Review Article

New insight of vitamin D in chronic liver diseases

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BACKGROUND: **Vitamin D is a fat-soluble sterol derivative that is predominantly synthesized in the liver and has multiple functions. The accumulative data showed that the clinical manifestations and prognosis of chronic liver diseases are associated with serum vitamin D levels.**

DATA SOURCES: **A PubMed and Google Scholar search using terms: "vitamin D", "25(OH)D", "liver disease", "viral hepatitis", "non-alcoholic fatty liver disease", "liver fibrosis", "cirrhosis", "hepatocellular carcinoma" and "autoimmune liver disease" was performed, and relevant articles published in English between January 2000 and March 2014 were reviewed. Full-text publications relevant to the field were selected and relevant articles from reference lists were also included.**

RESULTS: **The insufficiency or deficiency of vitamin D is common in various kinds of chronic liver diseases including viral hepatitis B and C. Serum 25-hydroxyvitamin D and vitamin D receptors are possibly interrelated with the incidence, treatment and prognosis of diseases. Though the evidence of vitamin D supplementation in viral hepatitis and associated liver diseases is still limited, there is great potential to apply this adjuvant therapy to improve the treatments.**

CONCLUSIONS: **Although the exact role and mechanisms of vitamin D have not been fully elucidated in chronic liver diseases, it is potentially beneficial in the treatment of chronic liver diseases. Further mechanistic studies are needed to validate its clinical application.**

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KEY WORDS: **vitamin D; deficiency; viral hepatitis; chronic liver diseases**

Introduction

Vitamin D, the sunshine vitamin, is now recognized not only for its importance of bone health in humans,[1] but also for other health benefits including reducing the risk or progression of chronic liver diseases (CLDs). Vitamin D produced in the skin or ingested in the diet is biologically inert and requires two successive hydroxylations first in the liver on carbon 25 to form 25-hydroxyvitamin D [25(OH)D], and then in the kidney for a hydroxylation on carbon 1 to form the most important biologically active form of vitamin D, 1, 25-dihydroxyvitamin D [1, 25$(OH)_2$D].[2] It is worthy to mention that extra renal hydroxylation of 25(OH)D is also important for the non-skeletal actions of vitamin D, because 1, 25$(OH)_2$D controls a variety of genes directly or indirectly to regulate cellular proliferation, differentiation, apoptosis and angiogenesis.[3]

In the past decades, methods have been developed to measure serum 25(OH)D and 1, 25$(OH)_2$D concentrations *in vivo*. In recent years, lots of evidences suggest that serum 25(OH)D is the best indicator of vitamin D status *in vivo*;[4] while serum 1, 25$(OH)_2$D provides limited information about vitamin D status, because it is often normal or even elevated due to secondary hyperparathyroidism associated with vitamin D deficiency. So serum 25(OH)D examination now has been widely used to evaluate vitamin D concentrations in clinical practice.[4]

Clinical and epidemiological data have shown that chronic viral hepatitis and their extrahepatic manifestations are associated with lower vitamin D concentrations.[5] In recent years, there has been considerable speculation about the potential role of vitamin D in the treatment of CLD patients with low serum vitamin D levels.[6, 7] It is encouraging that the therapeutic value of vitamin D supplement has been confirmed in autoimmune liver diseases.[8, 9] And a recent study[10] also showed the association between vitamin D shortage and the severity of chronic viral hepatitis, non-alcoholic fatty liver disease (NAFLD) and other CLDs. In this review, we briefly summarize the

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new progress of factors affecting vitamin D deficiency in common CLDs and the correlation of viral hepatitis and other CLDs with reduced serum 25(OH)D concentrations.

Factors associated with vitamin D deficiency

Serum 25(OH)D concentration is an objective variable reflecting vitamin D restoration in body, but there is no exact definition of its normal range in real clinical setting. In general population, the normal concentration of serum 25(OH)D is 75-120 nmol/L (30-50 ng/mL), inadequate concentration is 50-75 nmol/L (20-30 ng/mL), while shortage concentration is less than 50 nmol/L (<20 ng/mL); and there is no difference between male and female populations. According to this standard, approximately one billion people worldwide are vitamin D inadequate or shortage.

Most scholars believe that the lack of sun ultraviolet exposure is the main cause of vitamin D insufficiency, because air pollution induced by modern industry retard the necessary ultraviolet radiation which is essential for vitamin D synthesis.[11] Currently, modern lifestyle habits also play a pivotal role in vitamin D inadequate or shortage. To prevent skin aging or cancer, sun umbrella and sunscreen cosmetics are intentionally utilized to stay away from sunshine. The prolongation of life span is another factor of vitamin D deficiency, vitamin D synthesis in skin and absorption by intestinal tract declines along with increasing age.[11] Additionally, the vitamin D content in modern fortified foods is significantly less than that in wild oily marine fish, freshwater fish, cod liver oil, egg yolk and so on. In recent years, high heritability suggests that genetic factors could also play a role in vitamin D deficiency.[12, 13] For example, variants genes involved in cholesterol synthesis, hydroxylation, and vitamin D transport affect vitamin D status; and genetic variation at these loci identifies individuals who have substantially raised risk of vitamin D insufficiency.[12]

The distribution of the vitamin D in the body also affects the serum levels. Serum 25(OH)D is often decreased in obese people because of the retaining of vitamin D in adipose tissue. The vitamin D retaining capability of the adipose tissue is the same and therefore, the vitamin D is diluted in people with obese, leading to the decrease of serum vitamin D. The weight loss caused by malabsorption may also lower the serum vitamin D level. As there is no feedback regulation of hydroxylation of vitamin D in the liver, when liver parenchyma disease occurs, impaired hydroxylation of vitamin D can also lead to vitamin D deficiency or shortage.[14, 15] A genetic study[12] showed that vitamin D related gene polymorphisms, including vitamin D-binding protein (DBP), vitamin D receptor (VDR) and α1 hydroxylase gene, are associated with serum vitamin D concentrations.

Viral hepatitis

Clinical evidence indicated that patients with chronic hepatitis C (CHC) are always at higher risk of vitamin D deficiency.[16] In a large scale study,[17] serum 25(OH)D in CHC patients was significantly lower than that in healthy population (25.07±9.92 vs 43.06±10.19 ng/mL, $P<0.0001$), and serum 25(OH)D was less than 30 ng/mL in 73% of CHC patients whereas only 6% in the healthy controls. Current evidence[17, 18] suggested that HCV not only inhibits 25(OH)D synthesis by regulating lipid metabolism, but also decreases the production of previtamin D, which is an intermediate in the cascades of 1, $25(OH)_2D$ synthesis.[19] Low serum 25(OH)D level is associated with the severity of liver diseases and fibrosis damage in CHC patients.[20, 21]

Serum 25(OH)D deficiency is associated with the severity of liver diseases in human immunodeficiency virus (HIV)/HCV co-infected patients,[10, 22] and lower serum 25(OH)D may also impair virological response to pegylated interferon α (PEG-IFNα) and ribavirin (RBV) therapy in those HIV/HCV co-infected patients.[23] The low level of serum vitamin D may negatively affect the virological response of PEG-IFNα/RBV, and appropriate vitamin D supplement would improve sustained virological response in CHC and HIV/HCV co-infected patients.[22, 23] Gal-Tanamy et al[24] suggested that vitamin D inhibits HCV RNA replication directly, possessing natural antiviral activity, and its collaborative antiviral effect with interferon improves antiviral effect in CHC patients.[6, 25] Kondo et al[26] reported that 1, $25(OH)_2D$ supplement improves the sensitivity of PEG-IFNα/RBV therapy on HCV-infected hepatocytes by reducing the IP-10 production from PBMCs and ISGs expression in the liver. Additionally, the beneficial effect of vitamin D on decreasing insulin resistance and improving systemic inflammation may also contribute to the virological response of PEG-IFNα/RBV therapy in CHC patients.[6, 27, 28] These data indicate that CHC patients with low serum vitamin D need to supply this vitamin when they are treated with PEG-IFNα/RBV.[29] It is worthy to mention that serum DBP and the polymorphism of DBP are known to influence vitamin D levels; and in difficult-to-treat HCV genotypes, simultaneous pretreatment normal serum vitamin D levels and the carriage of DBP wild-type isoform strongly predicts the achievement of sustained virological response after PEG-IFNα/RBV antiviral

therapy.[30]

New evidence continues to suggest a relationship between serum vitamin D level and chronic hepatitis B (CHB). Farnik et al[31] quantitatively examined the levels of serum 25(OH)D in 203 untreated CHB patients, and found that there were 34% patients with severe vitamin deficiency (<10 ng/mL), 47% with vitamin D insufficiency, and only 19% with normal level. Whereas vitamin D level in HBeAg positive patients is notably lower than that in HBeAg negative patients. Meanwhile, vitamin D level presents opposite seasonal fluctuations compared with HBV DNA, and the low level of serum 25(OH)D is correlated with high HBV DNA.[31] Though, it is still uncertain whether the low level of serum vitamin D decreases the efficacy of PEG-IFNα or nucleos(t)ide analogs, some scholars speculated that appropriate vitamin D supplement may be helpful to improve or optimize curative efficacy of existing antiviral therapy for CHB patients with vitamin D deficiency. Because of the huge amount of CHB patients all over the world and the relative limited therapeutic drugs and antiviral strategies, it is very important and necessary to recognize the role of vitamin D in CHB progression, and potential value for increasing the antiviral efficacy of existing antiviral therapy and developing new targets for antiviral treatment in the future.

NAFLD

The morbidity of NAFLD is on the rise worldwide, and epidemiological data showed that NAFLD morbidity is significantly higher in the vitamin D deficiency population than that in normal subjects; similarly, NAFLD patients tend to have a lower vitamin D level.[32-34]

Nakano and coworkers[35] reported that in an animal study the lower level of vitamin D is associated with obesity and severity of liver steatosis, indicating that vitamin D deficiency may participate in NAFLD progression. Vitamin D deficiency may also up-regulate hepatic inflammation and oxidative stress genes via endotoxin and Toll-like receptor pathway to cause NAFLD.[36] Considering the significance of insulin resistance in NAFLD development,[37] the correlation between vitamin D deficiency and insulin resistance might be another important cause of the progression of NAFLD, as low vitamin D level is associated with the impaired function of islet beta cells.[38] Interestingly, current preclinical studies demonstrated that sunlight exposure and vitamin D supplements helped to ameliorate NAFLD histopathology. Kitson and Roberts[39] proposed that vitamin D plays an important role in the activation and regulation of both innate and adaptive immune systems, which indicate the beneficial effect of vitamin D on NAFLD. Although the exact mechanism is still not clear, we believe that vitamin D is an effective drug in the prevention and treatment of NAFLD.

Liver fibrosis and cirrhosis

Due to the severe liver functional damage, the construction of transport proteins in patients with fibrosis and cirrhosis is decreased. Thus, vitamin D deficiency is very common in these patients. In HIV/HCV co-infected patients, serum 25(OH)D levels are significantly correlated with the Metavir fibrosis score; and patients with severe fibrosis (Metavir F3/F4) have lower serum 25(OH)D levels compared with F2 and F1 patients (16.2±10.0 vs 18.9±8.5 and 20.9±11.1 ng/mL, respectively).[22] In genotype I CHC patients, lower serum vitamin D levels are significantly associated with the severity of liver fibrosis,[17] and correction of vitamin D deficiency in patients with CLD is a potential therapy to inhibit progression of fibrosis, as 1, 25$(OH)_2$D and its nuclear receptor repress human α1(I) collagen expression and type I collagen formation.[40] Indeed, those clinical findings are also supported by *in vitro* and *in vivo* experiments, showing that 1, 25$(OH)_2$D possesses anti-fibrosis effect both in bone marrow mesenchymal stem cells and fibrosis rat, with the increasing expression of VDR caused by 1, 25$(OH)_2$D, which inhibit the proliferation of hepatic stellate cells and the expression of cyclin D1, tissue inhibitor of metalloproteinase 1 and collagen.[41] In addition, vitamin D is also able to reduce the production of body smooth muscle actin and collagen, thus inhibiting the progression of liver cirrhosis induced by thioacetamide. All those clues strongly suggest that vitamin D is most likely to be an anti-fibrosis agent.[42]

In the past years, genome-wide studies have identified genetic variants (including DHCR7, CYP2R1 and DBP) that affect serum 25(OH)D levels in healthy populations; and GG homozygosis for DHCR7 gene and lower 25(OH)D levels in CHC patients are both independently associated with the severity of liver fibrosis.[43] Grünhage et al[44] also reported that the common variation in 25(OH)D metabolism is associated with liver stiffness in patients with CLD, and the stronger influence of 25(OH)D is on the initiation rather than progression of hepatic fibrosis. Moreover, the low level of VDR is also an important factor affecting fibrosis,[45] and VDR gene polymorphism is significantly linked with fibrosis and cirrhosis progression,[46] including the presence of cirrhosis in CHC patients.[21]

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the sixth most

common cancer in the world, approximately 630 000 new cases are diagnosed each year. Amany them, 82% of the cases are related to viral hepatitis, 55% to HBV; but 89% of the cases are in regions where HBV is endemic.[47]

There is a correlation between the progressive decline of active vitamin D and the progression of liver disease. Genetic analyses also revealed a role for vitamin D insufficiency in HCV-associated HCC development.[48] Thus, some researchers[49] proposed that serum vitamin D is also a potential biomarker of HCC, just like serum α-fetoprotein, and that vitamin D may be valuable for monitoring HCC in patients with high-risk, including those with CHB or CHC. In addition, vitamin D deficiency is common in HCC patients after liver transplantation and is closely related to prognosis, thus serum vitamin D levels also may be a prognostic indicator for HCC after treatment, and vitamin D supplementation may help to prevent acute cellular rejection in liver recipients with severe vitamin D deficiency.

Though current epidemiological data are not enough to completely uncover the correlation between vitamin D and HCC, lots of experimental evidences suggested that vitamin D and its analogs (such as EB1089 and seocalcitol) have inhibitory effect against HCC cell lines.[50-52] Active 1, 25$(OH)_2$D has anti-tumor effects in several aspects, including anti-proliferation, anti-inflammatory, anti-angiogenesis, promoting apoptosis and differentiation.[51, 53, 54] Moreover, DBP-macrophage activating factor activates macrophages, the latter has anti-angiogenic activity and tumor killing activity, which inhibit HCC growth.[55] All of the data above implied that vitamin D and vitamin D-related molecules may represent a new strategy for the treatment of HCC.

Autoimmune liver disease

The development of autoimmune disease is based on the interaction of genetic susceptibility and environmental causes. Vitamin D endocrine system plays important roles in host immune system responses. For example, activated macrophages (a type of immune cell) not only produce 1, 25$(OH)_2$D, but also express VDR.[56] And the liver-produced 1, 25$(OH)_2$D could further activate a negative feed-back loop at sites of inflammation and therefore contribute to the suppression of the occurrence of autoimmune liver disease.[56]

Actually, the active vitamin D acts its biological effects by binding to its own receptor VDR; and vitamin D also modulates the expression of VDR in human bile duct epithelial cells. D'Aldebert et al[57] demonstrated that biliary epithelial cells in human liver expressed both cathelicidin and VDR, and that VDR is also an important nuclear receptor for ursodeoxycholic acid (UDCA) inducing cathelicidin expression in biliary epithelial cells. Thus the hepatic expression of VDR increased the efficacy of UDCA therapy, and vitamin D and UDCA have synergistic effect on some autoimmune liver diseases such as primary biliary cirrhosis and primary sclerosing cholangitis.

Recent studies[58, 59] found that genetic factors appear to be involved in the pathogenesis of autoimmune liver diseases, and that VDR polymorphisms may be associated with autoimmune liver diseases such as autoimmune hepatitis and primary biliary cirrhosis. However, further studies are still needed to elucidate the mechanisms by which VDR polymorphisms contribute to the losing of immune tolerance in autoimmune diseases.

Summary

Vitamin D, along with its related VDR, is possibly interrelated with the incidence, treatment and prognosis of a variety of chronic liver diseases. Though the exact role and mechanisms of vitamin D in viral hepatitis have not been fully elucidated and the evidence for vitamin D supplement in those populations is still limited, vitamin D supplement may potentially optimize the current treatment. The role of vitamin D in CLD needs further study.

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