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Review Article

Cardiorenal syndrome and vitamin D receptor activation in chronic kidney disease ☆

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A B S T R A C T

Cardiorenal syndrome (CRS) refers to a constellation of conditions whereby heart and kidney diseases are pathophysiologically connected. For clinical purposes, it would be more appropriate to emphasize the pathophysiological pathways to classify CRS into: (1) hemodynamic, (2) atherosclerotic, (3) uremic, (4) neurohumoral, (5) anemic–hematologic, (6) inflammatory–oxidative, (7) vitamin D receptor (VDR) and/or FGF23-, and (8) multifactorial CRS. In recent years, there have been a preponderance data indicating that vitamin D and VDR play an important role in the combination of renal and cardiac diseases. This review focuses on some important findings about VDR activation and its role in CRS, which exists frequently in chronic kidney disease patients and is a main cause of morbidity and mortality. Pathophysiological pathways related to sub-optimal or defective VDR activation may play a role in causing or aggravating CRS. VDR activation using newer agents including vitamin D mimetics (such as paricalcitol and maxacalcitol) are promising agents, which may be related to their selectivity in activating VDR by means of attracting different post-D-complex cofactors. Some, but not all, studies have confirmed the survival advantages of D-mimetics as compared to non-selective VDR activators. Higher doses of D-mimetic per unit of parathyroid hormone (paricalcitol to parathyroid hormone ratio) is associated with greater survival, and the survival advantages of African American dialysis patients could be explained by higher doses of paricalcitol (> 10 μg/week). More studies are needed to verify these data and to explore additional avenues for CRS management via modulating VDR pathway.

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Introduction

Combined cardiac and renal dysfunction, referred to as cardiorenal syndrome (CRS), is common in people with primary cardiovascular disease and those with kidney function disorders. It is believed that the incidence and prevalence of CRS have increased in recent decades, not only because of increasing occurrence of cardiac or renal disease but also because of improved longevity of cardiac and renal patients. Pathophysiologically, heart and kidney diseases are connected to each other through a number of pathways, including, but not limited to, hemodynamic constellations, electrolyte disarrays, immunological disorders, metabolic dysfunctions, neurological derangement, and inflammatory and hormonal factors (Fig. 1).

Definition and classification of CRS

Recently, CRS has been more systemically defined and classified into five different types [1]. CRS Types I and II are described as the primary occurrence of an acute cardiac event or chronic heart disease, respectively, leading to kidney disorders, whereas in Types III and IV CRS, the primary disease is acute kidney injury or chronic kidney disease (CKD), respectively, and the cardiovascular disease is a secondary phenomenon. Type V is any combination of the above.

Despite the well-intended efforts in providing such novel definitions, the usefulness of this classification in clinical approaches and patient management is questionable. Perhaps, for clinical purposes, it would be more appropriate to emphasize the pathophysiological pathways, which are the main etiological role-players and which may have more clinical utility in patient management. We propose the following categories (Table 1): "hemodynamic CRS" (when heart failure leads to renal perfusion comprise and renal functional derangements, or when fluid retention due to primary kidney disease leads to decompensated heart failure); "atherosclerotic CRS" (when both atherosclerotic cardiovascular disease and renal artery disease coexist); "uremic CRS" (when primary kidney disease leads to myocardial or pericardial dysfunction); "neurohumoral CRS" (when primary electrolyte or acid–base disorders in renal disease or heightened catecholamine release in cardiac disease or other hormonal derangements lead to cardiac or renal compromise); "anemic–hematologic CRS (when anemia and/or iron deficiency lead to cardiac or renal compromise); "inflammatory CRS" (when proinflammatory pathways are activated in either organ and affect the other organ); and "vitamin D receptor (VDR)-related CRS" (when VDR activation is suboptimal, leading to a variety of combined heart and kidney diseases); and finally in situations where there are multiple pathophysiological connections, the term "multifactorial CRS" could be used.

In recent years, there have been a preponderance data indicating that vitamin D and VDR play an important role in the combination of renal and cardiac diseases. This review focuses on some important findings about VDR activation and its role in CRS.

Biological characteristics of vitamin D and VDR

Usually about 50–90% of required vitamin D for the body is engendered in the skin under the sunshine by converting dehydro-cholesterol into cholecalciferol (vitamin D_3), and the remainder comes from ingested food in the form of natural or added cholecalciferol, mostly animal origin, or ergocalciferol (vitamin D_2), mostly plant origin. In the liver, 25-hydoxylase coverts the latter to 25-OH vitamin D (which is usually measured in the blood as a screening test), and 1-α-hydoxylase in the kidneys coverts the latter to 1,25 di-hydroxycholecalciferol, which is also known as active vitamin D and which is the most potent activator of VDR (Fig. 2). Although small amounts of 1-α-hydoxylase also exist in peripheral (extrarenal) tissues, $>90\%$ of vitamin D activation occurs in

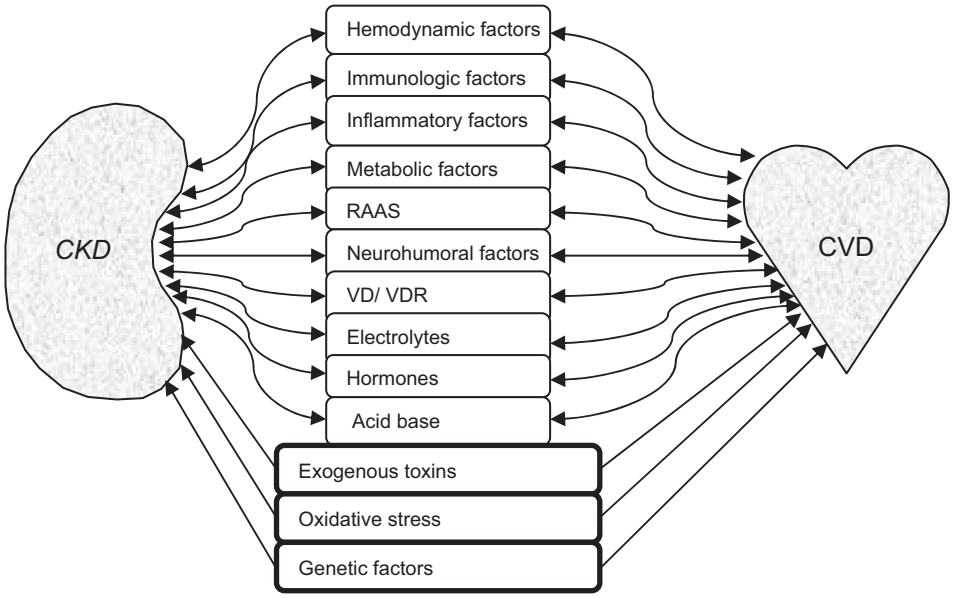

Figure 1. Putative pathophysiological connections in cardiorenal syndrome.
RAAS, renin–angiotensin–aldosterone system; VD/VDR, vitamin D/vitamin D receptor.