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**Hepatitis C infected patients need vitamin D3 supplementation in the era of direct acting antivirals treatment**

Kondo Y. Supplementation of vitamin D3 in DAAs treatment

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**Abstract**

It has been reported that the serum level of vitamin D3 (VitD3) could affect the natural course of chronic hepatitis C (CH-C) and the response to treatment with pegylated interferon (Peg-IFN) and ribavirin. Although several mechanisms for the favorable effects of VitD3 supplementation were reported, the total effect of VitD3 supplementation remains unclear. Previously, we reported that supplementation with 1(OH)VitD3 could enhance the Th1 response inducing not only a favorable immune response for viral eradication but also HCC control. Recently, the main treatment of CH-C should be direct acting antivirals (DAAs) without Peg-IFN. Peg-IFN is a strong immune-modulator. Therefore, an immunological analysis should be carried out to understand the effect of VitD3 after treatment of DAAs without Peg-IFN. The induction of a favorable immune response by adding VitD3 might be able to suppress the hepatocarcinogenesis after achieving SVR, especially in children and elderly patients with severe fibrosis lacking sufficient amounts of VitD3.

**Key words:** Vitamin D; Hepatitis C virus; DAAs; Hepatocarcinogenesis; Immune response

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**Core tip:** Although several mechanisms for the favorable effects of vitamin D3 (VitD3) supplementation were reported, the total effect of VitD3 supplementation remains unclear. Recently, the main treatment of chronic hepatitis C should be direct acting antivirals (DAAs) without pegylated interferon (Peg-IFN). Peg-IFN is a strong immune-modulator. Therefore, an immunological analysis should be carried out to understand the effect of VitD3 after treatment of DAAs without Peg-IFN. The induction of a favorable immune response by adding VitD3 might be able to suppress the hepatocarcinogenesis after achieving SVR, especially in children and elderly patients with severe fibrosis lacking sufficient amounts of VitD3.

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**INTRODUCTION**

It has been reported that the serum level of vitamin D3 (VitD3) could affect the natural course of chronic hepatitis C (CH-C) and the response to treatment with pegylated interferon (Peg-IFN) and ribavirin (RBV)[1,2]. Although several mechanisms for the favorable effects of VitD3 supplementation were reported, the total effect of VitD3 supplementation remains unclear. It has been reported that VitD3, as synthesized in the skin by photolysis from 7-dehydrocholesterol, is transported in the blood to the liver where it is hydroxylated at the C-25-position. Then, it is hydroxylated at the C-1α-position to form the active metabolite 1,25 (OH)2 VitD3 in the kidney. 1,25 (OH)2 VitD3 is known to regulate calcium and phosphorus metabolism in skeletal homeostasis. Moreover, 1,25(OH)2 VitD3 could affect various kinds of immune cells *via* vitamin D receptor[3,4]. Several groups reported that the amount of 25(OH)VitD3 affects the progression of CH-C and response to Peg-IFN/RBV treatment. Moreover several mechanisms for the favorable effects of VitD3 supplementation in CH-C patients have been reported[5]. Dr. Azza reported that the serum level of 25(OH)VitD3 in CH-C children was significantly lower than that in healthy children. In addition to the treatment response, the deficiency of VitD3 could affect bone density. Therefore, we should consider supplementation with VitD3 for CH-C patients even in the era of direct acting antivirals (DAAs).

**DISCUSSION**

After a sustained virological response, the risk of hepatocarcinogenesis remains. Previously, we reported that supplementation with 1(OH)VitD3 could enhance the Th1 response inducing not only a favorable immune response for viral eradication but also HCC control[5]. The induction of a favorable immune response by adding VitD3 might be able to suppress the hepatocarcinogenesis after achieving SVR, especially in children and elderly patients lacking sufficient amounts of VitD3. Another group reported that 1,25(OH)2VitD3 could inhibit HCC development through reducing secretion of inflammatory cytokines from immune-related cells[6]. Moreover, it has been reported that reduced 25(OH)VitD3 serum levels were found to be associated with HCV-related HCC[7]. In addition to the risk of HCC development, 25(OH)VitD3 deficiency could be associated with advanced stages of HCC and it could be a prognostic indicator for a poor outcome[8]. In Japan, hepatocarcinogenesis after achieving SVR is an important issue since many CH-C patients are old and have severe fibrosis. Especially, CH-C patients with severe fibrosis might not have sufficient VitD3 since hepatocytes are necessary to metabolize VitD3. Moreover, it has been reported that there might be a relationship between carcinogenesis and insufficient VitD3[6,9]. Therefore, we should analyze the effect of VitD3 supplementation on hepatocarcinogenesis after achieving SVR[7]. Additionally, the immunological effect of VitD3 might differ between DAAs with and without Peg-IFN.

**CONCLUSION**

Recently, the main treatment of CH-C should be DAAs without Peg-IFN. Peg-IFN is a strong immune-modulator. Therefore, an immunological analysis should be carried out to understand the effect of VitD3 after treatment of DAAs without Peg-IFN.

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