MINI REVIEW

Vitamin D and the vitamin D receptor in liver pathophysiology

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Summary  Vitamin D through the vitamin D nuclear receptor (VDR) plays a key role in mineral ion homeostasis. The liver is central in vitamin D synthesis, however the direct involvement of the vitamin D-VDR axis on the liver remains to be evaluated. In this review, we will describe vitamin D metabolism and the mechanisms of homeostatic control. We will also address the associations between the vitamin D-VDR axis and pathological liver entities, such as non-alcoholic fatty liver disease, autoimmune liver disease, viral hepatitis and liver cancer. The link between liver diseases and the vitamin D-VDR axis will be discussed in light of evidences arising from in vitro and in vivo studies. Finally, we will consider the therapeutic potential of the vitamin D-VDR axis in liver diseases.

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The vitamin D-VDR axis has a wide range of cellular and tissue activities. Increasing evidence tends to link the vitamin D-VDR axis to hepatic physiology and pathophysiology. However, the molecular mechanisms by which the vitamin D-VDR axis impacts the liver still need to be defined. The low VDR expression in the liver suggests indirect mechanisms that could arise from tissues with high VDR expression levels. However, a direct effect of the vitamin D-VDR axis cannot be ruled out, because VDR is expressed in non-parenchymal liver cells.

Vitamin D metabolism

Vitamin D is a secosteroid hormone whose principal biological action is to regulate mineral and skeletal homeostasis. Vitamin D can be obtained from exogenous sources (vitamin D\textsubscript{3}) or can be endogenously synthesized from cholesterol (vitamin D\textsubscript{2}). The endogenous synthesis of vitamin D is elicited in the skin by the conversion of 7-dehydrocholesterol to pre-vitamin D\textsubscript{3} by ultraviolet radiation \cite{1}. This initial step is followed by a thermal isomerization of pre-vitamin D\textsubscript{3} to vitamin D\textsubscript{3}. Irrespective
Endogenous synthesis of vitamin D occurs in the skin under sunlight exposure. Whether from endogenous or dietary origin, vitamin D is subjected to two consecutive hydroxylations, occurring first in the liver and then in the kidney. These sequential reactions lead to the production of the active form of vitamin D, 1,25(OH)2D. Vitamin D homeostasis is tightly regulated by hormonal and mineral control. Serum phosphate level directly regulates vitamin D synthesis, while calcium regulation is mediated by the parathyroid hormone. Finally, 1,25(OH)2D exerts a feedback control on its own synthesis and also positively regulates its catabolism.

The production of vitamin D is a tightly regulated process under the control of hormones, dietary calcium and phosphate levels. Vitamin D regulates its own synthesis by directly decreasing 1α-hydroxylase activity [4] and by inhibiting the parathyroid hormone (PTH) action [5]. PTH controls 1,25(OH)2D production by inducing the expression of renal 1α-hydroxylase through a cAMP-dependent pathway [5,6] (Fig. 1). High calcium serum level also directly suppresses the expression and activity of 1α-hydroxylase. Moreover, calcium indirectly regulates 1α-hydroxylase expression by decreasing PTH levels [7,8] (Fig. 1). Finally, high serum phosphate levels decrease the expression and activity of 1α-hydroxylase by a mechanism independent of PTH and calcium levels. Because serum FGF23 increases when serum phosphate rises, the effect of phosphate on the vitamin D synthesis pathway may be mediated by the FGF23-Klotho axis [9]. Yet, the mechanism by which FGF23 decreases circulating 1,25(OH)2D levels needs to be clarified.

Vitamin D metabolism may also be locally regulated by pro-inflammatory signals acting on monocytes/macrophages. In these cells, bacterial products or INF-γ induce the expression of 1α-hydroxylase [10,11], resulting in the local production of 1,25(OH)2D. Active vitamin D will then control the ability of monocyte/macrophage to avoid excessive inflammatory response while inducing innate defenses by an autocrine mechanism [11,12]. This local production of vitamin D has no influence on the circulating levels of vitamin D except in pathophysiological settings, such as granulomatous diseases [13]. Because almost 90% of all tissue macrophages are located in the liver [14], hepatic production of active vitamin D may be of local importance in inflammatory liver diseases.
Table 1  Examples of genes directly regulated by VDR.

<table>
<thead>
<tr>
<th>Gene function</th>
<th>Gene</th>
<th>Regulation</th>
<th>Tissue or cell type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism</td>
<td>Parathyroid hormone (PTH)</td>
<td>-</td>
<td>Parathyroid glands</td>
</tr>
<tr>
<td></td>
<td>24-hydroxylase</td>
<td>+</td>
<td>All VDR target tissues</td>
</tr>
<tr>
<td></td>
<td>FGF15</td>
<td>+</td>
<td>Intestine</td>
</tr>
<tr>
<td></td>
<td>1[alpha]-hydroxylase</td>
<td>-</td>
<td>Kidney</td>
</tr>
<tr>
<td></td>
<td>CYP3A4</td>
<td>+</td>
<td>Intestine, liver, hepatocytes</td>
</tr>
<tr>
<td></td>
<td>MRP3</td>
<td>+</td>
<td>Intestine</td>
</tr>
<tr>
<td></td>
<td>SULT2A1</td>
<td>+</td>
<td>Hepatocyte cell line, colon cells</td>
</tr>
<tr>
<td></td>
<td>Calbindin D9K</td>
<td>+</td>
<td>Intestine</td>
</tr>
<tr>
<td></td>
<td>TRPV6</td>
<td>+</td>
<td>Intestine</td>
</tr>
<tr>
<td>Detoxification and transport</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CYP3A4</td>
<td>+</td>
<td>Intestine, liver, hepatocytes</td>
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<tr>
<td></td>
<td>MRP3</td>
<td>+</td>
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<td>Calbindin D9K</td>
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<tr>
<td></td>
<td>TRPV6</td>
<td>+</td>
<td>Intestine</td>
</tr>
<tr>
<td>Immunity</td>
<td>Cathelicidin (LL37)</td>
<td>+</td>
<td>Biliary epithelial cells, immune cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(monocytes, neutrophils, myeloid cells,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>colon cells, keratinocytes</td>
</tr>
<tr>
<td></td>
<td>Defensin β2</td>
<td>+</td>
<td>Immune cells (monocytes, neutrophils,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>keratinocytes</td>
</tr>
<tr>
<td></td>
<td>FasL/CD95L</td>
<td>-</td>
<td>T lymphocytes</td>
</tr>
<tr>
<td></td>
<td>Alkaline phosphatase</td>
<td>+</td>
<td>Osteosarcoma cells</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>ASBT</td>
<td>+</td>
<td>Intestine, colon cells</td>
</tr>
<tr>
<td></td>
<td>EGFR</td>
<td>-</td>
<td>Breast cells</td>
</tr>
<tr>
<td></td>
<td>E-cadherin</td>
<td>+</td>
<td>Colon</td>
</tr>
</tbody>
</table>

Vitamin D homeostasis is also regulated through catabolic control. Indeed, 1,25(OH)_{2}D induces the expression of the catabolic enzyme, 24-hydroxylase (i.e. CYP24A1), in all vitamin D target tissues [15,16]. Furthermore, the expression and activity of 24-hydroxylase are repressed by PTH [17] and increased by phosphate levels [9]. Thus, the catabolism and synthesis of vitamin D are inversely regulated. The products of 24-hydroxylase activity are biologically inactive and are either excreted as calcitroic acid or converted to further excretion products [18].

The vitamin D and vitamin D metabolites circulating levels thus result from active synthesis and catabolism. While 1,25(OH)_{2}D serum levels do not vary, 25(OH)D levels increase according to vitamin D uptake and/or synthesis. Furthermore, serum 25(OH)D levels are usually a thousand time higher than 1,25(OH)_{2}D levels. Thus, 25(OH)D serum level is commonly used as an indicator of vitamin D status [19]. 1,25(OH)_{2}D and 25(OH)D do not circulate freely in the serum but are transported bound to the vitamin D binding protein (DBP). DBP is a liver synthesized protein able to bind vitamin D and its derivatives, with the highest affinity being observed for 25(OH)D [20]. The biological actions of vitamin D are thus in part controlled by DBP that protects the hormone from catabolism and excretion.

**Vitamin D mechanism of action**

The biological effects of 1,25(OH)_{2}D are mainly mediated by the vitamin D nuclear receptor (VDR), as evidenced by VDR gene mutations in type 2 vitamin D dependent rickets [21]. Furthermore, VDR null mice have a similar phenotype to patients with vitamin D deficiency or type 2 vitamin D dependent rickets, as they display severe rickets, osteomalacia, alopecia, hypocalcemia and hypophosphatemia [22–25]. VDR expression has been identified in all major vitamin D target tissues, such as bone, kidney, thyroid and intestine [26], but also in the skin, immune cells and non-parenchymal liver cells [27,28], suggesting that VDR may impact physiology besides mineral ion homestasis. Thus, the analysis of VDR null mice that are rescued from their altered mineral ion homestasis by a diet enriched in calcium, phosphorus and lactose, may allow to discriminate the impact of VDR, independently of mineral ion status [29].

VDR is part of the NR1I family, a subgroup of the nuclear hormone receptor superfamily [30]. Accordingly, VDR has four major domains conferring ligand-activated transcription factor activities. Thus, VDR is organized as follows: (1) a ligand-binding domain, (2) a retinoid X receptor (RXR) heterodimerization domain, (3) a DNA binding domain to vitamin D response elements and (4) a recruitment domain of VDR coregulators. Once vitamin D is bound, VDR forms a heterodimer with RXR that binds to DNA and recruits coactivators or corepressors to promote or repress transcription of 1,25(OH)_{2}D target genes (Table 1 and Supplementary Table 1).

Besides gene regulation activities, vitamin D also exerts rapid nongenomic actions through cell surface receptors [31,32]. Because VDR is required for rapid nongenomic effects of 1,25(OH)_{2}D on chloride and calcium channels in osteoblasts [33], it was suggested that VDR was also accountable for nongenomic effects of vitamin D. Furthermore, VDR was localized in caveolea-enriched plasma membranes of intestinal, lung, kidney cells and osteoblasts, where it efficiently binds 1,25(OH)_{2}D [34]. However, 1,25(OH)_{2}D rapid effects are identical in VDR+/+ and VDR−/− osteoblasts, indicating that VDR is not required for most vitamin D rapid responses [35]. Another vitamin D membrane receptor candidate is the membrane-associated rapid-response steroid-binding protein (1,25D-MARRS). 1,25D-MARRS or ERp57/GRp58/ERp60 is mostly known as a soluble protein
of the endoplasmic reticulum, where it promotes the folding and quality control of newly synthesized proteins as part of the calnexin/calreticulin chaperone system [36]. The 1,25D3-MARRS receptor was cloned in duodenal chick cells [37], where the existence of a membrane vitamin D receptor was first demonstrated [38]. 1,25D3-MARRS binds 1,25(OH)2D3 with a similar affinity to VDR [39]. Furthermore, the stimulation of phosphate uptake by 1,25(OH)2D3 in chick intestinal epithelial cells is abolished when 1,25D3-MARRS expression is decreased [40]. These observations suggest that 1,25D3-MARRS may be accountable for the rapid nongenomic effects of vitamin D. However, 1,25D3-MARRS tissue distribution and biological significance still needs to be defined.

These observations indicate that 1,25(OH)2D covers a wide spectrum of biological actions that are essentially mediated by VDR. Vitamin D serum levels have dramatically decreased during the past few years in northern populations [41], suggesting that homeostasis of mineral, immunity or detoxification may be altered. The latter assumption is of particular interest in gastrointestinal and liver diseases, in which vitamin D levels are decreased [42—44]. This observation also suggests that alterations in the vitamin D-VDR axis may precede or worsen gastrointestinal and liver diseases.

Vitamin D, VDR and hepatic pathophysiology

Vitamin D, VDR and non-alcoholic fatty liver disease (NAFLD)

Vitamin D serum levels negatively correlate with insulin resistance and the metabolic syndrome [45]. Like other members of the nuclear factor superfamily, that control metabolic and energy homeostasis, VDR may be involved in metabolic diseases. The hepatic component of the metabolic syndrome is considered to be the accumulation of fat in hepatocytes. Interestingly, lower vitamin D levels are associated with increased severity of steatosis, necroinflammation and fibrosis in NAFLD. Furthermore, serum vitamin D levels could predict the severity of NAFLD independently of other components of the metabolic syndrome, such as insulin resistance or body mass index [46]. This observation made in adults was confirmed in children, in which low levels of vitamin D are correlated with the histological severity of NAFLD independently of metabolic characteristics [47]. The molecular mechanisms by which the vitamin D-VDR axis controls hepatic lipid homeostasis and associated inflammation are however unclear. Because the development of inflammation and fibrosis in NAFLD may be linked to signals arising from extrahepatic sources [48], the vitamin D-VDR axis could be involved in NAFLD through its ability to modulate immunity.

Vitamin D, VDR and autoimmune liver diseases

VDR is expressed in almost all immune cells and mediates the immunoregulatory properties of vitamin D [20]. Indeed, vitamin D through VDR interferes directly with T cells by inhibiting the production of T-helper-1 (Th1) type cytokines, while promoting those of the Th2 subtype. Furthermore, vitamin D inhibits dendritic cell differentiation resulting also in a decreased in Th1 cell development [49]. Taken together, these observations indicate that vitamin D through VDR diminishes the effector T cell response suggesting that the vitamin D-VDR axis may be involved in autoimmune diseases [50]. Consistently, VDR polymorphisms have been identified in primary biliary cirrhosis (PBC) and autoimmune hepatitis (AIH). However, the difference in population origin and small sample sizes led to the identification of different VDR polymorphisms in PBC [51—55]. VDR polymorphisms have also been associated with decreased bone mineral density in PBC [56], indicating that VDR genetics might not only influence the susceptibility of the disease but also associated complications. Taken together, these observations indicate a potential link between the vitamin D-VDR axis and viral hepatitis.

Vitamin D, VDR and viral hepatitis

Cellular immunity is crucial in the pathogenesis of chronic viral infections caused by the hepatitis B and C viruses (HBV and HCV, respectively). Consistently, low vitamin D serum levels have been correlated with the severity of inflammation and fibrosis in chronic hepatitis C [57]. However, no genetic association between VDR polymorphism and HCV infection has yet been evidenced [58]. Moreover, the serum concentrations of DBP were inversely correlated with fibrosis in patients with HCV [59,60]. Because decreased DBP leads to increased vitamin D catabolism [61], the observation of decreased circulating DBP suggests a decreased efficacy of the vitamin D-VDR axis in HCV patients. In HBV, VDR polymorphisms have been associated with infection susceptibility and clinical course in Asian, African and Middle Eastern populations [62—65]. Taken together, these observations indicate a potential link between the vitamin D-VDR axis and viral hepatitis.

Vitamin D, VDR and liver cancer

HBV and HCV chronic infections are major risk factor for the development of hepatocellular carcinoma (HCC). HCC mainly occurs in the context of cirrhosis elicited by exogenous agents, but is also influenced by genetic status. The genetic analysis of VDR in HCC specimens of various etiologies showed a significant association between VDR polymorphisms and alcohol-related HCC [58]. Furthermore, VDR expression increases in HCC tissue compared to normal non-cancerous liver [66]. In human liver cancer cell lines, the activation of VDR by vitamin D or pharmacological ligand decreases cell proliferation [67,68], suggesting that the vitamin D-VDR axis may have anti-proliferative activity on cancerous hepatocytes. The levels of circulating DBP are also diminished in patients with HCC [59], suggesting that the vitamin D-VDR axis is less efficient in these patients. Moreover, VDR expression is also increased in cholangiocarcinoma when compared to normal biliary tissue [66,69]. In this neoplasm arising from the biliary epithelium, VDR expression increased with tumor differentiation and patients survival [69]. Thus, the vitamin D-VDR axis could represent a therapeutic target in hepatic cancers arising either from hepatocytes or biliary epithelial cells.
Altogether, these observations indicate that the vitamin D-VDR axis is linked to hepatic pathophysiology by yet unknown mechanisms. In this context, information originating from basic research studies may uncover the molecular mechanisms elicited by the vitamin D-VDR in the liver.

**Vitamin D action in the liver: evidences from basic research**

Few experimental studies have addressed the impact of vitamin D or VDR in hepatic pathophysiology, mostly because VDR expression is low or absent in the liver [26]. In adult rats, VDR is highly expressed in the intestine and kidney, but present in minute amounts in the liver [70]. This observation was however challenged by a study indicating that all liver cells are positive in the adult rat [71]. While VDR transcript expression was detected in fetal liver, RT-PCR signals were however barely detectable in the adult liver [71]. An in-depth analysis of VDR expression in all liver cell types showed that transcripts and proteins are virtually absent from hepatocytes, while clearly expressed in non-parenchymal cells, such as biliary epithelial cells [28].

Biliary epithelial cells, which are exposed to circulating vitamin D and to vitamin D present in bile [72], respond to VDR activation by increasing the expression of cathelicidin, an antimicrobial peptide with anti-endotoxin activities [73]. Surprisingly, vitamin D was also shown to have detoxifying activities in human primary cultured hepatocytes by increasing the expression of P450 cytochromes (i.e. CYP3A4, CYP2B6 and CYP2C9) [74]. The effect of vitamin D could be mediated by VDR, since the promoters of these genes display VDR response elements (VDRE). Moreover, the expression of CYP7A1 is also controlled by 1,25(OH)2D3 in human primary cultured hepatocytes [75]. However, the CYP7A1 promoter does not have any VDRE sequence, suggesting that 1,25(OH)2D3 exerts its effect through a nongenomc pathway. This pathway could involve the phosphorylation of VDR and the recruitment of c-Src. The VDR/c-Src complex may then activate a MAPK pathway that would lead to transcriptional control through the displacement of HNF-4[alpha] on bile acid response elements (BARE) [76]. A direct or indirect biological action of vitamin D through VDR is however controversial since normal hepatocytes have been reported to express little or no VDR.

Compared to normal hepatocytes, transformed hepatocytes strongly express VDR [77]. In the HepG2 human hepatoma cell line, 1,25(OH)2D3 activates VDR to directly induce the expression of the dehydroepiandrosterone sulfo-transferase (SULT2A1), a detoxifying enzyme that mediates the sulfo-conjugation of toxic compounds [78]. Besides this direct effect, VDR may also control gene expression by the sulfo-conjugation of toxic compounds [78]. This pathway could involve the phosphorylation of VDR and the recruitment of c-Src. The VDR/c-Src complex may then activate a MAPK pathway that would lead to transcriptional control through the displacement of HNF-4[alpha] on bile acid response elements (BARE) [76]. A direct or indirect biological action of vitamin D through VDR is however controversial since normal hepatocytes have been reported to express little or no VDR.

The possibility that vitamin D impacts liver physiology is however supported by experimental evidence indicating that vitamin D controls hepatic gene expression [81,82]. The weak or absent effect of 1,25(OH)2D3 on transcript expression in human and rat liver slices suggests that the signals regulating gene expression in hepatocytes may arise from extrahepatic cells or tissues [83]. The latter assumption is supported by an anti-cholestatic effect of 1(OH)D3 in bile duct-ligated (BDL) mice that may result from an action of the hormone on inflammatory cells [84]. Indeed, circulating inflammatory cytokines, such as IL-1β, IL-6 and TNFα, are decreased in BDL mice injected with 1(OH)D3, while no significant difference can be observed in the hepatic transcript levels of these cytokines [84]. In line with these observations, phototherapy or 1(OH)D3 ameliorate diet-induced steatohepatitis in the rat, in part through the control of inflammatory gene expression [85]. Furthermore, 1,25(OH)2D3 was also shown to decrease hepatic Cyp7a1 expression by increasing the expression of Fgf15 in the intestine [86]. Consistently, Cyp7a1 expression was increased in mice lacking VDR when compared to wild type mice, indicating that intestinal VDR activity controls the basal expression of Cyp7a1 [86]. The impact of the vitamin D-VDR axis on bile acid homeostasis is however controversial, since long-term injection of vitamin D in another mouse strain resulted in an increase in Cyp7a1 expression [84]. Thus, the involvement and mechanism of action of the vitamin D-VDR axis in the liver still needs to be clarified.

**Therapeutic potential of vitamin D in liver diseases**

Vitamin D or analogs have shown potential therapeutic benefit in preclinical model of diseases, such as autoimmune disorders or cancer [87]. Thus, vitamin D or analogs could be used as well in the treatment of liver diseases. In PBC, activation of the vitamin D-VDR axis could be of therapeutic interest. Indeed, VDR expression is increased by UDCA, the only efficient medical therapy available for inflammatory biliary diseases, in the liver of patients with PBC [73]. The latter observation could explain at least in part the therapeutic benefit of UDCA in PBC patients and suggests that combinatory therapy or the use of vitamin D analogs could be of benefit in PBC.

The potential use of vitamin D in NAFLD has become more apparent with preclinical models of steatosis [88]. Furthermore, a randomized controlled trial has shown that ursodeoxycholic acid (UDCA), which controls the VDR pathway in liver cells [73], decreases ALT, metabolic parameters, such as serum glucose, and Fibrotest values in NASH patients [89]. The potential of the vitamin D-VDR axis to diminish the extent of fibrosis has also been discussed in the context of chronic hepatitis C [90], following the observation that serum vitamin D levels are inversely correlated with fibrosis in HCV patients [57].

Because vitamin D decreases the proliferative capacity of transformed hepatocytes, a trial was developed to evaluate the use of a VDR agonist (i.e. EB1089 oresecalcitol) in HCC patients [91]. In this open, noncontrolled, multicenter study including 56 patients with inoperable HCC, the oral dose of seocalcitol was adjusted to avoid hypercalcemia. Out of the 33 patients that were assessed for antitumor effect, two showed a complete response, 12 had a stable
disease, while the remaining 19 patients did not respond to treatment [91]. These findings even though encouraging did not result in additional trials.

Conclusion

The vitamin D through VDR is involved in mineral ion homeostasis, immunity control and detoxification of xenobiotics or endogenous compounds. The liver, by transforming vitamin D into 25(OH)D, is a key organ in vitamin D synthesis. Together with an insufficient dietary absorption, the latter observation may explain the vitamin D deficiency observed in most liver diseases. Moreover, a deficit in the vitamin D-VDR axis signaling may represent a risk factor for the development of liver diseases. Indeed, low vitamin D, VDR polymorphisms or altered VDR expression have been associated with NAFLD, autoimmune liver diseases and liver cancer. Because VDR expression is low or absent from hepatocytes, the association of the vitamin D-VDR axis with liver pathophysiology may result from an alteration of signals that stem from non-parenchymal liver cells or extrahepatic cells. This observation is of particular importance in high prevalence diseases such as NAFLD, in which the vitamin D-VDR axis has been involved without identifying the responsible molecular mechanisms. The involvement of the vitamin D-VDR axis in biliary-type or fibrotic liver diseases may also be of interest, because these diseases involve either biliary epithelial cells or hepatic stellate cells, that both express high levels of VDR. These observations ask for the development of basic research studies that will elucidate the intimate relationship between the vitamin D-VDR axis and the liver.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.clinre.2011.02.003.

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