Adynamic bone in patients with chronic kidney disease

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Adynamic bone in patients with chronic kidney disease (CKD) is a clinical concern because of its potential increased risk for fracture and cardiovascular disease (CVD). Prevalence rates for adynamic bone are reportedly increased, although the variance for its prevalence and incidence is large. Differences in its prevalence are largely attributed to classification and population differences, the latter of which constitutes divergent groups of elderly patients having diabetes and other comorbidities that are prone to low bone formation. Most patients have vitamin D deficiency and the active form, 1,25-dihydroxyvitamin D, invariably decreases to very low levels during CKD progression. Fortunately, therapy with vitamin D receptor activators (VDRAs) appears to be useful in preventing bone loss, in part, by its effect to stimulate bone formation and in decreasing CVD morbidity, and should be considered as essential therapy regardless of bone turnover status. Future studies will depend on assessing cardiovascular outcomes to determine whether the risk/reward profile for complications related to VDRA and CKD is tolerable.

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The history of adynamic bone had its origins in the 1980s during the concern about aluminum overload. Initially, this form of low bone turnover was designated 'aplastic' bone, since it had the appearance of inert bone devoid of apparent bone cell activity.[1,2] The association of adynamic bone with aluminum overload made it seem likely that this was a clinically significant bone disease because of numerous examples of aluminum-induced fractures and associated morbidity.[3,4] Over time, it became apparent that adynamic bone or low bone formation exists without aluminum overload and that the presence of fractures was not a common feature.[5–7]

With its growing awareness, adynamic bone ultimately became associated with abnormal calcium balance[8] and possible links to calcific arteriolopathy[9] and cardiovascular disease (CVD).[10] As a consequence, recommended guidelines and protocols[11] have included provisions, which limit some forms of therapy based on whether adynamic bone might be present, the 'diagnosis' of which is usually made by a relatively low or normal parathyroid hormone (PTH) level. In particular, intravenous vitamin D therapy is one treatment that has received attention as being inappropriate in the setting of adynamic bone, owing to its assumed potential to further lower bone formation rates.[12] This issue has become relevant not only because of the possible increasing prevalence of adynamic bone but also because of the recent observations that intravenous vitamin D therapy is associated with improved survival in dialysis patients[13–17] and hence the need to consider vitamin D receptor activator (VDRA) therapy in every patient receiving dialysis.

The goal of this review will be to re-examine the clinical significance of adynamic bone in patients with chronic kidney disease (CKD) and to determine how the presence of this type of low bone formation should be reconciled with emerging data, suggesting that patients with relatively low PTH levels appear to have a survival advantage[14,18–20] when compared to dialysis patients who have high bone turnover and its attendant increased mortality risk.[16]

DEFINITION AND PREVALENCE

Adynamic bone is defined by the presence of low or absent bone formation as determined by tetracycline uptake into bone, in conjunction with a paucity of bone-forming osteoblasts and bone-resorbing osteoclasts.[7,20] While measurements of

tetracycline uptake into bone allow for precise quantification of bone formation, one inherent problem with the definition is in determining what constitutes normal bone formation. Because the range of bone formation in the iliac crest of normal subjects can include patients with very low or even absent tetracycline labels,[21–30] it becomes difficult to know exactly how to use this parameter to define adynamic bone. The same is true for the quantification of bone cell numbers, especially osteoblast number. Consequently, there are multiple variations of the definition of adynamic bone in the literature, some of which appropriately use 'in-house' normal biopsies to determine the range of normal bone formation,[4,21,31–36] while others have used the less stringent measure of historical controls to make their comparisons. Moreover, the recent identification of minimodeling, which represents localized areas of bone formation within generalized adynamic bone,[36] further complicates the diagnostic accuracy and assessment of its clinical importance.

Because of the lack of a common definition, the true prevalence of adynamic bone in CKD is unknown. In patients with stages 3 and 4 CKD, a prevalence range of 5–40% has been reported, while in stage 5 dialysis patients, the reported prevalence varies from 10 to 50%. Higher percentages of adynamic bone have been reported in peritoneal dialysis (PD) patients (40–70%) compared to patients on hemodialysis (20–50%). Data from one laboratory using the same classification system over the past 10 years suggest that the prevalence of adynamic bone in dialysis patients has been increasing.[20] In addition to there being several different arbitrary standards for adynamic bone, the multiple causes of low bone formation make it clear that its diagnosis depends largely on the population profile.

RISK FACTORS

There is a common misperception that low or normal serum PTH is a cause of adynamic bone when in fact what is meant is that there is a resistance to the bone stimulatory effect of PTH in CKD. Thus, PTH levels two- to fourfold above normal are more often associated with normal bone formation in many but not all dialysis patients[4,33,35] and a range of intact PTH of 150–300 pg ml^{-1} has been the suggested target during treatment of secondary hyperparathyroidism.[11] Bone resistance to PTH appears to be unique to CKD, since non-CKD patients with idiopathic hypoparathyroidism have preserved or increased bone mass during calcium and vitamin D therapy.[37–41]

The causes of low bone formation in CKD are multifactorial (Table 1) and include such remedial causes as vitamin D deficiency,[42] high serum phosphate,[43] metabolic acidosis,[44] elevated circulating cytokine levels (interleukin (IL)-I, tumor necrosis factor (TNF)),[45–47] and low estrogen and testosterone levels.[48–50] PTH receptor downregulation is one potential mechanism to explain the bone resistance effect to PTH[51] due, in part, to persistently elevated PTH (PTH downregulates its own receptor) and to low 1,25-dihydroxyvitamin D levels.[42] Other potential mechanisms of low bone formation include decreased osteoblast proliferation from the direct effect of accumulated uremic inhibitors,[52] and decreased circulating insulin-like growth factor (IGF)-I activity either from low IGF-I and/or IGF-binding protein (IGFBP)-5 levels or from excess IGFBPs that inhibit the action of IGF-I[53] (Table 1). Circulating levels of the bone anabolic factor, IGF-I, correlate directly with bone formation in dialysis patients, independent of PTH[54] and low IGFBP-5 levels[53] may contribute to low bone formation, since IGFBP-5 stimulates bone formation by both IGF-dependent and -independent mechanism.[55,56]

Three important clinical conditions are associated with low bone formation: diabetes, aging, and malnutrition. The apparent increase in the prevalence of patients with low bone formation, with or without adynamic bone,[20] may be due to the increase in the prevalence of diabetic and elderly patients who develop CKD and go on to require dialysis. This may also partially explain the variance in its prevalence among different dialysis units. The role of malnutrition in causing low bone formation may be most apparent when comparing PD patients to those who receive hemodialysis. Serum albumin levels are typically lower in PD patients, because of protein loss through the peritoneal membrane. While decreased serum albumin levels correlate with low bone formation,[57] it is still unclear how malnutrition reduces bone formation, particularly in the dialysis patient who often has concomitant inflammation and elevated cytokine levels. Reduced circulating IGF-I activity in malnourished PD patients may have a role in causing low bone formation in

Table 1 | Causes and proposed mechanisms of decreased bone formation in patients with CKD

Cause		Mechanism of ↓ osteoblast Activity
(1)	Low serum 1,25-D	↓ Osteoblast differentiation ↓ Osteoblast lifespan
(2)	Metabolic acidosis	↓ 1,25D production ↓ Collagen synthesis
(3)	High serum phosphate	↓ 1,25D production
(4)	Calcium loading/ hypercalcemia	↓ 1,25D production and ↑ 1,25D degradation (CaSR mediated)
(5)	High serum IL-1, IL-6, TNF	↓ Osteoblast lifespan
(6)	Low serum IGF-I activity	↓ IGF-I and IGFBP-5 levels ↑ Inhibitory IGFBPs (2, 4, 6) levels ↓ Osteoblast lifespan
(7)	Malnutrition, proteinuria	↓ IGF-I; ↓ 25D levels
(8)	Diabetes	↓ 25D & 1,25D levels; ↑ AGE; ↓ osteoblast lifespan
(9)	Age-related	↑ AGE; ↓ Osteoblast lifespan
(10)	*Hypogonadal*	
	Women (↓ E and ↑ SHBG)	↓ Osteoblast lifespan
	Men (↓ T and ↑ SHBG)	↓ Osteoblast lifespan
(11)	Uremic toxins (uric acid)	↓ 1,25D production, ↓ VDR activity ↓ Osteoblast proliferation
(12)	Aluminum toxicity	↓ Osteoblast activity

AGE, advanced glycemic end-product; CKD, chronic kidney disease; IGF, insulin-like growth factor; IGFBP, IGF-binding protein; IL, interleukin; TNF, tumor necrosis factor; VDR, vitamin D receptor; E, estrogen; SHB6, sex hormone binding globulin.

this setting.[58] Certainly, the PD patient has other risk factors for low bone formation: high dialysate calcium concentration[59] and possibly increased glucose levels.[60] These two factors, along with malnutrition, may also promote normal or low PTH levels, which function to unmask the adynamic lesion. Interestingly, despite the presence of long-standing adynamic bone, not all PD patients show low bone density or evidence of bone loss,[61] raising the question about the clinical significance of fracture risk in adynamic bone that is not due to aluminum loading (see below).

MECHANISMS

Multiple circulating factors contribute to low bone formation by interfering with VDR-dependent pathways, by decreasing PTH-receptor-dependent stimulation of bone formation, or by other mechanisms (Table 1). Low 1,25-dihydroxyvitamin D levels promote decreased VDR expression[62,63] and recent studies in VDR knockout mice have identified the VDR as being crucial in maintaining normal bone formation[64] and bone mineralization[65] by directly enhancing osteoblast differentiation. VDR activation of the osteoblast also functions to prevent apoptosis through genotropic (VDRE-dependent) as well as non-genotropic activation of Src kinase.[66] Transduction of kinase-mediated signals by these mechanisms is similar to those recently discovered for the estrogen and androgen receptors in their function to prevent apoptosis of osteoblasts and osteocytes.[67] In addition, osteoblasts contain the 1a-hydroxylase enzyme and can produce 1,25-dihydroxyvitamin D from circulating 25-hydroxyvitamin D[68] presumably to function in an autocrine/paracrine manner to maintain bone formation. Elevated PTH is known to downregulate the VDR,[63,69] which could contribute to further lowering of bone formation. Elevated phosphate lowers circulating 1,25-dihydroxyvitamin D[70] by downregulating renal expression of 1a-hydroxylase in stage 4 CKD and potentially contributing to reduced VDR expression in bone and parathyroid cells. Metabolic acidosis lowers 1,25-dihydroxyvitamin D levels by its inhibitory effect on renal 1a-hydroxylase activity,[71–73] while also having a direct effect on osteoblast function to decrease collagen synthesis,[44] a necessary component for normal bone formation. Metabolic acidosis also stimulates bone resorption by directly activating osteoclast activity.[44] Thus, in all patients with CKD progression, the plasma accumulation of phosphate and acid may further suppress already low 1,25-dihydroxyvitamin D levels, which may suppress bone formation by directly lowering osteoblast activity. Increased bone turnover, however, may occur in some patients in response to the direct effects of elevated PTH. The presence of diabetes can accentuate the vitamin D-deficient state[74,75] and may be one of the mechanisms for low bone formation in this disorder. Another potential mechanism for low bone formation in diabetes relates to the accumulation of advanced glycemic end products (AGEs) and their effect to induce osteoblast apoptosis (see Osteoblast apoptosis section below).

Table 2 | Relative contribution of factors that reduce bone formation according to CKD stage in patients not treated with active vitamin D

Factors	Stage 3	Stage 4	Dialysis
Low serum 1,25D	+	++	+++
Metabolic acidosis	+/−	+	++
High serum phosphate	No	+/−	+++
Calcium loading	No	+/−	+++
High serum IL-1, TNF	No	No	+++
Low serum IGF activity	No	No	++
Malnutrition	No	No	++
Uremic toxins	?	?	++
Diabetes	Yes	Yes	Yes
Age-related	Yes	Yes	Yes
Hypogonadism	Yes	Yes	Yes

CKD, chronic kidney disease; IGF, insulin-like growth factor; IL, interleukin; TNF, tumor necrosis factor.

Circulating cytokines, such as IL-1, IL-6, and TNFα, are intermittently elevated in dialysis patients[45] and may act to directly inhibit osteoblast function by mechanisms that are PTHR and VDR independent through pathways that promote Runx2 transcription factor degradation[46,76] and inhibit Runx2 expression.[77] The fact that these cytokines circulate at higher levels in stage 5 dialysis patients compared to patients with stage 3 or 4 CKD may partly explain the higher prevalence of adynamic bone in the dialysis population (Table 2).

Low IGF-I levels may be one of the mechanisms by which malnutrition contributes to low bone formation.[58] Diabetic patients in particular are prone to malnourishment in early stage CKD if heavy proteinuria is present. Proteinuria of this magnitude is associated with profound 25-hydroxyvitamin D deficiency and low bone formation[78] and its presence would likely add to the vitamin D deficiency that is more commonly seen in the diabetic CKD patient. The mechanisms for the age-related reduction in bone formation are incompletely understood, although several potential candidates include reduced growth hormone (GH) activity,[79] decreased expression of the Klotho gene,[80] reduced circulating sex-steroids,[49,50,81] oxidative stress,[82] and accumulation of AGE.[83] One therapeutic benefit common to estrogens,[67] androgens,[84] and activated vitamin D[66] is their effect to prolong the osteoblast lifespan by preventing apoptosis to improve bone formation (see Osteoblast apoptosis section below).

Reductions in serum estradiol in women and testosterone in men are associated with bone loss.[81] Women who are post-menopausal have an increased risk of CVD,[85,86] independent of the presence of CKD, and one apparent mechanism for this increased risk is accelerated aortic calcification as a result of accelerated bone loss from estrogen deficiency.[87] Interestingly, new data reveal that women who receive estradiol replacement therapy have reduced coronary artery calcification compared to women not taking estrogen,[88] presumably due to its effect to decrease bone loss by decreasing excessive bone resorption, although a direct protective effect on

vascular calcification may also be a contributing factor. Studies are needed in patients with CKD to determine whether similar correlations exist between vascular calcification and sex steroid deficiencies and whether estrogen therapy may mitigate vascular calcification.

Dialysis patients represent the end result of serum accumulation of many compounds that have the potential to suppress bone formation. Uric acid accumulation is known to suppress 1,25-dihydroxyvitamin D production[89] and uremic ultrafiltrate contains accumulated substances that interfere with VDR function.[90] Other inhibitors of osteoblast function have also been found,[52] although their exact identification remains for future study. While aluminum use as a phosphate binder is largely confined to the dialysis population, the recognition that aluminum accumulation causes low bone formation and fractures, through its effect to directly decrease osteoblast activity,[91] has not been sufficient to completely eradicate its use. For example, recent bone biopsy studies looking at the association of low bone formation and arterial calcification have been confounded by the presence of significant bone aluminum accumulation, which may also be important in the development of vascular calcification.[10]

OSTEOBLAST APOPTOSIS

The regulation of osteoblast apoptosis is now recognized as a major mechanism for determining rates of bone formation. It is estimated that 60–90% of osteoblasts within a remodeling unit die by apoptosis with the remainder becoming either osteocytes or bone lining cells.[92] Antiapoptotic proteins active in osteoblasts include TGFβ,[93] Wnt,[94] IGF-I,[95] FGF-2,[96] PTH-rP,[97] and IL-6[98] and antiapoptotic hormones include estrogen,[67] androgens,[84] and vitamin D analogues.[66] Intermittent injections of PTH also serve an antiapoptotic function to increase bone formation and bone mass[99] in contrast to continuous PTH infusions, which cause bone loss.[100] Circulating proapoptotic proteins that are relevant to the CKD patient include TNFα, IL-1, bone morphogenetic proton (BMP)-2,[101] and AGE.[83] Oxidative stress, as a component of aging,[82] and glucocorticoids, when used as therapy,[102] also potently stimulate apoptosis of osteoblasts and osteocytes. Thus, several clinically important causes of adynamic bone in patients with CKD have osteoblast apoptosis as the potential mechanism for reductions in bone formation (Table 1). Elevated levels of AGE, as seen with diabetes and aging, decreased sex steroids in idiopathic and secondary hypogonadism (also as part of aging), glucocorticoid therapy, GH resistance or IGF-I insufficiency, excess TNF exposure, and vitamin D deficiency or inadequate vitamin D therapy are all common occurrences in patients with CKD, and they likely play a role in suppressing bone formation by inhibiting the number of osteoblasts that can form bone.

CLINICAL SIGNIFICANCE AND DIAGNOSIS

The clinical relevance and diagnosis of adynamic bone in the CKD population ultimately depends on the number of risk factors present at the time of assessment. This in turn depends on whether the patient has diabetes and/or is elderly as well as on the severity of CKD (Table 2). Thus, the extent of depressed bone formation can be thought of as a continuum, which becomes reduced from normal to absent (true adynamic bone), as more risk factors are present. Progression of CKD adds to this risk profile as levels of 1,25-dihydroxyvitamin D become markedly reduced and the accumulation of phosphate and acid further suppresses 1,25-dihydroxyvitamin D production.

Among the studies that have identified fractures and fracture risk in patients with CKD, none have identified biopsy proven adynamic bone as a risk factor for fracture. Instead, surrogate markers of low bone turnover, mainly PTH levels, have been the comparator to define who is at risk for fracture, using relatively low or normal PTH as the identifier of fracture risk.[103,104] Unfortunately, low PTH is also associated with low protein intake and may be a risk factor for malnutrition,[105,106] which itself has been associated with low bone formation. Moreover, in CKD patients receiving dialysis, the histologic cause of hip fracture has never been identified, although the assumption that hip fractures in dialysis patients result from osteopenia or osteoporosis. However, β-2 amyloid deposition in the femoral neck is a common cause of hip fracture in patients who have received dialysis for more than 5 years.[107] Older age and a longer time on dialysis are risk factors for developing amyloid bone disease,[108] which are also risk factors for developing fractures and CV events.

Because of confounding by association of time on dialysis and age, it becomes difficult to know how the impact of low PTH contributes to fracture risk in this setting. Hip fracture rates were recently shown to be higher in dialysis patients compared to a matched cohort of non-CKD patients and PTH levels were not predictive of fracture.[109] To further complicate this interpretation, a recent analysis of dialysis patients who had undergone a parathyroidectomy showed that parathyroid ablation is associated with increased survival (relative risk lower by 15–35%) when compared to matched patients not having had the surgery.[19] A more recent analysis of this patient group indicates that parathyroidectomy is associated with a lower risk for fracture,[110] a finding that corroborates earlier literature defining low risk of bone loss after long-term follow-up of patients who received total parathyroidectomy.[111] Thus, normal or relatively low PTH levels may be the preferred long-term goal to effectively reduce fracture and mortality rates.

With the progression of CKD, the number of risk factors for the development of low bone formation increases (Table 2). Diabetes, aging, and hypogonadism are expected to have an impact throughout all stages of CKD. As patients approach stage 4 CKD, the accumulation of phosphate and organic acids is an additional contributor to suppressed bone formation. Stage 5 dialysis patients are the most severely affected by excess phosphate accumulation, retention of uremic toxins, high circulating cytokine levels, and

heightened catabolic rate, which leads to malnutrition. Finally, excess calcium loading from the use of calcium-based phosphate binders has been associated with suppression of bone formation,[112] bone loss,[113] accelerated vascular calcification,[114–116] and increased mortality.[116]

The diagnosis of adynamic bone ultimately is made by bone biopsy. However, because most patients are unwilling to undergo this invasive procedure, non-invasive diagnostic methods continue to be used most of the time. Risk stratification (Table 1) is helpful in defining susceptible patient populations. For example, a diabetic male older than 60 with hypogonadism will be more likely to have adynamic bone than a 40-year-old patient without diabetes. The presence of malnutrition/inflammation (for example, low serum albumin levels; high C-reactive protein), metabolic acidosis or calcium loading from calcium-containing phosphate binders, would further distinguish susceptible patients.

As a single serum test, PTH has been the most extensively used non-invasive method, employing assays that measure intact PTH plus PTH fragments or newer assays that measure only intact PTH. Early reports, suggesting that the use of both assays to quantify the amount of retained PTH fragments to predict bone histology,[117] have not been corroborated by subsequent studies.[118,119] This is likely due to the fact that serum PTH is not a product of bone and, because it is not the only regulator of bone formation, it will never have excellent predictability as a sole measurement. In contrast, serum bone alkaline phosphatase has very good predictive value in separating high from low bone turnover.[120,121] Serum bone alkaline phosphatase has also been useful when combined with PTH levels to identify patients with low bone formation (for example, bone alkaline phosphatase <20, PTH $<100\,\mathrm{pg\,ml^{-1}}$).[121]

TREATMENT

Calcium intake

Dialysis patients with adynamic bone are less able to incorporate a calcium load into bone compared to those with normal or high bone turnover[8] and consequently they are at an increased risk for soft-tissue and vascular calcification during periods of calcium and aluminum loading.[10] London *et al.* recently demonstrated that bone biopsy evidence of low bone formation correlated with higher calcification scores in a population that was receiving calcium and aluminum as the phosphate binders. Interestingly, those patients who had substantial bone aluminum accumulation tended to show a better correlation between bone formation and vascular calcification than those without aluminum deposits,[10] suggesting that aluminum itself may have had a role in promoting calcification. Whether the binding of aluminum to the calcium sensing receptor[122] is partly responsible for enhanced calcification remains to be determined. Appropriate treatments for a patient with suspected adynamic bone include: (1) stopping all forms of excess calcium loading by not exceeding a dialysate calcium concentration $>2.5\,\mathrm{mEq\,l^{-1}}$ and by limiting total oral elemental calcium intake to $1.0–1.4\,\mathrm{g\,day^{-1}}$,[123] (2) achieving optimal phosphate control using non-calcium-based phosphate binders, (3) optimizing dialysis to more effectively remove accumulated toxins and acids and to decrease inflammatory cytokine levels (daily dialysis to achieve a higher weekly K_t/v (for example, $>24\,\mathrm{h\,week^{-1}}$ of hemodialysis)),[124] and (4) improving bone formation with VDRA therapy. Other potentially useful forms of therapy to stimulate bone formation include testosterone and estrogen or estrogen analogues (selective estrogen-receptor modulators).

Vitamin D receptor activation

VDRA has only recently been appreciated to be an effective treatment of adynamic bone owing to its stimulatory effect on bone formation.[64,125] The findings that VDR activation is required for osteoblast development and normal bone formation,[64] as well as for normal mineralization,[65] by calcium-independent pathways are complemented by the more recent demonstration that active vitamin D treatment can decrease bone resorption by inhibiting osteoclast production.[126,127] Moreover, *in vivo* studies utilizing several different active vitamin D compounds have corroborated the stimulatory effect of active vitamin D on bone formation and bone accretion.[128] Especially, intriguing is the finding that paricalcitol treatment of LDL receptor knockout mice corrected low bone volume by enhancing bone mineralization and by decreasing bone resorption directly.[129] Treatment of low 25-hydroxyvitamin D levels may also be important for enhancing bone formation, since osteoblasts contain the 1a-hydroxylase enzyme,[65,68] which increases local production of 1,25-dihydroxyvitamin D. Interestingly, osteoblasts also contain megalin receptors,[68] which are known to function as 25-hydroxyvitamin D acceptor proteins that incorporate 25-hydroxyvitamin D into the cell. The upregulation of megalin[130] and 25-hydroxyvitamin D incorporation into cells by VDRA therapy[131] suggests that concomitant VDRA may be necessary with 25-hydroxyvitamin D therapy to optimize intracellular uptake of 25-hydroxyvitamin D. Low 25-hydroxyvitamin D levels have been correlated with the presence of low bone formation in dialysis patients[132] and treatment with ergocalciferol was recently shown to be effective in a dialysis patient with osteomalacia.[133]

Clinical studies lend support to the notion that VDR activation is anabolic for bone as seen in dialysis patients[134] as well as in patients with early and late stage CKD.[135,136] In both reports, longitudinal measurements of bone mineral density confirmed the ability of active vitamin D analogues to not only stop bone loss but also increase bone density. While bone biopsy evidence of bone formation was not present in these studies, previous results in pre-dialysis patients with adynamic bone showed that their bone formation rates improved following treatment with active vitamin D.[137] Thus, the VDRA-directed increase in bone mineral density (BMD) most likely occurs from reduced bone resorption (due to reduced PTH effects) and increased bone formation

Table 3 | Proposed effect of VDRA therapy to mitigate factors that reduce bone formation

Factors	Positive VDRA effect	Mechanism of VDR effect
Low serum 1,25D	Yes	↑ Osteoblast activity ↑ Osteoblast lifespan
High serum phosphate	Yes	↑ Osteoblast VDR activity
High serum IL-1, TNF	Yes	↓ IL-1 and TNF levels ↑ Osteoblast lifespan
Low serum IGF activity	Yes	↑ IGF-I and IGFBP-5 (obl) ↑ Osteoblast lifespan
Malnutrition	Possible	↓ IL-1 and TNF levels ↑ IGF-I activity
Diabetes	Possible	↑ 1,25D levels ↑ Insulin sensitivity
Age-related	Possible	↑ Osteoblast lifespan
Hypogonadal		
Women	Possible	↑ Osteoblast lifespan
Men	Possible	↑ Osteoblast lifespan

IGF, insulin-like growth factor; IGFBP, IGF-binding protein; IL, interleukin; TNF, tumor necrosis factor; VDRA, vitamin D receptor activator.

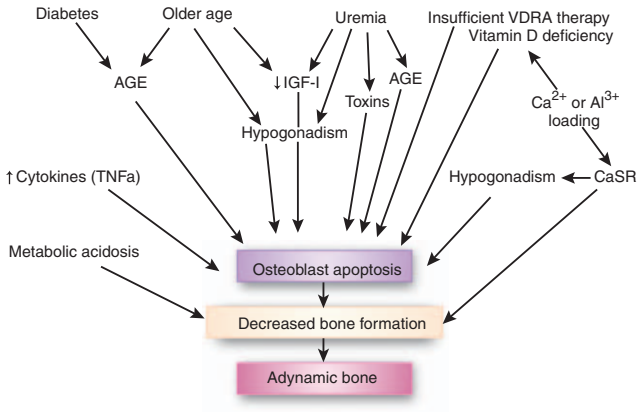

Figure 1 | Mechanisms of decreased bone formation in chronic kidney disease.

(from vitamin D stimulation of osteoblast function). Future studies in CKD patients should evaluate the newer vitamin D analogues for their effect on bone formation and bone accretion.

Therapy with active vitamin D analogues to treat and prevent low bone formation probably act through several mechanisms (Table 3). The effect of vitamin D therapy to upregulate VDR expression would be expected to stimulate osteoblast activity directly. Treatment of dialysis patients with IV calcitriol has been shown to effectively reduce elevated levels of IL-1, IL-6, and TNFα,[45] which are known inhibitors of bone formation. While high phosphate levels are known to interfere with the effectiveness of calcitriol therapy in dialysis patients, the effectiveness of paricalcitol to suppress PTH was not altered by high phosphate levels,[138] suggesting that this VDRA has selective effects on target tissues. This is corroborated by the demonstration that paricalcitol, in contrast to calcitriol and doxercalciferol, is less stimulatory of bone resorption[139] and intestinal calcium absorption[140] and more stimulatory for bone formation *in vitro*.[141] This may be explained, in part, by the effect of VDRA therapy to increase osteoblast production of IGF-I and IGFBP-5,[142] both of which enhance bone formation.[55,143]

Because of the recent finding that active vitamin D therapy is associated with a survival benefit in dialysis[13,14] as well as pre-dialysis patients,[144] there is a question about the importance of active vitamin D treatment in all CKD patients as a way to decrease CV mortality. Thus, determining the potential mechanisms for the apparent beneficial effect of VDRA therapy will be important. Vitamin D regulation of cytokine production may be an especially beneficial way not only to ameliorate bone loss but also to prevent or improve CVD.[145–152] Elevated levels of IL-1, IL-6, and TNFα are known risk factors for CVD,[145–147] which are suppressed by calcitriol treatment in dialysis patients.[45] Low levels of IL-10, in contrast, are associated with atherosclerosis[147,148] and bone loss.[149] Vitamin D deficiency is associated with low IL-10 levels[150] and calcitriol stimulates the production of IL-10 in T lymphocytes.[151] Thus, because IL-10 expression by T lymphocytes is intimately associated with the inhibition of atheroma formation,[152] it is possible that VDRA therapy may be useful in preventing or treating atherosclerosis (Figure 1).

DIABETES

Diabetic patients with CKD have lower rates of bone formation,[153] a complication that often precedes their development of CKD. Because patients with diabetes tend to develop more profound vitamin D deficiency during the progression of CKD, a potentially treatable cause of low bone formation would be early treatment with an active vitamin D analogue. Certainly, optimizing glucose control should be expected to improve bone formation[154] as well as decrease the risk for vascular comorbidities.[155]

HYPOGONADISM

Men with CKD have about a 40% prevalence of hypogonadism.[156] Both primary and secondary hypogonadism have been associated with uremia, thus LH levels may be either high or low relative to a low free testosterone concentration. Appropriate testosterone replacement therapy in men is expected to stop bone loss and increase bone density,[50,157] although studies are needed in patients with CKD to confirm that androgen therapy stimulates bone formation and reduces bone loss. Appropriate testing for prostate cancer (digital rectal exam, serum prostate specific antigen (PSA)) is recommended prior to long-term testosterone replacement therapy.

Most women older than 45 years who receive dialysis are post-menopausal.[158] Identifying such patients is important for risk assessment of CVD, since some, but not all, menopausal women with osteoporosis have accentuated rates of bone loss, which closely correlate with high rates of vascular calcification.[87] Optimal control of PTH levels is

paramount for reduction of bone resorption and bone loss. Whether the addition of raloxifene to active vitamin D treatment would be additive protection from bone loss remains to be determined. However, estrogen treatment can enhance VDR expression in some tissues,[159] and therefore it may potentially enhance the anabolic effect of vitamin D on bone. Moreover, estrogen treatment in the perimenopausal period offers protection from coronary artery calcification.[88] Studies are needed to determine the effectiveness of estrogen or raloxifene on bone loss and CVD in women with CKD.

AGE-RELATED BONE LOSS

Pediatric patients have unique problems because CKD so profoundly interferes with bone growth and mineralization.[160] Short stature is a common problem in pediatric CKD patients,[161] owing to the marked reduction in cartilage growth plate development. Several mechanisms appear to play a role in delayed growth, including decreased serum GH and IGF-I activity, vitamin D deficiency, and metabolic acidosis. Early treatment with GH[162] and active vitamin D[163] has been shown to improve growth velocity and bone mass.

The elderly suffer from reduced bone mass as a result of decreased bone formation and increased bone resorption.[164] While the exact mechanism of the age-related decrease in bone formation remains undefined, the problem is likely to be multifactorial, since serum levels of such stimulators of bone formation as sex-hormones, GH, and IGF-I all become reduced with advancing age while the accumulation of AGE becomes prominent. An intrinsic defect of osteoblast precursors may also play a role if it is true that only a finite number of osteoblasts are available during a given lifespan. Presumably, the addition of CKD enhances the rate of bone loss by further decreasing bone formation, although limited data are available to assess the effect of CKD longitudinally in this population.

FUTURE STUDIES

Additional work is needed to clarify several issues relating to the clinical consequences of low bone formation. The development of a risk assessment protocol would be useful to identify susceptible patients with CKD who are more prone to developing low or absent bone formation and CVD. Such studies would involve the concomitant measurement of bone histology, bone loss, vascular calcification, and serum markers of bone turnover. Clinical investigation of the potential impact of BMP-7 deficiency as a cause of vascular calcification and adynamic bone is now warranted, given the preclinical findings that BMP-7 levels fall with reductions in glomerular filtration rate and that BMP-7 treatment stimulates bone formation and mitigates vascular calcification.[165–167] Finally, standardized criteria for adynamic bone need to take into account not only the rate of bone formation but also the extent of bone loss systemically. Such data will enable researchers and clinicians to more fully appreciate the likelihood of individual patient risk for developing adynamic bone over time and how that relates to bone loss and CVD. In this respect, novel markers of bone turnover still need to be correlated with markers of vascular disease so that susceptible patients can be identified and followed during their progression with CKD.

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