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INVITED ARTICLE

The Role of Vitamin D Receptor Activation in Chronic Kidney Disease

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Abstract

The death rate from cardiovascular disease for dialysis patients is much higher than the general population, regardless of age. Observational data indicate that there is a close inter-relationship between progressive renal dysfunction in patients with chronic kidney disease cardiovascular disease and mortality.

Continuously evidence indicates that deficiencies in vitamin D receptor activation represents one of key players in adversely affecting cardiovascular health, as well as inducing to secondary hyperparathyroidism in chromic kidney disease patients. Vitamin D receptors are widely expressed throughout the body and modulations of vitamin D levels results in correlative regulatory effects on mineral metabolism homeostasis, cardiovascular disease, and vascular calcification. The management of SHPT has developed enormously in recent years and different drug classes are available to treat this disease. Potentially, selective VDR activators not only reduce serum parathyroid hormone levels minimizing the risk of hypercalcemia and hyperphosphatemia, but also may improve patient health, reducing the risk of cardiovascular disease.
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Key words: vitamin D, haemodialysis, cardiovascular disease

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Chronic Kidney Disease – Mineral and Bone Disorder (CKD-MBD) begins early in the course of kidney disease and is under-diagnosed. Decreased vitamin D receptor (VDR) activation is a major pathophysiologic factor in the development of secondary hyperparathyroidism (SHPT) and contributes to CKD morbidity and mortality. In contrast, VDR inactivation influences bone and cardiovascular disease (CVD) progression and mortality. Some data suggest that treatment choices influence patient survival. These data underline the need for early assessment and clear management strategies. It is important to identify patients at increased risk for a poor prognosis and to better understand whether early treatment will benefit these patients.

Observational data indicate that there is a close inter-relationship between progressive renal dysfunction in CKD patients, CVD, and mortality[1]. Causes of mortality in patients with even moderate kidney dysfunction (measured by estimated glomerular filtration rates, [GFR]) are commonly associated with cardiovascular-related events[1]. Data from a 5-year prospective longitudinal study involving more than 27,000 patients in the United States have shown that CKD patients are more likely to die than develop end stage renal disease (ESRD), and that congestive heart failure (CHF) and coronary artery disease were both more prevalent than haemodialysis in this patient population[2].

CKD is characterized by progressive kidney dysfunction, manifest at later stages through notably diminished GFR, endocrine dysfunction, extra-skeletal calcification, and mineral metabolism disorders[3]. Reduced vitamin D receptor (VDR) activation may occur early in the course of CKD as a consequence of vitamin D deficiency and CKD-associated mineral bone disease (MBD), effects frequently appearing before a significant rise in parathyroid hormone (PTH) levels[4]. VDR activators or agonists effectively lower elevated PTH levels and provide improved patient survival compared with untreated patients[5]. VDR activators initiate signaling through ligand binding to the ubiquitously-present VDR, followed by activation of downstream endocrine, paracrine, and/or autocrine loops to maintain homeostasis in the kidney, bone, immune, and cardiovascular systems[6]. The continued development of newer VDR activators has led to further improvement in VDR tissue selectivity and safety, showing equivalent or better PTH-reducing effects, and expanded clinical impact on cardiovascular endpoints beyond reducing PTH levels while minimizing effects on calcium and phosphorus absorption in the intestine[7-9].

VDR Activation in CKD and Cardiovascular Disease Epidemiology

It has been shown that in the presence of altered kidney function, 50% of the patients with vitamin D insufficiency and thus decreased VDR activation will have normal PTH levels[4]. This observation is more evident for those with lower levels of GFR. Additionally it is well known that the rate of cardiovascular events, as well as mortality rate, increase as GFR declines[1]. In a recent study, an increased relative risk was observed in hemodialysis dependent patients with low levels of calcitriol

(1,25(OH) vit. D), which was ameliorated by the treatment with VDR activators[10]. Similarly, in a well designed retrospective study which included more than 40,000 hemodialysis patients, the protective action of VDR activators was revealed[11]. These patients showed approximately 20% better total and cardiovascular survival over those who did not follow VDR activator treatment[11]. Another impressive finding of this study was the sustained advantage of VDR activation independent of age, gender, race, calcium, phosphorus and PTH levels. Following the same pattern, other ethnic observational studies have shown a clear survival advantage in favor of VDR activators in hemodialysis patients with elevated PTH levels[12].

On the other hand, other statistical approaches of the same data from the DOPPS study have shown no benefit for those under VDR activators treatment[13]. According to these authors, inevitably, a randomized controlled trial of vitamin D in hemodialysis patients is needed. Conversely, in a large number of patients who were followed for a period of a few years, it has been seen a dose dependent advantage for those receiving paricalcitol treatment[14]. Finally, even per os administration of VDR activators has been proven beneficial in hemodialysis patients, and has been associated with improved cardiovascular, infectious, neoplastic and overall mortality[15].

Interestingly, in a study sample of more than 3,000 people from the general population, who were scheduled for coronary angioplasty, the authors observed a much higher all cause (HR= 2.08) and cardiovascular mortality (HR= 1.53) for those with lower levels of vitamin D[16].

All things considered, VDR activation seems to play a key role in human survival, even though solid evidence will be provided by future randomized studies.

The Role of VDR Activation on SHPT and Cardiovascular Outcome

For many years, the administration of calcitriol has been the mainstay of treatment for SHPT in CKD patients[17]. However, several novel findings and issues have substantially influenced nephrologists` attitudes towards VDRAs administration in recent years. High serum calcium (Ca) and phosphate (P) levels have been convincingly associated with reduced survival in CKD patients[18]. Moreover, Tonelli et al investigated the impact upon outcome of even small increases in serum P levels at the time of an acute myocardial infarction. They found an association of higher - but still within the normal range - P levels with the occurrence secondary cardiovascular events in non-dialysis patients[19]. VC may result from high dosages of vitamin D administration, as seen in several animal models with renal insufficiency[19]. Moreover, some evidence exists that previous calcitriol treatment in humans with advanced CKD is one of the VC promoting factors[20].

There is consistent observational data available that the administration of active vitamin D in dialysis patients and patients with advanced renal failure is associated with improved survival, irrespective of underlying P and Ca levels[21]. This survival improvement may be attributable to both the traditional bone and mineral actions of vitamin D as well as to the pleiotropic actions. As a consequence of these divergent statements, and since prospective, randomized data are missing, nephrologists might well get "lost in translation" if they try to transfer all the available experimental and observational data into every-day patient care. Currently, the bedside treatment decision for SHPT in CKD is even more complex: In the beginning of active vitamin D treatment in ESRD there used to be only the simple question: to give calcitriol or not to give calcitriol. In contrast, nowadays, there are several so-called vitamin D receptor activators (VDRAs) available: 1,25-dihydroxy-22-oxavitamin D_3 (22-oxacalcitriol, OCT), 1,25-dihydroxy-19-norvitamin D_2 (19-norD_2, paricalcitol), 1α-hydroxyvitamin D_2 (1αOHD_2). These novel alternative agents all claim to imitate the typical calcitriol action, i.e. reduction of SHPT. On the other hand, they deny being comparable to vitamin D regarding some other less desirable actions such as induction of hypercalcaemia or hyperphosphataemia[17].

Numerous observational studies show a clinical advantage for VDR activator therapy. To date, no studies have demonstrated increased mortality in patients receiving VDR activator therapy. Intravenous VDR activator therapy confers a survival advantage in patients on dialysis[17]. Kalantar-Zadeh and coworkers[22] have shown an association between any time-varying administered dose of paricalcitol and relative risk of death in over 58,000 maintenance HD patients over 2 years. Moreover, Wolf and colleagues[23] have shown in the ArMORR prospective, cross-sectional studies that 1,25-D and 25D deficiencies in incident HD patients are associated with an increased mortality risk that is reduced following the introduction of VDR activator therapy given in conjunction with dialysis. The association of improved survival with VDR activation therapy can already be observed in patients with moderate renal impairment. VDR activators directly affect cardiovascular outcomes, apparently by mechanisms independent of SHPT. These include effects on the immune system, RAS, and development of atherosclerosis, cardiac remodelling, and LVH.

Conclusions

A mounting body of evidence indicates that a deficiency in vitamin D and VDR activation play a crucial role in CKD, as well as cardiovascular outcomes in both CKD patients and the general population. VDR activation pathways mediate widespread activities that include the maintenance of and interrelated effects between cardiovascular and renal integrity. Preclinical and clinical data continue to support that when VDR activators are used at clinically relevant doses, an efficacious response is shown with minimal risk of vascular calcification. Adverse effects such as hypercalcemia and phosphatemia are further lessened with the use of selective VDR activators. In addition, selective VDR activation differentially exerts a number of ameliorative effects on parameters outside

of cardiovascular and renal disease, such as immunologic effects. Some data now suggest that recognition of CKD and cardiovascular interrelated effects requires cumulative assessment of patient health for the appropriate selection of treatments that may influence patient survival. These data underline the need for early identification of vitamin D deficiency and clear management strategies. Data continue to accrue to help define the many potentially beneficial physiologic effects of VDR activators in CKD patients with CKD or CVD.

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