

Vitamin D and the Renal and Cardio Affairs

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The presence of vitamin D (1, 25 dihydroxvitamin D₃, the active form of Vitamin D₃) receptors in several organs and tissues, supports its pleiotropic role, beyond its function on mineral metabolism [1-3]. There is a bulk of evidence showing that vitamin D has anti-proliferative effects in cellular differentiation and is also an immuno modulator and inhibitor of the Renin-Angiotensin System (RAS) [4].

Recently, some experimental studies have documented the existence of 1, 25 dihydroxiVitamin D₃ Receptors (VDR) in podocytes and have demonstrated an association between this vitamin and the number of podocytes observed [5-6]. In glomerular disease structural changes of podocytes play an important role in the progression of kidney disease, namely in type 1 and type 2 diabetic nephropathy [5].

On the other hand, hyperglycaemia causes intra renal production of factors down regulating VDR and 1 α -hydroxylase in proximal tubule cells, resulting in decreased tubular megalin expression and consequently a decrease in 1, 25 dihydroxvitamin D₃ reabsorption with increased levels of protein urinary excretion [7]. The combination of hyperglycemia and the absence of VDR results in an intra renal increase of RAAS activation demonstrated by Zhang, and simultaneously there is evidence that deficits in the active metabolite of vitamin D indirectly stimulate the activation of TGF-1 β [8]. Vitamin D decreases proteinuria through

hemodynamic and also non-hemodynamic effects such as regulation of cell proliferation, apoptosis, angiogenesis and inflammation [9-13].

In some experimental models, administration of 1, 25-dihydroxyvitamin D₃ decreases the loss of podocytes and inhibits their hypertrophy [14]. This beneficial effect is due to a direct action in signal modulation for the inhibition of TGF- β 1 and Bone Morphogenetic Protein (BMP-7) expression [15].

In DN, the protective action of 1, 25 dihydroxvitamin D₃ is also due to its negative regulatory effect on the RAAS, by suppressing the production of renin which is one of the mechanisms responsible for renal injury, either by hemodynamic mechanisms, or through pro-inflammatory and pro-fibrotic mechanisms [16-18].

Several small studies have demonstrated the benefit of using 1, 25 dihydroxvitamin D₃ in reducing the levels of proteinuria in renal disease. Agarwal and colleagues evaluated the efficacy of oral paricalcitol in patients with stages 3 and 4 chronic kidney disease over a period of 24 months [19]. A total of 107 patients were randomized in a double-blind pilot trial, with 57 patients receiving oral paricalcitol. At the end of the study patients treated with paricalcitol showed a greater reduction of proteinuria, 51 vs 25.5 % in the placebo group (OR = 3.2 for reduction of proteinuria, 95% CI: 1.5-6.99). The effect of paricalcitol in reduction proteinuria was independent of demographic characteristics, comorbidities and use of antagonists of the renin-angiotensin system [19]. Also in a study with non-diabetic chronic kidney patients, Alborzi et al. showed the advantage of paricalcitol over placebo. In a shorter trial, these authors found that paricalcitol (1 and 2 μ g / day) reduced

albuminuria in about 50 %, comparing with placebo ($p > 0.001$) [12]. In a recent meta-analysis including 9 studies (832 patients), Cheng et al demonstrated the advantage of paricalcitol over placebo in reducing proteinuria in chronic kidney disease patients [20].

Specifically regarding diabetic patients, there are two clinical studies that only included type 2 diabetic patients. In both, all the patients were already medicated with antagonists of the renin-angiotensin system. The VITAL study was a prospective, randomized, double-blinded placebo-controlled, multi centric study that evaluated the efficacy of oral paricalcitol on reducing Albuminuria: Creatinine Ratio (ACR). In this trial the 281 patients were equally allocated to 3 groups to receive, 0, 1 or 2 μg of oral paricalcitol for a 24 weeks period. Patients on 2 μg showed a statistically significant reduction in ACR of 20 % ($p=0.014$ vs placebo) [21].

In a prospective observational study, Kim et al treated, with oral cholecalciferol, during four months, type 2 diabetic patients with low levels of 25 (OH)D. They found that cholecalciferol reduced albuminuria and urinary TGF- β 1 and concluded that dietary 1, 25 dihydroxivitamin D3 repletion with cholecalciferol could have a beneficial effect on progression of diabetic nephropathy [22].

More recently, the advantage of using paricalcitol in kidney transplanted patients have also been demonstrated. In a single-center prospective, randomized, crossover study, Trillini et al, found that paricalcitol decreased urinary deoxypyridoline/creatinine ratio and proteinuria in patient's submitted to renal transplantation [23]. Furthermore, it was shown that vitamin D deficiency is a risk factor of acute allograft rejection and the 1, 25-dihydroxyvitamin D supplementation may reduce the occurrence of rejections in patients with deficiency of vitamin D [24].

Although not designed to address the effect of paricalcitol on renal function, in the PRIMO study there was a trend to a greater progression of renal disease in the paricalcitol group; however this group had worse renal function at baseline [25]. Moreover Trillini et al also found that those patients under paricalcitol therapy showed worse renal function compared with

no paricalcitol therapy [23]. The increase of serum creatinine is attributed to decrease of creatinine tubular secretion, increase of its production, or both. It is argued that activators of vitamin D receptors do not affect glomerular filtration rate [26, 27].

Despite the evidence that vitamin D reduces proteinuria, a surrogate end-point, it is imperative to ascertain if these compounds can retard the renal disease progression in the long run. Prospective and well designed studies with a prolonged follow-up are required.

Cardiovascular is the main cause of morbidity and mortality in chronic kidney patients and there is a bulk of evidence showing that low levels of 1,25 dihydroxivitamin D3 are associated with greater risk of cardiovascular events in the general population [28,29].

Also in chronic kidney patients, low vitamin D levels are associated with greater cardiovascular morbidity and mortality [30, 31]. Moreover the administration of oral vitamin D3 [32] or vitamin D receptor activator [33] improves the survival of chronic hemodialysis patients. Teng and coworkers also found a survival advantage of paricalcitol over calcitriol, in chronic hemodialysis patients [34]. There are several mechanisms that may explain this beneficial effect of paricalcitol: the lower capacity of paricalcitol to promote gut absorption of calcium [34]; the greater capacity of calcitriol in inducing vascular calcification through an increased RANKL / osteoprotegerin expression [35]; vitamin D receptors are ubiquitous throughout the body, and when activated may modulate various beneficial functions at the cellular level [34].

Paricalcitol reduces the expression of genes involved in atherosclerosis: vascular cell growth, thrombus formation, fibrinolysis and endothelial regeneration related genes [36], and also mitigates disturbed aortic gene expression induced by uremia [37]. In rats, paricalcitol prevents the progression of Left Ventricular Hypertrophy (LVH) and the development of heart failure [38, 39]. It also decreases heart renin expression [40]. The combination of losartan and paricalcitol is able to maintain cardiac renin levels, which rise on mono therapy with losartan, adding effects in reducing LVH. Paricalcitol also decreases LVH and fibrosis secondary to uremia [41].

Despite these encouraging preclinical data, in the PRIMO randomized placebo-controlled trial, paricalcitol failed to reduce LVH in CKD patients with moderate LVH and iPTH 150–300 pg/ml [25]. Reduction in LVH was the primary endpoint of the study. Paricalcitol reduced BNP levels, left auricular volume and hospitalization for cardiovascular reasons [25].

It will be very important to ascertain if the treatment of CKD patients with 1,25 dihydroxyvitamin D₃ will decrease cardiovascular morbidity and mortality in this particular population, in a well designed prospective and randomized study; a study comparing 1,25 dihydroxyvitamin D₃ and paricalcitol, an activator of the 1,25 dihydroxyvitamin D₃ receptor, is also required, since their costs are quite different. The knowledge of the right moment of the intervention, with previous normalization of 1, 25 dihydroxyvitamin D₃ levels, also seems crucial and will it be useful the administration of paricalcitol in 1, 25 dihydroxyvitamin D₃ repleted patients?

Some important questions remain and must be answered regarding the role of vitamin D on renal and cardio affairs.

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