Review Article

A Review on role of vitamin-D in Chronic kidney disorders (CKD) with their sources, metabolism and deficiency

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ABSTRACT

Vitamin D deficiency is now recognized as a pandemic. The major cause of vitamin D deficiency is the lack of appreciation that sun exposure in moderation is the major source of vitamin D for most humans. Very few foods naturally contain vitamin D, and foods that are fortified with vitamin D are often inadequate to satisfy either a child's or an adult's vitamin D requirement. Vitamin D deficiency causes rickets in children and will precipitate and exacerbate osteopenia, osteoporosis, and fractures in adults. Vitamin D deficiency has been associated with increased risk of common cancers, autoimmune diseases, hypertension, and infectious diseases. A circulating level of 25-hydroxyvitamin D of >75 nmol/L, or 30 ng/mL, is required to maximize vitamin D's beneficial effects for health. In the absence of adequate sun exposure, at least 800–1000 IU vitamin D_3/d may be needed to achieve this in children and adults. Vitamin D_2 may be equally effective for maintaining circulating concentrations of 25-hydroxyvitamin D when given in physiologic concentrations.

Key words: *Hydroxyvitamin, Osteopenia and Osteoporosis*

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INTRODUCTION

Vitamins are organic compounds that are needed in small quantities to sustain life. Most vitamins need to come from food. This is because the human body either does not produce enough of them, or it does not produce any at all. Each organism has different vitamin requirements [1]. For example, humans need to consume vitamin C, or ascorbic acid, but dogs do not. Dogs can produce, or synthesize, enough vitamin C for their own needs, but humans cannot. People need to get most of their vitamin D from exposure to sunlight, because it is not available in large enough quantities in food. However, the human body can synthesize it when exposed to sunlight.[2]

Vitamin D

Chemical names: Ergocalciferol, cholecalciferol.

- It is fat soluble.
- Deficiency may cause rickets and osteomalacia, or softening of the bones.
- Good sources: Exposure to ultraviolet B (UVB) through sunlight or other sources causes vitamin D to be produced in the skin. Also found in fatty fish, eggs, beef liver, and mushrooms [3], [4]

ROLE OF VITAMIN-D IN KIDNEY DISORDERS

Vitamin D deficiency/insufficiency is an increasingly recognized public health problem in the general population. Chronic kidney disease (CKD) has been known to be a risk factor for development of vitamin D deficiency/insufficiency and is associated

with increased morbidity and mortality [5]. The vitamin D hormonal system is implicated in the regulation of calcium homeostasis and bone metabolism but also potentially has extra-mineral metabolism functions through activation of non-renal vitamin D receptors (VDR) and over the last decade, interest in the therapeutic potential of vitamin D has grown [6].

The active form of vitamin D is present in many tissues which are not associated with calcium or bone metabolism. Indeed, 1.25-dihydroxyvitamin D regulates cell proliferation, differentiation and apoptosis in many normal and cancer cells. Epidemiologic studies have shown that vitamin D deficiency increases the risk of cancer, cardiovascular disease, autoimmune disease, type 2 diabetes mellitus, and infectious disease; however, in this review we focus our attention on highlighting new information from recent studies on vitamin D deficiency/insufficiency and pathogenesis in renal disease, and vitamin D replacement therapy and outcomes in renal disease [7].

A. SOURCES AND METABOLISM OF VITAMIN D

In nature, vitamin D can be obtained in two forms - dietary ingestion or sunlight-induced endogenous synthesis by the skin (Figure 5). Humans derive vitamin D mostly from skin-exposure to sunlight and, to a lesser extent, from the diet and dietary supplements. Few foods naturally contain or are fortified with vitamin D. Therefore, without daily regular consumption of naturally-rich or fortified foods, individuals may be deficient in vitamin D. In the absence of daily exposure to sunlight, or with the use of sunscreens, this deficiency has been more pronounced. Solar ultraviolet B radiation converts 7-dehydrocholesterol in the epidermis to pre-vitamin D_3, which is immediately converted to biologically inactive vitamin D_3 in a heat-dependent process [8].

Vitamin D in these forms must be converted to the active hormone to be able to exert biological influence affecting mineral metabolism and other physiological functions. Vitamin D is transported in the blood by the vitamin D-binding protein (DBP) to the liver. In the liver vitamin D is hydroxylated at the C-25 position by one or more cytochrome P450 vitamin D 25 hydroxylases, resulting in the formation of 25(OH)D. 25-hydroxyvitamin D is the main storage form of vitamin D. In the proximal renal tubule (PCT), the enzyme 1-α-hydroxylase catalyzes the hydroxylation of 25 (OH) D (Figure 5) at the position of carbon 1 of the A ring resulting in the hormonally active form of vitamin D, 1.25-dihydroxyvitamin D (1.25 $(OH)_2$ D). Also called calcitriol, this is the biologically active form of vitamin D that acts on receptors in different target organs [9].

The renal synthesis of 1.25 (OH) D_2 is a tightly regulated step in itself, given its potent activity in calcium homeostasis (Figure 5). Dietary calcium can regulate vitamin D directly through changes in serum calcium and indirectly by altering parathyroid hormone (PTH) levels. 1-alpha hydroxylase can be suppressed by other factors such as phosphorus and chronic metabolic acidosis. However, high circulating calcium and fibroblast growth factor-23 (FGF-23) levels directly suppress renal 1-α-hydroxylase activity, via regulation of 1-α-hydroxylase gene transcription and indirectly through PTH suppression via cAMP-mediated changes. FGF-23 is a hormone produced by osteocytes and is a critical circulating hormone involved in phosphate metabolism [10].

B. VITAMIN D METABOLISM IN CKD (Chronic Kidney Disease)

The kidney is the key organ involved in production of bioactive forms of vitamin D from inert precursors. Consequently, chronic kidney disease is an important risk factor for development of vitamin D deficiency. There are several mechanisms by which $1.25(OH)_2D$ are lowered during the course of CKD, starting with decreased availability of the 25 (OD)D substrate for the

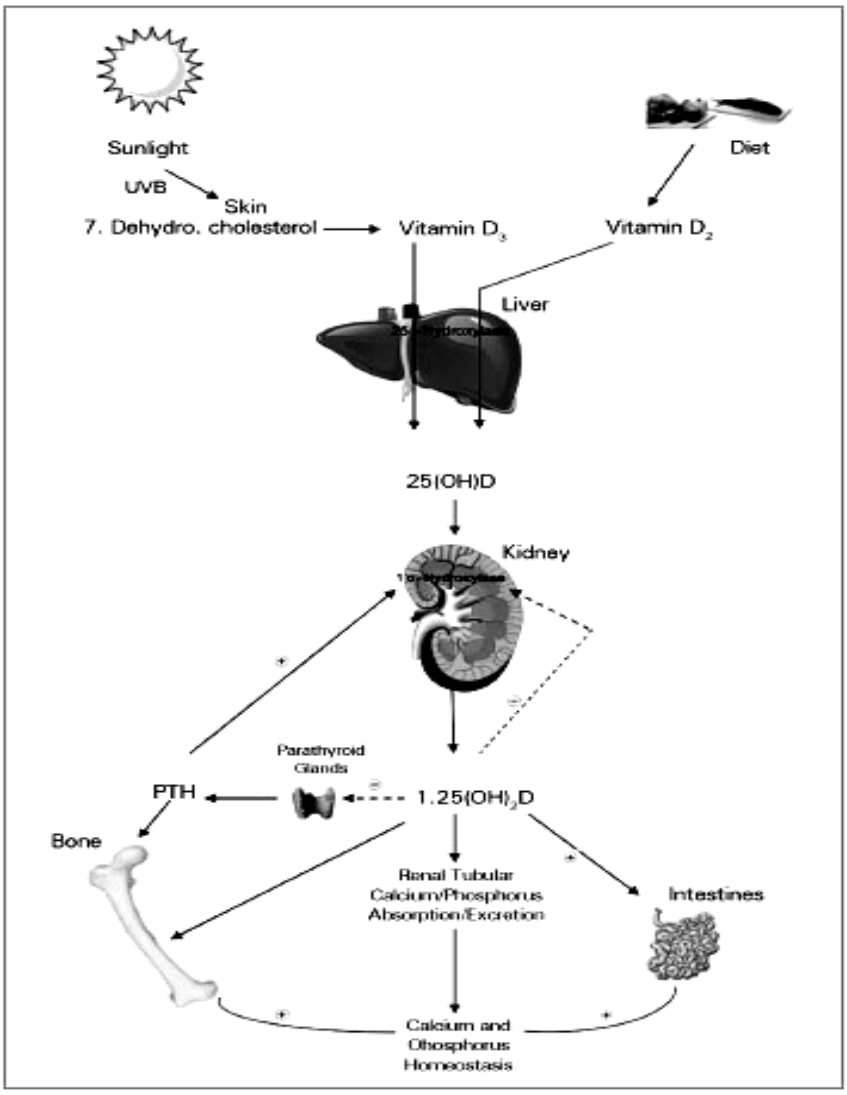

Figure 6: Sources and metabolism of vitamin D. UVB: Ultraviolet B; Vitamin D_3: cholecalciferol; Vitamin D_2: Ercalciferol; 25(OH)D: 25 hidroxyvitamin D; 1.25$(OH)_2$D: 1.25 dihydroxyvitamin D (calcitriol); PTH: Parathyroid hormone.

production of 1.25$(OH)_2$D (Figure 6). A reduction in glomerular filtration rates (GFR) limits the delivery of 25(OH) D to the 1-α-hydroxylase enzyme in the proximal renal tubule, and therefore restricts the ability of the kidney to produce 1.25$(OH)_2$D. Levels of phosphaturic hormone FGF-23 also increase early in CKD, presumably in response to phosphate retention, which also suppresses production of 1.25$(OH)_2$D. In addition to these factors, there may be additional contribution from potential suppressive effects of Carboxyl (C)-terminal fragments of PTH on 1.25$(OH)_2$D synthesis [11].

C. VITAMIN D DEFICIENCY IN CKD

The debate and speculation surrounding the role of Vitamin D supplementation is hindered in the inability to achieve consensus on a cut-off point to define Vitamin D deficiency. Adopting criteria based on levels

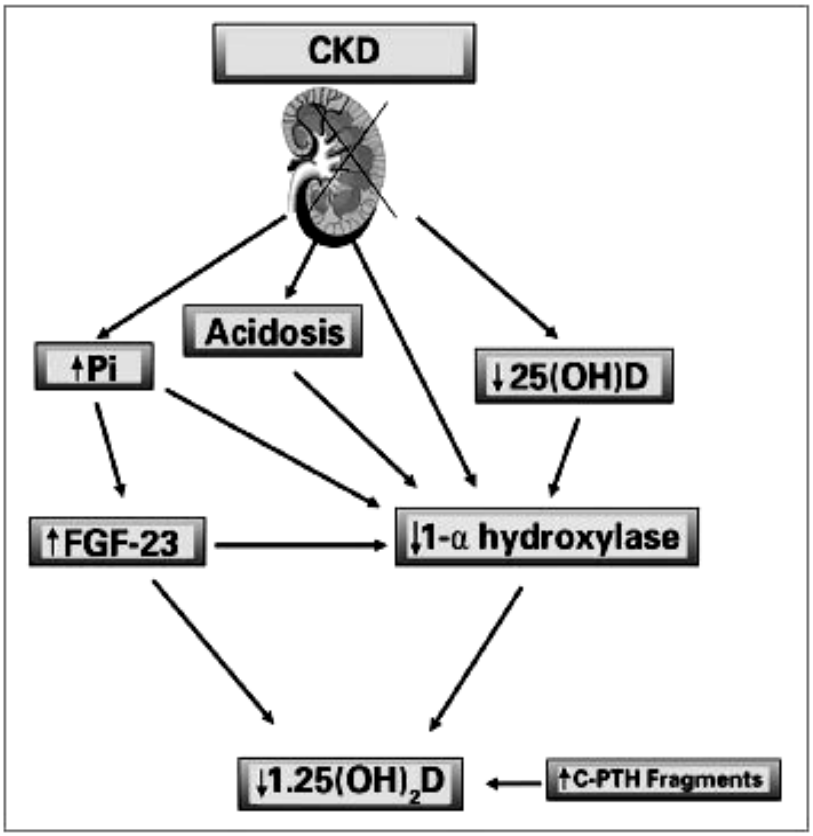

Figure 7: The mechanism contributing to the progressive decrease in the levels of 1.25 - dihydroxyvitamin D (calcitriol).

of 25(OH)D required to suppress PTH in mostly white populations, some experts have defined Vitamin D deficiency at serum 25(OH)D levels < 20 ng/mL and relative insufficiency as 21-29 ng/mL. A target ≥ 30 ng/mL has been suggested to be desirable for optimal health. It is important to remember that circulating $1.25(OH)_2D$ provides essentially no information with respect to the patient's nutritional vitamin D status [12].

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