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Vitamin D for your patients with chronic hepatitis C?

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Summary

Vitamin D is increasingly becoming recognized as an important physiological regulator with pleiotropic functions outside of its classical role in skeletal homeostasis. A growing body of clinical evidence highlights the prevalence and risks of vitamin D deficiency in patients suffering from chronic hepatitis C infection, and vitamin D supplementation has been proposed as an adjunct to current standards of care. This review considers the experimental evidence for the anti-inflammatory, antifibrotic and antiviral effects of vitamin D, and discusses the therapeutic potential of vitamin D supplementation to protect against liver disease progression and improve responses to treatment.

Introduction

Advances in hepatitis C virus (HCV) pharmaceutical development are being made at a blistering pace; however, highly effective, non-toxic therapies remain a hope for the future. This leaves an immediate need for interventions that can minimize disease progression and/or improve sustained virological response (SVR) rates in the short term. The aging of the HCV-positive population is creating an epidemic of end stage liver disease. Many patients cannot wait for second and third generation direct acting antiviral drugs to reach the clinic. As an *interim* measure, vitamin D supplements have been proposed as an adjunct to pegylated-interferon and ribavirin. This review integrates the known biological effects of the vitamin D system with recent clinical findings and discusses the therapeutic potential of vitamin D supplementation in HCV-positive patients.

Keywords: Hepatitis C; Vitamin D; 25(OH)D; $1,25(OH)_2D$; Inflammation.
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Abbreviations: HCV, hepatitis C virus; SVR, sustained virological response; 25(OH)D, 25-hydroxyvitamin D; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; VDR, vitamin D receptor; RXR, retinoid X receptor; VDREs, vitamin D response elements; PTH, parathyroid hormone; TLR, toll-like receptor; TNFR, tumor necrosis factor receptor.

Vitamin D metabolism

Unlike most vitamins, vitamin D is neither an enzyme co-factor nor an essential nutrient that must be obtained from food. Rather, it is a precursor of a seco-steroid hormone. Vitamin D can be manufactured endogenously from 7-dehydrocholesterol when skin is exposed to ultraviolet B radiation (Fig. 1). Historically, sun exposure was the main source of vitamin D, but food and supplements are now important sources, especially among urban populations and people who work indoors. During its conversion from a precursor to an active hormone, vitamin D is first modified in the liver by microsomal vitamin D 25-hydroxylases, which form 25-hydroxyvitamin D [25(OH)D], a stable metabolite that is the best single indicator of vitamin D status [1]. A second hydroxylation step, mediated by the mitochondrial cytochrome P450 oxidase, CYP27B1, produces the most biologically active metabolite, 1,25-dihydroxyvitamin D [$1,25(OH)_2D$]. In individuals with adequate renal function, most of the circulating $1,25(OH)_2D$ is produced by the kidney; however, CYP27B1 activity occurs in many extra-renal tissues, including innate immune cells, such as macrophages and dendritic cells. The local metabolism of 25(OH)D by these cells is likely to be an important factor in generating the high local concentrations of $1,25(OH)_2D$ needed for its paracrine and autocrine activities.

$1,25(OH)_2D$ mediates most of its biological effects by binding to the vitamin D receptor (VDR), which is expressed at some level in almost all human tissues. In the absence of its ligand, the VDR largely exists as an inactive homodimer. Upon binding $1,25(OH)_2D$, the VDR is phosphorylated and forms a heterodimer with its preferred binding partner, the retinoid X receptor (RXR), forming a nuclear transcription factor. This VDR/RXR heterodimer binds vitamin D response elements (VDREs) in DNA and recruits co-regulatory protein complexes to modulate the expression of hundreds of genes. In addition to acting as a ligand-activated transcription factor, the VDR is also thought to activate cell signaling pathways independent of its genomic effects [2].

The multiple steps in vitamin D bioactivation are controlled by intricate regulatory pathways [1]. CYP27B1 expression in the renal proximal tubule is stimulated by the parathyroid hormone (PTH), which is regulated by free serum calcium levels. $1,25(OH)_2D$ itself can directly and indirectly inhibit CYP27B1 expression, thereby providing a tight negative feedback loop. CYP27B1 expression in keratinocytes is stimulated by both PTH and inflammatory cytokines such as TNFα and IFNγ. $1,25(OH)_2D$ negatively regulates its own activity in these cells by inducing the expression of the $1,25(OH)_2D$ catabolic enzyme, CYP24A1. The functional expression of CYP27B1 and intracellular

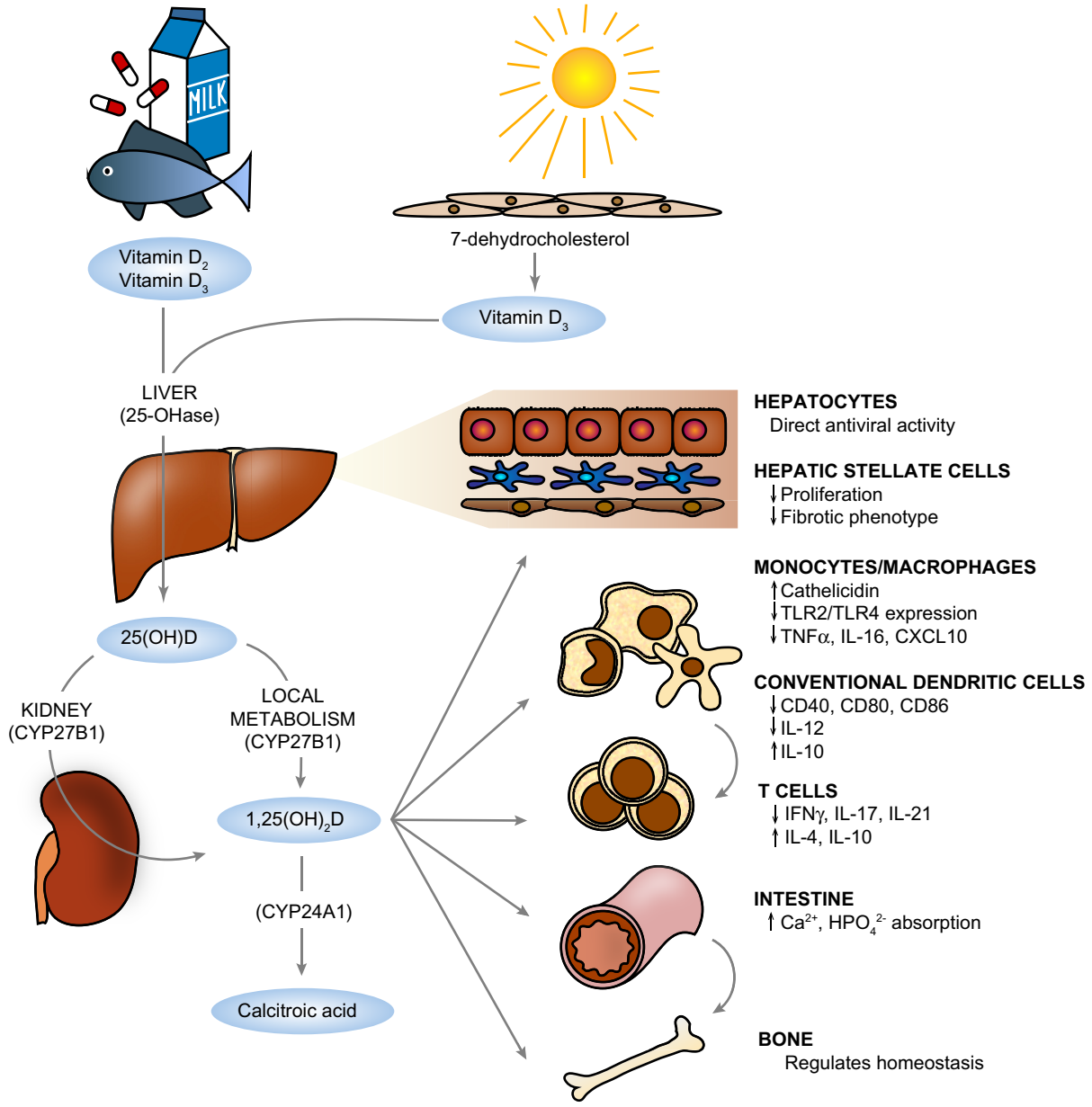

Fig. 1. Vitamin D is obtained from dietary sources and through the photochemical conversion of 7-dehydrocholesterol in the skin. It binds to vitamin D-binding protein and is transported to the liver, where it is hydroxylated by 25-hydroxylases to form 25(OH)D, a stable metabolite that is the best single indicator of vitamin D status. A second hydroxylation step, mediated by the 1a-hydroxylase CYP27B1 in the kidneys and other extrarenal tissues, produces the most active metabolite 1,25$(OH)_2$D, which signals primarily through the VDR, resulting in pleiotropic physiological effects, as highlighted in the Fig. 1,25$(OH)_2$D is catabolized by CPY24A1 to its inactive metabolite, calcitroic acid.

synthesis of 1,25$(OH)_2$D in macrophages are induced by both inflammatory cytokines, such as IFNγ, and toll-like receptor (TLR) ligands, such as lipopolysaccharide. Because vitamin D metabolism is controlled by multiple factors, the amount of vitamin D consumed in the diet is only one of many variables that determine the local activity of the vitamin D system. The levels of vitamin D binding protein and VDR are additional variables that strongly influence the magnitude of the biological effects of vitamin D.

VDR activation by 1,25$(OH)_2$D has long been known to increase intestinal calcium and phosphate absorption, fostering healthy bones. A growing number of recent studies reveal pleiotropic roles of 1,25$(OH)_2$D beyond bone and calcium metabolism, including the induction of antimicrobial genes and the reduction of inflammation and fibrogenesis [1]. Given the prevalence of bone disease, inflammation, and fibrosis in HCV-positive patients, both classical and newly-discovered effects of vitamin D may be relevant to disease management.

Vitamin D deficiency in patients with liver disease

Knowledge of the widespread physiological importance of vitamin D raises concern about the risks of vitamin D deficiency.