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Hypothesis

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Modulation of vitamin D signaling is a potential therapeutic target to lower cardiovascular risk in chronic kidney disease

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Summary

While it is true that many traditional cardiovascular risk factors are amenable to intervention in chronic kidney disease (CKD), the results of intervention may not be as efficacious as those obtained in the general population. Thus, there may also be a unique milieu established in CKD, which causes excess cardiovascular disease (CVD) burden by mechanisms that are as yet not fully recognized. Recently, vitamin D has sparked widespread interest because of its potential favorable benefits on CVD. However, the mechanisms for how vitamin D may improve CVD risk markers and outcomes have not been fully elucidated. Furthermore, hypovitaminosis D is highly prevalent in the CKD cohort. Given this background, we hypothesize that low vitamin D status may act as a new CVD risk marker, and modulation of vitamin D signaling may be a potential therapeutic target to lower cardiovascular risk in CKD. The data presented in this review support that the low vitamin D status may be linked with the high cardiovascular risk in CKD, based on both the biological effects of vitamin D itself on the cardiovascular system, and the cross-actions between vitamin D signaling and the multiple metabolic pathways. Considering the high prevalence of hypovitaminosis D, limited natural vitamin D food sources, and reduced sun exposure in CKD patients, recommendations for treatment of hypovitaminosis D mainly focus on exogenous supplementation with vitamin D and its analogues. Although promising, when to start therapy, the route of administration, the dose, and the duration remain need to be discussed.

key words: **vitamin D • chronic kidney disease • endothelial function • atherosclerosis • thrombosis**

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Background

The increased risk of cardiovascular disease (CVD) in patients with chronic kidney disease (CKD) has been well documented. Individuals requiring dialysis treatment have cardiovascular mortality rates that are 10 to 20 times greater than age- and sex-matched controls in the general population [1]. More specifically, a 50% contribution to the overall mortality makes CVD the leading cause of death in patients with CKD [2]. Indeed, even mild renal insufficiency is associated with increased rates of cardiovascular events, and moreover, this hazard may prove to be a long-term factor to be considered in childhood nephropathy which persists into adulthood [3,4]. The increase in cardiovascular risk associated with CKD may be due to several mechanisms, including hemodynamic overload due to hypertension and anemia, dyslipidemia, a high prevalence of diabetes and impaired glucose tolerance, prothrombotic changes, hyperhomocysteinemia, increased oxidant stress, neurohormonal overactivity, divalent ion abnormalities, a high calcium phosphate product, and chronic inflammation [5–12]. While it is true that above traditional cardiovascular risk factors are amenable to intervention in CKD, the results of intervention may not be as efficacious as those obtained in the general population [13,14]. Thus, it has been hypothesized that there is a unique milieu established in CKD, which causes excess CVD burden by mechanisms that are as yet not fully recognized.

Vitamin D refers to a group of compounds that have antirachitic activity. It was initially discovered as a substance responsible for healing rickets. During the period of its discovery it was realized that there were 2 antirachitic factors with distinct structures – vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol) [15]. Vitamin D can be produced in the skin as vitamin D_3 on exposure to ultraviolet-B (UVB) from the sun or obtained from the diet as vitamin D_2 or vitamin D_3. Both vitamin D_3 and vitamin D_2 can be further modified by corresponding enzymes to produce different vitamin D metabolites in a similar fashion. After vitamin D enters the body, it circulates bound to vitamin D-binding protein and is rapidly converted to its major circulating form, 25-hydroxyvitamin D [25-(OH)D], by the liver. 25-(OH)D is filtered at the glomerulus and actively reabsorbed into renal tubular cells via megalin and cubilin, where it is converted to the potent hormone 1,25-dihydroxyvitamin D [1,25-$(OH)_2$D] by the enzyme 1-α hydroxylase [16]. Circulating 1,25-$(OH)_2$D enters the target cell, either in its free form or facilitated by megalin, and binds to the vitamin D receptor (VDR) in the cytoplasm, which then translocates to the nucleus and heterodimerizes with the retinoic X receptor (RXR). The 1,25-$(OH)_2$D-VDR-RXR complex then binds to vitamin D response elements on DNA to increase transcription of vitamin D-regulated genes [17]. The predominant physiological function of vitamin D is to maintain the calcium and phosphate homeostasis, and this is accomplished by close coordination with parathyroid hormone (PTH) [18,19].

Recently, vitamin D has sparked widespread interest because of its potential favorable benefits on CVD [20,21]. Several cross-sectional and epidemiological studies suggested indirectly that vitamin D status could explain differences in mortality from CVD. Grimes et al recognized that mortality from ischemic heart disease was inversely proportional to the amount of hours of sunlight in the United Kingdom [22]. Douglas et al recognized that incidence and mortality rates from coronary heart disease demonstrated a strong seasonal pattern, with higher rates in the winter, when vitamin D levels are lowest [23]. Rostand reported that blood pressure increased with increasing distance from the equator and indicated that cutaneously synthesized vitamin D could be playing a role in the regulation of blood pressure [24]. In addition, several studies have also evaluated a baseline measurement of vitamin D status and prospectively evaluated long-term cardiovascular outcomes in subjects with no history of CVD. During a 10-year follow-up period, men in the Health Professionals Follow-up Study without previous CVD and hypovitaminosis D exhibited a 2-fold increased rate of myocardial infarction [25]. In the Framingham Offspring Study, subjects with no history of CVD and vitamin D deficiency [25-(OH)D ⩽15 ng/ml] experienced a hazard ratio of 1.80 (95% CI, 1.05–3.08) for developing a first cardiovascular event after 5 years of follow-up compared with subjects with higher levels of 25-(OH)D (>15 ng/ml) [26]. On the basis of the above epidemiologic associations between vitamin D and CVD, a randomized controlled trial of vitamin D supplementation demonstrated that modest amounts of vitamin D (400 IU) plus calcium given during an 8-week period significantly reduced systolic blood pressure by 9% in elderly German women [27]. However, the mechanisms for how vitamin D may improve CVD risk markers and outcomes have not been fully elucidated.

Hypovitaminosis D is highly prevalent in the CKD cohort. In terms of serum 25-(OH)D levels, 76% of CKD patients display either vitamin D deficiency [42%; 25-(OH)D ⩽15 ng/ml] or insufficiency [34%; 15 ng/ml <25-(OH)D ⩽30 ng/ml] [28]. Serum 25-(OH)D is below the recommended sufficiency values in >90% of patients if they progress to end-stage renal disease (ESRD) [29]. CKD patients are at particular risk of 25-(OH)D deficiency because of a range of factors that do not directly depend on renal function; these include reduced sun exposure, impaired production of the 25-(OH)D precursor molecule, and reduced dietary intake [30]. In contrast to 25-(OH)D, circulating levels of 1,25-$(OH)_2$D chiefly depend on the ability of renal 1-α hydroxylase to convert 25-(OH)D into 1,25-$(OH)_2$D. This ability is decreased by a reduction in the nephron mass, and the hyperphosphatemia-induced increase in levels of the phosphaturic hormone fibroblast growth factor-23 (FGF-23), which both inhibits the production of 1,25-$(OH)_2$D and increases its degradation [31].

The Hypothesis

The increased risk of CVD in patients with CKD has been well documented. While it is true that many traditional cardiovascular risk factors are amenable to intervention in CKD, the results of intervention may not be as efficacious as those obtained in the general population. Thus, there may also be a unique milieu established in CKD, which causes excess CVD burden by mechanisms that are as yet not fully recognized. Recently, vitamin D has sparked widespread interest because of its potential favorable benefits on CVD; however, the mechanisms by which vitamin D may improve CVD risk markers and outcomes have not been fully explained. Furthermore, hypovitaminosis D is highly prevalent in the CKD cohort. Given this background, we hypothesize that

low vitamin D status may act as a new CVD risk marker, and modulation of vitamin D signaling may be a potential therapeutic target to lower cardiovascular risk in CKD.

Evaluation of the Hypothesis

It is speculated that 25-(OH)D itself has important biological effects on the cardiovascular system. Although the kidney is the major organ that converts 25-(OH)D to 1,25-$(OH)_2$D by 1α-hydroxylase, many other cells, including vascular smooth muscle and endothelial cells, also express 1α-hydroxylase [32,33]. 1,25-$(OH)_2$D, synthesized from the circulating 25-(OH)D in these cells, binds the local VDR in the autocrine/paracrine pathways. 25-(OH)D circulates at a concentration about 1000-fold higher than that of 1,25-$(OH)_2$D; this suggests that adequate 25D levels may also be necessary, especially for cells that rely on autocrine/paracrine pathways [34]. However, this aspect will require investigation.

In addition, the data presented below focus on the cross-actions between hypovitaminosis D and the disturbances of multiple metabolic pathways in CKD. Clarification of these relationships may help to suggest possible underlying mechanisms, and might be of clinical importance in planning preventive and therapeutic strategies.

Vitamin D, calcium-phosphate metabolism, and cardiovascular function

In patients with CKD, the cardiovascular function is abnormal, characterized by increased cardiac contractility, arterial calcification, and structural remodeling. The link between vitamin D deficiency and cardiovascular dysfunction may be, in part, mediated through calcium-phosphate metabolism disorders such as hyperphosphatemia, hyperparathyroidism, and increased calcium-phosphate product [29]. Above all, vitamin D plays an important role in cardiac function. Cardiac muscle cells possess a VDR and calcitriol-dependent Ca^{2+} binding protein. Moreover, a calcitriol-mediated rapid activation of voltage-dependent Ca^{2+} channels exists in cardiac muscle cells, and the uptake of calcium by cardiac muscle cells is in part regulated by vitamin D_3 [35]. In experimental studies, vitamin D administration can normalize the impaired contractility of the myocardium. Baksi et al observed an increased contractility in response to increasing concentration of the extracellular calcium bath in the atria of rats maintained on a vitamin D-deficient diet [36]. The direct effects of vitamin D deficiency were suggested by Weishaar et al. Rats fed a vitamin D-deficient diet have increased amounts of collagen. This effect could not be suppressed by normocalcemia, suggesting that indeed this is a direct action/consequence of vitamin D deficiency [37].

On the other hand, a cross-sectional study in high-risk CVD patients showed an inverse relationship between vitamin D levels and extent of arterial calcification [38]. However, several small observational studies have reported the association of vitamin D levels with arterial calcification [39–41]. The hypotheses were that vitamin D enhances calcium and phosphate absorption from the intestine and increases the calcium-phosphate product [18]. Interestingly, consistent with these findings in humans, an animal model of CKD showed that the administration of clinically relevant doses of vitamin D reduced arterial calcification [42], while in another study rats fed a diet rich in cholesterol and extremely high in vitamin D (1.8 million units/kg) developed greater arterial calcification [43]. The recent discovery of FGF-23 has provided a unique tool to explain the effect of vitamin D in development of arterial calcification. Vitamin D stimulates FGF-23 secretion and is inhibited by increased FGF-23 [44]. Indeed, increased FGF-23 level has been associated with arterial calcification in patients with all stages of CKD, although its role is as yet incompletely understood [45–47]. Thus, evidence from clinical studies and from animal models supports the existence of biphasic relationships of vitamin D with calcium-phosphate metabolism and cardiovascular function, which demonstrates that lower doses suppress calcification and higher doses accelerate calcification [48].

Vitamin D, PTH, and cardiovascular mortality

Hyperparathyroidism may occur early in the course of CKD as a consequence of vitamin D deficiency [49]. Vitamin D levels decline in the early phase of renal failure; however, PTH stimulates the production of 1,25-$(OH)_2$D to return it to normal circulating concentrations [50]. Patients with elevated PTH concentrations are at higher risk of cardiovascular mortality. According to the statistical data reported by Hagström et al in a community-based cohort of 958 elderly men, a 1-SD increase in plasma PTH was associated with a 37% to 38% higher risk for cardiovascular mortality in the crude and multivariable models [51]. Several mechanisms may explain the link between PTH and cardiovascular mortality. First, PTH has been directly implicated in atherogenesis via vascular calcification and vascular remodeling [52,53]. Second, PTH appears also to have detrimental effects on the myocardium via induction of left ventricular hypertrophy, cardiac calcification, and fibrosis [54–56]. Third, secondary hyperparathyroidism may be involved in the pathophysiological mechanism of hyperlipidemia seen in chronic renal failure [57]. Fourth, higher PTH is associated with both established cardiovascular risk factors and more recently described risk factors such as inflammation markers, renal dysfunction, and cardiac pathology [51,58–60]. Finally, because PTH is one of the key regulatory hormones in the mineral homeostasis, it is possible that the plasma levels of PTH reflect other abnormalities along the same pathway, such as vitamin D deficiency, hypercalcemia, hyperphosphatemia, or renal failure, that predispose to a higher risk for cardiovascular mortality [51]. Thus the interplay between secondary hyperparathyroidism due to vitamin D deficiency and cardiovascular mortality in CKD is very complex.

Vitamin D, inflammation, and endothelial function

CKD is now considered a prototypical situation of chronic inflammatory state, and C-reactive protein (CRP), a nonspecific marker of inflammation, is regarded as a fundamental biomarker for endothelial dysfunction in these patients [61]. Endothelial dysfunction usually describes binding of monocytes to the endothelial surface, down-regulation of nitric oxide (NO) activity, reduced dilatory capacities, and an early event of arteriosclerosis [62]. The synthesis of CRP in the liver is induced by pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-1 or IL-6 [63–65]. Vitamin D deficiency is associated with elevated

levels of CRP and pro-inflammatory cytokines, and a lower flow-mediated dilation [66,67]. Activated vitamin D has potent anti-inflammatory effects and endothelial modulation. Various groups have shown that the nuclear factor kappa-B (NFκB) family is linked to the VDR signaling pathway, and that Vitamin D inhibits monocyte NFκB p65 activation with down-stream suppression of various pro-inflammatory cytokines including TNF-α, IL-1, and IL-6 [68]. Subsequently, a number of genes associated with endothelial function and regeneration are modulated. These encompass increased endothelin B receptor expression, which, in turn, increases NO synthesis; and reduced oxytocin receptor expression, which causes vasoconstriction [69]. Should this be the case, vitamin D may improve endothelial function mediated by anti-inflammatory activities.

Vitamin D, Renin-angiotensin system (RAS), and blood pressure

One specific pathway that appears to be regulated by the vitamin D signaling in CKD patients is the renin-angiotensin system *(*RAS). This cascade features a sequential activation of angiotensin II, which in patients with CKD is likely to have deleterious effects on blood pressure and its associated disorders [70,71]. Pioneering work by Y.C. Li at the University of Chicago has reinvigorated interest in vitamin D as an antihypertension agent [72]. His group clearly established that VDR knockout mice have elevated activation of the RAS and high blood pressure, which can be reversed with an angiotensin-converting enzyme inhibitor. However, with intact VDR activity or vitamin D supplementation, evidence suggests that these deleterious effects may be relieved through modulation of the RAS [73]. The following mechanism may account for the negative regulation of RAS dependent on vitamin D signaling. Experimental studies indicate that 1,25-$(OH)_2$D participates in the transcriptional suppression of renin by sequestering cyclic adenosine monophosphate response element binding, a necessary factor for the transcription of renin mRNA [74,75].

Vitamin D, beta-cell function, and glucose metabolism

Recent observational data has highlighted an association between hypovitaminosis D and increased cardiovascular mortality in patients with CKD, possibly mediated via vitamin D effects on beta-cell dysfunction, impaired insulin secretion, and insulin resistance [76,77]. Glucose metabolism has been examined as an outcome in these studies, and before-after treatment comparisons have demonstrated the improvement of glucose metabolism after a relatively short duration of vitamin D therapy. However, the long-term effects of vitamin D on glucose metabolism in CKD, and how these effects translate into clinical health outcomes, are not clear [78].

Further data regarding the relationship between vitamin D and glucose metabolism are available in the general population. In a longitudinal study of Finnish men and women, a 40% reduction in the risk of developing type 2 diabetes was observed after 17 years of follow-up in those with 25-(OH)D levels >28 ng/ml at baseline [79]. One prospective study evaluated the effect of vitamin D supplementation (400 IU daily) on fasting glucose and found that subjects with impaired fasting glucose at baseline had less of a rise in fasting glucose concentrations during a 3-year period compared with subjects randomized to placebo [80]. Three mechanisms may explain this improvement. First, VDR is present in the beta cells of islets, and the islets can express 1-alpha hydroxylase, thereby activating 25-(OH)D. An indirect effect of vitamin D on insulin secretion is postulated by means of increased intracellular calcium in the islets [81,82]. Second, VDR has also been identified in cells of the immune system. Modulation of the immune system has been proposed as an additional mechanism through which vitamin D may preserve long-term beta-cell function via effects on cell proliferation, differentiation, and apoptosis [83]. Third, a vitamin D response element has been described in the promoter region of the human insulin receptor gene, and vitamin D stimulated insulin receptor expression and insulin responsiveness for glucose transport in cultured human promonocytic cells [84,85].

Vitamin D, lipid metabolism, and atherosclerosis

Lipid abnormality is not only a striking feature of CKD but also contributes to the onset of atherosclerosis [6,86,87]. Derived from cholesterol, vitamin D is characterized by cleavage of the B ring of the core structure, hence the "seco" prefix vitamin D. Various forms of vitamin D belong to the sterol-class of lipids [15]. Increasing evidence suggests that vitamin D is related to lipid abnormality in CKD, which has been found to be associated with lower levels of serum 25-(OH)D [88]. Strong inverse associations between vitamin D and serum cholesterol, low density lipoprotein cholesterol (LDL-C), and triglyceride (TG) have been reported, and more importantly, supplementation of vitamin D could result in the improvement of lipid profiles [88,89]. In a report by Gupta et al. [90], treatment of logarithmically growing rat intestinal epithelial cells (IEC-6) in culture with vitamin D_3 caused an inhibition of the cholesterol biosynthetic pathway at 2 separate sites. At concentrations >2 pg/ml, vitamin D3 caused an accumulation of methyl sterols, indicating an inhibition of lanosterol demethylation. A second site of inhibition occurs at 3-hydroxy-3-methy1g1utay1 coenzyme A reductase, the rate-limiting enzyme in cholesterol biosynthesis at concentrations <2 pg/ml. In another study, Oh et al. [91] found that diabetes-derived macrophages cultured in 1,25-$(OH)_2$D-supplemented media had decreased oxidized LDL-C and acetylated LDL-C uptake both qualitatively and quantitatively by 40% to 50%, respectively, compared with macrophages cultured in vitamin D-deficient media. In addition, a possible mechanism of action by which vitamin D lowers TG levels and protects against atherosclerosis is through an increased activity of the lipoprotein lipase, which has been shown to be regulated by vitamin D in adipocytes [92].

On the other hand, in a survey of cardiovascular risk factors in 185 men and 173 women in Belgium, 25-(OH)D was shown to be consistently and independently associated with both the apolipoprotein A-I (apo A-I) and the high density lipoprotein cholesterol (HDL-C) concentration [93]. Although the mechanisms for the influence of vitamin D on serum apo A-I and HDL-C are not clearly elucidated, these findings support the postulate that avoidance of hypovitaminosis D could contribute to reductions in the risk of atherosclerosis [94]. Because apo A-I and LDL-C are involved in the reverse transport system that clears tissue cholesterol,

lowering the availability of these will increase the risk of vascular damage associated with foam cell formation [95,96].

Vitamin D, coagulation homeostasis, and thrombosis

Patients with CKD exhibit features of a hypercoagulable state, which may contribute to their increased thrombosis [97,98]. VDR is expressed in monocyte cells and vascular endothelial cells, suggesting potential roles of vitamin D in antithrombotic function [99,100]. Ohsawa and colleagues found that 1,25-$(OH)_2$D exerted anticoagulant effects by up-regulating the expression of the anticoagulant glycoprotein thrombomodulin (TM) and by down-regulating the expression of a critical coagulation factor, tissue factor (TF), in cultured monocytic cells and human peripheral monocytes [101]. Furthermore, to clarify whether activation of VDR plays any antithrombotic actions *in vivo*, Aihara et al. [102] examined the hemostatic and thrombogenic systems in normocalcemic VDR knockout mice on a high calcium diet and compared them with wild type and hypocalcemic VDR knockout mice. Their results demonstrated that the gene expression of antithrombin in the liver as well as that of TM in the aorta, liver and kidney was down-regulated in hypo- and normocalcemic VDR knockout mice, whereas TF mRNA expression in the liver and kidney was up-regulated in VDR knockout mice regardless of serum calcium level. Therefore, the activation of VDR elicits down-regulation of TF and up-regulation of TM gene expression.

Consequences of the Hypothesis and Discussion

Taken as a whole, the data presented above which come from observational or experimental studies support the hypothesis that low vitamin D status may be linked with the high cardiovascular risk in CKD, based on both the biological effects of vitamin D itself on the cardiovascular system, and the cross-actions between vitamin D signaling and the multiple metabolic pathways. Thus, modulation of vitamin D signaling is a potential therapeutic target to lowering cardiovascular risk in CKD. Considering the high prevalence of hypovitaminosis D, limited natural vitamin D food sources, and reduced sun exposure in CKD patients, recommendations for treatment of hypovitaminosis D mainly focus on exogenous supplementation with vitamin D and its analogues [28–30]. Although promising, when to start vitamin D therapy, the route of administration, the dose, and the duration remain to be determined.

In CKD, supplementation with 25-(OH)D is recommended at the inception of the disease, with the addition of 1,25-$(OH)_2$D replacement beginning in stage 3 [103]. Because of a wide margin between doses recommended for repletion and doses considered unsafe, supplementation may be safely achieved with the use of vitamin D in oral form [31,104]. The National Kidney Foundation clinical practice guidelines for bone and mineral metabolism focus on the use of vitamin D to suppress elevated PTH in CKD [30]. Although there is a general consensus that the serum 25-(OH)D concentration must be at least 20 ng/ml, recent studies suggest the possibility that it must be much higher. Several papers have shown that the level of serum 25-(OH)D required for complete PTH suppression was 30~32 ng/ml [105,106]. According to the common estimation that each 100 IU of vitamin D administration can raise the serum level of 25-(OH)D by 1 ng/ml, recent quantitative studies now suggest that doses as high as 4000 IU daily may be required to maintain optimum levels of vitamin D in normal populations, and it is extrapolated that higher doses may be required in CKD patients to overcome the more profound deficits to which they are prone [31]. Holick [107] recommends a standard supplementation protocol for adult patients with CKD stage 2 and 3 to treat vitamin D deficiency using a 2-phase protocol: 50,000 IU of vitamin D_2 once per week for 8 weeks; repeat for another 8 weeks if 25-(OH)D <30 ng/ml. As for adult patients with CKD stage 4 and 5: 0.25–1.0 μg of 1,25-$(OH)_2D_3$ by mouth twice a day or 1 of the following, 1–2 μg of paricalcitriol IV every 3 days, 0.04–0.1 μg/kg paricalcitriol IV every other day initially and can increase to 0.24 μg/kg, 2–4 μg by mouth 3 times per week, or doxercalciferol 10-20 μg by mouth 3 times per week or 2–6 μg paricalcitriol IV 3 times per week. However, specific recommendations for vitamin D intake for pediatric patients with CKD have yet to be proposed.

Conflicts of interest statement

None declared.

References:

1. Foley RN, Parfrey PS, Sarnak MJ: Epidemiology of cardiovascular disease in chronic renal disease. J Am Soc Nephrol, 1998; 9(12 Suppl.): S16–23
2. Oh J, Wunsch R, Turzer M et al: Advanced coronary and carotid arteriopathy in young adults with childhood-onset chronic renal failure. Circulation, 2002; 106(1): 100–5
3. Mann JF, Gerstein HC, Dulau-Florea I et al: Cardiovascular risk in patients with mild renal insufficiency. Kidney Int Suppl, 2003; (84): S192–96
4. Groothoff JW, Lilien MR, van de Kar NC et al: Cardiovascular disease as a late complication of end-stage renal disease in children. Pediatr Nephrol, 2005; 20(3): 374–79
5. McMahon LP: Hemodynamic cardiovascular risk factors in chronic kidney disease: what are the effects of intervention? Semin Dial, 2003; 16(2): 128–39
6. Tsimihodimos V, Dounousi E, Siamopoulos KC: Dyslipidemia in chronic kidney disease: an approach to pathogenesis and treatment. Am J Nephrol, 2008; 28(6): 958–73
7. Crutchlow MF, Robinson B, Pappachen B et al: Validation of steady-state insulin sensitivity indices in chronic kidney disease. Diabetes Care, 2007; 30(7): 1813–18
8. Fried L, Solomon C, Shlipak M et al: Inflammatory and prothrombotic markers and the progression of renal disease in elderly individuals. J Am Soc Nephrol, 2004; 15(12): 3184–91
9. Kielstein JT, Salpeter SR, Buckley NS et al: Two cardiovascular risk factors in one? Homocysteine and its relation to glomerular filtration rate. A meta-analysis of 41 studies with 27,000 participants. Kidney Blood Press Res, 2008; 31(4): 259–67
10. Oberg BP, McMenamin E, Lucas FL et al: Increased prevalence of oxidant stress and inflammation in patients with moderate to severe chronic kidney disease. Kidney Int, 2004; 65(3): 1009–16
11. Desir GV: Renalase is a novel renal hormone that regulates cardiovascular function. J Am Soc Hypertens, 2007; 1(2): 99–103
12. Menon V, Greene T, Pereira AA et al: Relationship of phosphorus and calcium-phosphorus product with mortality in CKD. Am J Kidney Dis, 2005; 46(3): 455–63
13. Rakhit DJ, Marwick TH, Armstrong KA et al: Effect of aggressive risk factor modification on cardiac events and myocardial ischaemia in patients with chronic kidney disease. Heart, 2006; 92(10): 1402–8
14. Kaisar MO, Isbel NM, Johnson DW: Recent clinical trials of pharmacologic cardiovascular interventions in patients with chronic kidney disease. Rev Recent Clin Trials, 2008; 3(2): 79–88
15. Beale MG, Chan JC, Oldham SB et al: Vitamin D: the discovery of its metabolites and their therapeutic applications. Pediatrics, 1976; 57(5): 729–41

16. Stamp TC: Vitamin D metabolism. Recent advances. Arch Dis Child, 1973; 48(1): 2–7
17. Haussler MR, Haussler CA, Jurutka PW et al: The vitamin D hormone and its nuclear receptor: molecular actions and disease states. J Endocrinol, 1997; 154(Suppl): S57–73
18. Amizuka N, Kwan MY, Goltzman D et al: Vitamin D3 differentially regulates parathyroid hormone/parathyroid hormone-related peptide receptor expression in bone and cartilage. J Clin Invest, 1999; 103(3): 373–81
19. Sypniewska G, Sobanska I, Pater A et al: Does serum osteoprotegerin level relate to fragility fracture in elderly women with low vitamin D status? Med Sci Monit, 2010; 16(2): CR96–101
20. Holick MF: Vitamin D and sunlight: strategies for cancer prevention and other health benefits. Clin J Am Soc Nephrol, 2008; 3(5): 1548–54
21. Judd SE, Tangpricha V: Vitamin D deficiency and risk for cardiovascular disease. Am J Med Sci, 2009; 338(1): 40–44
22. Grimes DS, Hindle E, Dyer T: Sunlight, cholesterol and coronary heart disease. QJM, 1996; 89(8): 579–89
23. Douglas AS, Dunnigan MG, Allan TM et al: Seasonal variation in coronary heart disease in Scotland. J Epidemiol Community Health, 1995; 49(6): 575–82
24. Rostand SG: Ultraviolet light may contribute to geographic and racial blood pressure differences. Hypertension, 1997; 30(2 Pt 1): 150–56
25. Giovannucci E, Liu Y, Hollis BW et al: 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. Arch Intern Med, 2008; 168(11): 1174–80
26. Artaza JN, Mehrotra R, Norris KC: Vitamin D and the cardiovascular system. Clin J Am Soc Nephrol, 2009; 4(9): 1515–22
27. Pfeifer M, Begerow B, Minne HW et al: Effects of a short-term vitamin D(3) and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. J Clin Endocrinol Metab, 2001; 86(4): 1633–37
28. Barreto DV, Barreto FC, Liabeuf S et al: Vitamin D affects survival independently of vascular calcification in chronic kidney disease. Clin J Am Soc Nephrol, 2009; 4(6): 1128–35
29. London GM, Guérin AP, Verbeke FH et al: Mineral metabolism and arterial functions in end-stage renal disease: potential role of 25-hydroxyvitamin D deficiency. J Am Soc Nephrol, 2007; 18(2): 613–20
30. National Kidney Foundation: K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis, 2003; 42(4 Suppl.3): S1–201
31. Williams S, Malatesta K, Norris K: Vitamin D and chronic kidney disease. Ethn Dis, 2009; 19(4 Suppl.5): S5-8–11
32. Somjen D, Weisman Y, Kohen F et al: 25-hydroxyvitamin D3-1alpha-hydroxylase is expressed in human vascular smooth muscle cells and is upregulated by parathyroid hormone and estrogenic compounds. Circulation, 2005; 111(13): 1666–71
33. Hewison M, Burke F, Evans KN et al: Extra-renal 25-hydroxyvitamin D3-1alpha-hydroxylase in human health and disease. J Steroid Biochem Mol Biol, 2007; 103(3–5): 316–21
34. Hur SJ, Kim DM, Lim KH et al: Vitamin D levels and their relationship with cardiac biomarkers in chronic hemodialysis patients. J Korean Med Sci, 2009; 24(Suppl.1): S109–14
35. Covic A, Voroneanu L, Goldsmith D: The Effects of Vitamin D Therapy on Left Ventricular Structure and Function – Are These the Underlying Explanations for Improved CKD Patient Survival? Nephron Clin Pract, 2010; 116(3): c187–95
36. Baksi SN, Hughes MJ: Deficiency in dietary vitamin D, not calcium, alters noradrenergic responsiveness in rat atria *in vitro*. J Mol Cell Cardiol, 1986; 18(7): 653–56
37. Weishaar RE, Kim SN, Saunders DE et al: Involvement of vitamin D3 with cardiovascular function. III. Effects on physical and morphological properties. Am J Physiol, 1990; 258(1 Pt 1): E134–42
38. Watson KE, Abrolat ML, Malone LL et al: Active serum vitamin D levels are inversely correlated with coronary calcification. Circulation, 1997; 96(6): 1755–60
39. Milliner DS, Zinsmeister AR, Lieberman E et al: Soft tissue calcification in pediatric patients with end-stage renal disease. Kidney Int, 1990; 38(5): 931–36
40. Goldsmith DJ, Covic A, Sambrook PA et al: Vascular calcification in long-term haemodialysis patients in a single unit: a retrospective analysis. Nephron, 1997; 77(1): 37–43
41. Kingma JG Jr, Roy PE: Ultrastructural study of hypervitaminosis D induced arterial calcification in Wistar rats. Artery, 1988; 16(1): 51–61
42. Mathew S, Lund RJ, Chaudhary LR et al: Vitamin D receptor activators can protect against vascular calcification. J Am Soc Nephrol, 2008; 19(8): 1509–19
43. Kunitomo M, Kinoshita K, Bandô Y: Experimental atherosclerosis in rats fed a vitamin D, cholesterol-rich diet. J Pharmacobiodyn, 1981; 4(9): 718–23
44. Zisman AL, Wolf M: Recent advances in the rapidly evolving field of fibroblast growth factor 23 in chronic kidney disease. Curr Opin Nephrol Hypertens, 2010; 19(4): 335–42
45. Mirza MA, Larsson A, Lind L et al: Circulating fibroblast growth factor-23 is associated with vascular dysfunction in the community. Atherosclerosis, 2009; 205(2): 385–90
46. Ix JH, Shlipak MG, Wassel CL et al: Fibroblast growth factor-23 and early decrements in kidney function: the Heart and Soul Study. Nephrol Dial Transplant, 2010; 25(3): 993–97
47. Shimada T, Urakawa I, Isakova T et al: Circulating fibroblast growth factor 23 in patients with end-stage renal disease treated by peritoneal dialysis is intact and biologically active. J Clin Endocrinol Metab, 2010; 95(2): 578–85
48. Reis JP, Michos ED, von Mühlen D et al: Differences in vitamin D status as a possible contributor to the racial disparity in peripheral arterial disease. Am J Clin Nutr, 2008; 88(6): 1469–77
49. Cozzolino M, Malindretos P: The role of vitamin D receptor activation in chronic kidney disease. Hippokratia, 2010; 14(1): 7–9
50. Malluche HH, Monier-Faugere MC, Koszewski NJ: Use and indication of vitamin D and vitamin D analogues in patients with renal bone disease. Nephrol Dial Transplant, 2002; 17(Suppl.10): 6–9
51. Hagström E, Hellman P, Larsson TE et al: Plasma parathyroid hormone and the risk of cardiovascular mortality in the community. Circulation, 2009; 119(21): 2765–71
52. Coen G, Mantella D, Sardella D et al: Asymmetric dimethylarginine, vascular calcifications and parathyroid hormone serum levels in hemodialysis patients. J Nephrol, 2009; 22(5): 616–22
53. Song GJ, Fiaschi-Taesch N, Bisello A: Endogenous parathyroid hormone-related protein regulates the expression of PTH type 1 receptor and proliferation of vascular smooth muscle cells. Mol Endocrinol, 2009; 23(10): 1681–90
54. Cha H, Jeong HJ, Jang SP et al: Parathyroid hormone accelerates decompensation following left ventricular hypertrophy. Exp Mol Med, 2010; 42(1): 61–68
55. Di Leo C, Gallieni M, Bestetti A et al: Cardiac and pulmonary calcification in a hemodialysis patient: partial regression 4 years after parathyroidectomy. Clin Nephrol, 2003; 59(1): 59–63
56. Amann K, Ritz E, Wiest G et al: A role of parathyroid hormone for the activation of cardiac fibroblasts in uremia. J Am Soc Nephrol, 1994; 4(10): 1814–19
57. Nishizawa Y, Miki T, Okui Y et al: Deranged metabolism of lipids in patients with chronic renal failure: possible role of secondary hyperparathyroidism. Jpn J Med, 1986; 25(1): 40–45
58. Ogard CG, Engelmann MD, Kistorp C et al: Increased plasma N-terminal pro-B-type natriuretic peptide and markers of inflammation related to atherosclerosis in patients with primary hyperparathyroidism. Clin Endocrinol (Oxf), 2005; 63(5): 493–98
59. De Boer IH, Gorodetskaya I, Young B et al: The severity of secondary hyperparathyroidism in chronic renal insufficiency is GFR-dependent, race-dependent, and associated with cardiovascular disease. J Am Soc Nephrol, 2002; 13(11): 2762–69
60. Walker MD, Fleischer JB, Di Tullio MR et al: Cardiac structure and diastolic function in mild primary hyperparathyroidism. J Clin Endocrinol Metab, 2010; 95(5): 2172–79
61. Tripepi G, Mallamaci F, Zoccali C: Inflammation markers, adhesion molecules, and all-cause and cardiovascular mortality in patients with ESRD: searching for the best risk marker by multivariate modeling. J Am Soc Nephrol, 2005; 16(Suppl.1): S83–88
62. Galle J, Quaschning T, Seibold S et al: Endothelial dysfunction and inflammation: what is the link? Kidney Int Suppl, 2003; (84): S45–49
63. Mackiewicz A, Speroff T, Ganapathi MK et al: Effects of cytokine combinations on acute phase protein production in two human hepatoma cell lines. J Immunol, 1991; 146(9): 3032–37
64. Fantuzzi G, Zheng H, Faggioni R et al: Effect of endotoxin in IL-1 beta-deficient mice. J Immunol, 1996; 157(1): 291–96
65. Marino MW, Dunn A, Grail D et al: Characterization of tumor necrosis factor-deficient mice. Proc Natl Acad Sci USA, 1997; 94(15): 8093–98
66. Fiscella K, Franks P: Vitamin D, race, and cardiovascular mortality: findings from a national US sample. Ann Fam Med, 2010; 8(1): 11–18

67. Silvestro A, Scopacasa F, Ruocco A et al: Inflammatory status and endothelial function in asymptomatic and symptomatic peripheral arterial disease. Vasc Med, 2003; 8(4): 225–32
68. Guijarro C, Egido J: Transcription factor-kappa B (NF-kappa B) and renal disease. Kidney Int, 2001; 59(2): 415–24
69. Wu-Wong JR, Nakane M, Ma J et al: Effects of Vitamin D analogs on gene expression profiling in human coronary artery smooth muscle cells. Atherosclerosis, 2006; 186(1): 20–28
70. Hu P, Qin YH, Pei J et al: Beneficial effect of all-trans retinoic acid (ATRA) on glomerulosclerosis rats via the down-regulation of the expression of alpha-smooth muscle actin: a comparative study between ATRA and benazepril. Exp Mol Pathol, 2010; 89(1): 51–57
71. Renke M, Tylicki L, Rutkowski P et al: The effect of N-acetylcysteine on blood pressure and markers of cardiovascular risk in non-diabetic patients with chronic kidney disease: a placebo-controlled, randomized, cross-over study. Med Sci Monit, 2010; 16(7): PI13–18
72. Li YC, Kong J, Wei M et al: 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. J Clin Invest, 2002; 110(2): 229–38
73. Wang AY, Lam CW, Sanderson JE et al: Serum 25-hydroxyvitamin D status and cardiovascular outcomes in chronic peritoneal dialysis patients: a 3-y prospective cohort study. Am J Clin Nutr, 2008; 87(6): 1631–38
74. Yuan W, Pan W, Kong J et al: 1,25-dihydroxyvitamin D3 suppresses renin gene transcription by blocking the activity of the cyclic AMP response element in the renin gene promoter. J Biol Chem, 2007; 282(41): 29821–30
75. Wang TJ, Pencina MJ, Booth SL et al: Vitamin D deficiency and risk of cardiovascular disease. Circulation, 2008; 117(4): 503–11
76. Chonchol M, Cigolini M, Targher G: Association between 25-hydroxyvitamin D deficiency and cardiovascular disease in type 2 diabetic patients with mild kidney dysfunction. Nephrol Dial Transplant, 2008; 23(1): 269–74
77. Petchey WG, Hickman IJ, Duncan E et al: The role of 25-hydroxyvitamin D deficiency in promoting insulin resistance and inflammation in patients with chronic kidney disease a randomised controlled trial. BMC Nephrol, 2009; 10: 41
78. de Boer IH: Vitamin D and glucose metabolism in chronic kidney disease. Curr Opin Nephrol Hypertens, 2008; 17(6): 566–72
79. Mattila C, Knekt P, Männistö S et al: Serum 25-hydroxyvitamin D concentration and subsequent risk of type 2 diabetes. Diabetes Care, 2007; 30(10): 2569–70
80. Pittas AG, Harris SS, Stark PC et al: The effects of calcium and vitamin D supplementation on blood glucose and markers of inflammation in nondiabetic adults. Diabetes Care, 2007; 30(4): 980–86
81. Penckofer S, Kouba J, Wallis DE et al: Vitamin D and diabetes: let the sunshine in. Diabetes Educ, 2008; 34(6): 939–40, 942, 944 passim
82. Billaudel BJ, Delbancut AP, Sutter BC et al: Stimulatory effect of 1,25-dihydroxyvitamin D3 on calcium handling and insulin secretion by islets from vitamin D3-deficient rats. Steroids, 1993; 58(7): 335–41
83. Rojas-Rivera J, De La Piedra C, Ramos A et al: The expanding spectrum of biological actions of vitamin D. Nephrol Dial Transplant, 2010; 25(9): 2850–65
84. Maestro B, Dávila N, Carranza MC et al: Identification of a Vitamin D response element in the human insulin receptor gene promoter. J Steroid Biochem Mol Biol, 2003; 84(2–3): 223–30
85. Maestro B, Molero S, Bajo S et al: Transcriptional activation of the human insulin receptor gene by 1,25-dihydroxyvitamin D(3). Cell Biochem Funct, 2002; 20(3): 227–32
86. Hu P, Lu L, Hu B et al: Recapture of hepatic apolipoprotein B mRNA editing may be a promising strategy to relieve nephrotic dyslipidemia. Med Hypotheses, 2010; 75(6): 561–63
87. Hu P, Qin YH, Jing CX et al: Association of polymorphisms at restriction enzyme recognition sites of apolipoprotein B and E gene with dyslipidemia in children undergoing primary nephrotic syndrome. Mol Biol Rep, 2009; 36(5): 1015–21
88. Khajehdehi P: Effect of vitamins on the lipid profile of patients on regular hemodialysis. Scand J Urol Nephrol, 2000; 34(1): 62–66
89. Bonakdaran S, Ayatollahi H, Mojahedi MJ et al: Impact of treatment with oral calcitriol on glucose intolerance and dyslipidemia(s) in hemodialysis patients. Saudi J Kidney Dis Transpl, 2008; 19(6): 942–47
90. Gupta AK, Sexton RC, Rudney H: Effect of vitamin D3 derivatives on cholesterol synthesis and HMG-CoA reductase activity in cultured cells. J Lipid Res, 1989; 30(3): 379–86
91. Oh J, Weng S, Felton SK et al: 1,25(OH)2 vitamin d inhibits foam cell formation and suppresses macrophage cholesterol uptake in patients with type 2 diabetes mellitus. Circulation, 2009; 120(8): 687–98
92. Rejnmark L, Vestergaard P, Heickendorff L et al: Simvastatin does not affect vitamin d status, but low vitamin d levels are associated with dyslipidemia: results from a randomised, controlled trial. Int J Endocrinol, 2010; 2010: 957174
93. Auwerx J, Bouillon R, Kesteloot H: Relation between 25-hydroxyvitamin D3, apolipoprotein A-I, and high density lipoprotein cholesterol. Arterioscler Thromb, 1992; 12(6): 671–74
94. John WG, Noonan K, Mannan N et al: Hypovitaminosis D is associated with reductions in serum apolipoprotein A-I but not with fasting lipids in British Bangladeshis. Am J Clin Nutr, 2005; 82(3): 517–22
95. Dansky HM, Charlton SA, Barlow CB et al: Apo A-I inhibits foam cell formation in Apo E-deficient mice after monocyte adherence to endothelium. J Clin Invest, 1999; 104(1): 31–39
96. McNeish J, Aiello RJ, Guyot D et al: High density lipoprotein deficiency and foam cell accumulation in mice with targeted disruption of ATP-binding cassette transporter-1. Proc Natl Acad Sci USA, 2000; 97(8): 4245–50
97. Adams MJ, Irish AB, Watts GF et al: Hypercoagulability in chronic kidney disease is associated with coagulation activation but not endothelial function. Thromb Res, 2008; 123(2): 374–80
98. Brophy DF, Martin RJ, Gehr TW et al: A hypothesis-generating study to evaluate platelet activity in diabetics with chronic kidney disease. Thromb J, 2005; 3(1): 3
99. Hewison M, Freeman L, Hughes SV et al: Differential regulation of vitamin D receptor and its ligand in human monocyte-derived dendritic cells. J Immunol, 2003; 170(11): 5382–90
100. Merke J, Milde P, Lewicka S et al: Identification and regulation of 1,25-dihydroxyvitamin D3 receptor activity and biosynthesis of 1,25-dihydroxyvitamin D3. Studies in cultured bovine aortic endothelial cells and human dermal capillaries. J Clin Invest, 1989; 83(6): 1903–15
101. Ohsawa M, Koyama T, Yamamoto K et al: 1alpha, 25-dihydroxyvitamin D(3) and its potent synthetic analogs downregulate tissue factor and upregulate thrombomodulin expression in monocytic cells, counteracting the effects of tumor necrosis factor and oxidized LDL. Circulation, 2000; 102(23): 2867–72
102. Aihara K, Azuma H, Akaike M et al: Disruption of nuclear vitamin D receptor gene causes enhanced thrombogenicity in mice. J Biol Chem, 2004; 279(34): 35798–802
103. Jones G: Expanding role for vitamin D in chronic kidney disease: importance of blood 25-OH-D levels and extra-renal 1alpha-hydroxylase in the classical and nonclassical actions of 1alpha, 25-dihydroxyvitamin D(3). Semin Dial, 2007; 20(4): 316–24
104. Kunitomo M, Futagawa Y, Tanaka Y et al: Cholesterol reduces and corticosteroids enhance the toxicity of vitamin D in rats. Jpn J Pharmacol, 1989; 49(3): 381–88
105. Drüeke TB, Ritz E: Treatment of secondary hyperparathyroidism in CKD patients with cinacalcet and/or vitamin D derivatives. Clin J Am Soc Nephrol, 2009; 4(1): 234–41
106. Kuwabara A, Tsugawa N, Tanaka K et al: Improvement of vitamin D status in Japanese institutionalized elderly by supplementation with 800 IU of vitamin D(3). J Nutr Sci Vitaminol (Tokyo), 2009; 55(6): 453–58
107. Holick MF: Vitamin D deficiency. N Engl J Med, 2007; 357(3): 266–81