RENOPROTECTIVE EFFECTS OF VITAMIN D AND RENIN-ANGIOTENSIN SYSTEM

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Abstract

Vitamin D has many physiological functions. First it is a primary regulator of calcium homeostasis. Beyond that, vitamin D and its receptors (VDR) play important role in the immune system, cardiovascular system, reproductive system and insulin resistance. An important aspect of vitamin D pleiotropic effects is the interaction with components of renine-angiotensine system (RAS). It was demonstrated that vitamin D–null mice have a sustained elevation of renin expression. The combination of both the AT1 blockers and the vitamin D analogues, leads to a marked amelioration of the molecular and clinical markers of diabetic nephropathy.

This combination may protect the kidney through the effects on both the glomerular and the tubulointerstitial compartments. There are different studies that corroborate the renoprotective action of vitamin D in CKD. In fact the renoprotective mechanisms in humans remain to be discovered, but these are realized through reduction of proteinuria, high blood pressure, inflammation as well as hemodynamic effects.

An important mechanism is the role of vitamin D as a potent negative endocrine regulator of renin expression. Actually we can accept that low vitamin D levels are a candidate novel risk factor for the progression of renal disease but it is not demonstrated yet that vitamin D can prolong the time to end-stage renal disease.

This question remains to be answered in other future controlled clinical trials.

Introduction

Department of Nephrology and Dialysis, University Hospital Center, Tirana, Albania Vitamin D is a primary regulator of calcium homeostasis. Genetic inactivation of either the vitamin D receptor (VDR), a member of the nuclear receptor superfamily that mediates the action of 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$], or 25-hydroxyvitamin D_3 1á-hydroxylase, the rate-limiting enzyme for the biosynthesis of 1,25 $(OH)_2D_3$, results in impaired calcium homeostasis, leading to hypocalcemia, secondary hyper parathyroidism, and rickets (1,2,3,4,5). However, the wide tissue distribution of VDR suggests that the vitamin D endocrine system has additional physiological functions beyond calcium homeostasis. There are many experimental and clinical data that corroborate the pleiotropic actions of vitamin D. Indeed, vitamin D and VDR have been shown to play important roles in the immune system, cardiovascular system, reproductive system, and hair growth (1). Many of these actions of vitamin D are realized indipendently from the effects on PTH and the level of calcium and phosphorus. Although VDR-deficient mice do not have a

spontaneous increase in cancer, they are more prone to oncogene- or chemocarcinogen-induced tumors (6). Also, it was shown that, low levels of vitamin D in the circulation are associated with a high incidence of autoimmune diseases, insulin resistance, and peripheral arterial diseases (7,8). Epidemiological evidence suggest that diabetes mellitus type 1 is more prevalent in countries with lower ambient winter ultraviolet light, supporting the theory that vitamin D supplementation in early childhood may offer protection against diabetes mellitus type1 (9). In different animal models, 1,25(OH)2D or its analogues reduced proteinuria levels, preserved glomerular podocyte structure, decreased levels of TGF-â 1, an inducer of renal fibrosis and inhibited mesangial cell proliferation, a marker of renal injury (8). Also, it has been demonstrated an inverse association of circulating vitamin D levels with blood pressure and it has been shown that the treatment with vitamin D analogues reduces blood pressure (10).

An important aspect of vitamin D pleiotropic effects is the interaction between receptors of vitamin D(VDR) and the components of renine- angiotensine system (RAS). 1,25 (OH) D3 reduces plasma renine activity, angiotensin II (Ang II) and myocardial hypertrophy (11). This makes possible, the inhibition of profibrotic and proinflammatory as well as the endothelial dammage caused by RAS. In a previous study (1) it was demonstrated that VDR-null mice have a sustained elevation of renin expression while still maintaining a normal level of blood electrolytes. The augmentation of renin synthesis leads to increased plasma Ang II production from angiotensinogen, which drives VDR-null mice to increase water intake and intestinal salt absorption, since Ang II is a very potent thirst-inducing agent that acts on the CNS, as well as a potent stimulator of intestinal sodium absorption (12). As a result, the mutant mice have to excrete more urine and salt to maintain volume and electrolyte homeostasis.

Since Ang II is a potent vasoconstrictor, its augmentation also leads to the development of hypertension and cardiac hypertrophy in VDR null mice, although the latter effect still needs more experimental verification.

This is not unexpected, as hypertension and cardiac hypertrophy have been well documented in patients and animals with high renin and Ang II (13). Thus, a new steady state of the renin-angiotensin system is established in VDR-null mice, in which the basal renin expression is higher but still responds appropriately to the same tubular salt load and volume stimuli as in the normal state. Based on these assessments, it is believed that the upregulation of renin expression is a primary defect in VDR-null mice (1).

An interesting study investigated the combined effect of ARB: Losartan and non-calcamic vitamin D analogue paricalcitol on the development and progression of diabetic nephropathy (14). In this experimental study it was shown that combination of both the AT1 blocker losartan and the vitamin D analogue paricalcitol, leads to a marked amelioration of the molecular and clinical markers of diabetic nephropathy. It was demonstrated absence of glomerulosclerosis in the combined treatment group, whereas thickening of glomerular basement membrane and podocyte effacement was shown in the groups where either paricalcitol or losartan was used alone.

Lowest values of blood glucose levels were encountered in the combined treatment group as well as

significant lower level of creatinine in comparison with the single treatment groups. Another more recent study of Li and colleagues (15) is an extension of a previous work by the authors that demonstrated that the combination of angiotensin receptor blockers plus paricalcitol therapy abrogates progression of streptozotocin induced diabetes (14).

In this study the authors demonstrated that combination therapy is better than sum of the parts with respect to progression of kidney disease as measured by kidney structure (kidney histology) and function (albuminuria, serum creatinine) in mice with type 2 diabetic nephropathy.

The mechanism of renal protection appears to be the protection of podocytes and blockade of the TGF-β system in the glomerulus (15).

TGF-β also activates interstitial fibroblasts and induces tubular epithelial to mesenchimal transition.

This way, VDRAs by blocking TGF-β may have the potential to abrogate tubulo-interstitial fibrosis. Further more, VDRAs have an anti inflammatory effect. Taken together these studies suggest that VDRA may protect the kidney through their effects on both the glomerular and the tubulointerstitial compartments (16).

Epidemiological and clinical studies in the last two decades have suggested an inverse relationship between vitamin D and blood pressure and/or plasma renin activity (17). Cutaneous production of vitamin D is influenced by sunlight, seasonal changes and skin pigmentation. Data from the INTERSALT study have revealed a linear correlation between the rise in blood pressure or the prevalence of hypertension and the latitudes north or south of the equator (18). Blood pressure tends to be higher in the winter than in the summer, and is affected by variations in skin pigmentation as well. In fact, ultraviolet light has been reported to lower blood pressure in patients with mild essential hypertension (19).

In patients where disturbances of RAS are important in the progression of disease such as diabetic nephropathy, the positive effects of ARB and ACE-I has been shown since many years but one can expect also that the inhibitory action of vitamin D on RAS , can be useful in slowing the progression of renal damage. Any way although there is strong evidence from the studies described above implicating the RAS in the mechanism of renal protection among animals with diabetic nephropathy, whether the same holds true in humans is unclear.

Actually there are at least four studies on the renoprotection by VDRA among patients with CKD not on dialysis (16). In the first study it was reported a reduction of proteinuria in stage 3 and 4 CKD patients who participated in 3 controlled trials of oral paricalcitol (20). Moreover, reduction of proteinuria occurred despite the use of of agents that block the RAS. Alborzi et al (21) studied 24 patients with stage 3 CKD who were allocated randomly to three equal groups to receive either 0, 1, or 2 μg paticalcitol orally for 1 month. At 1 month the treatment –baseline ratio of high-sensitivity C reactive protein was improved with a 2 μg dose of paricalcitol. At 1 month the treatment-base line ratio of 24–h albumin extretion rate was improved with paricalcitol. This study suggest that paricalcitol may evince reduction in albuminuria and inflammation independent of its effects on hemodynamics (measured in this study by glomerular filtration rate and ambulatory blood pressure monitoring) and parathyroid hormone suppression.

In another uncontrolled trial, ten patients with Ig-A nephropathy and

persistent proteinuria despite angiotensin converting enzyme inhibition and angiotensin II receptor blockade were treated with 0.5 μg Calcitriol twice weekly for 12 weeks (22). After this period there was a significant overall decrease in urine protein-creatinine ratio. No significant change in blood pressure or renal function was noted. There was a simultaneous decrease in serum TGF-b level and the percentage of decrease in serum TGF-b level significantly correlated with percentage of change in proteinuria.

The fourth study comprised 61 patients with CKD and proteinuria greater than 400 mg/d assigned equally to either 1 μg paricalcitol/per day or placebo (23). In this study, changes in protein excretion from baseline to last evaluation were +2.9% for controls and -17.6% for the paricalcitol group (P=0.04). Anyway the magnitude of reduction of proteinuria at 6 months was much less compared with that seen at 1 month by Alborzi et al (21).

Trying to understand the mechanism of the vitamin D and RAS interaction, it was shown that VDR-null mice maintain a high level of renin expression that is, to our knowledge, a novel finding, but the underlying physiological cause can be complicated. The observation that renin expression in VDR-null mice reacts properly to high salt load or dehydration indicates that the mechanism underlying the sustained renin elevation is independent of the pathways activated by tubular salt load or volume depletion. In fact, the involvement of cyclooxygenase-2 (COX-2), which may play an important role in macula densa–mediating renin release, in renin elevation in VDR-null mice is unlikely, since it was observed the same low COX-2 protein level in the kidneys of both VDR-null and wild-type mice (24). Since adult VDR-null mice develop hypocalcemia and secondary hyper parathyroidism, the upregulation of renin expression could be due to VDR inactivation per se, hypocalcemia, and/or high PTH. However, several lines of evidence from our study strongly suggest that vitamin D regulation of renin gene expression is direct and independent of the calcium status. Many facts provide very compelling evidence to establish that vitamin D is a potent negative endocrine regulator of renin expression in vivo (1).

If VDRAs effectively block the RAS, one would expect to share the side effects of RAS blockers such as hypokalemia, renal failure and hypotension. These side effects are absent in humans, so the mechanisms that afford renal and cardiovascular protection in humans may not be the same as that seen among rodents (25). In fact the renoprotective mechanisms in humans remain to be discovered.

It can't be exluded at this time, the possibility that, in vivo, secondary hyperparathyroidism may also contribute to the renin upregulation in VDR-null mice. Previous studies have shown that intravenous infusion of PTH increases plasma renin activity and renin release in humans and animals but the molecular mechanism whereby PTH regulates renin expression in vivo remains unknown. PTH may indirectly regulate renin expression in vivo (1).

Black patients who start dialysis tend to have lower levels of vitamin D than non-hispanic white patients, and are therefore presumably more likely to receive intravenous activated vitamin D. A recent study indicates that this difference in vitamin D treatment might contribute to the extended survival of black patients on dialysis compared to white patients.

Wolf et al.: analysed data from 9303 patients (55% white, 35% black) in the US (26). At the initiation of dialysis, black patients had a higher mean parathyroid hormone level and a lower mean 1,25-dihydroxyvitamin D level than white patients (P<0.05 for both). More black patients than white patients received activated vitamin D (88% vs 71%; P<0.05). And baseline parathyroid hormone level was the strongest predictor of

vitamin D treatment. Black ethnicity was associated with a 32% (95%CI 23-29%) lower risk of death than white ethnicity, and use of activated vitamin D was associated with a 52% (95% CI 46-57%) decrease in the risk of death. Multivariate analysis revealed that black people who received vitamin D had a 16% lower risk of death than than white people who received vitamin D ($P<0.05$); however the survival advantage of black ethnicity disappeared when the dose of vitamin D was taken into account. By contrast, among vitamin D untreated individuals, black patiens had a 35% higher risk of death than white ones ($P<0.05$).

On the basis of its suppression of the RAS and on animal models showing beneficial effects on albuminuria, mesangial cell proliferation, inflammation, and extracellular matrix formation, low vitamin D levels are a candidate novel risk factor for the progression of renal disease (8). Until now we can say that vitamin D must be given to patients with CKD in order to maintain bone health as well as immunological, cardiovascular and renal health. An adequate dose is considered when the serum level of vitamin D is greater than 30 ng/ml (16). But regarding renal effects, although vitamin D reduce proteinuria and hypertension, it was not demonstrated yet that it can prolong the time to end-stage renal disease. This question remains to be resolved more precisely in other future controlled clinical trials.

Disclosure

The authors declared no conflict of interest.

REFERENCES:

1. **Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP:** 1,25-Dihydroxyvitamin D_3 is a negative endocrine regulator of the renin-angiotensin system. J Clin Invest. 2002; 110: 229–238.
2. **Yoshizawa T. Handa Y, Uematsu Y, Takeda S, Sekine K et al.** Mice lacking the vitamin D receptor exhibit impaired bone formation, uterine hypoplasia and growth retardation after weaning. Nat Genet. 1997. 16:391-396
3. **Panda DK. Miao D, Tremblay ML, Sirois J, Farookhi R, Hendy GN et al.** Targeted ablation of the 25-hydroxyvitamin D1alpha-hydroxylase enzyme: evidence for skeletal, reproductive, and immune dysfunction. Proc Natl Acad Sci USA. 2001. 98:7498-7503.
4. **Li YC, Pirro AE, Amling M, Delling G, Baron R, Bronson R et al.** Targeted ablation of the vitamin D receptor: an animal model of vitamin D-dependent rickets type II with alopecia. Proc Natl Acad Sci USA. 1997; 94: 9831-9835.
5. **Dardenne, O, Prud'homme, J, Arabian, Glorieux FH, St-Arnaud R.** Targeted inactivation of the 25-hydroxyvitamin D(3)-1(alpha)-hydroxylase gene (CYP27B1) creates an animal model of pseudovitamin D-deficiency rickets. Endocrinology. 2001; 142:3135-3141.
6. **Agarwal R.** Vitamin D, Proteinuria, Diabetic Nephropathy, and Progression of CKD. Clin J Am Soc Nephrology. 2009; 4: 1523-1528,
7. **Muller D, Muller DN.** Battle against the rennin-angiotensin system: help from an unexpected party. Nephrol Dial Transplant. 2009; 24;1110-1112.
8. **Melamed ML, Astor B, Michos ED, Hosteter TH, Powe NR, Muntner P et al.** 25-Hydroxyvitamin D Levels, Race, and the Progression of Kidney Disease. J Am Soc Nephrol. 2009; 20: 2631-2639.

9. **Martin RJ, McKnight AJ, Patterson CC, Sadlier DM, Maxwell AP, Warre 3/UK Go KinD Study Group et al.** A rare haplotype of the vitamin D receptor gene is protective against diabetic nephropathy. Nephrol Dial Transplant. 2010; 25 : 497-503
10. **Scrag R, Soers M, Bell C.** Serum 25-hydroxyvitamin D, ethnicity, and blood pressure in the Third National and Nutrition Examination Survey. Am J Hypertension. 2007; 20: 713-719.
11. **Bodyak N, Ayus JC, Achinger S.** Activated vitamin D attenuates left ventricular abnormalities induced by dietary sodium in Dahl salt sensitive animals. Proc Natl Acad Sci USA. 2007; 104: 16801-16815
12. **Fitzsimons, JT.** Angiotensin stimulation of the central nervous system. Rev Physiol Biochem Pharmacol. 1980; 87:117-167
13. **Geisterfer, AA, Peach, MJ, Owens, GK.** Angiotensin II induces hypertrophy, not hyperplasia, of cultured rat aortic smooth muscle cells. Circ Res. 1988; 62:749-756.
14. **Zhang Z, Zhang Y, Ning G, Deb DK, Kong J, Li YC.** Combination therapy with AT1 blocker and vitamin D analog markedly ameliorates diabetic nephropathy blockade of compensatory renin increase. Proc Natl Acad Sci USA. 2008; 41:15896-15901
15. **Deb DK, SunT, Wong KE, Zhang Z, Ning G, Zhang Y et al.** Combined vitamin D analog and AT1 receptor antagonist synergically block the development of of kidney disease in a model of type 2 diabetes. Kidn Int. 2010; 77:1000-1009
16. **Agarwal R.** Are vitamin D receptor agonists like angiotensin-convering enzyme inhibitors without side effects? Kidn Int. 2010; 77: 943-945
17. **Li YC.** Vitamin D regulation of the Renin Angiotensin System. Journal of Cellular Biochemistry. 2003; 88: 323-331
18. **Rostand SG.** Ultraviolet light may contribute to geographic and racial blod pressure differences. Hypertension. 1997; 30: 150-156
19. **Krause R, Buhring M, Hopfenmuller W, Holick MF, Sharma AM.** Ultraviolet B and blood pressure. Lancet. 1998; 352: 709-710
20. **Agarwal R, Acharya M, Tian J, hippensteel RL, Melnick JZ, Qiu P et al.** Antiproteinuric effect of oral paricalcitol in chronic kidney disease. Kidn Int. 2005; 68: 2823-2828
21. **Alborzi P, Patel NA, Peterson C, Bills JE, Bekele DM, Bunaye Z et al.** Paricalcitol reduces albuminuria and inflammation in chronic kidney disease: a randomized double blind pilot trial. Hypertension. 2008; 52: 249-255.
22. **Szeto CC, Chow KM, Kwan BC, Chung KY, Leung CB, Li PK.** Oral calcitriol for the treatment of persistent proteinuria in immunoglobulin A nephropathy: an un controlled trial. Am J Kidn Dis. 2008;51: 724-731.
23. **Fishbane S, Chittienni H, Packman M, Dutka P, Ali N, Durie N.** Paricalcitol in the treatment of patients with CKD and proteinuria: a randomized trial. Am J Kidn Dis. 2009; 54: 647-652.
24. **Cheng HF. Wang JL, Zhang MZ, Wang SW, McKanna JA, Harris RC.** Genetic deletion of COX-2 prevents increased renin expression in response to ACE inhibition. Am J Physiol Renal Physiol. 2001; 280: 449-456.
25. **Bodyak N, Ayus JC, Achinger S, Shivalingappa V, Ke Q, Chen YS et al.** Activated vitamin D attenuates left ventricular abnormalities induced by dietary sodium in Dahl salt-sensitive animals. Proc Natl Acad Sci USA. 2007; 104: 16810-16815.
26. **Wolf M, Betancourt J, Chang, Y, Shah A, Teng M, Tamez H.** Impact of activated vitamin D and race on survival among hemodialysis patients. J Am Soc Nephrol. 2008; 19:1379-1388.