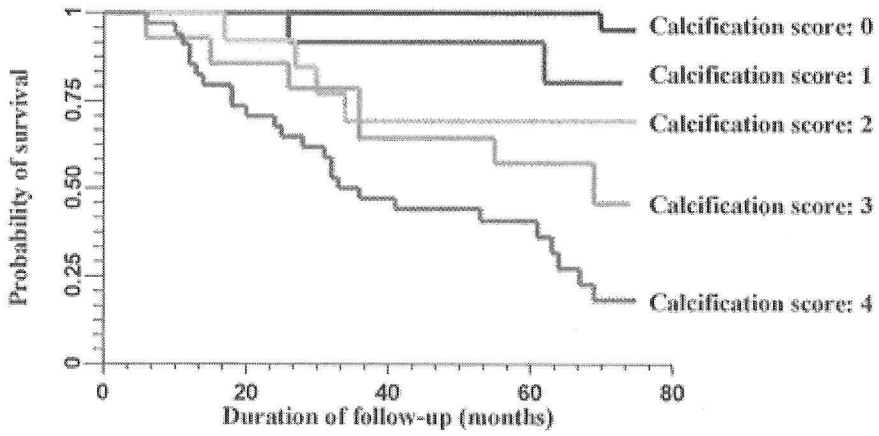
Cardiovascular disease (CVD) accounts for 50% of deaths in the end stage renal disease (ESRD) population (6), with lower extremity amputation approximately 10 times higher as compared to non-ESRD patients despite controlling for diabetes (7). A National Kidney Foundation task force compared CVD prevalence and outcome in chronic renal failure patients using data from the US Renal Data System to that of the general population using data from the US National Center for Health Statistics to characterize risk status of chronic renal failure patients (8). Mortality in dialysis patients was found to be approximately 9%/yr, which is 30 times the risk in the general population. Despite stratificaton for age, CVD (including arrythmia, cardiomyopathy, cardiac arrest, myocardial infarction, atherosclerotic heart disease and pulmonary edema) was 10-20 times higher than the general population (8). (Fig1)

Fig. 1 Cardiovascular Mortality in the General Population (NCHS) & in ESRD Treated Dialysis Patients (USRDS)



Limb amputation is 10 times that of the general population with cumulative post amputation 1year survival in dialysis patients of 45% vs those with renal transplant of 85% and those with transplant failures of 52% (9). Blacher and colleagues evaluated and scored for the presence of arterial calcifications at the carotid artery, abdominal aorta, iliofemoral axis and legs ultrasonographically and found that the presence and extent of vascular calcifications were strong predictors of cardiovascular all-cause mortality (10) (Fig 2).

Fig 2: Probability of All-cause Survival According to Calcification Score ($p < 0.0001$)



Furthermore, EBCT evaluation of coronary artery calcification in 39 ESRD patients age range 7-30 years showed that presence of coronary artery calcification was significantly greater in those who were on dialysis longest and had greater intake of calcium containing phosphate binders. BP control was similar between those with calcification

and those without cacification. Only one diabetic patient was in the study and his cacification score was 0 (11). Taken together, these studies indicate that vascular calcification may be acclerate in the presence of advanced renal failure and cause significant morbidity and mortality.

Pathology of Vascular Calcification

Generally calcification of the vasculature can be found as 2 types: discrete intimal lisions in association with atheromatous plaque or diffuse medial calcification (Monkeberg's sclerosis) resembling railroad tracks with linear calcification noted along the elastic lamella (12,13).

Calcified Plaque

Focal calcified lesions are usually discrete areas of lipid laden foam cells at the base of the atheromatous plaque primarily involving the vascular intima (2). Initial injury stimulates mononuclear leukocyte infiltration into the intima with release of adhesion molecules, selectins (P-selectin) and vascular cell adhesion molecule-1 (VCAM-1), stimulating initially transient deposition and then more adherent deposition of leukocytes to the endothelium (14). A number of other factors including oxidized lipoproteins, local hemodynamics further potentiate adherence and chemokines initiate migration of cells into the intima. Nitric oxide release from the endothelium acts to inhibit leukocyte adhesion by interfering with NFK-B signaling and VCAM-1 gene expression in the endothelial cells (14). With leukocyte diapedesis into the intima, there is lipid accumulation and foam cells form. Further foam cell accumulation in the intima represents the atheromatous plaque (14). This plaque progresses to become more fibrotic as smooth muscles migrate to the area of the lesion to release macromolecules which stimulate formation of a fibrous matrix and subsequent osteogenesis. Calification around an atheromatous lesion increases plaque fragility and makes the vessel wall more vulnerable to shear stress, eventually precipitating plaque rupture and thrombosis (14).

Medial Calcification

With renal failure, there is diffuse mineral deposition throughout the vascular tree (Monkebergs sclerosis) with significant fibroelastic intimal thickening, and calcification of the internal elastic lamella, medial ground substance and medial elastic fibers and disruption and reduplication of the internal elastic lamella as seen with aging or diabetes, suggesting an acceleration of the normal arterial aging process(15,16). Evaluation of the calcified vascular architecture reveals bone substance. Examination of the calcific deposits reveal the consistency of bone mineral apatite (hydroxyapatite crystals), C10(PO4)6(OH)2. Investigators identified both white and red marrow and cartilage early on in calcified vascular lesion (17,18,19). More recently other markers for bone mineralization have also been identified, including collagen 1, the major bone collagen, hydroxyapatite and other non-collagenous bone matrix proteins including osteonectin,

osteopontin, matrix GLA protein, and osteoglycin as well as matrix vesicles and initiation sites for mineralization (19).

This confluent mineralization induces morbidity and mortality by stiffening the vessel wall and reducing vascular compliance. Stiff vessels lead to a widened pulse pressure, increase pulse wave velocity and increased LV afterload and coronary morbidity (20). Similarly there is also occlusive intimal proliferation of cutaneous and subcutaneous arteries resulting in necrotizing painful rash and digital gangrene with high morbidity (21). Is this metastatic calcification or dystrophic calcification? Metastatic calcification usually is calcification in previously normal tissue exposed to an abnormal chemical environment whereas dystrophic calcification is abnormal tissue in a normal chemical environment. In uremia both is seen, an abnormal tissue vasculature since many patients are smokers, have diabetes, hypertension, and lipid abnormalities and an abnormal chemical environment from the inability of adequate toxin clearance.

Cell culture and In Vivo Models of Vascular Calcification/ Parallels to Bone Ossification

Mineralization Process

The process of calcification requires specialized cells and a specific environment in order to mineralize. This is obvious from bone and teeth which calcify under normal conditions whereas other tissues facing similar ion concentrations do not normally calcify. Osteoblasts, a key cell in bone matrix synthesis and mineralization originates from pluripotent marrow mesenchymal stem cells stimulated by transcription factor core binding factor 1 (Cbfa-1) and bone morphogenetic factor 2, 4 (BMP-2, BMP-4) (22,23,24). Osteoblasts then produce factors including type 1 collagen, cell adhesions proteins, calcium binding proteins, mineralizing proteins, enzymes, growth factors, and cytokines necessary for mineralization to occur (22) (Table1).

Table 1: PROTEINS OF BONE MATRIX
Osteoblast-Derived Proteins

Type 1 collagen
Cell adhesion proteins
Osteopontin, fibronectin, thrombospondin
Calcium-binding proteins
Osteonectin, bone sialoprotein
Proteins involved in mineralization
Osteocalcin
Enzymes
Collagenase, alkaline phosphatase
Growth factors
IGF-1, TGF-beta, PDGF
Cytokines
Prostaglandins, IL-1, IL-6
Adapted from Cotran 1999 6th Edition

Interestingly, vascular smooth muscle cells originate from the same lineage as osteoblasts. Therefore these cells may have the ability to transform to similar functions as the osteoblast when needed. In fact, Bostrom has isolated a sub-population bovine medial cells which express osteoblastic markers and produce hydroxyapatite mineral in vitro(23,25). They are pericyte like cells and termed calcifying vascular cells. Whether these cells originate from dedifferentiation of pluripotent intimal or medial vascular smooth muscle cells or from circulating stem cells from the bone marrow is not clear. What stimulates these cells to go from non-calcifying cells to becoming calcifying cells is also still speculative. From cell culture of bovine aortic smooth muscle cells (BVSMC), Giachelli etal have found that these cells lose their lineage markers SM22α and smooth muscle α actin under conditions amenable to calcification and gained osteogenic phenotype as noted by expression and DNA binding activity of trancription factor Cbfa1 (26). Similarly, genes containing the Cbfa1 binding site OSE 2, osteopontin, osteocalcin and alkaline phosphatase were elevated. Shanahan and colleagues examined gene expression of human vessels with monkeberg's sclerosis by immunohistochemistry, in situ hybridization and semiquantitative RTPCR and found that calcified vessels expressed high levels of alkaline phosphatase, bone sialoprotein, bone Gla protein and low levels of osteonectin and matrix GLA protein, indicating upregulation of markers of osteogenesis (27).

Calcification starts with crystallizaton within matrix vesicles as intravesicular Ca concentration increases due to its affinity for acidic phospholipids of the vesicle membrane. Phosphatases such as alkaline phosphatase, ATPases, pyrophosphatase at vesicle membranes act on ester phosphates of matrix fluids to produce a local increase PO4 concentration, thereby raising the intravesicular ionic product of Ca and phosphate (28). This leads to amorphous CaPO4 deposition which over time becomes insoluble hydroxyapatite. Factors then that can naturally inhibit this process are 1) in adequate Ca levels, 2) inadequate phosphate levels, 3) and presence of organic phosphates which prevent crystal growth such as pyrophosphates, adenosine phosphate, noncollagenous phosphoproteins including osteopontin, and gamma-carboxyglutamic acid containing proteins of bone. Factors which can promote mineralizaton are then 1) elevated levels of Ca and Phosphorus , collagen, phosphatases, which serves as a link protein between and collagen and hydroxyapatitie.

Table 2: Bone Mineralization

Inhibitors	Promoters
Low calcium	High calcium
Low phosphorus	High phosphorus
MGP	Phosphatases
Pyrophosphates	Vitamin D3
Osteopontin	
Osteoprotegerin	
Osteonectin	
Klotho	
PTHrP	

As noted previously these factors are also found in the calcified vasculature and the time course of expression is similar to that found in osteoblast differentiation (29). The presence of these bone regulatory proteins in calcified vasculature suggests a similar regulated process of calcification in arterial vessels.

It follows then that either the absence of possible functional inhibitors or increased presence of factors which promote calcification may cause diffuse calcification of the vasculature. Interestingly, several rodent models as well as human counterpart diseases with absence of these natural inhibitors suggest a possible link to increased arterial calcification.

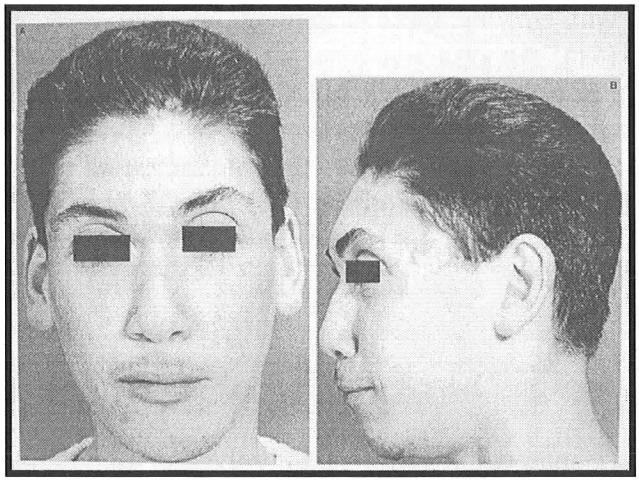
Inhibitors of Calcification

Matrix GLA Protein

Matirx GLA protein (MGP) is a sleletal extracellular matrix protein 14 Kda in mice and 10 Kda in humans and present in cartilage, bone matrix, and the arterial wall. Human MGP consists of 84 aa mature protein and 19 aa transmembrane signal peptide. It is a member of the Gla protein family which includes osteocalcin, another skeletal matrix protein. Glutamic acid residues of the MGP protein are undrgo necessary modification for funtion to gamma carboxyglutamic acid by a specific gamma carboxylase in the endoplasmic reticulum using vitamin K as a cofactor. The modified glutamic acid residues of Gla protein confer a high afffinity for mineral ions such as calcium, phosphate, and hydroxyapatite crystals, the mineral components of skeletal extracellular matrix. MGP binds to BMP-2 and blocks the osteogenic properties of this protein (24,30).

In vivo, mice null for the matrix GLA protein (MGP) spontaneously calcify their arteries and die soon after birth (31). The arteries of these mice display similar loss of smooth muscle markers and gain of osteopontin and Cbfa1. In fact MGP expression is lower in the media of arteries of diabetics with Monkeberg's sclerosis than those of normal vessels (24). While MGP deficient mice have diffuse vascular calcification, MGP deficient humans as described in Keutels syndrome calcify their cartilage but not the vasculature (32). Keutels syndrome is an autosomal recessive disorder characterized by abnormal cartilage calcification, peripheral pulmonary stenosis and midfacial hypoplasia (33,34) (Fig 3). MGP deficiency is also postulated in the Singleton-Merton syndrome characterized by aortic calcification, short stature, osteopenia, and decreased muscle mass (35). Therefore while MGP may be an important inhibitor to vascular calcification in the rodent, other factors in addition to MGP may be playing a role in humans.

Fig 3: Keutels Syndrome with midfacial hypoplasia (ref 33)



Pyrophosphate

Pyrophosphate is an important inhibitor to hydroxyapatite formation in the bone. Hydroxyapatite is the primary salt found in bone and in calcified vasculature. Absence of pyrophosphate may then increase calcification (36). Interestingly, a genetic form of diffuse calcification of the media of large muscular arteries that resembles the acquired Monkebergs sclerosis is a syndrome called idiopathic infantile arterial calcification (IIAC) (37,38). IIAC proband demonstates a plasma cell membrane glycoprotein-1 deficiency (PC-1). This glycoprotein is the most abundant isozyme of the phosphodiesterase nucleotide pyrophosphatase (PDNP) family of isozymes with NTPPH (nucleoside triphosphate pyrophosphohydrolase) and acts to cleave the phosphodiester bond-1 in both purine and pyrimidine nucleoside triphosphatases and thus release free pyrophosphates in the ECF. Thus the inability to generate pyrophosphates causes diffuse calcification of the arterial vasculature in these infants with IIAC (39).

So one thought that naturally comes to mind is the possibility of and acquired deficiency of this isozyme PC-1 in renal patients. While this has not been evaluated, pyrophosphate levels in patients on dialysis appear not to be decreased as compared to the normal population (36).

Osteopontin

Another inhibitor of bone calcification is osteopontin (OPN) (40). A protein with various functions, OPN can promote cell adhesion and migration and also binds calcium and inhibits hydroxyapatite formation (41). Osteopontin has been found in association with calcified deposits in Monkebergs sclerosis, aortic stenosis, prosthetic valves, renal stones, and tumor associated calcifications. The inhibitory effect of OPN is dependent on the number of phosphorylated sites. OPN treated with alkaline phosphatase generates

dephosphorylated OPN which fails to inhibit human smooth muscle cell culture calcification. When levamisole is added to cell culture to inhibit alkaline phosphatase action, OPN then appropriately inhibits HSMC calcification (41). Similarly, when dephosphorlated OPN is phosphorylated with enzyme, there is again appropriate inhibition of HSMC culture calcification (41). An attractive hypothesis for renal failure patient with acclerated atherogenesis may be decreased levels of OPN or presence of perhaps nonfunctional or dephosphorylated OPN especially as many patients have elevated alkaline phosphatase. Recently soluble osteopontin levels were measured in dialysis patients and found to be elevated as compared to controls (42). The level of protein phosphorylation was not assessed in this study. In recent studies OPN null mice are not reported to have arterial calcification (24).

Osteoprotegerin

Another protein recently identified with vascular calcification and involved in modulating bone osteoclastogenesis, osteoprotegerin (OPG), may be important in preventing mineralization. OPG acts as a souble decoy for the receptor ligand RANKL (RANK ligand) on osteblasts. RANK (receptor activator of NFκβ) on osteclasts precursors ordinarily binds to RANKL on osteblasts to stimulate osteoclast differentiaion. OPG can occupy the RANKL site and inhibit osteoclastogenesis (24,43,44,45,46). The deficiency of this protein in OPG null mouse presents phenotypically as mice who develop siginificant osteopororosis and medial calcification of the aorta and renal arteries (47). In the elderly or estrogen deficient we also observe osteoporosis and arterial calcification (43). Similarly, in patients with advanced renal failure, Parfitt and coworkers have noted substantially decreased bone density with bone pain and fractures disproportionate to the radiographic and histologic features noted either as low or high bone turnover (48). However osteoprotegerin levels measured in elderly postmenapausal women are actually increased (43). In fact when relative risk is evaluated relative to osteoprotegerin levels, there is a 4 –fold greater risk for those women in the highest quintile. A seeming explanation for this may be that there is incomplete defense for keeping mechanisms under control which contribute to vascular calcification (43). Osteoprotegrin levels have not yet been measured in the renal failure population.

Osteonectin

Osteonectin, also known as secreted protein acidic and rich in cysteine (SPARC) or BM40 is expressed in areas of active remodeling in skeleton and other tissues . Osteonectin binds to collagen and hydroxyapatite and can regulate cell proliferation and cell matrix interactions (24). In vitro, it is a potent inhibitor of hydroxyapatite crystal formation (49). Vascular smooth muscle cells (VSMC) in normal arteries express osteonectin at high levels but in Monkeberg's sclerosis, osteonectin expression is significantly reduced or absent (27). Osteonectin null mouse have decreased osteoblats and osteoclasts with subsequent impaired bone remodeling and decreased trabecular bone density, low turnover osteopenia. However these null mice are not reported to have arterial calcification (24).

Klotho

Another important inhibitor of calcification and aging may be the Klotho protein. The Klotho gene is homologous to β-glucosidase enzyme and encodes a novel protein that appears to function outside the cells as a secreted protein and may prevent premature aging including arteriosclerosis(50,51). Mutant Klotho mouse have osteoprorosis and extensive vascular meidal calcification, twice the seum phosphorus levels found in wild type mouse, skin atrophy, short life span and infertility (50). Phenotypically they appear similar to the advanced chronic renal failure patient with diffuse Monkeberg's sclerosis. The gene is expressed primarily in the distal convoluted tubule of the kidney and the brain. Therefore loss of nephron function should lead to decreased Klotho protein. In fact, Koh et al have demonstrated in a recent paper that Klotho protein as measured by Western Blot and immunohistochemistry from kidney tissues of advanced chronic renal failure and dialysis patients is indeed markedly decreased as compared to control kidney tissues without renal failure (52). This may provide a clue to the advanced atherogenesis seen in renal failure patients. Data is yet to be generated which shows that in patients with advanced renal failure, replacing Klotho protein can reverse this process.

If inhibitors of mineralization are present in patients with advanced renal failure, then there may be at least 2 reasons for failure of these inhibitors of calcification in the renal failure population, 1) inhibitors nonfunctional in uremic environment, 2) inhibitors are overwhelmed by other factors which promote calcification.

Promotors of Calcification

Alkaline Phosphatase

An important inhibitor of pyrophosphate is the enzyme alkaline phosphatase which is frequently elevated in patients with advanced renal failure. Alkaline phosphatase is an extracellular universal phosphatase acting as an organic phosphatase, pyrophosphatase, protein phosphatase, DNA phosphatase (53,54). It is a phosphate/calcium binding protein and has collagen binding domain on its surface. Therefore its expression on cell surfaces may alter the physical properties of the membrane, leading to changes in cell adhesion. Alkaline phosphatase is an essential component of matrix vessicles where it increases orthophosphates for the growing hydroxyapatite crystals (28,55). Defective bone mineralization is evident with alkaline phosphatase deficiency as found in hypophosphatasia (53). Therefore the presence of this enzyme is necessary for bone mineralization to occur. Some believe that inorganic pyrophosphates may cover the bone surface and prevent the amorphous calcium and phosphorus from organizing into hydroxyapatite. In the presence of pyrophosphatases such as alkaline phosphatase, the pryophosphate inhibition is removed and hydroxyapatite formation ensues (36). Certainly in many of our dialysis patients this enzyme is elevated, often in association with an elevated phosphorus and calcium and elevated PTH. However this enzyme is also

elevated in patients without elevated levels of calcium, phosphorus, PTH, perhaps just suggesting the process of active mineralization.

Elevated Phosphate and Calcium levels

Increased calcium and phosphorus levels in the ECF increase bone mineralization. In renal failure, levels of phosphate can be significantly elevated. Recent USRDS epidemiologic data shows that average phosphate level is 6.2 mg/dl with 30% of dialysis patients having serum phosphorus above 7.0 mg/dl and 10% with levels greater than 9 mg/dl (56). Furthermore elevated phosphorus levels greater than 6.5 mg/dl increases the relative risk of death to 1.27 those of serum phos < 6.5 mg/dl (57) (Fig 4). A high CaxP product is an independent risk factor for cardiovascular mortality (57) (Fig 5).

Fig 4: Relative Risk in Relation to Phosphorus

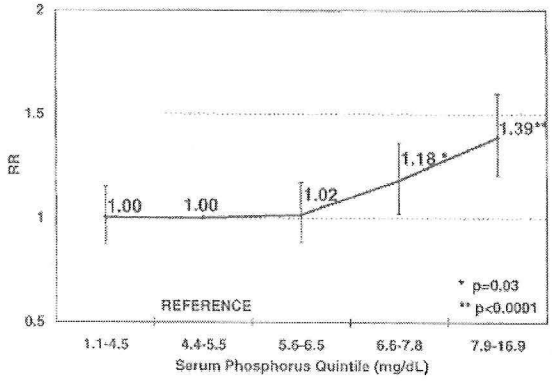
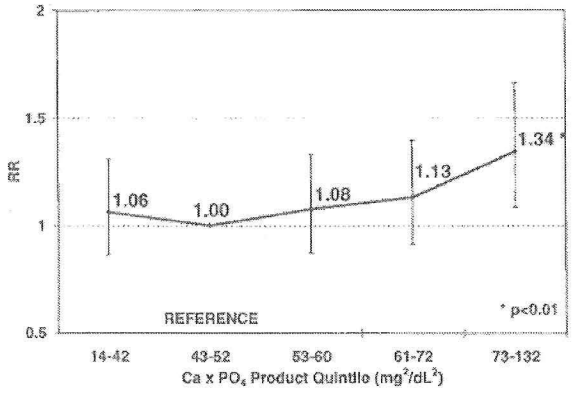


Fig 5: Relative Risk in Relation to CaxPO4 Product

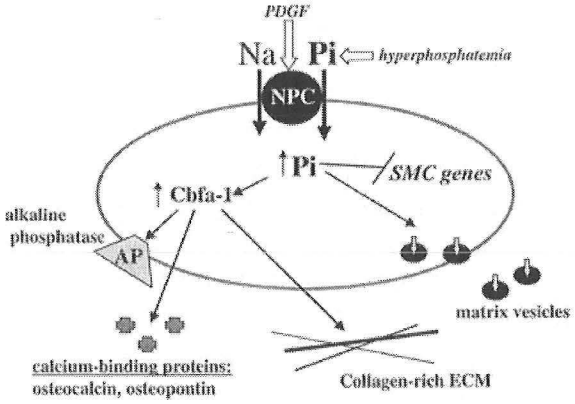


Elevated levels occur because renal failure patients are unable to excrete their phosphate load. Initially low levels of calcium and 1,25(OH)2 vitamin D3 stimulate the

parathyroid gland to increase PTH and stimulate bone reabsorption as well as the enzyme alpha 1-hydroxylase to make more vitamin D3 so as to normalize serum calcium. However this also further increases serum phosphorus levels. Elevated phosphorus levels also stimulate PTH to induce renal phosphate excretion which cannot occur in the advanced renal failure patient. Therefore elevated phosphorus levels maintain increased levels of PTH which further act on bone. Intervention with oral phosphate binders, primarily in the form of calcium is done to decrease gut phosphorus reabsorption, and increase gut calcium reabsorption. Also in order to suppress PTH activity and prevent significant bone loss, Vitamin D supplementation is given which further increases gut calcium and phosphorus reabsorption. Excess suppression of PTH with Vitamin D supplements can result in adynamic bone where the mineralization front in bone is decreased, so the reservoir for increased calcium and phosphorus to deposit is no longer available. Furthermore, vascular smooth muscle cells have receptors for PTH, and PTHrP. 1,25(OH)2D3 dose dependently decreased secretion of PTHrP by BVSMC in a dose dependent manner and depressed gene expression (58). PTHrP secreted by VSMC act as an endogenous inhibitor of vascular calcification although the mechanism is unclear. Therefore increased Vit D decreases another inhibitor important in the prevention of vascular calcification. Vitamin D also acts to stimulate effects of alkaline phosphatase (58) further promoting calcification. As a result, levels exceeding normal serum calcium/phosphorus are generated and deposited in soft tissues and vasculature, likely in places of injury where initial cellular phenotypic changes have occurred as possibly a part of the repair process (6).

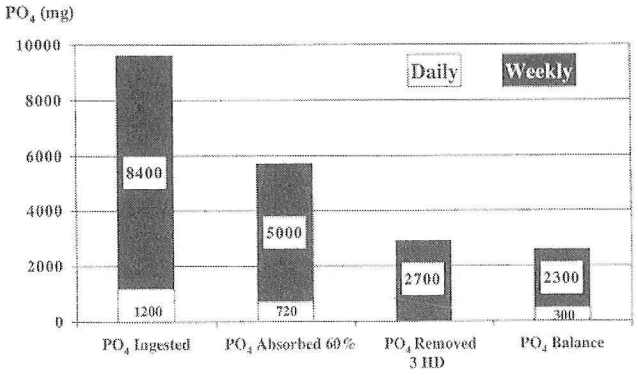
Recent data suggests that inorganic phosphorus stimulates the type III Na phosphate cotransporter (NPC) Pit1 (Glvr-1) in human smooth muscle cells (HMSC) to increase phosphorus transport, thereby raising intracellular phosphorus (59). In fact Jono et al have shown that under normal phosphatemic conditions (1.4 mmol/l or 4.3 mg/dl Pi) HSMC cultures do not mineralize and calcify. However under increased hyperphosphatemic conditions (2 mmol/L or 6.2 mg/dl Pi), calcification was increased (59). Both light and electron microscopy showed the presence of mineralization in the form of hydroxyapatite in the ECM, particularly collagen. Furthermore elevated inorganic phosphorus of 2 mmol/l induced phenotypic transformation of HSMC characterized by gain of mineralization markers osteocalcin, and Cbfa-1 gene expression. This was blocked by phosphoformic acid which inhibits NPC type 3 (Glv, Pit-1) co-transporter (59). This data is provocative in hypothesizing that elevated phos levels in patients with advanced renal failure may be a good reason for the stimulation of smooth muscle cells in the media of their artery to undergo phenotypic transformation such that mineralization is possible. These authors hypothesize that phosphorus internalizes via the NPC type III co-transproter and then likely stimulates gene synthesis for the phenotypic changes to occur such that further enzymes and proteins can be generated for mineralization to progress (60) (Fig 6).

Fig 6: Possible Pathogenesis of Phosphorus Induced Calcification



During conventional 4 hour HD, 3X per week hemodialysis, phosphate removal is approx 300mg per session or 900 mg per week. (Fig 7) (61). Intake, though recommended to restrict to 800 mg/day is impossible with the recommended protein diet of 1.1-1.2 mg/day to avoid malnutirtion in the dialysis population. Therefore usual intake is approx 1100 to 1200 mg /day. Absorption is approx 60% in the gut and 50% with binders therefore is approx 500-600 mg /day, leaving a positive balance of approx 300 mg /day or 2300 mg/week (57,61).

Fig 7: Phosphorus Removal by Conventional Hemodialysis



Additive to this is the fact that in many patients with advanced renal failure, large doses of calcium binders are administered in order to decrease phosphate absorbtion. Hsu estimates a net positive calcium balance with dietary intake and net dialysis calcium influx (62). In addition, many patients ingest as much as 13-18 gm of CaCO3 as a phosphate binder just to bring the serum phosphorus level to 5 mg/dl. Along with often a high calcium bath and or oral intake, there is a net positive calcium balance in patients with advanced renal failure. This adds to the environment favorable for mineralization.

Treatment Options

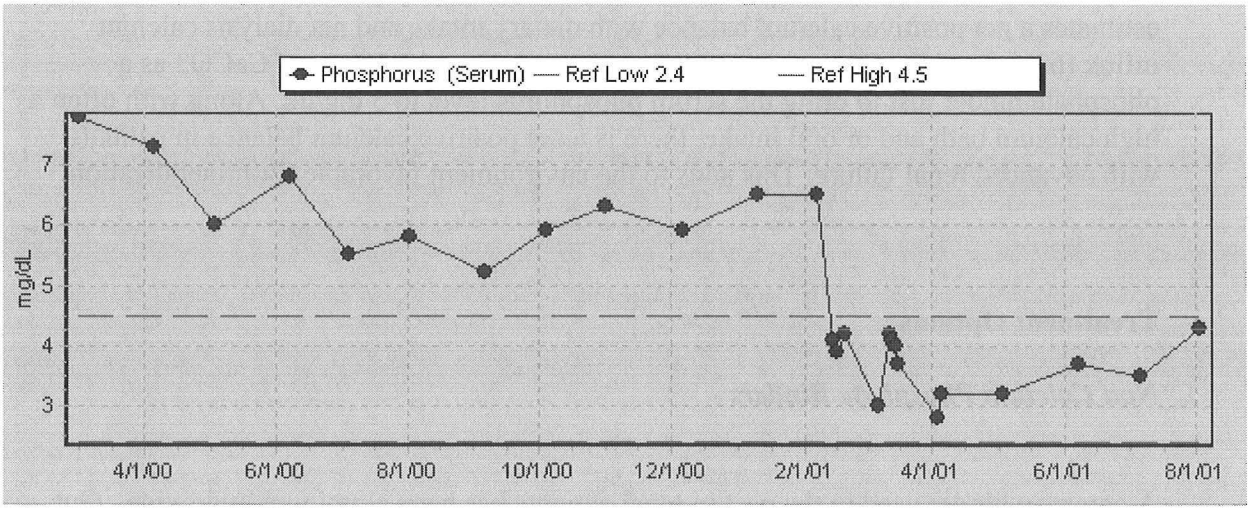
Non Calcium Phosphate Binders

A common binder used in the past in renal patients has been aluminum hydroxide. Gut binding of ingested phosphorus is excellent. However in large quantities as is consumed by the renal failure population, there is a greater risk of aluminum toxicity and aluminum bone disease, frequently 8-10 years ago in longterm dialysis patients. Therefore its use is currently limited. Another more recent binder, sevalamer which is a polyamine dihydrochloride seems to be at least as effective as the binder calcium acetate (63). However many patients still need to ingest an average of 6-12 tabs per day in addition to numerous other antihypertensive agents, vitamins, cardiac medications, and anti-platelet agents and strict phosphate restriction which makes compliance with phosphate binders an important issue. Cost also becomes a prohibitive issue as average monthly binders may be from $100 to $ 400 per month.

Nocturnal Dialysis

Data from Europe, Canada and more recently from the US is now able to show that patients who dialyse longer have improved mortality (64,65,66,67,68). As a result we initiated a program at the Dallas VAMC of in-center nocturnal dialysis for patients with severe hyperphosphatemia, difficult to control blood pressure, and with inadequate volume control on conventional hemodialysis 4 hours 3x/wk. Nocturnal patients dialyzed 9 –10 hours 4 days per week while sleeping. Average phosphorus decreased from 7 mg/dl on 15-18 tabs of phosphate binders to average of 3 mg/dl on no phosphate binders in 1-2 months of nocturnal dialysis. (fig 8) . Amount of phosphorus removed on high flux polysulfone dialyzer (F70NR) over 9 hours is 1900 mg. Therefore weekly removal is approximately 7600 mg. In fact with this treatment we are much closer to meeting weekly phosphate intake. In patients who are doing prolonged nightly dialysis at home, for 6-7 days per week actually require phosphate supplementation in the dialysate to maintain adequate phosphate balance. Case reports suggest that metastatic calcification and uremic arteriopathy can improve with prolonged daily dialysis (69).

Fig 8: Change in Serum Phosphorus Levels with Nocturnal Dialysis



Summary

The presence of vascular calcification is a marker for significant cardiovascular morbidity and mortality. Vasculature calcify in a regulated fashion in the appropriate environment. Plagued with other comorbid factors predisposing to cardiovascular disease including diabetes, hypertension, lipid abnormalities, and smoking, patients with advanced renal failure are especially prone to diffuse vascular calcification given the burden of uremia and inability to appropriately excrete their daily phosphate load. While current oral agents may improve serum levels of phosphorus, prolonged dialysis may be the more important solution at this time to decrease phosphate burden and improve vascular morbidity.

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