Role of Vitamin D Receptor Activators in Cardio-Renal Syndromes

Mario Cozzolino, MD, PhD, Elena Bruschetta, MD*, Andrea Stucchi, MD†, Claudio Ronco, MD†, and Daniele Cusi, MD**

Summary: The involvement of vitamin D deficiency in cardiovascular morbidity and mortality is attracting great interest. In patients with chronic kidney disease this association is stronger because vitamin D levels decrease as a result of renal progressive impairment. In chronic kidney disease secondary hyperparathyroidism commonly occurs in response to persistent hypocalcemia and hyperphosphatemia; moreover, parathyroid gland volume increases, vascular calcification is accelerated, and structural and functional modifications of the left ventricle are observed. These alterations entail both cardiac and renal involvement, resulting in cardio-renal syndrome. Recent studies concluded that vitamin D administration seems to have cardioprotective and renoprotective effects and improve peripheral vascular disease, vascular calcification, cardiac outcome, and blood pressure control. In clinical practice, therefore, the use of this hormone may play an important role in cardio-renal syndrome prevention.

Semin Nephrol 32:63-69

Keywords: Vitamin D, mineral metabolism, chronic kidney disease, dialysis

Vitamin D belongs to a group of secosteroid molecules and it plays an important role in calcium-phosphate homeostasis and bone mineralization. Serum calcium concentration control is the principal aim of 1,25 $(OH)_2D_3$ (calcitriol), which increases active calcium and phosphate intestinal transport and bone calcium resorption.[1] Vitamin D exists in two different forms: ergocalciferol (vitamin D_2), which derives from a vegetal precursor under action of ultraviolet (UV) light; and cholecalciferol (vitamin D_3), which is produced in the skin from 7-dehydrocholesterol through UV light exposition. The first molecule can be found in vegetables, the second one in fishes and mammals. Two conversions are necessary to obtain an active form of vitamin D: in the liver 25-hydroxylation occurs and subsequently in the kidney 1-α-hydroxylasis transforms vitamin D in its active form (1,25-dihydroxy vitamin D). The active form binds the vitamin D receptor (VDR), forming a heterodimer complex. This complex binds together other factors of vitamin D responsive elements on DNA, activating altered gene expression. Renal hydroxylation is controlled by hypocalcemia, hypophosphatemia, and parathyroid hormone (PTH), a hormone produced by the parathyroid gland when hypocalcemia occurs. PTH has direct effects on calcium and phosphate renal transport, resulting in decreased calcium excretion in the distal tubule and inhibited phosphate reabsorption in the proximal tubule. Furthermore, PTH effects on bone include osteoclast activation and consequent increased bone turnover, resulting in increased serum calcium and phosphate concentrations.[2] Figure 1 summarizes the pathogenesis of secondary hyperparathyroidism in chronic kidney disease (CKD).

During the past decade, it has been shown that VDRs are present in a wide range of tissues, such as liver, brain, immune cells, vascular smooth muscle cells, pancreatic β-cells, endothelial cells, and cardiomyocytes (Table 1).[3-5] This discovery shows that vitamin D has different effects not only on mineral and bone metabolism. This molecule in fact also rules hormone secretion because it inhibits PTH synthesis and prevents parathyroid gland tissue proliferation. In addition, the presence of VDR in pancreatic β-cells promotes insulin secretion and vitamin D deficiency is associated with an increased risk of type I and type II diabetes mellitus. Furthermore, vitamin D has important immunomodulatory effects, controlling T-cell activation through T-cell antigen–receptor signaling. Moreover, vitamin D rules cellular proliferation and differentiation of malignant cells that express VDR. Finally, the discovery that vitamin D seems to play a considerable role in cardiovascular protection has stimulated great interest.[6]

SELECTIVITY OF VDR ACTIVATORS

VDR activators (VDRAs) have a wide range of affinity for the components of the vitamin D system, both for the vitamin D–binding protein and for nuclear VDR. The mechanism of action of VDRAs is genomic and is the result of change in the structural configuration of the vitamin

**Renal Division, Dipartimento di Medicina, Chirurgia e Odontoiatria, University of Milan School of Medicine, San Paolo Hospital, Milan, Italy.*

†Department of Nephrology Dialysis & Transplantation, International Renal Research Institute, San Bortolo Hospital, Vicenza, Italy.

Financial support for this work: none.

Financial disclosure and conflict of interest statements: Mario Cozzolino received in the past honoraria from Abbott, Amgen, Shire, Sanofi, and Roche. Dr. Claudio Ronco receives speaking honoraria from Alere, Abbot, Gambro and Pfizer.

Address reprint requests to Mario Cozzolino, MD, PhD, Renal Division, San Paolo Hospital, University of Milan, Via A. di Rudinì, 8-20142, Milan, Italy. E-mail: mario.cozzolino@unimi.it or mariocozzolino@hotmail.com

0270-9295/ - see front matter

doi:10.1016/j.semnephrol.2011.11.009

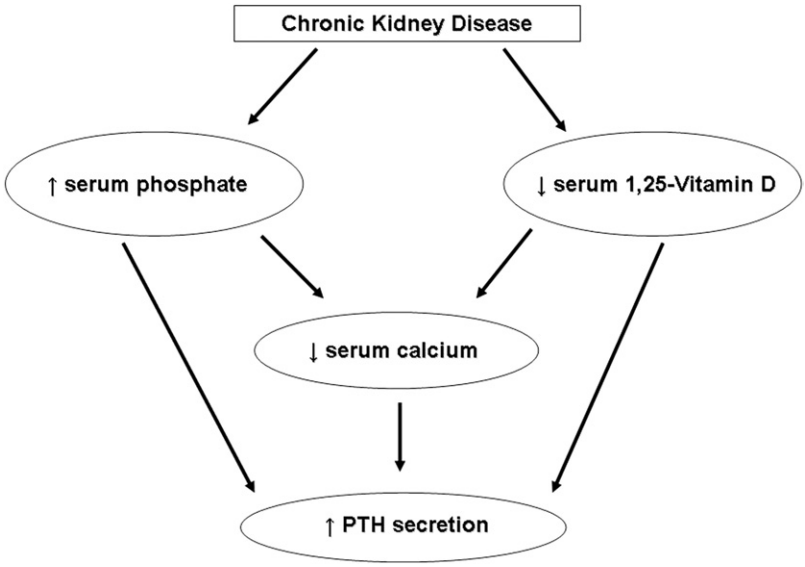

Figure 1. Pathogenesis of SHPT in CKD. In CKD patients, both increased serum phosphate levels and reduced plasma 1,25-vitamin D levels lead to a decrease of serum calcium levels. All these factors result in enhancement of PTH synthesis and secretion.

D–VDR complex or in the affinity of the vitamin D–VDR complex. Therefore, paricalcitol is considered a selective VDR activator; the term *selective* means that this molecule acts greatly to parathyroid gland than to intestine and bone, resulting in lower serum calcium and phosphorus increases but in improvement of hyperplasia of the parathyroid gland and secondary hyperparathyroidism (SHPT).

The selectivity is explained by the C-terminal portion of the VDR, which is the ligand-binding region and determines the specificity of a given ligand. When a ligand binds to the VDR, a particular domain of the receptor (the AF-2 domain) changes its conformation, increasing the recruitment of VDR-interacting proteins, known as co-activators and co-repressors, able to modulate the biological activity of the ligand-VDR complex.

Table 1. VDR Distribution in the Body

System	Tissue
Cardiovascular	Vascular smooth muscle cells, endothelial cells, cardiomyocytes
Central nervous system	Brain neurons
Connective tissue	Fibroblasts, stroma
Endocrine	Parathyroid, pancreatic β-cells, thyroid C cells
Exocrine	Parotid gland, sebaceous gland
Epidermis/appendage	Skin, breast, hair follicles
Gastrointestinal	Esophagus, stomach, small intestine, large intestine
Hepatic	Liver parenchyma cells
Immune	Thymus, bone marrow, B cells, T cells
Muscle	Striated muscle
Renal	Proximal and distal tubules, collecting duct, podocytes
Reproductive	Testis, spermatocytes, ovary, placenta, uterus, endometrium, yolk sac
Respiratory	Lung alveolar cells
Skeletal	Osteoblasts, osteocytes, chondrocytes

Recent studies have assessed the importance of VDRA selectivity in clinical practice. The wide VDR diffusion in human tissues allows potential ameliorative effects on cardiovascular (CV) structure and function, decreasing the risk of CV disease and death, especially in CKD patients. VDRAs seems to improve some other factors implicated in enhanced CV risk.[7]

Vitamin D administration inhibits PTH synthesis and secretion and it reduces parathyroid gland hyperplasia. However, calcitriol increases serum calcium and phosphate levels, worsening vascular calcification progression. The use of selective VDRAs seems to have a minor effect on increasing calcium and phosphorus concentrations, and a minor impact on vascular calcifications. Recent studies have shown that in uremic rats the use of calcitriol increases intestinal VDR content, although paricalcitol administration is not associated with this effect. Furthermore, a 10-fold higher dose of paricalcitol than calcitriol is needed to obtain the same increase of serum calcium concentration. Instead, equal doses of paricalcitol and calcitriol are able to reduce PTH levels, whereas paricalcitol has less effects on phosphate absorption. Nakane et al[8,9] have shown that calcitriol in uremic rats fed a high-phosphorus diet enhances intestinal calcium absorption because it promotes calbindin expression, whereas paricalcitol does not have this effect. Moreover, paricalcitol is less powerful than doxercalciferol and calcitriol in inducing calcium mobilization from bone.[1,10,11]

Direct effects on the gene transcription may be considered to explain different effects of VDRAs in tissues. Differential effects of paricalcitol and calcitriol on the induction