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Kidney Bone Disease and Mortality in CKD: Revisiting the Role of Vitamin D, Alkaline Phosphatase and Minerals

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Abstract

Recent evidence indicates that the traditional syndromes known as renal osteodystrophy, secondary hyperparathyroidism and vitamin D deficiency are related to mortality in persons with chronic kidney disease (CKD). The so-called "*Kidney Bone Disease*", also know as "*Mineral-and-Bone-Disorders*", is defined to include 3 interrelated entities: bone disorders, mineral disarrays, and vascular calcification. These disorders are common in individuals with moderate to advanced CKD and may be related to cardiovascular disease and risk. We have identified 13 common and clinically relevant conditions of contemporary nature that are related to the *Kidney Bone Disease*, including: calcitriol (active vitamin D) deficiency, 25(OH)-vitamin D deficiency, biochemical hyperparathyroidism, relatively low parathyroid hormone level, increased serum alkaline phosphatase (hyperphosphatasemia), elevated fibroblast growth factor-23, high turnover bone disease, adynamic bone disease, vascular calcification, hyper- and hypophosphatemia, and hyper- and hypocalcemia. We present a critical review of these 13 conditions with emphasis on CKD patient survival and other pertinent clinical outcomes. We also review unresolved controversies surrounding the administration of nutritional vitamin D, activate vitamin D analogs, calcimimetics and recombinant parathyroid hormone teriparatide; compare mortality predictability of parathyroid

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hormone and alkaline phosphatase; and examine potential risks of mineral disarrays and abnormally high and low levels of calcium and phosphorus in CKD patients.

Keywords

Hyerparathyroidism; vitamin D; calcimimetic; hypocalcemia; hypophosphatemia; alkaline phosphatase; parathyroid hormone (PTH)

Introduction

Bone disorders, mineral disarrays, and vascular calcification are the 3 closely interrelated and common conditions in individuals with moderate to advanced chronic kidney disease (CKD).[1, 2] These conditions appear to be related to progressive deficiency of active vitamin D and worsening secondary hyperparathyroidism (SHPT) that happen with gradual loss of renal function and lead to renal osteodystrophy.[3] Some opinion leaders have suggested the designation of "CKD *Mineral and Bone Disorder*" (CKD-BMD) for the constellation of the foregoing disorders.[1, 2] Even though the term CKD-MBD may sound more inclusive than the traditional term "renal osteodystrophy", many physicians and health care professionals as well as many patients continue to refer to these disorders as "*Renal Bone Disease*"[4, 5] or simply "*Kidney Bone Disease*".[6, 7] Table 1 includes the list of most commonly encountered conditions related to the *Kidney Bone Disease* in individuals with CKD. We present a critical review of the 13 conditions listed in Table 1 with emphasis on CKD patient survival and other pertinent clinical outcomes.

I. Calcitriol (Active Vitamin D) Deficiency

The SHPT is engendered, at least in part, as a result of the progressive decline in circulating level of 1,25 dihydroxycholecalciferol (1,25(OH)2D3 or calcitriol), also known as activate vitamin D, across worsening stages of CKD.[8–10] Replacement of activate vitamin D has thus become the main strategy in the treatment of SHPT. The introduction of a number of analogues of the activate vitamin D molecule, together also known as *vitamin D receptor activators* (VDRA), has broadened our therapeutic armamentarium,[11, 12] but has also made decisions about which drug to use more complicated.[13]

We recently examine the rationale for the therapeutic use of activate vitamin D and summarized the available scientific evidence supporting the use of them, alone or in combination with other therapeutic agents such as calcium sensing receptor (CSR) agonists, also known as calcimimetics, and/or nutritional vitamin D, i.e., precursor of 25(OH) vitamin D.[312] In particular, we reviewed the recent observational data on the association of VDRA and survival in CKD and expanded our discussion on interpretation of such associative data in the setting of clinical practice and current and anticipated treatment guidelines.[3, 12] There are increasing number of observational studies published to date indicating survival advantages of active vitamin D in CKD patients, including several studies in maintenance dialysis patients[14–21] and 2 additional studies in non-dialysis dependent (NDD) CKD patients.[22, 23] To our knowledge, only one observational study has not uniformly confirmed the association of vitamin D agents and CKD survival, in which apparently both active and

nutritional vitamin D agents were examined combined as treatment group.[24] The consistency of the epidemiologic data is remarkable, making a strong point about the potential of causality given other features of Hill's causality criteria[25] such as biological plausibility and scientific coherence.[3]

Some experimental studies using animal models have shown an association between active vitamin D and vascular calcification[26–28] or myocardial fibrosis,[29] whereas other studies have shown salutary effects including improved left ventricular hypertrophy[30] or lack of vascular calcification with more selective VDRA that may have less effect on vitamin D receptors of the gastrointestinal tract, leading to less calcium and phosphorus absoption.[31] Nevertheless, the survival advantages of VDRA should eventually be tested in randomized controlled trial, not withstanding the fact that many fundamental beliefs of the contemporary medicine and public health, such as the association between smoking and lung cancer, have never been tested in any randomized controlled trial.

Differences in survival-advantages between *paricalcitol* and *calcitriol* observed in a large epidemiologic study[32] may also be explained by virtue of their differential effects on diverse PTH segments. Monier-Faugere *et al.*[33] found that *calcitriol* and *paricalcitol* have trivial but biologically significant differences between their effects on circulating levels of PTH-(1-84), intact PTH, large C-terminal PTH fragments (C-PTH), and the ratio of PTH-(1-84) to C-PTH fragment or PTH-(7-84), i.e., iPTH minus PTH-(1-84). The PTH-(7-84), has been shown to act as a partial antagonist of PTH-(1-84), with opposite biologic activities.[34, 35] In CKD patients reduction in renal function is accompanied by a higher increase in C-PTH than in PTH-(1-84).[36] The administration of *cinacalcet* to dialysis patients with SHPT[37] or to patients with parathyroid cancer[38] does not change the ratio between intact PTH and PTH-(1-84).[34] Among VDRAs, *paricalcitol* has less hypercalcemic and hyperphosphatemic effects and does not induce low bone turnover in a rat model of renal failure.[39] Also, the affinity of *paricalcitol* for vitamin D receptor is three times less than that of *calcitriol*, whereas its calcemic and phosphatemic effects have been shown to be 10 times lower.[33] Biologically plausible mechanisms that can explain survival advantageous of different VDRAs are yet to be discovered and confirmed in clinical trials.

II. 25(OH) Vitamin D Deficiency

The *Kidney Disease Outcome Quality Initiative* (KDOQI) guidelines recommend measuring 25(OH) D (calcidiol) levels in individuals with CKD and hyperparathyroidism and, if below 30 ng/ml, to replace it with nutritional (inactive) vitamin D_2 (ergocalciferol) or D_3 (cholecalciferol).[40] The recommended ergocalciferol dose is 50,000 units (one pill) per week to per month for 3 to 6 months, according to the severity of vitamin D deficiency.[41] Assuming liver function is intact, the administered nutritional (inactive) vitamin D precursor or substrate is expected to be converted to 25(OH) D and ready for further 1α-hydroxilation in the kidney or in non-renal (peripheral) organs.[12] Although many studies have shown meaningful epidemiologic or pathophysiologic association between low 25(OH) D level and outcomes in the general population,[42] such findings need yet to be confirmed in observational or interventional studies in CKD patient populations.[43] A recent prospective cohort study showed that lower levels of 25(OH) D were associated with increased mortality

in incident hemodialysis patients, but VDRA administration virtually nullified the mortality-predictability of 25(OH) D deficiency.[44]

Prior to the VDRA-era, nutritional (inactive) vitamin D agents such as ergocalciferol or cholecalciferol were used with less success in dialysis patients. A controlled trial by Berl et al[45] found that vitamin D_3 was not effective in decreasing serum PTH level in dialysis patients, whereas calcitriol was. Nine of 12 patients on D_3 showed histologic deterioration of bone disease, whereas in six of seven patients who received calcitriol, improved to unchanged bone histology was observed.[45] In another study by Malluche et al[46] vitamin D_3, in doses that normalized intestinal absorption of calcium, failed to restore bone histology to normal, although mineralization and collagen texture of osteoid were consistently improved.

There is ongoing debate as to whether in the absence of renal 1α-hydroxilation in renal failure, the peripheral (non-renal) 1α-hydroxilase is adequate to generate the required magnitude of circulating $1,25(OH)_2D$, especially if the availability of the *substrate*, i.e., 25(OH) D is enhanced by increasing the intake of nutritional vitamin D.[47] Apart from above unanswered question, 25(OH) vitamin D may have a more widespread role beside being a mere precursor or substrate to activate vitamin D.[43] Even though currently there is no convincing data about usefulness of nutritional vitamin D in CCKD,[12] there is heightened debate in the pharmaceutical industry related circles as to whether the combination of nutritional D plus calcimimetic can be as good as active vitamin D alone. Despite less encouraging results pertaining to the administration of nutritional D to dialysis patients in the past, it is possible that the combination of nutritional (inactive) vitamin D and a calcimimetic[48] is more promising than nutritional D alone, a hypothesis that needs to be tested in well-designed randomized controlled trials.

III. Biochemical Hyperparathyroidism

In individuals with normal renal function, a serum intact PTH of 65 pg/mL or above is considered abnormal and likely a sign of primary hyperparathyroidism. Indeed in the face of normal to high serum calcium level, even PTH levels in mid to high 50's pg/ml may be already abnormal.[49] The most recent version of the KDOQI, however, has recommended higher cutoff levels as the definition of treatment-eligible SHPT, i.e., PTH levels above 75 pg/ml, 110 pg/ml and 300 pg/ml, for CKD stages 3, 4 and 5, respectively.[49] Whereas the *Kidney Disease Initiative Global Outcome* (KDIGO) has proposed the target range within the approximately 2 to 9 times higher than the upper PTH threshold level of each region or country, both KDOQI and KDIGO guidelines recommend PTH target levels that are much higher than normal range of the general US population (<65 pg/ml). Assuming that PTH is a uremic toxin and associated with poor survival in CKD, as recently shown by Kovesdy *et al.*,[50] normalization of PTH levels using active or nutritional vitamin D agents or calcimimetics appears prudent, provided reliable PTH assays can be used.[51]

A recent study showed that in over 58,000 maintenance hemodialysis patients, PTH levels above 300 pg/ml were associated with increased death risk (Figure 1).[15] In this epidemiologic analysis using time-dependent models, intact PTH levels in 300 to 600 pg/ml were incrementally associated with higher death risk when compared to the 150 to 300 pg/ml (reference) group. However, PTH levels above 600 pg/ml, although still associated

with high death risk, did not show further increase in mortality as would be expected for a dose-response phenomenon. The aforementioned attenuated mortality with a PTH above 600 pg/ml may be due to the fact that most dialysis patients with very high PTH levels often received higher than usual doses of the active vitamin D analogs (Figure 1).[15] Consistent with this notion a recent study showed that the survival advantages of the African American dialysis patients, who usually have higher PTH levels, can also be explained by virtue of their higher likelihood of receiving active vitamin D agents.[21] In another recent study, the ratio of paricalcitol dose per unit of PTH was linearly associated with greater survival.[20]

IV. Syndrome of Apparent Low Serum PTH

The KDOQI guidelines recommend against PTH levels below 150 pg/ml in CKD stage 5 in order to mitigate the risk of adynamic bone disease.[40] However, significant discrepancies may exist between the histopathologic diagnosis of adynamic bone and the biochemical detection of “low PTH”. A recent epidemiologic study in NDD-CKD found that the lower the PTH the greater the survival.[50] Interestingly, a large epidemiologic study in maintenance hemodialysis patients showed a similar trend in the conventional Cox model using baseline PTH measures at the start of the cohort, whereas time-dependent survival model showed that a low PTH appeared associated with higher death risk, i.e., a so-called U-shaped phenomenon (Figure 1).[15] This may be due to several reasons listed in Table 2 and depicted in Figure 2. In particular, the KDOQI guidelines recommend withholding active vitamin D agents and calcimimetics when PTH is below certain range,[40] and this very recommendation may indeed lead to increased death risk as discussed above. High calcium load from calcium based binders[52] or dialysate bath[53] may lead to vascular calcification and cardiovascular death and may also suppress PTH at the same time exaggerating the artificial association between low PTH and poor outcomes. Serum PTH level may also be confounded by such non-bone related factors such as obesity[54] or pentosidine mediated carbonyl stress.[55] PTH assay discrepancies may lead to seemingly low PTH levels as well.[56, 57] Different subtypes and/or fragments of PTH may be measured via different assays, such as the inhibitory (7–84) portion that is related to one of the large the carboxy-terminal and that is measured along with the active (1–84) PTH when the so-called “intact PTH assay” is used.[4] Finally, the administration of *teriparatide*, a synthetic recombinant 1–34 PTH,[58] to osteoporotic patients with or without CKD, may increases bone turnover by stimulating osteoblasts more than osteoclasts, leading to elevated serum calcium and suppressed serum phosphorus and circulating (measurable) intact PTH levels. A recent case report indicated that teriparatide was successfully used in a parathyoridectomized CKD patient with severe hypocalcemia due to "hungry bone syndrome.[59] Currently there is no data available about the consequenses of *teriparatide* therapy in uremia.

A recent epidemiologic study found that even among dialysis patients with an intact PTH below 150 pg/ml a high serum alkaline phosphatase (>120 IU/L) was associated with higher death risk compared to lower alkaline phosphatase levels.[60] In a large cohort of Japanese dialysis patients, low PTH (<150 pg/ml) was associated with the greatest survival.[61] We have recently found that low PTH is yet another facet of the malnutrition-inflammation complex and that after adjusting for this confounder, the PTH in 100 to 150 pg/ml range is associated with best 5-year survival in a cohort of hemodialysis patients.[62]

V. Increased Serum Alkaline Phosphatase

Hyperphosphatasemia or hyperphosphatasia refers to disorders that feature elevated serum alkaline phosphatase activity in the blood.[63] High serum alkaline phosphatase level in CKD patients is usually from excesses of the bone isoforms of the enzyme, but it may also happen in certain types of liver disorders and biliary obstruction.[64, 65] Whereas serum alkaline phosphatase used to be a traditional measure for the management of kidney bone disease, in recent years it appeared to have fallen out of favor, probably since the KDOQI guidelines did not include it in its recommendations, nor did they suggest any cutoff levels or target ranges for it.[40] A recent epidemiologic study has shown robust associations between higher serum alkaline phosphatase (esp. if > 120 U/L) and poor survival in hemodialysis patients.[60] Indeed, compared to serum PTH, which has a U-shaped association with mortality (Figure 1), serum alkaline phosphatase appears to have a linear and incremental association with both all-cause and cardiovascular mortality (Figure 3) and this association appears to hold across different PTH strata including PTH below 150 pg/ml.[15]

Since lower alkaline phosphatase is associated with lower PTH (and ultimately with hypOdynamic bone), some might expect a higher, rather than lower, mortality associated with low serum levels. Our epidemiologic findings[15, 60] are contrary to this expectation, suggesting that alkaline phosphatase may be more than a mere marker of bone turnover. Higher alkaline phosphatase has indeed been shown to result in increased hydrolysis of pyrophosphate,[66, 67] which is a potent inhibitor of vascular calcification.[68–70] The effect of alkaline phosphatase on pyrophosphate could be the link that explains why lower levels of the former are associated with a linear decrease in mortality.[71] Indeed, a recent epidemiologic study found that higher levels of alkaline phosphatase, and no other biomarkers such as PTH or minerals, were associated with coronary artery calcification in hemodialysis patients.[72] Another possible explanation for the observed association is a link between higher alkaline phosphatase levels and lower 25(OH) vitamin D level,[73–75] which is per se associated with increased mortality.[44] Alkaline phosphatase is a marker of bone resorption, and as such it is closely associated with PTH levels.

Alkaline phosphatase can be effectively lowered by both active vitamin D products[12, 76, 77] and calcimimetics.[78] Indeed a recent meta-analysis, which questioned the PTH lowering effect of active vitamin D analogs, showed that these agents can decrease serum alkaline phosphatase effectively.[79] Recent data indicate a link between pyrophosphate and tissue-nonspecific alkaline phosphatase as a causative pathway to vascular calcification.[66, 71] A recent study suggested that the lower serum alkaline phosphatase the better is the response of dialysis patients to erythropoietin stimulating agents during anemia management.[80] The consistency of epidemiologic and experimental data on alkaline phosphatase and the fact that vitamin D and calcimimetics can both lower its circulating level makes this traditional marker a promising tool for the management of *Kidney Bone Disease*, notwithstanding that lack of adequate recommendations by current KDOQI guidelines.

VI. Fibroblast Growth Factor-23

Similar to PTH, FGF-23 has phosphaturic properties, but it also inhibits 1-α hydroxylation and, hence, may aggravate calcitriol deficiency leading to further PTH production and

release.[81, 82] It is unclear to what extent the different pathophysiologic mechanisms, i.e., intrinsic loss of enzymatic activity vs. suppression by FGF-23, contribute to the lower 1-alfa hydroxylase activity, but the net effect is a progressive decline in activate vitamin D levels with advancing stages of CKD. It is speculated that VDR activation may increase whereas calcimimatic administration may decrease FGF-23.[82] The latter may explain why calcimimetics lead to paradoxical hyperphosphatemia in patients with CKD stages 3 and 4 and some urine output, whereas in dialysis patients with no significant residual renal function serum phosphorus tends to decrease similar to hungry bone syndrome after parathyroidectmy.[82] Similar to hyperglycemia associated increase in A1c level,[83] persistent hyperphosphatemia may lead to higher FGF-23 levels, which *per se* independent of serum phosphorus is associated with both increased death risk and increased serum alkaline phosphatase in maintenance dialysis patients.[84] Further epidemiologic and clinical studies are needed to examine the association between FGF-23 with vascular calcification and mortality in CKD patients.

VII. High Turnover Bone Disease and Osteoporosis

Even though changes in bone structure in histopathologic examinations are the hallmarks of the high turnover bone disease, such biomarkers as increased serum PTH and/or alkaline phosphatase are often used as screening and detection tools.[4, 85] To date no reliable biomarker of bone histopathology has been found. Diminished bone mineral density may be observed with this or other types of renal osteodystrophy.[86, 87] Indeed low bone mineral density and osteoporosis is often associated with increased risk of aortic calcification in the general population.[88] A recent study showed that diminished bone mineral density was related to protein-energy wasting and poor survival in dialysis patients.[89] Additional studies to examine the association between the nature of bone disease or its histopathology and survival in CKD patient population are needed to show consistency of such findings. Nevertheless, emerging studies that indicate robust and incremental association between serum alkaline phosphatase and mortality (see above) may indicate deleterious effect of high turnover bone disease on survival.

VIII. Adynamic (Low Turnover) Bone

Notwithstanding the pathognomonic histopathologic features of adynamic bone disease in CKD, recent evidence implies that adynamic bone status might indeed be a secondary phenomenon and a consequence of the malnutrition-inflammation-complex syndrome (MICS), which is per se associated with hypoalbuminemia, increased serum levels of pro-inflammatory cytokines, protein-energy wasting[90] and increased cardiovascular disease and death in maintenance dialysis patients.[91] A recent study in 44 chronic peritoneal dialysis patients showed that low serum albumin was associated with adynamic bone.[92] Although we are not aware of any study that indicates a direct causal effect of inflammation on adynamic bone disease in CKD, in vitro PTH secretion is suppressed by interleukin-6,[93] a strong pro-inflammatory cytokine that is associated with poor outcome in maintenance dialysis patients. Interleukin-1 beta (IL-1β), another pro-inflammatory cytokine, may also suppress PTH secretion; in another in vitro study, PTH secretion from cultured parathyroid tissue slices was significantly inhibited in media containing IL-1β.[94] This effect may be mediated through the specific IL-1 receptors that upregulate calcium-sensing receptor mRNA leading

to apparent low bone turnover.[94] Indeed in the foregoing study, the inhibitory effect of IL-1β could be counteracted by the IL-1 receptor antagonist (IL-1ra),[94] indicating that the inflammation induced suppression of PTH can potentially be overcome by treatment of MICS in individuals with CKD. Hence, interventions that can improve hypoalbuminemia and kidney disease wasting by correcting malnutrition and/or by mitigating inflammation, e.g., via agents that counteract tumor-necrosis-factor-alpha or other pro-inflammatory cytokines,[95] may be more promising approaches for the management of adynamic bone disease rather than decreasing the dose of or withholding activated vitamin D analogs or calcimimetics.

IX. Vascular Calcification

The recent literature is oversaturated with exponential numbers of studies indicating a high prevalence of vascular calcification in CKD[96, 97] and its association with death risk.[98] Medial calcification, which happens more frequently in CKD, is associated with increased death risk as compared to no vascular calcification, but intimal calcification has the strongest association with death risk.[99] There are mixed data about the association of calcium based phosphorus binders and vascular calcification.[100, 101] A recent controlled trial did not show any conclusive association between type of binder and short-term survival, even though a trend towards better survival was observed with non-calcium binder sevelamer.[102, 103] Another trial showed no advantage of sevelamer over calcium acetate in conjunction with statin, but both treatment arms were associated with increased calcification.[104] There are conflicting data and opinions about the association of vitamin D or calcimemtics with worsening or amelioration of vascular calcification.[13] The highly competitive nature of the binder marketing in the current environment and a lack of conclusive data has lead to major confusion among both physicians and patients as to whether any medication or intervention is associated with significant vascular calcification and if so, whether the calcification that is engendered in this way is related to poor survival.[13]

X. Hyperphosphatemia

The link between phosphorus retention and SHPT has been known for decades.[105] Recent evidence puts more emphasis on the FGF-23 pathway as the link between hyperphosphatemia and active vitamin D deficiency due to inhibition of 1-α hydroxylation of 25(OH) vitamin D. Several recent epidemiologic studies have found an incremental association between phosphorus levels above 6 or 7 mg/dL and increased death risk.[15, 106] As to which cutoff level of serum phosphorus is accepted in which stage of CKD, is a matter of ongoing debate, despite the clear-cut cutoff levels recommended by KDOQI guidelines.[40] A recent study suggested that dietary protein restriction to lower serum phosphorus may cause more harm, i.e., increased mortality, than good in dialysis patients.[107] A similar concern appears to exist with regard to restricting or discontinuing active vitamin D medications to lower serum phosphorus, esp. in the current era of ongoing performance pressure of achieving “good phosphorus level” at all costs.

XI. Hypophosphatemia

Two large epidemiologic studies from Fresenius[106] and DaVita national databases[15] showed that even after extensive multivariate adjustment including for surrogates of malnutrition,

serum phosphorus levels below 3.0 g/dL were associated with increased death risk in maintenance hemodialysis patients. Indeed in unadjusted survival models, consistent with the real world of dialysis patients, a low serum phosphorus, which is often observed in patients with malnutrition-inflammation complex, is a by far stronger marker of poor survival than normal to high serum phosphorus.[108] Because of the high risk of death associated with low appetite[109] and poor protein intake,[110] it is possible that imposing protein restriction to control phosphorus may cause more harm in CKD patient populations.[105] Hence, more diligent use of potent phosphorus binders and more emphasis on restricting non-protein sources of phosphorus such as in preservatives or fast food may be the preferred future approaches to this end.

XII. Hypercalcemia

Whereas several epidemiologic studies have shown an incremental association between high serum mineral level and mortality in dialysis patients,[106, 111] a recent epidemiologic study found somewhat different calcium threshold levels above which mortality starts to increase, i.e., 8.5 mg/dL vs. 10.5 mg/dL, when conventional Cox survival model with fixed covariates and time-dependent survival models using calendar quarterly varying values where used, respectively.[15] As shown in Figure 4, in conventional (non-time-dependent model) only baseline values at the start of the cohort are used, whereas changes over time are ignored. It is not clear which of these two models are more consistent with the real world scenario, but conventional models that ignore changes in biochemical value over time and that assume that baseline values represent subsequent values may be far fetched.

XIII. Hypocalcemia

Much more controversy exists as to whether a low serum calcium, e.g. below the KDOQI recommended level of 8.4 mg/dL is harmful or not.[112, 113] In the post-calcimimetic era such low calcium values in dialysis patients are no rarities.,[114–116] not to mention a lowering trend of dialysate calcium concentration (bath) from 3.5 mEq/L in 1990's to 2.5 or even 2.25 mEq/L in recent years. Lowered calcium levels may lead to more frequent use of calcium based binders as shown in some controlled trials where more calcium based binders are in use in the calcimimetic arm by the end of the study.[117] Time-dependent survival analyses recently showed that such low calcium levels, similar to high calcium values, may be associated with increased death risk.[15] Furthermore, a decline in serum calcium over 6 months was associated with increased death risk in the same study.[15] Low serum calcium may be associated with cardiac arrhythmias.[118] A recent epidemiologic study showed that low calcium level showed a tendency towards higher rates of CKD progression in a group of male NDD-CKD patients.[119] Nevertheless, calcimimetics also offer a number of important advantages including reduction of fracture rate and parathyrdoidectomy.[120] The concomitant use of active vitamin D analogs with calcimimetics may reduce the risk of severe hypocalcemia and reinforce their beneficial effect. Future studies are required to better address the issue of hypocalcemia in CKD.

Epilogue

The SHPT, vitamin D deficiency and mineral disarrays are associated with multiple skeletal and cardiovascular disorders in CKD. There is a large volume of epidemiologic evidence

suggesting a broader beneficial effect from treatment of the *Kidney Bone Disease* by modulating vitamin D and calcium sensing receptors. Whereas there are insufficient well-designed randomized controlled trials in the field, this shortcoming should not lead to a nihilistic approach to the relevant clinical problems of CKD patients. Nevertheless, due to insufficient clinical data, a single treatment modality, be it nutritional or activate vitamin D, calcimimetics, phosphorus binders, or recombinant PTH, may not claim to be uniformly superior to the others, and a wider therapeutic window often prompts the use of a combination of these agents. Since the ultimate goal is improving the poor survival of CKD patients, any suggested approach to the management of *Kidney Bone Disease* should be tested to this end.

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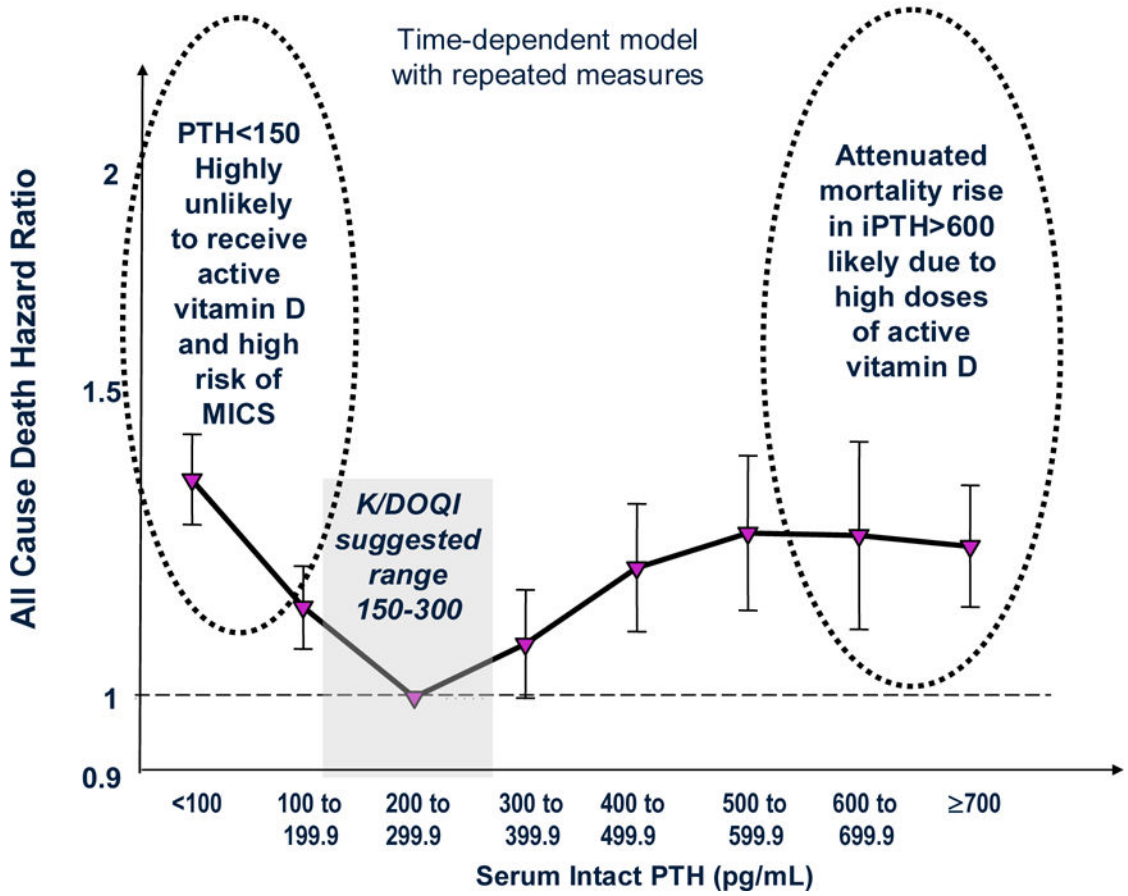

Figure 1.

The U-shaped association between serum intact PTH and survival in 58,058 maintenance hemodialysis patients over 2-years (adapted from[15]).

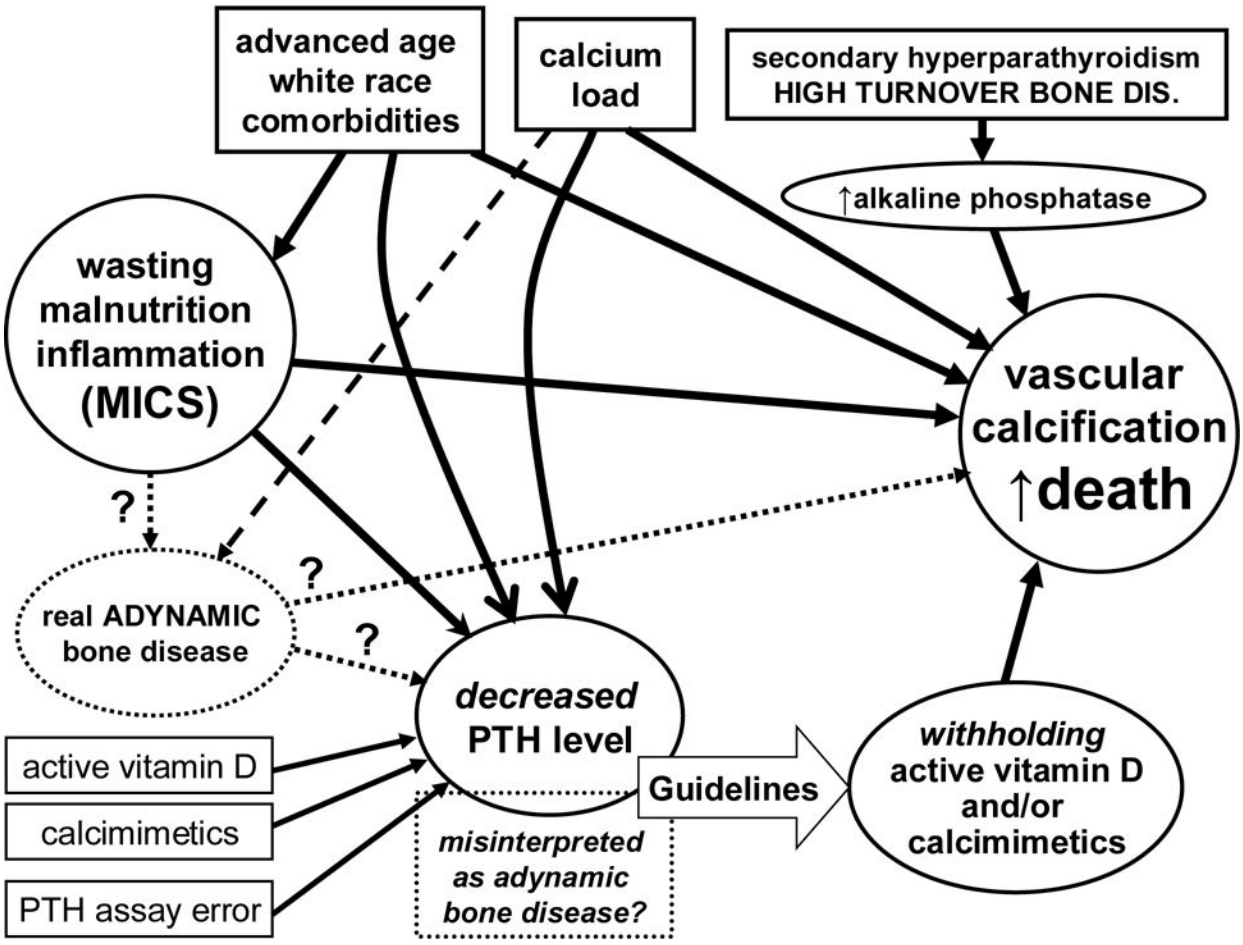

Figure 2.

Schematic representation of the links between components of Kidney Bone Disease and vascular calcification. Note potential contributors of low PTH level and its confounded association with poor outcomes.

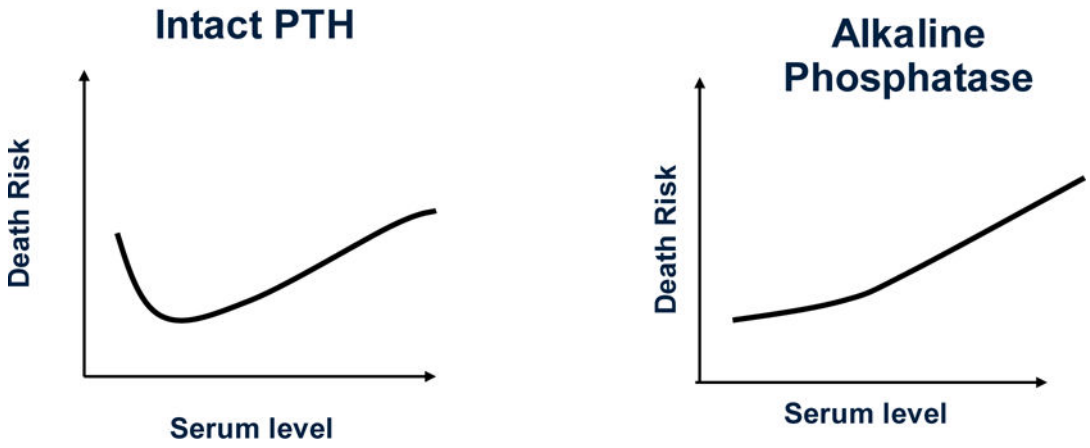

Figure 3.

A comparison between survival predictability of serum PTH (as shown in Figure 1) and serum alkaline phosphatase in dialysis patients.

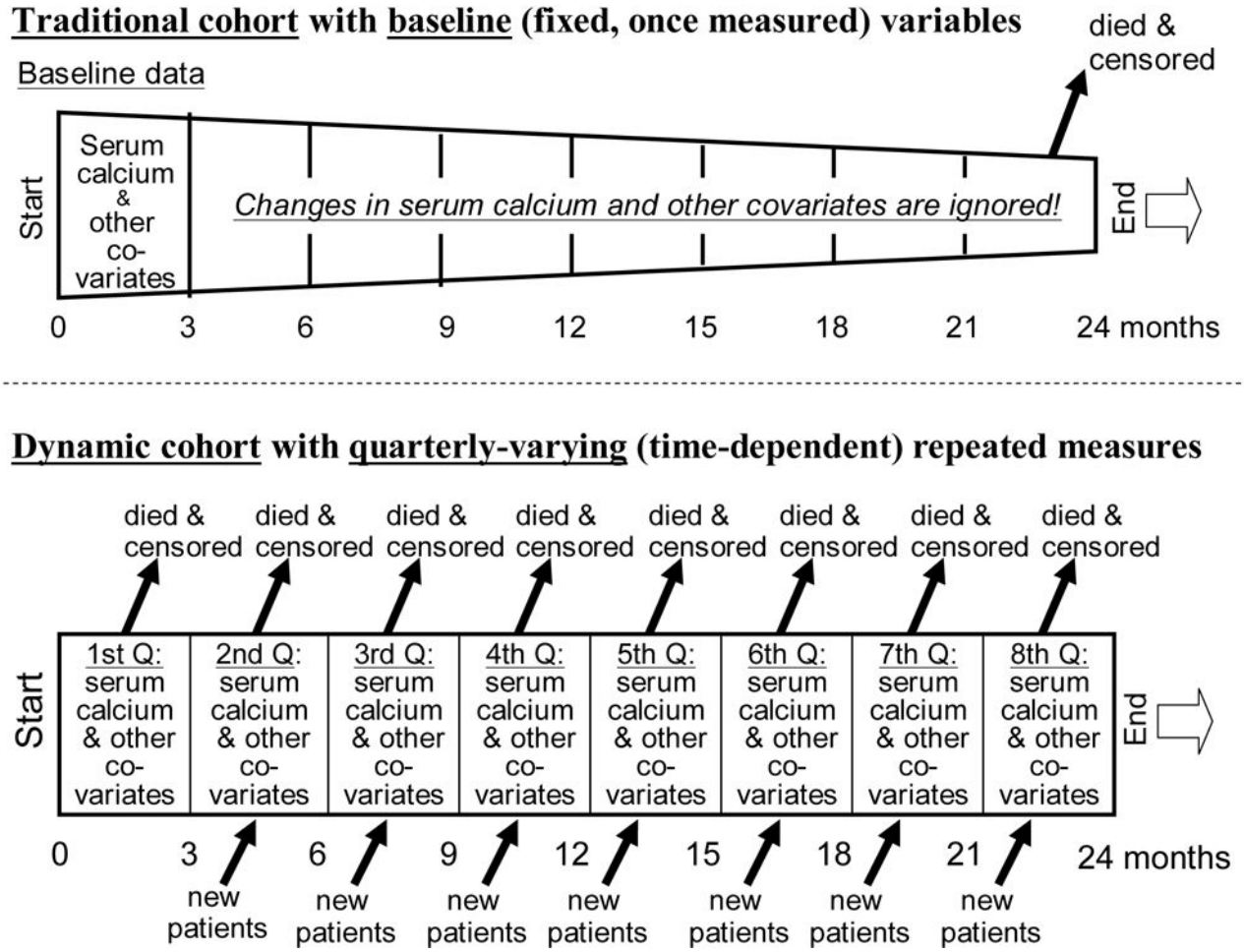

Figure 4.

Comparing conventional (fixed covariate) survival models vs. time-dependent (repeated measure) models in examining the association between serum calcium and survival in CKD patients.

Table 1

Disorders related to kidney bone disease

	Disorder/Condition	Possible Cause	Potential Consequence
1	1,25 dihydroxy vitamin D (calcitriol) deficiency	insufficient renal 1-alpha hydroxylation, ↑FGF-23, hyperphosphatemia, ↑PTH	probably the main driver of SHPT and renal osteodystrophy, MICS, vascular calcification, atherosclerotic CV disease and death, poor survival
2	25(OH) vitamin D deficiency	Nutritional (reflecting background population), MICS	MICS, vascular calcification, atherosclerotic CV disease and death, poor survival
3	Hyperparathyroidism	↓cacitriol, hypocalcemia, hyperphosphatemia, ↓ vitamin D receptor, ↓ calcium-sensing receptor, PTH resistance, ↑FGF-23	renal osteodystrophy, uremic toxin, vascular calcification, atherosclerotic CV disease and death, poor survival, refractory anemia resistant to ESA,
4	Low PTH	MICS, calcium load, administration of native or active vitamin D or calcimimetics, PTH assay error	questionable primary (causal) link to adynamic bone disease or other outcomes
5	increased level of circulating alkaline phosphatase (hyperphosphatasemia)	SHPT, calcitriol deficiency, high turnover bone disease	Worsening renal osteodystrophy, vascular calcification, atherosclerotic CV disease and death, poor survival
6	Elevated FGF-23	↓GFR, hyperphosphatemia	Phosphaturic effect (with adequate residual renal function), inhibition of 1-alpha hydroxylation, ↓cacitriol, hypocalcemia
7	High turnover bone disease	SHPT, calcitriol deficiency, 25(OH) D deficiency (?), uremia per se	Renal osteodystrophy, decreased bone mineral density, osteitis fibrosa, pathological fractures, hyperphosphatesemia
8	Adynamic bone disease	Calcium load (both high calcium bath and high po calcium intake), diabetes mellitus, peritoneal dialysis, intake of vitamin D and calcimimetic (?), aluminum deposition	Hypercalcemia (cause vs. consequence?), bone fracture (?)
9	Vascular calcification	MICS, diabetes mellitus, vitamin D deficiency, SHPT	Peripheral vascular disease, CV disease and death, poor survival
10	Hyperphosphatemia	↓GFR, increased phosphorus ingestion in protein and preservatives, ↓FGF-23, vitamin D analogs, calcimimetics (in NDD-CKD)	↑SHPT, ↑FGF-23, ↑vascular calcification, ↑ mortality
11	Hypophosphatemia	Malnutrition-inflammation complex, protein-energy wasting, low protein intake, imposed (overzealous) dietary restrictions, calcimimetics (in dialysis patients)	Increased death risk (as a surrogate of malnutrition and poor PO intake)
12	Hypercalcemia	Calcium load, calcium-based binder, dialsyate cakcium, vitamin D, refractory (tertiary) hyperparathyroidism, adynamic bone disease	↑vascular calcification, ↑ mortality
13	Hypocalcemia	↓GFR, calcimimetics	Potential risk of arrhythmias, possible increased risk of death

Table 2

Causes of biochemically measured, relatively low serum intact PTH level in CKD patients, e.g. PTH <150 pg/ml, using conventional PTH assays

Calcium based binders
Calcium rich diet
Higher calcium concentration in dialysate bath
Metabolic syndrome
Diabetes mellitus
Malnutrition-inflammation complex
Oxidative stress
Carbonyl (pentosidine) stress
Peritoneal dialysis
Advanced age
Caucasian race
PTH assay errors
Administration of nutritional or active vitamin D agents
Administration of calcimimetics
Administration of recombinant PTH (Teriparatide)*
Adynamic bone disease

* Footnote: Administration of recombinat PTH, known as Teriparatide (injectable Forteo™) may suppress the measurable naïve PTH level based of the PTH assay employed.