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D-livering the message: The importance of vitamin D status in chronic liver disease

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Summary

Vitamin D is synthesized predominantly in the liver and functions as an important secosteroid hormone with pleiotropic effects. While its key regulatory role in calcium and bone homeostasis is well established, recently there is increasing recognition that vitamin D also regulates cell proliferation and differentiation, and has immunomodulatory, anti-inflammatory and anti-fibrotic properties. These non-skeletal effects are relevant in the pathogenesis and treatment of many causes of chronic liver disease. Vitamin D deficiency is frequently present in chronic liver disease and may predict non-response to antiviral therapy in chronic hepatitis C. Small studies suggest that vitamin D supplementation improves sustained viral response rates, while 1α-hydroxylase polymorphisms and vitamin D-binding protein are also implicated in therapeutic outcomes. Vitamin D deficiency also closely relates to the severity of non-alcoholic fatty liver disease (NAFLD) and is implicated in the pathogenesis of insulin resistance, a key factor in the development of NAFLD. In preclinical studies, phototherapy and vitamin D supplementation ameliorate NAFLD histopathology, while vitamin D is a powerful anti-fibrotic against thioacetamide liver injury. In liver transplant recipients severe vitamin D deficiency predicts, and vitamin D supplementation prevents, acute cellular rejection. The role of vitamin D in the activation and regulation of both innate and adaptive immune systems may explain its importance in the above liver diseases. Further prospective studies are therefore warranted to investigate the therapeutic impact of vitamin D supplementation in chronic liver disease.

Introduction

Vitamin D is an important secosteroid hormone with pleiotropic effects (Table 1). While its role in the regulation of calcium and bone homeostasis is well established, recently there is increasing recognition that vitamin D has immunomodulatory, anti-inflammatory and anti-fibrotic properties and plays an important role in the regulation of cell proliferation and differentiation. These extraskeletal effects are relevant in the pathogenesis and treatment of many causes of chronic liver disease.

Vitamin D synthesis and metabolism

Vitamin D undergoes a 3-step activation process before it interacts with the vitamin D receptor. The majority of circulating vitamin D is synthesized in the skin as a result of exposure to sunlight. The initial step involves ultraviolet-B radiation (wavelength 290–315 nm) converting the cholesterol metabolite 7-dehydrocholesterol into previtamin D_3 in the lower epidermis, which is rapidly converted to vitamin D_3 in a heat-dependent process. However, excessive sunlight exposure does not cause vitamin D intoxication because excess vitamin D_3 is destroyed by sunlight [1]. Only a small proportion of vitamin D is obtained from dietary sources such as fatty fish, eggs, UV-irradiated mushrooms, supplements, and artificially fortified foods (Table 2). Dietary-derived vitamins D_2 (ergocalciferol) and D_3 (cholecalciferol) are absorbed via a bile-acid dependent process whereby vitamin D is incorporated into micelles in the intestinal lumen, then absorbed by enterocytes and packaged into chylomicrons that are then transported to the venous circulation via lymphatic drainage. Vitamin D from both skin synthesis and dietary sources can either be stored in adipocytes or undergo 25-hydroxylation in the liver. This process is mediated by the 25-hydroxylases, which are cytochrome P450 isoforms that include the important microsomal CYP2R1 and the mitochondrial CYP27A1 enzymes. This produces the main circulating, though biologically inactive, form 25-hydroxyvitamin D [25(OH)D], or calcidiol, which has a long half-life of 2–3 weeks and is therefore used to assess vitamin D status. The vast majority (88%) of serum 25(OH)D is bound to vitamin D-binding protein (DBP), which is also known as Gc or the group-specific component of globulin. DBP is a 58 kDa α-macroglobulin almost exclusively synthesized by the liver and a member of the albumin gene family located on chromosome 4, with high sequence homology to albumin and α-fetoprotein [2]. It is highly polymorphic, having three common isoforms, Gc1F, Gc1S, and Gc2, that display marked racial variation [3], with the Gc1F isoform having the highest affinity for vitamin D metabolites. DBP has anti-inflammatory and immunomodulatory functions independent of its role as the carrier of vitamin D [4,5].

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Table 1. Pleiotropic effects of vitamin D.

Target	Action
Hepatic	
	Inhibits *in vitro* HCV replication in a dose-dependent manner [30-32]
	Supplementation may improve SVR rate in HCV [36-38]
	Vitamin D-binding protein is one of 3 metaproteins associated with SVR in HCV [40]
	Supplementation/phototherapy improves liver histology in preclinical studies of NAFLD [58]
	Supplementation prevents liver fibrosis in preclinical studies [62,63]
	Supplementation decreases risk of acute rejection post-transplantation [125]
Extra-hepatic	
Mortality	Supplementation decreases mortality by 7% [16]
Calcium and bone homeostasis	Enhances Ca and PO_4 absorption from small intestine [6]
	Suppresses PTH secretion [6]
	Induces osteoclast maturation [6]
Pancreas/adipocytes	BMI inversely associated with 25(OH)D level [46]
	Normal vitamin D status associated with 67% lower prevalence of metabolic syndrome [47]
	Activates transcription of insulin gene [50]
	Supplementation improves insulin sensitivity and lowers risk of developing type 2 diabetes [52-54]
Immune system	
Innate	Activates macrophage TLR response to TB infection [95]
	Hastens sputum culture conversion in pulmonary TB in those with tt *Taq*I *VDR* allele [100]
	Downregulates expression of TLR2, TLR4 and TLR9 [107-110]
	Necessary for NK cell development and function [114]
	Enhances NK cell cytotoxicity [115]
	Promotes tolerant DC phenotype by suppressing DC maturation [116]
	Enhances secretion of IL10 and decreases secretion of IL12 from DCs [122]
Adaptive	Activates naïve T cells [117]
	Inhibits proliferation of Th1 lymphocytes [118]
	Shifts balance to a Th2 phenotype [119]
	Increases Treg cells [120,121]
	Inhibits Th17 cell development [121]
	Supplementation decreases risk of developing MS in women [85] and type 1 diabetes in children [86]
Carcinogenesis	Higher 25(OH)D levels associated with lower incidence of colorectal adenoma [135]
	Sunlight exposure associated with reduced risk of NHL [145]

The final step in the synthesis of vitamin D is 1α-hydroxylation that predominantly occurs in the proximal tubule of the kidney but also to a lesser extent in lymphocytes and parathyroid tissue. It is mediated by 1α-hydroxylase (CYP27B1) that produces the active form 1α,25-dihydroxyvitamin D [1α,25$(OH)_2$D] or calcitriol, which is also highly bound to DBP (85%) [2] and has a half-life of only 4 h. 1α,25$(OH)_2$D is the ligand that activates the vitamin D receptor (VDR). This then forms a heterodimer with the retinoid X receptor that acts as a transcription factor that binds to vitamin D response elements in the promoter region of target genes. 1α-hydroxylation is under the influence of factors such as serum phosphate and calcium concentration, parathyroid hormone (PTH), fibroblast growth factor 23 and genetic polymorphisms of *CYP27B1*. 1α,25$(OH)_2$D acts in a negative feedback loop to decrease its own synthesis and increase the expression of 25-hydroxyvitamin D-24-hydoxylase (CYP24A1), which catabolizes 1α,25$(OH)_2$D into calcitroic acid, a biologically inert agent excreted in the bile (Fig. 1).

VDR is expressed in most tissues and cells of the human body, including liver, pancreas, and several immune cells including monocytes, macrophages, T lymphocytes, B lymphocytes, natural killer (NK) cells, and dendritic cells (DC), with expression most abundant on the epithelial cells of the gastrointestinal tract. As a transcription factor activated by 1α,25$(OH)_2$D, VDR directly or indirectly regulates the expression of more than 200 genes that influence cell proliferation, differentiation and apoptosis, as well as immunomodulation and angiogenesis [6]. Studies in VDR null mice highlight the broad physiologic function of vitamin D [7].

Vitamin D deficiency

Vitamin D deficiency is broadly defined as a serum 25(OH)D level <50 nmol/L (<20 ng/ml). Levels between 75 and 125 nmol/L (30–50 ng/ml) are considered optimal as PTH levels rise when 25(OH)D is <75 nmol/L (30 ng/ml); hence, levels between 50