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REVIEW

Theoretical basis of a beneficial role for vitamin D in viral hepatitis

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Abstract

Abnormal bone metabolism and dysfunction of the calcium-parathyroid hormone-vitamin D axis have been reported in patients with viral hepatitis. Some studies suggested a relationship between vitamin D and viral hepatitis. Genetic studies have provided an opportunity to identify the proteins that link vitamin D to the pathology of viral hepatitis (i.e., the major histocompatibility complex class Ⅱ molecules, the vitamin D receptor, cytochrome P_{450}, the renin-angiotensin system, apolipoprotein E, liver X receptor, toll-like receptor, and the proteins regulated by the Sp1 promoter gene). Vitamin D also exerts its effects on viral hepatitis *via* non-genomic factors, i.e., matrix metalloproteinase, endothelial vascular growth factor, prostaglandins, cyclooxygenase-2, and oxidative stress. In conclusion, vitamin D could have a beneficial role in viral hepatitis. Calcitriol is best used for viral hepatitis because it is the active form of the vitamin D_3 metabolite.

Key words: Calcitriol; Hepatitis; Hepatitis B virus; Hepatitis C virus; Vitamin D

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INTRODUCTION

Abnormal bone metabolism and dysfunction of the calcium-parathyroid hormone (PTH)-vitamin D axis have been reported in patients with viral hepatitis. In these patients, bone mineral density (BMD) was reduced in the lumbar spine and femoral neck[1-4]. The prevalence and severity of bone loss increases based on the severity of the liver disease[2]. Biochemical markers of bone resorption, such as urinary telopeptide (NTX) and pyridinoline, bone-specific alkaline phosphatase, and serum levels of PTH, were increased in patients with chronic viral hepatitis[1,4-9]. Serum insulin-like growth factor-1 (IGF-1) and 25-hydroxyvitamin D_3 (25OHD) were lower in patients with viral hepatitis[1,8-10]. However, other studies demonstrated contradictory results with respect to bone metabolism in patients with chronic viral hepatitis. Osteosclerosis was reported in patients with hepatitis C virus (HCV) and was associated with normal levels of IGF-1. It is also associated with an increased levels of osteoproterin (OPG) and the ligand for receptor activator of nuclear factor-κB (RANK)[11,12]. Serum levels of PTH were lower in patients with HCV compared to controls[6,13]. These findings suggested that there might be a relationship between vitamin D and viral hepatitis. In this paper, we review the role of vitamin D in patients with viral hepatitis.

GENETIC FACTORS RELATED TO VITAMIN D IN VIRAL HEPATITIS

The major histocompatibility complex (MHC) class Ⅱ molecules play an important role in immune functioning

and are essential to the body's defense against infection. The human MHC class Ⅱ is encoded by three different isotypes, *HLA-DR*, *HLA-DQ*, and *HLA-DP*. Studies have suggested that several genes in the MHC region promote susceptibility to viral hepatitis. Human leukocyte antigen (HLA) genes, which are located in the MHC region, have been implicated in viral hepatitis susceptibility. *HLA-DRB1*12* is significantly more common in children with autoimmune hepatitis with positive hepatitis A IgM than in children with negative hepatitis A IgM[14]. In addition, the *HLA-DPA1* and *HLA-DPB1* genes are known to be associated with hepatitis B virus (HBV) infection in Han Chinese, Japanese, and Thai populations[15-18]. However, *HLA-DPA1* was not associated with the development of cirrhosis or hepatocellular carcinoma (HCC) in Han Chinese populations[19]. Genetic variants in the *HLA-DPA1* region may also affect treatment-induced hepatitis B e antigen (HBeAg) sero-conversion[20]. In the normal human liver, mRNA expression of *HLA-DPA1* and *HLA-DPB1* are important for control of HBV[21]. *HLA-DRB1*1101* correlates with less severe hepatitis in Taiwanese male carriers of HBV[22]. *HLA-DRB1*1302* was reported to be associated with protection against persistent HBV infection in Gambian populations[23]. In South Indian populations, a significantly higher frequency of *HLA-DRB1*0701* was observed in patients with chronic viral illness compared with individuals who spontaneously recover (SR), but *HLA-DRB1*0301* was noted to be of higher frequency in the SR group than the chronic HBV group[24]. In patients from Eastern Turkey, *DQ2* and *DQ8* have been noted to be markedly higher in patients with chronic HBV than those with SR[25]. The presence of *DQw1* may protect against chronic active HBV infection[26]. In addition, patients with chronic HBV infection and the *DQB1*0303* and *DRB1*08* haplotypes may be less responsive to interferon alpha (IFNα) treatment[27]. Moreover, *DRB1*11*, *DRB1*0301*, and *DRB1*04* were found to confer a significant protective advantage against HCV infection[28-31]. These alleles might be responsible for the selection of viral epitopes for presentation to $CD4^+$ T cells, leading to a more efficient immune response against the virus. In a meta-analysis study, both *DQB1*0301* and *DRB1*1101* were protective alleles and presented HCV epitopes more effectively to $CD4^+$ T lymphocytes than other epitopes, Indeed, subjects with these two alleles were at a lower risk of developing chronic HCV infection[32]. On the other hand, calcitriol is known to stimulate phagocytosis but suppresses MHC class Ⅱ antigen expression in human mononuclear phagocytes[33,34]. In peripheral blood leukocytes, the expression of *HLA-DR* decreased after calcitriol administration in renal transplant recipients[35]. Calcitriol also decreases interferon-gamma-induced HLA-DR antigen expression on normal and transformed human keratinocytes and cultured epithelial tumor cell lines[35,36]. Both DR and DQ protein levels on the surface of a myeloma cell line were decreased after calcitriol treatment[37]. Moreover, calcitriol inhibits the expression of all three subtypes of MHC class Ⅱ antigens (*HLA-DR*, *HL-ADP*, and *HLA-DQ*) as well as the accessory activity of monocytes, both in a dose- and time-dependent manner[38]. These findings suggest that calcitriol may have an impact on viral hepatitis by suppressing the expression of MHC class Ⅱ antigens.

Genetic studies provide an opportunity to link molecular variations with epidemiological data. DNA sequence variations, such as polymorphisms, exert both modest and subtle biological effects. Vitamin D exerts immunomodulatory and anti-proliferative effects through the vitamin D receptor (VDR) in numerous diseases. VDR gene polymorphisms are reported to be associated with distinct clinical phenotypes in Taiwanese hepatitis B virus (HBV) carriers[39]. There is an association between *Taq1* and *Fok1* polymorphisms of VDR and HBV outcomes in Chinese patients[40]. The *tt* genotype of VDR polymorphism is linked to persistent HBV infection in African patients[41]. Polymorphisms in the *TT* allele of exon 9 of VDR are associated with occult HBV infection in Iranian patients[42]. Significant differences in the frequency of the allelic distribution of the *Apa1* of VDR are reported to occur more frequently in patients with HBV complicated by severe liver disease as well as those with higher viral loads[43]. These observations suggest that alterations in VDR function may play a role in viral hepatitis.

The cytochrome P_{450} (*CYP*) system is responsible for the oxidation, peroxidation, and/or reduction of vitamins and for the metabolism of steroids, xenobiotics, and various drugs. The *CYP27B1-1260* promoter polymorphism has been reported to be associated with vitamin D deficiency and an increased risk of fracture in the elderly[44]. Reduced 25OHD levels associated with the *CYP27B1-1260* promoter polymorphism results in reduced 1,25OHD levels and are associated with failure to achieve sustained virologic response (SVR) in patients with hepatitis C virus (HCV) genotypes 1, 2, and 3[45]. In Huh7.5 hepatoma cells, HCV infection increased calcitriol production by inhibiting *CYP24A1* induction, the enzyme responsible for the first step in calcitriol catabolism[46]. *CYP24A1* methylation tended to correlate with better prognosis in HCV-related HCC[47].

The primary function of the renin-angiotensin system (RAS) is to maintain fluid homeostasis and regulate blood pressure. Angiotensin converting enzyme (ACE) is a key enzyme in the RAS and converts angiotensin (AT) I to the potent vasoconstrictor AT Ⅱ[48]. Hepatic stellate cells (HSCs) are recognized as the main collagen-producing cells in injured hepatic tissue. Angiotensin Ⅱ (AT Ⅱ) mediates key biological actions involved in hepatic tissue repair, including myofibroblast proliferation, infiltration of inflammatory cells, and collagen synthesis. Activated HSCs secrete AT Ⅱ[49]. ACE2 expression is significantly increased in the context of liver injury, in both humans and rats[50]. In addition, AT Ⅱ levels are much higher in patients with HBV when compared to controls. These levels were directly related to the severity of the illness and decrease markedly with captopril, which is an ACE inhibitor[51]. A statistically significant correlation has been

noted between polymorphisms in the promoter region of the *AT* gene and the development of progressive hepatic fibrosis in patients with chronic HCV[52]. In recurrent hepatitis C infection, male liver recipients who were carriers of the *D* allele of *ACE* appeared to gain more weight after liver transplantation; in female recipients, however, carriers of the *D* allele appear to experience more severe allograft fibrosis[53]. Losartan, an AT1 receptor blocker, attenuates liver fibrosis in experimental models and in patients with chronic hepatitis C and significantly decreases the expression of several profibrogenic and NADPH oxidase (NOX) genes[54]. The administration of AT-blocking agents reduced the development of graft fibrosis in hepatitis C recurrence after liver transplantation[55]. However, there is also an interaction between vitamin D and the RAS. The combination of ACE inhibitors with the ACE *DD* genotype has been shown to decrease the level of calcitriol[56]. In Turkish populations of hypertensive patients, the presence of the *ACE D* allele is associated with a higher risk of left ventricular mass index and ambulatory blood pressure measurement, which is negatively correlated with serum 25OHD levels[57]. In addition, genetic disruptions of the VDR gene result in overstimulation of the RAS, resulting in increased renin and AT Ⅱ productions and subsequently leading to elevated blood pressure and cardiac hypertrophy. Treatment with captopril reduced cardiac hypertrophy in VDR knockout mice[58], suggesting that calcitriol could function as an hormonal suppressor of renin biosynthesis. Moreover, calcitriol suppresses renin gene transcription by blocking the activity of the cyclic AMP response element in the renin core promoter[59] and decreases ACE activity in bovine endothelial cells[60].

Apolipoprotein E (ApoE) is critical to systemic and local lipid transport and is a major genetic factor in viral hepatitis. The hepatitis virus is associated with serum lipoproteins, including ApoE and ApoB, and may enter cells *via* the low-density lipoprotein receptor (LDL-R). In *in vitro* models, the co-culture of hepatocytes with liver sinusoidal endothelial cells (LSEC) significantly increases the ability of hepatocytes to uptake low-density lipoprotein (LDL) and also results in a high level of HCV-like particle uptake[61]. The cell surface expression of LDL-R has been reported to correlate well with LDL-cholesterol and HCV-viral load[62]. ApoE antibody can block both HCV entry an the knockdown of the LDL-R reduced HCV infection of cells[63]. Human ApoE is required for the infectivity and assembly of HCV[64,65]. The *ApoE ε4* allele protects against severe liver disease caused by HCV[66], while *ApoE ε3* is associated with persistent HCV infection[67]. In addition, patients with chronic hepatitis C who do not carrying an *ApoE* ε3 allele, as well as carriers of a single *ApoE* ε3 allele with a serum cholesterol concentration over 190 mg/dL, were more likely to have a favorable outcome[68]. Moreover, lipoprotein abnormalities found in the early phases of acute hepatitis; low levels of serum cholesterol and ApoA associated with the severity of liver cell injury in chronic liver disease[69]. The nonstructural protein 5A (NS5A) of the HCV has been shown to interact with $ApoA_1$[70]. A decreased level of $ApoA_1$ was found in the LDL fractions of HCV-infected patients; the specific siRNA-mediated down-regulation of $ApoA_1$ led to a reduction in both HCV RNA and viral particle levels in culture[71]. On the other hand, the *ApoE4* allele is reported to be associated with decreased bone mass in postmenopausal Japanese women[72]. The common *ApoE* polymorphism has a complex effect on bone metabolism in peri-menopausal Danish women: those with *ApoE2* have lower bone mineral losses in the femoral neck and hip region than other women, whereas those with *ApoE4* gain more bone mineral than other women[73]. Calcitriol has been shown to induce macrophages to exhibit specific saturable receptors for LDL and acetyl-LDL; the LDL receptor of 1,25OHD-induced macrophages has been found to exhibit specificity for ApoB and E-containing lipoproteins[74]. In ApoE knockout mice, an animal model of dyslipidemia, high oxidative stress, and pronounced atherosclerosis after unilateral nephrectomy, animals developed less plaque growth and calcification with vitamin D analog treatment (paricalcitol) compared to healthy controls[75,76]. *ApoE ε4*, however, is associated with higher serum 25OHD levels[77]. Moreover, hypovitaminosis D is associated with reductions in serum $ApoA_1$[78] and a highly significant positive correlation was found between serum concentrations of 25OHD and *$ApoA_1$*[79]. In addition, calcitriol was reported to suppress *$ApoA_1$* gene expression at the transcriptional level in hepatocytes[80].

Lipids have been shown to play important roles in the viral life cycle and pathogenesis of infection. HBV infection of primary hepatocyte cultures is dependent on the presence of cholesterol in the viral envelope. The extraction of cholesterol from HBV purified from the plasma of HBV-infected patients leads to a strongly reduced level of infection, whereas infectivity is only regained by adding cholesterol back[81]. A number of lipid metabolic pathways were disrupted by HCV infection, resulting in an increase in cholesterol and sphingolipid levels[82]. Higher serum triglycerides, total cholesterol and LDL levels were correlated with higher HCV RNA levels[83]. Ceestatin, a novel small molecule inhibitor of hepatitis C virus replication, inhibits 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase in a dose-dependent manner[84]. Polyunsaturated liposomes are reported to be antiviral against hepatitis B and C viruses by decreasing cholesterol levels in infected cells[85]. Moreover, HCV and HBV X protein increases the hepatic lipogenesis is mediated predominantly by the liver X receptor (LXR)[86-88]. LDL receptor-related protein 5 (LRP5) is essential for normal cholesterol and glucose metabolism. Mice lacking LRP5 develop both increased plasma cholesterol levels when fed a high-fat diet markedly impaired glucose tolerance when fed a normal diet[89]. HCV core protein activates Wnt/β-catenin signaling molecules, such as LRP5/6 co-receptors[90], whereas calcitriol regulates the expression of LRP5 *via* DNA sequences elements located downstream of the transcription start site[91]. Notably,

high serum 25OHD concentrations are associated with a favorable serum lipid profile, e.g., total cholesterol and high-density cholesterol (HDL-C)[92]. Low levels of active vitamin D (calcitriol) are also associated with low HDL-C levels[93]. Moreover, calcitriol has been shown to suppress foam cell formation by reducing acetylated LDL (AcLDL) and oxidized LDL (oxLDL) cholesterol uptake by macrophages[94]. In addition, calcitriol also inhibits the activity of HMG-CoA reductase, an enzyme required for cholesterol biosynthesis[95]. In male VDR knockout mice, serum total cholesterol and LXRβ levels were significantly higher than those in wild type mice[96]. The crosstalk between LXRα and VDR signaling in the regulation of bile acid metabolism suggests a possible contribution of the VDR to the modulation of bile acid and cholesterol homeostasis[97].

Toll-like receptors (TLRs) are a group of glycoproteins that functions as surface trans-membrane receptors and are involved in innate immune responses to exogenous pathogenic microorganisms. Substantial evidence supports an important role for TLRs in the pathogenesis and outcomes of viral hepatitis. There is a correlation between hypo-responsiveness to TLR ligands and liver dysfunction in HCV infection[98]. The disruption of TLR-3, TLR-7, and TLR-9 signaling was reported in viral hepatitis[99-101]. *In vivo*, TLR signaling also inhibits HBV replication[102]. TLR-2 polymorphisms that impair the recognition of HCV core and nonstructure 3 proteins may be associated with allograft failure and mortality after liver transplantation for chronic HCV[103,104]. These polymorphisms affect HCV viral loads and increase the risk of HCC in patients infected with HCV genotype 1[105]. The TLR-3 polymorphism may predispose Asian Indian populations to HCV infection[106] and protect Han Chinese populations from HBV recurrence after liver transplantation[107]. TLR-7 polymorphisms are protective against from development of inflammation and fibrosis in male patients with chronic HCV infection and are predictive of the response to IFN treatment[108-110]. TLR-2 and TLR-4 polymorphisms are not associated with liver cirrhosis in HCV infected Korean patients[111]. RNA levels of TLRs 2, 4, 6, 7, 8, 9 and 10 were up-regulated in both the monocytes and T cells of HCV-infected patients when compared to controls[112,113]. In obese rats, vitamin D deficiency increases the expression of hepatic mRNA levels of TLR-2, TLR-4, and TLR-9[114]. However, calcitriol is also known to suppress the expression of the TLR-2 and TLR-4 protein and mRNA in human monocytes; it also triggers hypo-responsiveness to pathogen-associated molecular patterns[115]. Calcitriol has also been shown to down-regulate intracellular TLR-2, TLR-4 and TLR-9 expression in human monocytes[116]. TLR activation results in the expression of VDR and 1α-vitamin D hydroxylase in human monocytes[117]. Calcitriol can cause vitamin D-induced expression of cathelicidin in bronchial epithelial cells[118] and may enhance the production of cathelicidin LL-37[119]. The addition of a VDR antagonist has been shown to inhibit the induction of cathelicidin mRNA by more than 80%; consequently, the protein expression of this antimicrobial agent was reduced by approximately 70%[118].

The HBV major surface antigen promoter contains four functional transcription factor Sp1 binding sites, which likely contribute to the level of expression from this promoter during viral infection[120-122]. HCV-core protein functions as a positive regulator of IGF-Ⅱ transcription *via* the protein kinase C (PKC) pathway, and Sp1 and Egr1 are direct targets of the transcriptional regulation of the IGF-Ⅱ, which plays an important role in HCV pathogenesis during the formation of HCC[122,123]. Steatosis is an important clinical manifestation of HCV infection. Sp1 is involved in sterol regulatory element-binding protein-1c (SREBP-1c) activation, which activates the transcription of lipogenic genes by HCV-3a NSSA[124]. Moreover, Sp1 might participate in triggering HCV core protein up-regulation of the extracellular matrix metalloproteinase (MMP) inducer expression and progression of metastasis[125]. On the other hand, binding sites for the transcription factor Sp1 have been implicated in the hormone-dependent transcription of several genes. In cultured human fibroblasts, the level of CYP24 (25-OHD 24-hydroxylase) mRNA plays a key role in the metabolism of 1,25OHD and increases responsiveness to calcitriol by 20 000-fold. Two vitamin D-responsive elements (VDREs) located upstream of the *CYP24* gene are primarily responsible increased mRNA levels, and Sp1 has been noted to act synergistically with these VDREs in this induction[126]. The mVDR promoter is controlled by Sp1 sites[127] and functions as the transactivation component of the VDR/Sp1 complex to trigger gene expression[128]. Moreover, the genes encoding Sp1, VDR, the locus for the vitamin D-dependent rickets type Ⅰ, and hepatitis B virus-positive hepatocellular carcinomas from Thai patients were mapped to human chromosome 12q[129,130].

THE NON-GENETIC ROLE OF VITAMIN D IN HEPATITIS

A high prevalence of vitamin D deficiency was reported in HCV patients[10,131]. Low serum 25OHD levels are also found in patients with human immuno-deficient virus (HIV) and HCV and are correlated with severe liver fibrosis[132,133]. Preparations containing vitamin D_3 were shown to be effective in reducing the severity of the syndrome associated with osteo-arthropathy, including a decrease in BMD in Ukrainians with chronic hepatitis B and C[134]. The combination of vitamin A (25 000 IU) and vitamin D_2 (2500 IU) enhances the re-vaccination reaction against HBV in Chinese children[135]. *In vitro*, vitamin D_2 is reported to inhibit HCV RNA replication and its combination with β-carotene and linoleic acid also causes an additive and/or synergistic effect with respect to HCV RNA replication[136]. VDR mRNA and protein were found in the rat liver throughout the animal's life span[137]. In another study, however, human and mouse hepato-

cytes were found to have very low nuclear VDR (nVDR) mRNA and protein levels, whereas the sinusoidal endothelial, Kupffer, and stellate cells of the normal rat liver as well as a mouse biliary cell line clearly expressed the nVDR gene transcript[138]. Vitamin D_3 dramatically inhibits HCV production in Huh7.5 hepatoma cells and in combination with INF-α, also synergistically suppresses HCV production in human hepatocytes[47]. Serum vitamin D levels are complimentary to the IL-28B polymorphism in enhancing the accurate prediction of the SVR in patients undergoing treatment for chronic HCV[139]. Low vitamin D is linked to severe liver fibrosis and low SVR in response to IFN-based therapy in genotype 1 chronic HCV patients[10]. Vitamin D supplementation also improves SVR in chronic HCV-naïve patients[140] and in response to antiviral treatment for recurrent HCV infection in liver transplant patients[141]. These findings suggest that vitamin D may play a role in the treatment of HCV. Chronic infection with viral hepatitis is a major risk factor worldwide for the development of HCC. Vitamin D analogs have been reported to reduce tumor volume in patients with inoperable HCC[142] and to increase apoptosis of hepatocarcinoma cells by 21.4%[143]. In another pilot study, an intra-arterial injection of calcitriol in lipiodol into the hepatic artery was given to eight refractory HCC patients and led to the stabilization of α-fetoprotein levels[144].

MMPs are proteolytic enzymes that are responsible for extracellular matrix remodeling and the regulation of leukocyte migration through the extracellular matrix, which is important step for inflammatory processes and infectious diseases. MMPs are produced by many cell types including lymphocytes, granulocytes, astrocytes and activated macrophages. During the course of chronic HCV infection, hepatic mRNA expression of MMPs has been shown to either increase steadily with disease progression (MMP-1, MMP-2, MMP-7, and MMP-14) or increase transiently (MMP-9, MMP-11, and MMP-13), depending on the type of MMP[145]. Serum and tissue MMP-9 expression were reported to decrease in chronic HCV patients treated with pegylated INF-α2b and ribavirin[146]. The ratio of MMP-9 to MMP-2 is useful in distinguishing between patients with early stage and advanced HCC[147]. Serum TIMP-1 levels decreased significantly during and after treatment in sustained responders[148]. MMP-3 polymorphisms are associated with persistent HBV infection and advanced liver cirrhosis in Korean populations[149,150]. MMP-1, MMP-3, and MMP-9 polymorphisms are associated with the progression of HCV-related chronic liver disease in Japanese populations and may be a risk factor for poor prognosis in HCC patients[151,152]. However, VDR knock-out mice demonstrated an increased influx of inflammatory cells, phospho-acetylation of NF-κB associated with increased pro-inflammatory cells, and up-regulation of MMP-2, MMP-9, and MMP-12 in the lung[153]. The VDR *TaqI* polymorphism is associated with a decreased production of TIMP-1, which is a natural inhibitor of MMP-9[154]. Calcitriol modulates tissue MMP expression under experimental conditions[155], down-regulates MMP-9 levels in keratinocytes, and may attenuate the deleterious effects caused by the excessive TNF-α-induced proteolytic activity associated with cutaneous inflammation[156]. Calcitriol inhibits both basal and the staphylococcus-stimulated production of MMP-9 in human blood monocytes and alveolar macrophages[157]. Moreover, a vitamin D analog was also reported to reduce the expression of MMP-2, MMP-9, vascular endothelial growth factor (VEGF) and PTH-related peptide in Lewis lung carcinoma cells[158]. Furthermore, calcitriol significantly attenuated *Mycobacterium tuberculosis* (*M. tuberculosis*)-induced increases in the expression of MMP-7 and MMP-10, while suppressing the secretion of MMP-7 by *M. tuberculosis*-infected PBMCs. MMP-9 gene expression, secretion and activity were significantly inhibited, irrespective of infection status[159]. Calcitriol also suppressed the production of MMPs (MMP-7 and MMP-9) and enhanced the level of TIMP-1 in tuberculosis patients[160]. In human articular chondrocytes, calcitriol significantly suppresses the increased production of MMP-9 that is induced by phorbol myristate acetate (PMA)[161]. These studies suggest that calcitriol may play an important role in the pathological process of viral hepatitis by down-regulating the levels of MMPs and regulating the levels of TIMPs.

Angiogenesis is a complex process involving the coordinated steps of endothelial cell activation, proliferation, migration, tube formation and capillary sprouting, which require the participation of intracellular signaling pathways. VEGF is a key mediator of angiogenesis. Vascular changes associated with angiogenesis usually occur in cancer; however, they have also been reported to occur in inflammatory disease processes. HCV C protein can activate the expression of VEGF in hepatoma cell lines ($HepG_2$) and might contribute to viral carcinogenesis[162]. Co-expression of the HBV X gene and the HCV core gene also increase the expression of VEGF in $HepG_2$ cells and act synergistically in carcinogenesis[163]. The expression levels of TNFα mRNA and VEGF mRNA showed a positive correlation with the progression of viral hepatitis to cirrhosis, i.e., the higher levels of TNFα and VEGF mRNA, the higher the prevalence of HCC[164]. HBV X protein is known to up-regulate the expression of VEGF, thereby promoting angiogenesis in HCC *via* NFκB signaling pathway[165]. Serum VEGF concentration is a predictor of invasion and metastasis in HCC[166] and positively correlates with the recurrence rate of HCC after curative resection[167]. In contrast, calcitriol was reported to inhibit angiogenesis *in vitro* and *in vivo*[168]. Calcitriol significantly inhibits VEGF-induced endothelial cell spouting and elongation in a dose-dependent manner and decreases the production of VEGF[169]. Calcitriol is a potent inhibitor of retinal neovascularization in a mouse model of oxygen-induced ischemic retinopathy[170]. Vitamin D and its analog also reduce the expression of VEGF in various cancer cell lines[158,171]. Moreover, *DBP-maf* was reported to inhibit angiogenesis and tumor

growth in mice[172] and inhibits the VEGF signaling by decreasing VEGF-mediated phosphorylation of VEGF-2 and ERK1/2, a downstream target of the VEGF signaling cascade[173]. These findings suggested that vitamin D modulates angiogenesis in viral hepatitis and may impact the mechanism of progression to HCC in patients with viral hepatitis.

Prostaglandins (PGs) play a role in inflammatory processes. Cyclooxygenase (COX) participates in the conversion of arachidonic acid to PGs. HBV X protein was reported to up-regulate levels of COX-2, 5-lipoxygenase and phosphorylated extracellular signal-regulated protein kinase ½ (p-ERK1/2) and releases arachidonic acid metabolites in liver cells[174]. In liver samples from patients with chronic HCV infection, there is a significant correlation between the dominant intensity of COX-2 and the presence of histological steatosis and an inverse correlation was observed between COX-2 and viral load[175]. COX-2 up-regulates VEGF expression and tumor angiogenesis in HBV-associated HCC *via* PG production; selective COX-2 inhibitors may block HCC-associated angiogenesis and an increase in platelet counts when used with pegylated TFNα2a[176,177]. Indomethacin also cleared HBV DNA in chronic healthy carriers, and 5 patients with positive HBeAg became negative after 4 mo[178]. On the other hand, calcitriol has been reported to regulate the expression of several key genes involved in the PG pathway, resulting in a decrease in PG synthesis[179]. Calcitriol and its analogs have been shown to selectively inhibit the activity of COX-2[180]. These findings suggested that vitamin D plays a role in modulating the inflammatory process in viral hepatitis.

Reactive oxygen species (ROS) are produced by activated phagocytes as a part of their microbicidal activities. Intracellular hydrogen peroxide (H_2O_2) levels are significantly higher in patients with chronic HCV infection than in asymptomatic carriers and positively correlates with alanine amino-transferase (ALT) levels[181]. ROS can also modulate the intracellular level of HBV X protein. The direct addition of H_2O_2 to cells significantly increased the level of HBV X protein in HBV X protein ChangX-34 cells, while antioxidants completely abolished the increase in HBV X protein[182]. There is a significant decrease glutathione (GSH) levels in the patients with HBV-infected[183]. Superoxide dismutase (SOD) was present in peripheral blood mononuclear cells (PBMC) but was absent in the liver of patients with chronic HCV infection[184]. Levels of lipid peroxidation products are increased in serum, leukocyte, and liver specimens in HCV patients[185]. Similarly, calcitriol has been reported to exert a receptor-mediated effect on the secretion of H_2O_2 by human monocytes[186]. Human monocytes in culture gradually lose their capacity to produce superoxide when stimulated. The addition of calcitriol, lipopolysaccharide or lipoteichoic acid restored the ability of stimulated monocytes to produce superoxide and increased their oxidative capacity when compared with unstimulated monocytes[187]. Calcitriol can also protect nonmalignant prostate cells from oxidative stress-induced cell death by eliminating ROS-induced cellular injuries[188]. Vitamin D metabolites and vitamin D analogs were reported to induce lipoxygenase mRNA expression, lipoxygenase activity and ROS in a human bone cell line[189]. Vitamin D can also reduce the extent of lipid peroxidation and induce SOD activity in the hepatic anti-oxidant system of rats[190]. These findings suggested that vitamin D modulates oxidative stress in viral hepatitis.

Nitric oxide (NO) is a reactive nitrogen species (RNS) that is critical in the redox biology of hepatocytes and is formed by nitric oxide synthase (NOS). In the liver, iNOS was found to be important in the development and propagation of inflammation. Viral hepatitis is associated with an increased iNOS expression[191,192]. HCV infection can also stimulate the production of iNOS through the activation of the iNOS gene by the viral core protein and the NS3 protein[191]. In patients with HCC, the combined negative expression of iNOS and COX-2 on histology has a significant impact on patient survival[193]. Oxidative DNA damage has been reported to increase chromosomal aberrations associated with cell transformation, and oxidative stress has also been suggested in the development of HCV-associated HCC. Oxidative DNA damage was observed in circulating leukocytes and occurs as an early event in chronic HCV infection[194]. NO often damage mitochondria, leading to the induction of double-stranded DNA breaks and the accumulation of oxidative DNA damage[195]. The viral core and NS3 proteins were shown to be responsible for inhibition of DNA repair, which is mediated by NO and ROS[196]. On the other hand, the activation of macrophage 1α-hydroxylase results in an increase in 1,25 OHD, which inhibits iNOS expression and reduces the NO produced by LPS-stimulated macrophages[197]. This calcitriol production by macrophages could provide protection against the oxidative injuries caused by the NO burst. Calcitriol is known to inhibit LPS-induced immune activation in human endothelial cells[198]. Calcitriol enhances intracellular GSH pools and significantly reduces the nitrite production induced by LPS[199]. In human macrophage-like cells, calcitriol induces iNOS and suppresses the growth of *M. tuberculosis*[200]. Moreover, calcitriol protects against doxorubicin-induced chromosomal aberrations in rat bone marrow cells[201]. Calcitriol also acts synergistically with vanadium in inhibiting diethylnitrosamine-induced chromosomal aberrations and DNA-strand breaks in the rat liver[202]. In regenerating liver cells, calcitriol regulates the synthesis of DNA polymerase-alpha, generates functional ribonucleotide reductase subunits, and induces DNA replication[203,204]. In addition, calcitriol appears to be effective in suppressing liver-specific early chromosomal damage as well as DNA damage during the process of rat hepatocarcinogenesis[205].

CONCLUSION

The relationship between vitamin D and viral hepatitis

has been discussed. Vitamin D may have a beneficial role in viral hepatitis. Genetic studies have provided the opportunity to determine what proteins link vitamin D to the pathology of viral hepatitis. Vitamin D also exerts its effect on viral hepatitis *via* non-genomic mechanisms. As a result, it is imperative that vitamin D levels in patients with viral hepatitis be followed. Many studies use the relationship between serum PTH and 25OHD to define the normal range of serum 25OHD. According to the report on Dietary Reference Intakes for vitamin D and calcium by the Institute of Medicine (IOM), persons are at risk of deficiency at serum 25OHD levels less than 30 nmol/L. Recently, Saliba *et al*[206] suggested that a 25OHD threshold of 50 nmol/L is sufficient for PTH suppression and prevention of secondary hyperparathyroidism in persons with normal renal function. Calcitriol is best used for viral hepatitis, because of its active form of vitamin D_3 metabolite and inhibits inflammatory cytokine expression. Adjusting dose for calcitriol depends on serum calcium and PTH levels. However, monitoring of serum 25OHD after calcitriol intake is not necessary because calcitriol inhibits the production of serum 25OHD in the liver[207,208]. Further investigation with calcitriol in viral hepatitis is needed.

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