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PERSPECTIVES IN RENAL MEDICINE

Parathyroid hormone, vitamin D, and cardiovascular disease in chronic renal failure

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Background. Parathyroid hormone and vitamin D have been shown to influence cardiac and vascular growth and function experimentally in human subjects with normal renal function. Because of the increased prevalence of hyperparathyroidism and altered vitamin D status in chronic renal failure, these alterations have been considered to contribute to the increased prevalence of cardiovascular disease and hypertension seen in this patient population.

Methods and Results. In this article, we review experimental and clinical literature on the cardiovascular effects of parathyroid hormone and vitamin D and relate them to the development of cardiac and vascular dysfunction in uremia, such as: cardiomyopathy, myocardial hypertrophy, and fibrosis, as well as to myocardial ischemia; uremic glucose intolerance, dyslipidemia, and atherosclerosis; hypertension; and vascular and cardiac calcifications.

Conclusions. The hyperparathyroid state and altered vitamin D status found in uremia contribute to the cardiovascular pathology seen clinically in uremia and also to the excess mortality from cardiovascular causes found in this patient group. The therapeutic implications of these observations are also discussed.

End-stage renal disease (ESRD) is associated with numerous changes in cardiac structure and function that may account for the sustained high prevalence of morbidity and mortality from cardiovascular disease, particularly ischemic heart disease and heart failure [1]. Among the structural changes that have been noted most frequently are left ventricular hypertrophy (LVH), coronary artery disease, valvulopathies, and pericarditis. LVH is characterized not only by an increased myocardial fiber mass but also by interstitial fibrosis. Heart vessel changes are the result of decreased compliance (arteriosclerosis) and atherosclerosis, which favor hypertrophy and ischemia, respectively [2]. Cardiac calcification is a frequent event that occurs mainly at the level of the coronary arteries and heart valves, but that may also be seen as more diffuse deposits throughout the myocardium and as diffuse calcification of peripheral arteries. Although the etiologies for altered myocardial structure and performance in renal failure are multiple, there is evidence suggesting that disturbances of calcium and phosphorus metabolism may play important roles in uremic cardiovascular disease. Such changes include elevated plasma calcium and phosphate, increased circulating parathyroid hormone (PTH) caused by secondary hyperparathyroidism, changes of local PTH-related protein (PTHrP) synthesis and systemic metabolism, reduced production of active vitamin D metabolites, altered tissue responsiveness to these calciotrophic hormones, decreased calcium-sensing receptor expression, and frequent administration of pharmacological doses of calcium supplements and active vitamin D derivatives. This review focuses on the effects of PTH and vitamin D on cardiovascular structure and function in chronic renal failure (Tables 1 and 2).

Key words: uremia, hyperparathyroidism, PTH, blood pressure, end-stage renal disease, hypertension, myocardial ischemia, fibrosis.

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CARDIAC FUNCTION

Calcium ions are central to myocardial excitation-contraction coupling and to cardiac contraction and relaxation cycles. Excitation-contraction coupling begins when sarcolemmal depolarization permits cellular calcium entry via calcium channels. The release of calcium stored in the sarcoplasmic reticulum ensues, and this calcium reacts with troponin C, allowing actin and myosin to interact, thereby initiating muscle contraction. Dissociation and resequestration of calcium by an energy-dependent pump produce relaxation. Intracellular calcium steady state is maintained by membrane-bound Na^+-Ca^{++} exchanger and Ca-ATPase for the extrusion of cytosolic calcium, which, in addition, depends on Na^+,K^+-ATPase and the Na^+-H^+ exchanger [3].

Table 1. Effects of excess parathyroid hormone on cardiovascular structure and function in chronic renal failure

A. Blood pressure
  1. ↓ Blood pressure (acute)
  2. ↑ Blood pressure (chronic)
    a. ↑ VSMC$[Ca]_i$
    b. ↑ VSM wall: lumen ratio
B. Cardiac contractility
  1. ↑ Contractile force and rate (acute)
  2. ↑ Contractile force (chronic)
    a. ↓ Cardiomyocyte mitochondial energy production (chronic)
C. ↑ Cardiomycyte $[Ca]_i$
  1. ↓ Cellular Ca^{++} extrusion
  2. ↓ Sarcoplasmic reticulum Ca^{++} reuptake
D. ↑ Left ventricular mass, via
  1. Cardiomyocyte hypertrophy
  2. ↑ Interstitial fibrosis
E. ↑ Atherosclerosis (chronic), via
  1. Disturbed lipoprotein metabolism
  2. ↑ Insulin resistance
  3. ↑ VSMC $[Ca]_i$
  4. ↑ Ca-Phos deposition in vessel wall (mediacalcosis)
  5. Hypertension,
  6. but: Inhibition of VSMC migration/proliferation by PTH and PTHrP
F. Myocardial calcification (?) (chronic)
G. Heart valve calcification (chronic)

Abbreviations are: VSMC, vascular smooth muscle cells; Ca-Phos, calcium-phosphate; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related protein.

Table 2. Vitamin D effects on cardiovascular structure and function in chronic renal failure

A. Blood pressure
  1. ↓ Blood pressure
    a. opposing PTH excess (?)
  2. ↑ Blood pressure
    ↑ a. ↑ VSM force generation
    ↑ b. ↑ VSMC $[Ca^{2+}]_i$ (vitamin D excess)
    ↑ c. ↑ PTH production (decreased vitamin D concentration)
B. Cardiac introphy
  1. ↓ Introphy at low calcitriol concentration
  2. ↑ Introphy with severe calcitriol depletion
C. Left ventricular mass
  1. ↑ Heart weight (vitamin D depletion)
  2. ↑ Myocardial collagen content (vitamin D depletion)
  3. ↓ Endothelin-induced myocardial hypertrophy
D. VSMC growth and proliferation
  1. ↑ Cell proliferation (low calcitriol concentration)
  2. ↓ Cell proliferation/↑ cell maturation (high calcitriol concentration)
E. Atherosclerosis via:
  1. ↑ Apo A-1 and HDL-cholesterol
  2. ↓ Insulin resistance (direct and indirection actions)
  3. ↓ VLDL-triglycerides (direct and indirect actions)
F. Atherosclerosis via:
  1. ↑ Ca-Phos deposits in vessel wall (mediacalcosis)
  2. ↑ Blood pressure (?)
G. ↑ Heart valve calcification (chronic vitamin D excess)

Abbreviations are in Table 1 and: apoA-1, apolipoprotein A-1; HDL, high density lipoprotein; VLDL, very low density lipoprotein.

Parathyroid hormone and PTHrP have been shown to increase acutely the force and frequency of contraction of isolated, beating rat cardiomyocytes [4–6]. It has been suggested that increased inotropy produced by PTH and PTHrP is due to effects on coronary flow and heart rate and not to effects on contractile function [6]. However, changes induced by PTH occur in association with an increase of cell calcium and cAMP. Such effects have been shown to require extracellular calcium, to be mimicked by a calcium ionophore, to be blocked by verapamil, and to be independent of α- or β-adrenergic activity, suggesting mediation by enhanced calcium entry [5, 7, 8]. Baczynski et al and Bogin et al have also reported that in isolated myocardial mitochondria, PTH uncoupled oxidative phosphorylation and inhibited myocardial energy production from long- and short-chain fatty acids, the major substrates for cardiac metabolism [9–11]. These changes reduced cellular ATP concentrations and impaired myofibrillar activity of creatine kinase. Like the PTH effects on myocardial contractility, these responses were inhibited with verapamil [5, 12]. Verapamil has also been shown to prevent structural disorganization of cardiac myofibrils and their mitochondria observed in subtotally nephrectomized rats [13]. Moreover, Qing et al have shown that in a uremic rat model, elevated cytosolic Ca^{++} concentrations in cardiomyocytes were associated with attenuated insulin-like growth factor-1–stimulated protein synthesis that could be reversed either by parathyroidectomy (PTX) or treatment with felodipine, suggesting yet another mechanism by which elevated intracellular calcium and secondary hyperparathyroidism might modulate myocardial growth and structure in uremia [14]. The previously noted experimental studies suggest that prolonged exposure to PTH is associated with a greater intramyocardiocyte Ca^{++} concentration and with adverse effects on myocardial metabolism, structure, and function.

An increase of cytoplasmic Ca^{++} by excessive PTH levels has also been demonstrated for uremic patients in whom elevated platelet Ca^{++} was found to be correlated with plasma PTH concentration [15] and that could be corrected by PTX or calcitriol treatment [15]. Although increased calcium entry is felt to be most important in sustaining a high intramyocyte Ca^{++} concentration, reductions in sarcolemmal Na^+,K^+-ATPase and Na^+-Ca^+ exchange rates suggest that impaired calcium extrusion may contribute to altered cellular Ca^+ homeostasis [5]. In this regard, reduced Na^+,K^+-ATPase activity has long been observed under uremic conditions [16].

In rats with renal failure, the PTH/PTHrP receptor is down-regulated in the kidney and in the heart [17, 18]. This may serve to desensitize tissues to PTH effects and thus minimize increases in cellular calcium, possibly as part of a negative feedback mechanism [19]. Moreover, in a similar model, one may observe the same changes in cardiomyocyte Ca^+ concentration and mitochondrial function as in normal rats chronically exposed to PTH,

and these changes are reversed with PTX or, as in the case of normals + PTH, with verapamil [5].

In humans with ESRD, as in primary hyperparathyroidism, the presence of secondary hyperparathyroidism, or its markers, has also been associated with increased myocardial calcium content and impaired ventricular systolic and diastolic function [20–24]. However, despite an inverse association between plasma PTH concentration and left ventricular function, PTX is not consistently associated with improvement in cardiac contractile function [21, 23, 25–27], suggesting that either PTH-induced changes became irreversible in the case of long-standing severe hyperparathyroidism, for example, by the induction of interstitial fibrosis, or that other factors contributing to myocardial dysfunction were more important than PTH excess.

In this regard, receptors for $1,25(OH)_2D_3$ have been identified in myocardial cells and may be of clinical relevance. Recently, 26% of patients with congestive heart failure, New York Heart Association (NYHA) class III or IV, were found to have low serum concentrations of $1,25(OH)_2D_3$ [24], and the administration of vitamin D to patients with renal failure has improved cardiac function either indirectly by suppression of PTH synthesis and secretion or directly via a vitamin D-dependent process in cardiac muscle [28]. The correction by calcitriol of increased cytoplasmic Ca^{++} due to excess PTH may play a role [15]. However, experimentally severe vitamin D depletion can also stimulate contractile function and increase rates of relaxation of perfused rat hearts, irrespective of the serum Ca^{+} concentration [29, 30]. Thus, alterations in vitamin D metabolism can contribute either directly or indirectly to the regulation of cardiac muscle function. The balance between the degree of hyperparathyroidism, PTH/PTHrP receptor availability, and vitamin D status probably accounts for the variability in myocardial function and responses to PTX seen in ESRD.

MYOCARDIAL HYPERTROPHY AND FIBROSIS

Left ventricular hypertrophy is seen most frequently in ESRD and, together with increased cardiomyocyte Ca^{++} content, contributes to systolic and diastolic dysfunction, myocardial ischemia, and increased cardiac mortality in ESRD [1, 31–33]. The mechanisms underlying this process are many, including hypertension, decreased aortic and large artery compliance, perhaps, in part, as a consequence of vessel wall calcification, anemia, and possibly arteriovenous shunting [34, 35]. Both primary and secondary hyperparathyroidism and their marker, elevated alkaline phosphatase, are also associated with LVH and increased left ventricular mass index (LVMI) [31, 36–38]. The mechanisms by which hyperparathyroidism could favor LVH are theoretically several and include direct trophic effects on myocardial myocytes and on interstitial fibroblasts and indirect effects such as an increase in blood pressure via hypercalcemia, anemia, and large and small vessel changes. Thus, in cultured ventricular myocytes isolated from adult rats, PTH induces trophic effects manifested by increased protein synthesis and induction of creatine kinase [39]. Recent reports also suggest a permissive role for PTH in interstitial fibrosis [40]. In these studies, PTH caused significant increases in the volume density of nonvascular interstitial spaces without affecting the volume density of cardiac myocytes in rats with short-term uremia and in PTX-uremic rats replaced with PTH. Increased cardiac mass results, in part, from myocardial fibrosis, which has long been observed in uremia. This interstitial fibrosis has been found to occur independently of hypertension and may contribute significantly to diastolic dysfunction and to the rate of arrhythmia seen in patients with ESRD [33]. However, like the effects of PTH on cardiac functions, the results of PTX have been inconsistent. In some studies, PTX has been shown to produce small reductions in cardiac mass [41, 42], but in others, myocardial hypertrophy has also been dissociated from secondary hyperparathyroidism in experimental uremia and in humans with primary and secondary hyperparathyroidism [21, 23, 43, 44].

In ESRD, cardiac hypertrophy may also be related to altered vitamin D status by effects on vascular smooth muscle cell (VSMC) growth and blood pressure (discussed later in this article). Calcitriol may modulate the cell cycle in a dose-dependent fashion. High concentrations may slow cell proliferation and induce cell differentiation. It has been observed that depending on its concentration *in vitro*, calcitriol may be either stimulatory (10^{-12} M) or inhibitory (10^{-10} to 10^{-6} M) for cell proliferation, as shown in chondrocytes by Klaus et al [45]. Similar biphasic effects of calcitriol on cell proliferation were observed in keratinocytes by Pillai et al, with peak stimulatory effects at 10^{-12} to 10^{-10} M and a decline at higher concentrations [46]. In addition to its direct actions, vitamin D also modulates the effects of other growth factors. Thus, calcitriol has been found to antagonize endothelin-stimulated hypertrophy in neonatal rat cardiomyocytes [47]. In addition, in this model, it may also suppress ANP gene transcription by liganded vitamin D receptor and thus retard myocardial hypertrophy because atrial natriuretic peptide (ANP) gene expression is one of the earliest and most reliable markers of cardiac hypertrophy [48]. Conversely, its reduction in ESRD may allow trophic activities of endothelin and other peptide hormones to proceed unabated. In this regard, in recently reported studies in ESRD subjects, Park et al show that intravenous calcitriol treatment produced a significant regression of LVMI and concomitant significant reductions in plasma concentrations of PTH, angiotensin II (Ang II), and ANP [49].

Vitamin D_3 deficiency in rats is associated with an increased heart weight independently of serum calcium. However, because this type of cardiomegaly is associated with an increase in extracellular space, it could also be due to the concomitant secondary hyperparathyroidism leading to interstitial fibrosis [50]. Thus, in renal failure, vitamin D deficiency and/or impaired action may not only favor myocyte hyperplasia, but may also contribute to myocardial fibrosis.

MYOCARDIAL ISCHEMIA AND ATHEROSCLEROSIS

Numerous alterations in lipid metabolism have been noted in ESRD and have been proposed as causes for the high prevalence of symptomatic and silent cardiac ischemia seen in uremia [32]. Among the many uremia-associated factors contributing to atherosclerosis and ischemia, PTH has been implicated, and a role for altered vitamin D status is suggested. Both PTH infusion and hypocalcemic hyperparathyroidism in normal rats are associated with increased serum concentrations of total cholesterol and triglycerides and a decrease of plasma postheparin lipolytic activity. These effects could be prevented or reversed by PTX [51]. In experimental animals, uremic patients and those with primary hyperparathyroidism PTX produced long-lasting reductions in serum triglyceride concentrations, whereas only short-lasting reductions in total and high-density lipoprotein cholesterol were seen [52, 53]. Klin et al have also shown that in rats with chronic renal failure, there is a down-regulation of the mRNA of hepatic lipase and that hepatic lipase production, activity, and release are impaired [54]. These defects could be prevented by either PTX or verapamil. These studies suggest that hyperlipidemia in renal failure is dependent on excess PTH and that normal parathyroid function is necessary for normal lipid metabolism in renal failure [52, 53, 55]. Recent studies show a role for vitamin D in atherogenesis. One study suggested that vitamin D_3 is positively correlated with concentrations of apo A-I and high-density lipoprotein cholesterol, and another showed an inverse association with very low-density lipoprotein triglycerides, suggesting that vitamin D_3 may be cardioprotective [56, 57]. Moreover, vitamin D can also inhibit macrophage function and may thereby slow the atherogenic process [58]. If confirmed, insufficient vitamin D intake, reduced synthesis of its active metabolites, and impaired action at target tissues in ESRD may all contribute to atherogenesis.

Impaired carbohydrate tolerance, long known as an independent risk factor for atherosclerosis, is a common finding in chronic renal failure, and associations between hyperparathyroid states and glucose intolerance have been described [59–63]. The mechanism underlying this association is controversial. Several studies suggest that excess PTH causes carbohydrate intolerance in uremia by reducing pancreatic islet cell ATP, thereby raising intracellular calcium and impairing insulin secretion [60–63]. On the other hand, increased blood levels of insulin have been observed in primary hyperparathyroidism [64] and in hemodialysis patients with secondary hyperparathyroidism [65]. In both circumstances, PTX could reduce the observed increased blood levels of insulin. DeFronzo et al, in an elegant series of studies in patients with chronic renal disease, have also observed elevated plasma insulin concentrations and reduced tissue sensitivity to insulin [66]. This insulin resistance was found to occur at the level of peripheral tissues and not as a result of altered hepatic glucose production. In this regard, vitamin D may also be important because $1,25(OH)_2D_3$ has been shown to correct glucose intolerance, insulin resistance, and hypertriglyceridemia in uremic patients on hemodialysis, even in the absence of changes in plasma PTH [67].

Insulin has been shown to stimulate Na^+-H^+ exchange and Na^+,K^+-ATPase in frog skeletal muscle, thereby hyperpolarizing and alkalinizing the cell and stimulating glycolysis [68–70]. However, PTH and PTHrP have been shown to reduce the activity of Na^+-H^+ exchange in opossum kidney cells [71, 72], an effect that could be reversed by the addition of $1,25(OH)_2D_3$ [71]. Thus, it may be that by affecting cell pH, and thus its allosteric control of the enzyme, phosphofructokinase, a key regulator of glycolysis, the interplay of vitamin D and PTH may, in part, contribute to the degree of glucose tolerance and atherosclerosis.

Nonatherogenic cardiac ischemia is found often in ESRD patients as well. Altered coronary vasodilator reserve caused by hypertension, LVH, and anemia contribute, but altered small vessel structure and function have also been suggested [32]. Amann et al have described decreased myocardial capillary density and increased wall:lumen ratios in small intramyocardial arteries from uremic rats; the latter changes were unrelated to blood pressure [73, 74]. Remarkably, they could be reversed by PTX. PTH excess may also affect VSMC function by altering the production of endothelium-derived relaxing and contracting factors [75]. Moreover, because PTH/PTHrP receptors are expressed in VSMCs, a chronic excess of PTH might enhance vascular tone directly, for instance, by an increase in cytoplasmic Ca^{++}, in contrast to acute vasodilatory effects of PTH seen in animal studies. Alternatively, altered PTH and PTHrP binding caused by down-regulation of their receptor, as described in several tissues [17, 18], could oppose cellular Ca^{++} entry, thus favoring decreased tone in resistance vessels [76]. PTH and PTHrP may also be involved via indirect actions. It has been suggested that PTHrP may act locally to oppose vasoactive or growth-promoting effects of vasoactive peptides such as Ang II, which stimulate the induction

of the PTH/PTHrP receptor. In this regard, it has been shown that increased hydrostatic pressure is associated with increased PTHrP receptor gene expression, suggesting that the receptor is partly under the control of mechanical forces [77]. It has been proposed that up-regulation of the PTHrP receptor may exert at least some of its vasodilatory effects through stimulating interleukin-1β–induced nitric oxide synthesis [78]. Thus, down-regulation of this receptor in uremic hearts may enhance the trophic and vasoconstrictor actions of Ang II and other peptide hormones [19, 76].

A role for vitamin D is uncertain. *In vitro* studies have shown VSMC proliferation to be stimulated by vitamin D [79, 80], but another found that vitamin D3 suppressed VSMC [^{3}H]-thymidine incorporation and growth stimulated by epidermal growth factor [58]. Thus, it may be that depending on plasma calcitriol concentration in renal failure, VSMC proliferation may be enhanced or depressed, leading to increased wall:lumen ratios and to myocardial hypertrophy. Taken together, available data suggest that hyperparathyroidism and altered vitamin D status contribute significantly to the increased susceptibility for myocardial ischemia in chronic renal failure.

HYPERTENSION

Parathyroid hormone and vitamin D have both been implicated in blood pressure control. Short-term incubation of isolated VSMCs and intact arterioles with PTH produced vascular relaxation [4, 19, 76]. In whole animals, acute exposure to PTH produces hypotension, but the effect may be species specific because short-term infusion of 1,34-PTH in healthy normal human subjects either had no effect on blood pressure or, depending on metabolic state, increased it [81]. It has been well noted in animal studies, however, that chronic exposure to PTH is associated with elevated blood pressure. Studies in hypertensive animals, particularly in the spontaneously hypertensive rat of the Okamoto-Aoki strain, have demonstrated increased PTH secretion, increased parathyroid gland mass, and reduced plasma calcitriol concentration together with a decrease in intestinal calcium absorption and renal calcium reabsorption leading to hypercalciuria [82, 83]. In such studies, calcium deprivation raised blood pressure and PTX, and calcium supplementation reduced it [84–88]. In some forms of human hypertension, increased PTH has also been found, although concentrations of $1,25(OH)_2D_3$ have been variable [89–91]. As in animal studies, calcium supplementation in humans has been shown to lower blood pressure [92]. In renal failure, maneuvers that reduce PTH secretion may also lower blood pressure. Thus, PTX in dialysis patients has produced sustained reductions in blood pressure [93]. Moreover, blood pressure could be decreased in dialysis patients by exposure to ultraviolet light, a manipulation that lowered PTH concentration through increased production of $1,25(OH)_2D_3$ [94].

The mechanism of PTH-induced hypertension is thought to be through increasing intracellular Ca^{++}. As noted earlier in this article, PTH effects on vascular endothelial function and on growth may also contribute to increased vascular tone and stiffness [4, 6, 39, 74, 75, 77, 78, 95–98]. In this regard and contrary to a view suggesting an increased rate of sodium-hydrogen exchange activity in essential hypertension [99, 100], the fact that PTH can inhibit sodium-hydrogen exchange may also contribute to its hypertensive effect because selective inhibition of Na^+-H^+ exchange has been shown to increase blood pressure in the spontaneously hypertensive rat [101].

Short- and long-term administration of calcitriol has also been shown to have vasoconstrictive and blood pressure-elevating properties, and is thought to mediate their effects through increasing intracellular Ca^{++} and through altering adrenergic responsiveness [102–107]. Thus, one might expect that in renal failure, reduced calcitriol concentrations would be associated with lower blood pressures. However, as noted earlier in this article, in uremia, lower plasma calcitriol concentrations may actually increase blood pressure indirectly through elevated PTH secretion, whereas high concentrations may do the opposite. Thus, the action of calcitriol appears to depend heavily on the concomitant parathyroid status. In addition, as noted earlier in this article, vitamin D_3 deficiency in uremia may facilitate atherogenesis, myocyte proliferation, and collagen production, thus causing vascular stiffness and reduced compliance. In this regard, recent studies in humans with essential hypertension [57, 108, 109] or with chronic renal failure [94] and in Dahl salt-sensitive rats [110] have shown inverse associations between blood pressure and concentrations of $1,25(OH)_2D_3$, $25(OH)D_3$, or both.

VASCULAR AND CARDIAC CALCIFICATION

Soft tissue calcification occurs commonly in patients with ESRD. Numerous studies have shown increased myocardial calcium content in patients and animals with uremia [20, 111]. Widespread calcification of the cardiovascular system has also been reported, including the myocardium, mitral and aortic valves, the cardiac conduction system, and large and small arteries localized either as calcified plaques at the endothelial site or as diffuse calcium-phosphate deposits in the media ("mediacalcosis"; Fig. 1A) [96, 112–117]. Such calcification can contribute to mitral and aortic insufficiency, myocardial ischemia, systolic and diastolic cardiac dysfunction, significant and sometimes fatal arrhythmia, and symptomatic peripheral vascular disease, including gangrene. Valvular calcification and attendant dysfunction may also contribute to stroke, pulmonary hypertension, and

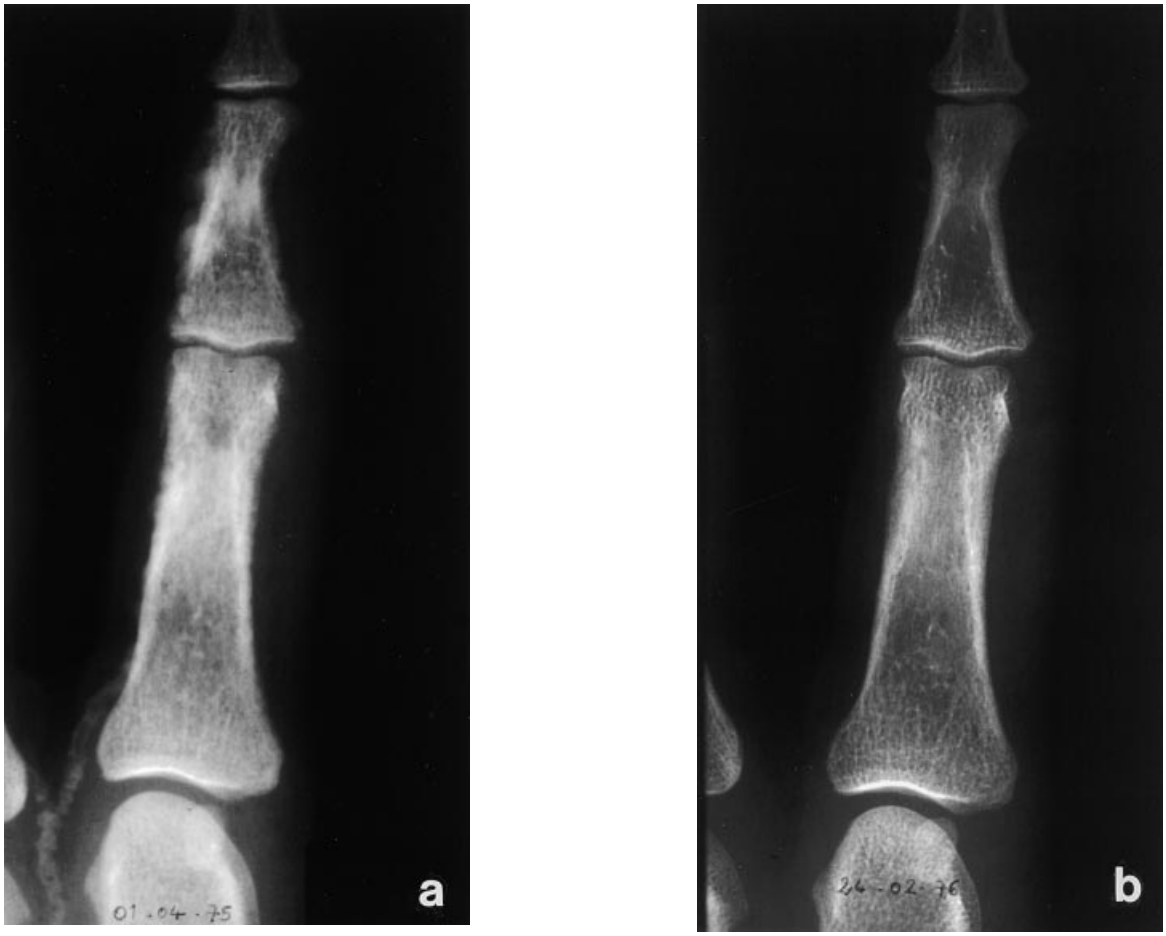

Fig. 1. Radiograph of a single digit and calcified digital artery of a 36-year-old woman with ESRD from congenital uropathy (*a*) before subtotal PTX and (*b*) 11 months later when calcification had completely disappeared.

dialysis-associated hypotension. Using two-dimensional echocardiography, we have found mitral valve calcification in 46.3% of hemodialysis patients and that such calcification was associated with left ventricular dysfunction, clinical heart failure, and infective endocarditis more often than in those in whom it was absent (Table 3). Our observed prevalence of mitral valve calcification (46.3%) was somewhat less than the 59% reported by Braun et al, who measured cardiac calcification in 49 hemodialysis patients using more sensitive electron beam computed tomography [118].

Mechanisms associated with myocardial and vascular accumulation of calcium in uremia have been discussed earlier in this article. Age and hypertension have been implicated in the process, as has secondary hyperparathyroidism [115, 118]. However, the role for secondary hyperparathyroidism is not clear. In animal studies, PTX could prevent the development of vascular calcification, suggesting that secondary hyperparathyroidism plays a role in the calcific arteriopathy seen in uremia [116]. Regression of vascular calcification may, on occasion, be seen following PTX in uremic patients (Fig. 1B). However, Rostand et al were unable to find an association between a PTH concentration and myocardial calcium content using either univariate or multiple variable analysis, but they did show that there was a strong association with calcium-phosphorus product and with PTX [20]. These data suggest that hyperparathyroidism severe enough to require PTX contributed to increased myocardial calcium content. Unfortunately, when a group of 10 patients was studied prospectively, PTX, though lowering plasma PTH and alkaline phosphatase activity, had no effect on myocardial calcium content [21], which is in keeping with similar findings on the effects of PTX on myocardial calcifications in primary hyperparathyroidism [43]. These data suggest that once accumulated in vascular and cardiac tissues, calcium is difficult to displace.

An alternative explanation would be that the induction of low-turnover bone disease by excessive reduction of plasma PTH favors the deposition of calcium phosphate in soft tissues, possibly the result of decreased bone buffer capacity in response to calcium and phosphorus

Table 3. Mitral valve calcification in ESRD: Frequency, distribution, and effects in 140 dialysis patients assessed by 2-dimensional echocardiography

	Mitral valve calcification	
	Present	Absent
Number	67 (47.9)	73 (52.1)
Male	26 (38.8)	32 (43.8)
Female	41 (61.2)	41 (56.2)
Age *years*	54.2 ± 11.8	49 ± 13.1
Mitral valve dysfunction	31 (46.3)	19 (26)
Insufficency	30	19
Stenosis	1	0
Tricuspid valve insufficiency	24 (35.8)	15 (20.5)
Infective endocarditis	2	0
Mitral valve surgery	4	0
LV ejection fraction, *average (%)*	48.3 ± 14.6 [61]	49.2 ± 14.5 [64]
EF < 50 percent	25 (40.9)	20 (31.3)
EF < 40 percent	21 (34.4)	14 (21.8)
Heart failure, clinical	19 (28.3)	10 (13.7)

Values are mean ± SD or actual counts. Numbers in parentheses are percent. Bracketed numbers are sample size if incomplete.

input from the gut [119]. The role of vitamin D in soft tissue calcification seen in renal failure is complex. Excessive intake of vitamin D or its metabolites and analogues may lead to arterial calcification [120, 121]. However, appropriate doses of vitamin D metabolites given to uremic patients for control of secondary hyperparathyroidism should actually induce a decreased propensity for vascular calcification. In keeping with this, it is noteworthy that an inverse, not direct, association between plasma calcitriol and arterial calcification has been found in subjects with normal renal function [122]. This observation was interpreted as reflecting calcium influxes into and out of bone, with a low vitamin D status favoring calcium deposition in soft tissues rather than in bone.

THERAPEUTIC IMPLICATIONS

The foregoing discussion suggests that altered vitamin D, PTH, and calcium metabolism may contribute significantly to the numerous cardiovascular complications found in and to the mortality of chronic renal failure. Throughout this discussion, we have alluded to studies showing that many of the PTH effects on myocardiocyte and VSMC calcium accumulation and metabolism and function, myocardial hypertrophy and fibrosis could be reversed or prevented by calcium channel blockade. Although some experimental studies suggest that calcium channel blockade does not reduce increased cardiovascular calcium content seen in uremia [44], others do [123]. The latter findings together with observations from numerous studies discussed earlier in this article suggest the use of calcium channel blockers early in the course of renal insufficiency nevertheless may be beneficial in reducing cardiovascular accumulation of calcium, thus decreasing the risk of calcifying the myocardium, mitral valve, conducting system, and small resistance arteries, thereby reducing the risk for myocardial ischemia, heart failure, arrhythmia, and death.

Moreover, efforts should be made to reduce PTH secretion through strict phosphorus control and oral supplementation with calcium or vitamin D derivatives into a range that is normal for a uremic patient, that is, with intact plasma PTH concentrations two to three times the upper limit of normal. Recently, it has been observed that the elevated Ca × PO_4 product (>72) and serum phosphorus concentration (>6.5 mg/dl) significantly increased the risk of mortality in ESRD, most probably as a result of cardiovascular complications [124]. Thus, these interventions, together with rigorous control of the Ca × PO_4 product, may help to minimize cardiac morbidity and mortality in renal failure.

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