Vitamin D and Calcimimetics in Cardiovascular Disease

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Summary: Cardiovascular disease has earned its place as one of the leading noncommunicable diseases that has become a modern-day global epidemic. The increasing incidence and prevalence of chronic kidney disease (CKD) has added to this enormous burden, given that CKD is now recognized as an established risk factor for accelerated cardiovascular disease. In fact, cardiovascular disease remains the leading cause of death in the CKD population, with significant prognostic implications. Alterations in vitamin D levels as renal function declines has been linked invariably to the development of cardiovascular disease beyond a mere epiphenomenon, and has become an important focus in recent years in our search for new therapies. Another compound, cinacalcet, which belongs to the calcimimetic class of agents, also has taken center stage over the past few years as a potential cardiovasculoprotective agent. However, given limited well-designed randomized trials to inform us, our clinical practice for the management of cardiovascular disease in CKD has not been adequately refined. This article considers the biological mechanisms, regulation, and current experimental, clinical, and trial data available to help guide the therapeutic use of vitamin D and calcimimetics in the setting of CKD and cardiovascular disease.

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Over the course of the past century, the world has witnessed a striking epidemiologic transition in the predominant causes of death from infectious diseases and nutritional deficiencies to noncommunicable diseases.[1] Among the noncommunicable diseases, cardiovascular diseases (CVD) has become the modern-day global epidemic and a leading cause of death.[2] The staggering health and health care economic burden of these noncommunicable diseases taxed on both developing and developed nations alike became the focal point of the global heads of state assembly at the United Nations High-Level Meeting in 2011. This is the first time the United Nations has tackled a health issue since the human immunodeficiency virus/acquired immune deficiency syndrome epidemic in 2001 and formally recognized the threat that noncommunicable conditions such as CVD constitutes for the 21st century.[3]

Models that include population aging, increasing rates of urbanization and globalization, and health behaviors that increase the burden of cardiovascular risk factors for ischemic heart disease partially account for this CVD epidemiologic transition.[4] Other well-established modifiable risk factors for CVD include hyperlipidemia, smoking, hypertension, and diabetes. However, in recent years, chronic kidney disease (CKD) has emerged as a powerful risk factor for the development of accelerated CVD.[5] In fact, CVD is the leading cause of death in patients with CKD and renal function decline has significant prognostic implications.

End-stage renal disease (ESRD) patients on dialysis have a 10- to 30-fold higher cardiovascular mortality rate compared with the general population despite stratification for sex and race.[5] Most cardiovascular deaths in ESRD are attributable to arrhythmia, congestive heart failure, and ischemic heart disease, which can lead to sudden cardiac death.[6] Among patients who experience an acute coronary syndrome (ACS), 40% of these patients have at least a moderate degree of decline in kidney function with an estimated glomerular filtration rate (GFR) less than 60 mL min^{-1} 1.73 m^{-2}.[7] The

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risk of ACS is related directly to declining renal function.[3] Furthermore, these patients have a 1-year mortality rate of approximately 25%, compared with 5% in patients with normal renal function.[8]

The development of accelerated CVD that occurs as renal function declines involves a multitude of highly complex pathogenic pathways, involving abnormal mineral and bone metabolism, uremic toxins, inflammation, anemia, sympathetic nerve activation, activation of the renin-angiotensin-aldosterone system (RAAS) and endothelial dysfunction.[9] Central to these pathways are complex interactions between several target organs that include the kidney, bone, and vascular and cardiac systems. Interactions between these organ systems form critical homeostatic endocrine loops that help ensure that calcium and phosphorus are highly regulated. The effect of this tight regulation is to maintain appropriate skeletal mineralization and avoid extraskeletal calcification.[10] Failure of this system therefore leads to two inter-related disease processes: overt mineral bone disease (MBD) and CVD. As kidney function decreases, breakdown of the kidney-bone, kidney-vascular, and kidney-heart axes can lead to high calcium and phosphate levels and increasing parathyroid hormone (PTH), fibroblast growth factor (FGF)-23 levels, low Klotho levels, and reduced synthesis of active 1,25-dihydroxyvitamin D levels. Alterations in each of these component variables have been linked invariably to the development of progressive CVD and accelerated age-related changes of the cardiovascular system.[5,11]

Therapeutic strategies to prevent or treat accelerated CVD in renal failure have largely focused on targeting one or more of these endocrine or mineral alterations. Traditionally, dietary phosphate control or use of various phosphate binders in parallel with the control of hypertension and statin therapy have been the mainstay of CVD prevention in CKD. However, therapeutic strategies involving vitamin D and its analogues, and calcimimetics, have garnished increasing attention over the past few years. Both vitamin D and calcimimetics are widely used for the treatment of secondary hyperparathyroidism in CKD. Many experimental and observational studies have linked vitamin D deficiency and the high PTH, high phosphate, and high calcium milieu associated with advanced secondary hyperparathyroidism to various cardiovascular outcomes in CKD.[12,13] Therefore, it has made sense for nephrologists to target these changes with vitamin D and calcimimetics. Careful follow-up evaluation of these component alterations therefore are important in CKD-MBD management as outlined in the Kidney Disease Improving Global Outcomes clinical practice guidelines.[14]

However, alterations of the serum levels of these individual components are insufficient to guide therapy and studies that look beyond these changes to cardiovascular outcomes, and hard clinical end points such as cardiovascular or all-cause mortality are demanded. Despite this, few well-designed, randomized, controlled trials are available to help guide vitamin D and calcimimetic therapy for the treatment of MBD and life-limiting CVD in the CKD population. As a result, clinicians are left with potentially equivocal recommendations that place a large reliance on serum PTH level to help guide these therapies. This has left uncertainty in the field of nephrology. This article reviews the plausible biological mechanisms, human studies, and available clinical trial data for the use of vitamin D and calcimimetics. Given the multiple redundant pathways that link the cardiac and renal systems, we focus specifically on the application of vitamin D and calcimimetics for the management of CVD in patients with advanced CKD.

VITAMIN D THERAPY

Vitamin D is indispensable to human health and plays a critical role in the integration and regulation of multiple physiological and metabolic systems. Vitamin D effects can be thought of as having two main functional arms: endocrine or classic functions mediated by circulating vitamin D produced by the kidney, and autocrine/paracrine nonclassic functions that are exerted by locally produced extrarenal vitamin D (Fig. 1). Endocrine functions of vitamin D mediate a complex interplay between the kidney, bone, parathyroid gland, and intestine that is largely involved in regulating mineral homeostasis. Given the widespread expression of 1α-hydroxylase and the vitamin D receptors (VDR) across many organ systems, both endocrine and locally produced autocrine/paracrine vitamin D have been found to exert pleiotropic effects in the regulation of normal organ physiology and exert cytoprotective functions (Fig. 1).

Vitamin D deficiency is a global public health problem and is a highly prevalent condition in CKD patients, with estimates as high as 70% to 80% in some studies.[15] Despite the introduction of international and European guidelines to supplement vitamin D in the dialysis population, reports over the past decade consistently have shown vitamin D deficiency in this population. Both active 1,25-dihydroxyvitamin D and nutritional 25-hydroxyvitamin D, from here on referred to as *calcitriol* and *calcidiol*, are deficient in the majority of patients with CKD. Vitamin D metabolism is ubiquitously altered in CKD and concentrations decrease early before PTH levels begin to increase as GFR decreases. Plasma calcidiol levels decrease when the glomerular filtration rate decreases to less than 45 mL/min/1.73 m^2.[16] Active calcitriol levels decrease to the lower limits of normal when patients reach the