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Role of vitamin D in chronic hepatitis C

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Vitamin D deficiency and a CYP27B1-1260 promoter polymorphism are associated with chronic hepatitis C and poor response to interferon-alfa based therapy.

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The prevalence of hepatitis C virus (HCV) infection in adults over age 40 is 1.29%, and the common HCV genotypes are Ib (40-59%) and 2a (33-52%) in Korea.[1,2] The best predictor of long-term response for chronic hepatitis C (CHC) to treatment is sustained virological response (SVR), defined as undetectable serum HCV RNA by PCR assay at 24 weeks after cessation of therapy.[3] The standard of choice for HCV treatment is the combination of a pegylated interferon alpha and ribavirin (Peg/RBV). According to Korean data, the response rates to the recommended strategies have been observed to be high compared to Western data, but 20-40% of patients did not achieve an SVR.[4-6] Two major predictors of SVR are genotypes and viral load.[3] Other baseline predictors include the doses of Peg/RBV, gender, age, race, body weight, and fibrosis stage.[3]

Recently, two emerged predictors of response to antiviral treatment are interleukin-28B (IL-28B) rs12979860 C/T polymorphism and serum vitamin D concentration. IL-28B polymorphism is associated with SVR, and SVR rates are doubled in patients with the C/C homozygotes compared with the carrier of the T/T or T/C alleles.[7,8] However, this polymorphism represents a nonmodifiable factor that predicts SVR, and plays a smaller role in Korean patients due to high frequency of favorable allele.[9] Pre-treatment serum vitamin D concentrations affect SVR, and vitamin D deficiency shows low SVR in Peg/RBV treatment.[10,11] Clinicians have increasing interest in vitamin D because it is easily modifiable and its supplementation may improve response to antiviral treatment.[12] Patients with CHC have higher incidence of severe vitamin D deficiency (25-hydroxy-vitamin D, 25(OH)D <10 ng/mL) compared to the normal control (25% versus 12%, P<0.0001).[13] The prevalence of vitamin D deficiency (25(OH)D <20 ng/mL) was 47.3% of males and 64.5% of females,[14] but there was no report on that in patients with CHC in Korea.

Vitamin D, as a regulatory factor of phosphorus and calcium absorption in intestine and renal reabsorption of calcium, plays a role in calcium metabolism. Through hydroxylation process of liver and kidney, vitamin D from the skin and diet is converted into the major circulating form, 25(OH)D, and then into the active form, 1,25-dihydroxyvitamin D (1,25(OH)D), respectively.[15] In relation to vitamin D synthesis in the liver, mild to moderate liver dysfunction causes malabsorption of vitamin D and dysfunction of 90% or more results in inability to make sufficient

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Abbreviations: CHC, chronic hepatitis C; CYP, cytochrome P450; HCV, hepatitis C virus; IL, interleukin; Peg, pegylated interferon alfa; RBV, ribavirin; SVR, sustained virologic response; VDRs, vitamin D receptors; Th, helper T cell; 25(OH)D, 25-hydroxyvitamin D; 1,25(OH)D, 1,25-dihydroxyvitamin D

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25(OH)D.[15] Therefore, low vitamin D serum level in patients with CHC is correlated to severity of fibrosis.[11] In addition to CHC, 25(OH)D serum level is an independent predictor of risk for cancer, autoimmune disease, cardiovascular disease, and metabolic disease.[15]

1,25(OH)D is activated by binding with the vitamin D receptors (VDRs), which are found in almost immune cells such as $CD4^+$ and $CD8^+$ T cells, B cells, neutrophils, and antigen presenting cells, and is an important mediator of innate immune and adaptive immune systems.[16] 1,25(OH)D enhances chemotactic and phagocytic responses of macrophage as well as induces antimicrobial actions with the upregulation cathelicidin via VDRs.[17] At the level of antigen presenting cells (like dendritic cells), 1,25(OH)D decreases antigen recognition by inhibited expression of MHC II molecules and co-stimulatory molecules (CD40, CD80, CD86). Furthermore, by suppressing production of IL-12 and IL-23, which are important Th1 and Th17 development, 1,25(OH)D inhibits the production of Th1 cytokines (IL-2 and IFN-γ) and Th17 cytokines (IL-17 and IL-23). A shift from Th1 to Th2 development stimulates Th2 cytokine production (IL-4). In addition, it induces regulatory T cells via modulation of dendritic cells and regulatory T cells and produce IL-10, which has the ability to interfere the development of the other Th subclasses. Finally, the action of 1,25(OH)D on B cells blocks proliferation, maturation to plasma cells, and immunoglobulin production.[16]

Petta et al[11], by analyzing retrospectively a cohort of 197 patients, detected an association between lower vitamin D serum levels and failure to achieve SVR. Of different isoforms of cytochrome P450 (CYP) involved in vitamin D metabolism, CYP2R1 and CYP27A1 exist in liver and CYP27B1 exists in kidney. Levels of CYP27A1, but not CYP2R1, were directly related to vitamin serum D levels and inversely correlated with necro-inflammation.[11] Bitetto et al[10] suggested that correction of vitamin D serum levels may play a complementary role to improve SVR in patients with difficult-to-treat HCV genotype and with IL-28B polymorphism. Based on the relationship between follow-up viral response rates and baseline 25(OH)D serum level, Bitetto et al[10] suggested that vitamin D plays an important role in early HCV decline after antiviral treatment. In two reports about additional effect of vitamin D on SVR in patients with CHC, Abu Mouth et al[18] showed vitamin D supplementation to Peg/RBV treatment significantly improved SVR in naïve genotype 1 patients (86% versus 43%, $P<0.001$), and Bitetto et al[12] showed the increase of SVR to antiviral treatment for recurrent hepatitis C (5/18 versus 5/27, $P<0.02$). The latter two studies have limited value due to small number of patients.

Together with these studies, Lange et al[13] retrospectively analyzed serum vitamin D levels and genetic polymorphisms in 468 naïve patients with CHC. As above mentioned, 25(OH)D is converted to the 1,25(OH)D by 1-α-hydroxylase (CYP27B1) in the kidney and the biological activities of vitamin D are mainly mediated via the VDRs. Unlike other studies,[10,11] subjects were investigated about correlation between polymorphisms within genes of vitamin D cascade (VDR and CYP27B-1260 promoter) and serum vitamin D levels.[13] Three main findings are as follows. First, in similar to recent reports, the occurrence of vitamin D deficiency was more frequently observed in the patients (66%) than in the controls (41%). In addition, severe vitamin D deficiency was more observed in the patients (25%) than in the controls (12%). Second, pretreatment serum vitamin D level was related to high responsiveness of Peg/RBV treatment in patients with HCV genotype 2/3, but not in patients with HCV genotype 1. This point is different from recent reports. Interestingly, in HCV genotype 1 patients, authors reported a positive association between SVR and 1-α-hydroxylase promoter polymorphism (CYP27B1-1260) and they suggested that 25(OH)D serum levels might not be an optimal predictor of SVR. Therefore, further researches are needed to investigate the effect of vitamin D according to race, polymorphism, and genotypes. Third, SVR rates were significantly higher in patients with CYP27B1-1260 genotype AA or AC compared to CYP27B1-1260 genotype CC (77% and 65% versus 42%, respectively; $P=0.02$), but VDR polymorphism is not associated with SVR. This study has some limitations due to retrospective data, absence of on-treatment vitamin D serum levels, and absence of potential confounders.

In conclusion, this study showed that the incidence of vitamin D deficiency is high in patients with CHC, vitamin D serum levels is linked to SVR, and a CYP27B-1260 promoter polymorphism is related with poor response to Peg/RBV treatment. To date, there are a few published reports on the role of vitamin D supplementation in patients with CHC and no domestic data on the relationship between vitamin D and CHC. Adding vitamin D to standard interferon therapy may increase SVR rates without serious adverse events. However, to prove these findings, well designed and large prospective studies are needed.

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