Review Article

Vitamin D and chronic hepatitis C: effects on success rate and prevention of side effects associated with pegylated interferon-α and ribavirin

Bassem Refaat¹, Adel Galal El-Shemi¹,², Ahmed Ashshi¹, Esam Azhar³,⁴

¹Department of Laboratory Medicine, Faculty of Applied Medical Sciences, Umm Al-Qura University, Al Abdeyah, Makkah, PO Box 7607, KSA; ²Department of Pharmacology, Faculty of Medicine, Assiut University, Egypt; ³Special Infectious Agents Unit, King Fahd Medical Research Center, King Abdulaziz University, Jeddah, KSA; ⁴Department of Medical Laboratory Technology, Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah, Saudi Arabia

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Abstract: Chronic hepatitis C (CHC) is one of the most common causes of liver diseases worldwide, affecting 3% of the world population and 3 to 4 million people acquire new infection annually. Despite the recent introduction of novel antiviral drugs for the treatment of CHC, these drugs are expensive and the access to them is not an option for many patients. Hence, the traditional therapy by pegylated interferon-α (Peg-IFN-α) and ribavirin may still have a role in the clinical management of CHC especially in developing countries. However, this standard therapy is associated with several severe extra-hepatic side effects and the most common adverse events are hematological abnormalities and thyroid disorders and they could result in dose reduction and/or termination of therapy. Vitamin D has been shown to be a key regulatory element of the immune system, and its serum concentrations correlate with the severity of liver damage and the development of liver fibrosis/cirrhosis. Furthermore, supplementation with vitamin D with Peg-IFN-α based therapy for the treatment of CHC could be beneficial in increase the response rate to Peg-IFN-α based therapy. Vitamin D has also been shown to regulate the thyroid functions and the process of erythropoiesis. This review appraises the data to date researching the role of vitamin D during the treatment of CHC and the potential role of vitamin D in preventing/treating Peg-IFN-α induced thyroiditis and anemia during the course of treatment.

Keywords: Chronic hepatitis C, vitamin D, pegylated interferon-α, anemia and thyroid disorder

Introduction

Infection with hepatitis C virus (HCV) is a major health problem and is one of the most important causes of chronic liver diseases. According to the World Health Organization (WHO) at least 170 million people are infected worldwide with HCV and 3 to 4 million new infections occur per year [1]. Only 20-30% of HCV infected individuals recover spontaneously while the remaining 70-80% progress to chronic hepatitis C (CHC) infection, that is association with the development of liver fibrosis, cirrhosis, end-stage liver disease, and hepatocellular carcinoma (HCC) [2-5].

The traditional treatment for CHC is a combination of a weekly injection of pegylated interferon-α (Peg-IFN-α) with daily oral ribavirin (RBV) [1-3] and the duration of the treatment is based on the viral genotype [1-3]. Although new direct acting antiviral (DAA) drugs have been developed, the treatment of CHC could still be based on a weekly injection of Peg-IFN-α-2a or -2b plus a daily weight-based dose of RBV with or without the new antiviral therapy depending on the progression of liver damage and the presence of other extrahepatic manifestations [2, 6-8]. Furthermore, the new antiviral drugs are expensive and therefore Peg-IFN-α based therapy could still be the standard of care especially for treatment naïve patients with no liver cirrhosis and/or for those living in developing countries and for whom access to the new drugs is not definite due to its high cost [9-12].
Several disadvantages are associated with Peg-IFN-α based therapy during the treatment of CHC. These include low response rate (e.g. 50% for genotypes 1&4) and the development of several drug induced side effects that could lead to dose reduction or termination of treatment [2, 13-15]. CHC and its treatment with Peg-IFN-α based therapy are associated with several extra-hepatic complications including hematological and endocrinological abnormalities. The most prevalent side effects associated with the traditional treatment of CHC are anemia and thyroid disorders [2, 16, 17].

Vitamin D (VitD) is involved in many biological processes beside its role in the regulation of bones and calcium homeostasis [18]. VitD supplementation has recently been recommended by several research groups to increase the response rate and achieving sustained viral response (SVR) during the treatment of CHC with Peg-IFN-α based therapy [19-23]. Additionally, abnormal low levels of VitD has been shown to play an important role in the development of many autoimmune diseases, and a significant VitD deficiency has been detected in patients affected with autoimmune thyroiditis [24, 25]. VitD has also been shown to be involved in the process of hematopoiesis by regulating the production of erythropoietin hormone (EPO) and its receptors, and erythrocyte progenitor cells [17]. Therefore, supplementation with VitD during the treatment of CHC with Peg-IFN-α and RBV could provide an alternate management option to increase the response rate and prevention/treatment of drug induced adverse effects, especially in those patients who require longer duration of treatment and cannot access to the new antiviral therapy due to financial limitations.

This review summarizes the role of VitD supplementation in CHC and the potential mechanisms by which it could increase the response rate to Peg-IFN-α based therapy and prevention of the secondary anemia and thyroid disorders during the course of treatment with Peg-IFN-α based therapy.

Methods


Publications in English and within the past 6 years were mostly selected, but commonly referenced and important older publications were not exclude. The reference lists of articles identified by this search strategy were also searched and those judged as relevant were also included. For a study to be included, it needed to be focused on incidence, diagnosis, clinical management and side effects of CHC infections and its treatment with Peg-IFN-α based therapy. Studies that were solely focusing on the treatment of CHC using medical agents other than Peg-IFN-α based therapy were not included.

Treatment of chronic hepatitis C

CHC is the most predominant cause of liver cirrhosis, HCC and liver transplantation [26-29]. The choice Peg-IFN-α plus RBV was based upon the results of three randomized clinical trials that demonstrated the superiority of this combination treatment over standard IFN-α and RBV [3, 14, 30-32]. Two types of pegylated IFN, which differ in their pharmacokinetic and chemical properties, have been developed. Both have demonstrated significantly superior efficacy to non-pegylated IFN in several controlled randomized clinical trials [2, 3, 8, 13, 33] with a significantly improved SVR as compared with standard IFN [3, 8].

HCV genotype is the most significant baseline predictor of response to therapy, and therefore the adjustment of HCV treatment, including the optimal duration and treatment protocol, is based on the genotype [2, 33]. Most of the published literature on the management of HCV have shown that the benefit is mostly achieved in patients with HCV genotype 2 and 3 infections while genotype 1 and 4 have significantly lower response rates [34, 35]. If Peg-IFN-α based therapy to be used, the guidelines state that all patients infected with HCV genotypes 2 or 3 should be treated for 24 weeks with an estimated SVR of about 80%. Coherently, patients with genotypes 1 and 4 could be treated with Peg-IFN-α plus standard weight-based RBV for 48 weeks with an estimated SVR of about 50% of cases [2, 3, 7, 8, 13, 14, 33, 35].
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Due to low response rate with viral genotype 1&4 and the development of drug induced complications, new antiviral drugs sparing IFN have been developed. These drugs are NS3A and NS5A inhibitors and the reported success rate for these novel agents by several registered trials is promising, ranging between 98-100% cure rate and the duration of treatment is relatively short (3-6 months) compared with the traditional Peg-IFN-α based therapy [36, 37]. However, the new agents are expensive and the cost of treatment is expected to be between 60,000-100,000 US dollars [9, 10, 38-40]. Hence, it has been postulated that access to the new treatment will not be available for all patients, especially those living in developing countries. Peg-IFN-α based therapy could therefore still be the only available option for those patients despite its associated disadvantages [11, 17].

Almost all patients treated with Peg-IFN-α and RBV experience one or more adverse events during the course of therapy. One of the barriers to adherence in combination therapy for CHC is the incidence of treatment associated adverse events that can lead to dose reductions or sometimes premature discontinuation [2, 3, 7, 8, 13, 14, 33, 35]. In the registered trials of Peg-IFN-α-2a and 2b plus RBV, 10% to 14% of patients had to discontinue therapy due to an adverse event [2].

Side effects associated with Peg-IFN-α based therapy during the treatment of CHC

The treatment regimen with Peg-IFN-α and RBV for either 24 or 48 weeks is associated with the several adverse effects that could result in the termination of therapy [8, 13, 35]. The adverse effects include flu like syndrome, hematological disorders, thyroiditis and depression [2, 41-45].

Anemia associated with CHC and IFN-α therapy

Hematological side effects are common during Peg-IFN-α based therapy and anemia is the most frequent complication [4, 46-48]. The reported incidence of developing anemia is about 12% by the registered trials using the combination of Peg-IFN-α with RBV and 2.5-3 g/dL decrease in hemoglobin during the first 4 weeks of treatment was reported. Additionally, these studies have shown that the severity of anemia is mainly dependent on the dose of RBV [16, 48-50].

Several pathogenic mechanisms for the development of anemia during the treatment of CHC by Peg-IFN-α and RBV have been proposed (Figure 1), including autoimmune hemolysis and suppression of erythropoiesis [16, 17, 50]. Peg-IFN-α have been reported to suppress the proliferation of progenitor cell, increase the destruction of erythroid precursor cells, induce autoimmune hemolytic reaction and reduce renal function [4, 16, 51-53].

On the other hand, RBV is considered the main cause of anemia during the treatment. It is believed that the majority of anemia during the course of therapy are hemolytic in nature due to the intoxication of human red blood cells (RBCs) with RBV [50, 53-56]. Peg-IFN-α could also exaggerate the hemolytic effect of RBV in the currently applied treatment protocol [46, 52, 57-59]. However, the prevalence of anemia was significantly lower in Peg-IFN-α monotherapy compared to Peg-IFN-α and RBV dual therapy [31].

Anemia associated with RBV appears to be dependent on the plasma concentration of the drug rather than the dose/Kg body weight [16, 50]. The accumulation of RBV and its metabolites in RBCs, causes oxidative stress, mitochondrial toxicity and RBCs hemolysis [53-56,
However, the uptake rate of RBV by erythrocytes has been reported to differ according to dose and species [61]. The largest accumulation of RBV was observed in monkey, followed by human and the lowest accumulation was detected in rat erythrocyte [61]. Moreover, in vitro incubation of erythrocytes from the 3 species with RBV showed that the retention rate of the drug was 77% in monkey, 45% in human and 20%, in rat red cells [61]. Nevertheless, exposure of RBCs to RBV in vitro did not alter the osmotic fragility and deformability of the cells [61-63].

RBV induced anemia could also be due the inhibiting effect of RBV on the process of erythropoiesis through the suppression of bone marrow and decreasing the expression of both EPO and its receptor [17, 47, 64]. RBV was also shown to decrease RBCs survival as well as inhibit the release of red cell from the bone marrow in monkey and rat [61-63, 65, 66]. However, RBV had no effect on erythrocyte mean cell volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentrations in both species [61-63].

The administration of Peg-IFN-α and RBV in human was also associated with a decrease in serum EPO concentrations [64]. RBV have also been reported to decreasing endogenous EPO in a rat experimental model at the kidney and serum levels and subsequently suppressing erythropoiesis and cause normocytic normochromic anemia [17]. Therefore, the authors postulated that RBV produces normocytic normochromic anemia in rat by suppressing the bone marrow through decreasing the production of EPO from the kidney.

Thyroiditis associated with CHC and IFN-α therapy

Liver diseases are known to induce thyroid disorders and abnormal serum concentrations of thyroid hormones. Hypothyroidism and thyroid autoimmunity are more common in patients with CHC, even in the absence of cirrhosis, HCC, or IFN-α treatment in comparison with normal individual or those who are infected with hepatitis B infection [67, 68].

Strong correlations between liver damage and thyroid disorders have been also reported [69]. Non-alcoholic fatty liver diseases (NAFLD) and abnormal liver enzymes are significantly associated with hypothyroidism and the prevalence of liver diseases and enzymes increase steadily with increasing grades of hypothyroidism [69]. Furthermore, a decrease in serum triiodothyronin (T3) concentration and T3: thyroxine (T4) ratio is frequently observed in patients with liver cirrhosis probably due to impaired conversion of T4 to T3 in the liver [70]. Thyrotoxicosis is also associated with a variety of abnormalities of liver function [71] and results from a recent study suggests that low free T4 (FT4) concentrations are associated with hepatic steatosis [72]. Serum thyroid stimulating hormone (TSH) level was also significantly higher in NAFLD and it has also been suggested that measurement of free T3 and T4 levels may all be useful as predictors of mortality in intensive care patients who have cirrhosis [73].

Thyroiditis is a major clinical problem especially for patients with chronic HCV infection [74-76]. Thyroiditis can also be associated with interferon and it is known as interferon induced thyroiditis (IIT), which can be classified as autoimmune and non-autoimmune types (Figure 2) [77, 78]. The estimated prevalence of thyroid disorders induced by CHC and its treatment with Peg-IFN-α based therapy ranges between 2.5% to 35% in different countries [42, 74, 76, 79, 80]. This variability can be attributed either to an underestimation of the true prevalence of thyroid disorders or to the diverse genetic predisposition of the subjects [42, 68].

Thyroid abnormalities following interferon therapy have also been described in children receiving interferon for hepatitis C infection [81]. Some of these complications of IFN therapy, especially thyrotoxicosis, can be severe and may interfere with adequate interferon therapy in patients with hepatitis C infection [77, 81]. Moreover, because the symptoms of hypothyroidism such as fatigue, hair loss, myalgia, and weight gain may be attributable to hepatitis C or IFN therapy, the diagnosis of hypothyroidism in these patients may be delayed [82]. This delay may lead to development of further complications. Thus, IIT represents a major clinical problem for patients with chronic HCV infection and who receive interferon for treatment that may interfere with their treatment course [43, 76, 77].

Autoimmune thyroid diseases (AITD) are strongly influenced by genetic factors and therefore they are likely to affect the etiology of IIT.
Actually, the presence of HCV infection and IFN-α therapy might induce thyroiditis in genetically inclined individuals [42, 79]. IFN-α and RBV could also act against thyroid cells by inducing a direct toxic effect [43, 68, 76, 80]. While it is not clear which factors contribute to the susceptibility to IIT, recent evidence suggests that genetic factors, gender, and hepatitis C virus infection may play a role [82]. However, viral genotype and therapeutic regimen do not influence susceptibility to IIT [81].

IIT is more common in females than in males [43, 68, 76, 83, 84]. According to different studies, females appeared to have a 4.4 times higher risk of developing secondary thyroid disease to IFN-α based therapy in comparison with males [43, 68, 76, 84]. Females’ susceptibility may be due to the effects of estrogenic sex steroids in promoting autoimmunity, or it could be due to the susceptibility gene on the X-chromosome, since females have two X-chromosomes, so males are less likely to inherit the gene [43, 76, 83]. IIT is considered a major complication for those who are treated with IFN-α based therapy [68, 76, 83]. IIT is classified mainly into two types: either autoimmune (i.e., Hashimoto’s thyroiditis and Grave’s disease) or non-autoimmune (e.g. destructive thyroiditis and non-autoimmune hypothyroidism) [68, 76, 83].

The commonest of autoimmune IIT is Hashimoto’s thyroiditis (HT) and it is more likely in people who are positive to thyroid antibodies (TAbs) before starting the therapy with Peg-IFN-α based therapy [42, 43, 76]. However, development of HT could also occur in CHC patients and who are negative to TAbs during the course of therapy [42, 68, 80]. A less common manifestation of autoimmune IIT is Graves’ disease (GD) [41, 42, 68, 80, 83]. In a retrospective study, 321 patients diagnosed with hepatitis B or C and treated with IFN-α, 10 patients developed thyrotoxicosis, which was characterized by a completely decreased TSH [83]. Six of those patients developed GD and all of them had symptomatic thyrotoxicosis, which failed to resolve even after IFN-α cessation [83].

GD and HT are both known of formation of thyroid-reactive T cells that infiltrate the thyroid gland [77, 85]. HT is characterized by Th1 switching of the thyroid infiltrating T cells, which induce apoptosis of thyroid follicular cells and clinical hypothyroidism. In GD, most of T cells undergoes a T helper (Th) 2 differentiation and activates B cells to produce antibodies against the thyroid stimulating hormone receptors, which are the hallmark of GD, and eventually they will cause clinical hyperthyroidism as a result of thyroid stimulation [86]. Indeed, IFN-α therapy in patients with hepatitis C has been strongly associated with both GD and HT, as well as the production of thyroid antibodies without clinical disease [77, 87].

Several studies have shown that the treatment of hepatitis C with IFN can induce the production of TAbs de novo, or cause a significant increase in TAb levels in individuals who were positive for TAbs prior to interferon therapy [43, 84]. The incidence of de novo development of thyroid autoantibodies secondary to IFN therapy varied widely in different studies from 1.9% to 40% [43, 77]. The wide variations in the reported incidence of TAbs in interferon treated
patients could be related to the used detection assays and different cut-off values applied in the different studies [88].

However, up to 50% of patients who develop thyroid abnormalities during IFN-α therapy do not develop autoantibodies, which suggests that thyroid dysfunction may be caused by a direct effect on thyroid cells [89]. A previous in vitro study reported that TSH-induced gene expression of thyroglobulin was inhibited following the culture of human thyroid follicular cells with interferon type I [41].

Destructive thyroiditis is a self-limited inflammatory disorder is another form of thyroid abnormality associated with Peg-IFN-α based therapy during the treatment of CHC. This disorder consists of three phases: hyperthyroidism, followed by hypothyroidism phase, and finally normalization of thyroid function and usually it takes weeks to months to resolve [74, 80, 89].

Subacute thyroiditis due to IFN therapy for hepatitis C infection is usually benign. In addition, a subset of these patients may progress to permanent hypothyroidism, usually accompanied by the development of TAbs suggesting an underlying autoimmune thyroiditis [43, 77]. Alternatively, the hypothyroidism may be due to a direct toxic effect of IFN on the thyroid. Clinical and subclinical hypothyroidism without TAbs during IFN therapy have been described and in many of these cases thyroid insufficiency is transient but permanent hypothyroidism is likely to develop if patients were positive for thyroid antibodies [90].

**Vitamin D and CHC**

VitD is synthesized in the skin following exposure to ultraviolet B radiation or ingested with the diet and stored in fat cells. The production of the biologically active form involves two steps of hydroxylation of which the first occurs in the liver to form 25-OH vitamin D and the second in the kidney, which produces the active form known as 1, 25-OH vitamin D. The active form of vitamin D enters the cells and binds to its receptor and the complex then heterodimerizes with the retinoid X receptor and binds to vitamin D response elements in the promoter of target genes, there by affecting their transcription [91]. The major circulating form of vitamin D is the 25-OH and its serum concentrations are used as an indicator of vitamin D status [92, 93]. Serum levels of vitamin D are affected by various parameters, including season, sunlight exposure, nutrition, and the metabolic syndrome [92-95].

Serum concentrations of 25(OH)-Vit D < 50 nmol/L (20 ng/mL) is accepted as a marker of deficiency, whereas a concentration of 51-74 nmol/L (21-29 ng/mL) indicates insufficiency [91, 93, 96]. VitD deficiency has been shown to associate with increased susceptibility to both infections and cancer [24, 25, 96-101].

Recent findings in HCV mono-infected patients have also shown a correlation between low serum levels of 25-OH vitamin D3 and severe liver fibrosis [102-104]. Vitamin D deficiency is very common (92%) among patients with chronic liver disease [91, 92, 105]. Significantly lower VitD levels have been observed in CHC patients with advanced fibrosis compared to those with mild or absent fibrosis. Inverse relationship was also reported between the viral load and VitD plasma concentrations [106-108]. Furthermore, certain polymorphisms in vitamin D receptor gene have also been shown to either represent potential predictors for treatment outcome [104, 109-113] while others to be a risk of developing hepatocellular carcinoma in CHC [114-116].

Patients with severe VitD deficiency had significantly lower chance to achieve SVR following the treatment of CHC with Peg-IFN-α based therapy [21-23, 91, 92, 104, 117, 118]. On the other hand, those with near-normal or normal vitamin D obtained an SVR rate in about half of the cases [103, 117-120]. A recent meta-analysis has reported that the diagnosis of advanced liver fibrosis was doubled when plasma vitamin D levels were ≤ 10 ng/mL with an odd ratio of 2.37 (95% confidence interval = 1.20-4.72). Additionally, SVR rates were twice in those patients with serum VitD levels > 20 ng/mL [108].

The latest reports have also shown that VitD supplementation improves the probability of achieving SVR following treatment with Peg-IFN-α based therapy and these findings indicate a potential causal relationship between VitD and HCV infection [21, 103, 117, 118, 121]. Some studies have also suggested that VitD possesses antiviral activity, and that sup-
Role of Vitamin D in Improving Peg-IFN-α Based Therapy in CHC

The immune system is not always able to control the infection and 70-80% of cases progress to chronic stage due to the escape of HCV from the immune system [135]. The release of IFN-α and -β is essential for the control of HCV during the acute phase [136, 137]. IFN-α/β activates a number of cellular genes, known as INF stimulated genes (ISGs), which inhibit the replication and spread of the virus to other non-infected liver cells [138]. However, HCV is able to block type 1 IFN induction by the non-structural proteins (NS3 and NS5A) and structural protein E2. HCV NS5A protein also inhibits the actions of endogenous IFN-α by upregulating the expression of interleukin (IL)-8 [135, 137].

Natural killer (NK) and natural killer T (NKT) cells consist the first line of immune response against HCV [139]. Infected liver cells release IFN-α and -β to activate of NK and NKT cells [140]. Furthermore, dendritic cells (DCs) release IL-12 that also activates the NK cells [140-142]. NK cells produce their antiviral activities by producing IFN-γ and tumour necrosis factor-α (TNF-α), which inhibit the replication of the virus but without destroying normal liver cells [143, 144]. In addition, they stimulate T helper 1 (Th1)/T cytotoxic (Tc) 1 responses [139, 145]. However, their role in controlling the infection is usually eliminated by HCV through blocking the production of IFN-γ via an interaction between HCV E2 protein and NK cell CD81 molecule [135, 137, 146, 147].

DCs also process and present viral antigens to specific immune system cells via class I and class II major histocompatibility complex molecules. Viral particles are captured by DCs through Toll-like receptors (TLRs) [148-150]. Activated DCs release a variety of cytokines including IL-12, TNF-α, IFN-α and IL-10. These cytokines subsequently regulate and polarize the response of adjacent cells [149-152]. Mature DCs enter the lymph nodes after collec-

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Vitamin D supplementation of VitD significantly improved Peg-IFN-α based therapy outcome in CHC patients, most probably by exerting a direct inhibitory effect on viral production (Figure 3) [92, 122-125].

Nevertheless, other research groups reported that the baseline 25(OH)D level is not associated with SVR to Peg-IFN-α plus RBV therapy in chronic HCV infection, regardless of genotype and there was no correlation between VitD levels and the stage of liver fibrosis in these patients [126-130]. One possible explanation for the discrepancies between the previously reported study could be related to the methods applied for the measurement of VitD levels in clinical laboratories, which could generate different levels of plasma VitD levels depending on the used method and target molecule [131-133]. Hence, further randomized controlled studies with sufficient number of patients and appropriate detection methods for both VitD2 and VitD3 (total and free) are still required to reach a definite conclusion on whether VitD supplementation during the course of CHC treatment is beneficial in achieving SVR.

Vitamin D in the regulation of the immune response to HCV

Infection with HCV leads to acute and chronic necro-inflammatory liver disease [134, 135].
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tion of viral epitopes to activate T cells in the specific immune system [138, 153].

The progression to chronic/adaptive response is initiated by CD4+T cells, which provide help in activating cytotoxic and humoral responses. These cells can secrete Th1-cytokines including IFN-γ, leading to inflammatory response or Th2 cytokines (e.g. IL-4 and IL-10), which limit Th1 cytokine-mediated response and favour the development of humoral response [135, 154]. A multi-specific, strong, sustained, CD4-T-cell-specific Th1 response may be seen in infections with HCV progressing to resolution [137, 155]. However, when infection becomes chronic, a weak CD4-T-specific response with few specificities and scarce type 1 cytokine production is observed [137, 145, 149].

When specific immune response fails to control viral replication, the infected liver cells releases chemokines resulting in the migration of non-specific mononuclear cells into the liver, which are unable to control infection but lead to sustained liver damage [155-157]. Persistent inflammation also stimulates hepatic stellate cells, myofibroblasts, and fibroblasts, which lead to the development of liver fibrosis [137, 157].

The classical action of VitD is the regulation of calcium homeostasis and bone metabolism. A relationship has recently been suggested between VitD status and susceptibility to infectious diseases and its role in the regulation of innate and humoral immunity in human has recently emerged [91, 93, 95, 101, 122, 158-160]. The bioactive form of VitD is an important immune modulator as shown by the results of several studies that calcitriol is crucial for the functions of T cells, NK cells, DCs and macrophages in various conditions [161-163]. These cells are known to be involved in the immune response to HCV and play an important role in the eradication of the viral infection [11].

Immunomodulatory roles for VitD during HCV infection have recently been proposed [164, 165]. VitD is a critical regulator of immunity, playing a role in both innate and cell-mediated immune responses [100, 101, 166]. VitD regulates the production of Th-1 cytokines, such as IFN-γ and IL-2, and also Th2 cytokines, such as IL-4 and IL-5. VitD also endorses innate immunity by directly inducing gene expression of antimicrobial peptides, cathelicidin and β-defensin, in various human cell types [97, 159, 160, 167]. Additionally, VitD supplementation could increase the sensitivity to Peg-IFN-α based therapy by downregulating the production of IP-10, increasing the production of Th-1 cytokines and ISGs by the hepatocyte and peripheral blood mononuclear cells [168]. It has also been suggested that VitD could also enhance the response to the conventional therapy by modulating the production of Th-17 cell including IL-17 and -23 [169, 170].

How could vitamin D enhance response rate to Peg-IFN-α based therapy?

INF therapy stimulates a large number of ISGs including TLRs [171], TNF-α [172] and ILs [173]. IFN-α also enhances the activity of lymphocytes, macrophages, and NK cells and it activates neutrophils and monocytes [139, 145, 155, 174]. IFN-α alters the immune response in patients with CHC from Th-2 to a Th-1 mediated pattern [175]. Th-1 cytokines mediate response and favour the eradication of the virus [135, 155]. INF-α promotes Th-1 response through the increase in the production of IFN-γ, IL-2 and TNF-α by the hepatocyte and immune cells [138, 157]. IFN-α also inhibits the release of IL-6 and IL-10, which regulates Th-1/Th-2 Cytokine balance, in patients with CHC [176, 177]. Additionally, IFN-α alters the production of immunoglobulin and decreases T-regulatory cell function [137, 178].

As mentioned earlier, VitD plays crucial roles in the regulation of immune system. NK, NKT cells and DCs are known to be major regulators of immune response against HCV and their activation is essential to prevent viral replication and spread [139]. VitD modulates the production of NK cells in vitro [179], functions of both NK and NKT cells and significantly lower numbers of NKT cells was observed in vitamin D receptor null mice [180, 181]. VitD3 also enhanced and facilitated the immune-attack of NK cells against malignant cells in vitro [182]. The active metabolite of vitamin D3, calcipotriol, also augmented the lysis effects of NK cells in vitro [183].

VitD3 has recently also been reported to promote the development of human DCs and to enhance their antimicrobial properties [184]. It also modulates the response of human DCs and their produced cytokines during their maturation [185, 186]. VitD has also been shown to
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Possible Mechanisms to prevent anemia

Figure 4. Possible mechanisms by which vitamin D supplementation could prevent the development of anemia during the treatment of chronic hepatitis C with pegylated interferon-α based therapy.

be a major modulator of the tolerogenic DCs functions by modulating its metabolic pathways [187]. Furthermore, 1,25-dihydroxyvitamin D3 promotes the generation of CD4+CD25+Foxp3+ regulatory T cells by treated mouse DCs [188].

Vitamin D has also been shown to regulate the release of several cytokines that are known to be involved in the immune and/or treatment response to IFN-α therapy. Several studies have demonstrated that vitamin D3 decreases the production of IL-8 [189-191], which is known to be induced by HCV NS3 and NS5A to inhibit the effects of INF-α on the production of IFN-γ [135, 137]. VitD2 and D3 also modulates the production of IL-6, IL-10, TNF-α and IFN-γ in a dose dependent manner [192-196]. Hence, supplementation with VitD could enhance the response to Peg-IFN-α based therapy by increasing the production of TNF-α and IFN-γ and decreasing the levels of IL-6, IL-10 and IL-8 [197]. Further studies are still required to identify the mechanisms by which vitamin D levels modulate the immune system during CHC.

Role of vitamin D in the prevention/treatment of anemia

Vitamin D regulates the process of erythropoiesis by stimulating erythroid progenitor cells in a synergistic fashion with other hormones and cytokines, including EPO, and it has been reported that vitamin D is crucial for normal production of RBCs [198]. VitD3 stimulates the proliferation of erythroid progenitor cells independently from EPO [17, 199] and vitamin D responsive element has been localized on the promoter region of the EPO receptor gene [198].

The prevalence of anemia and the use of erythropoiesis-stimulating agents (ESA) have been found to be negatively correlated with serum VitD levels regardless of kidney function in the general population [200]. The role of vitamin D in erythropoiesis has also been suggested by several clinical observations, especially in hemodialysis patients, where administration of VitD has been associated with dose reductions in ESA and increased reticulocytosis [201, 202]. Furthermore, vitamin D3 (calcitriol), in synergism with EPO, increases the production of EPO receptor at the mRNA and protein levels in vitro [198]. A recent study has also reported that 1,25-dihydroxyvitamin D3 was associated with decreased hepcidin and increased ferroportin expression in vitro. The authors further reported that VitD decreased the release of pro-hepcidin cytokines, IL-6 and IL-1β, which are also known to be associated with the development of anemia [203]. In vivo, high-dose vitamin D therapy also decreased systemic hepcidin levels in subjects with early stage chronic kidney disease [203].

Despite the aforementioned observations on the effects of VitD in the treatment of CHC and the prevention of anemia, few studies have only reported on a potential beneficial effect of adding vitamin D to Peg-IFN-α based therapy to prevent the associated anemia. Vitamin D could prevent anemia during the course of CHC treatment by modulating the immune system, increasing erythrocyte production and preventing RBV induced oxidative stress (Figure 4) [17]. Although these observations are promising, the results need to be confirmed in human as the rate of RBCs absorption and intoxication by RBV is species dependent [61-63].
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Role of vitamin D in the prevention/treatment of thyroid disorders

Vitamin D has been shown to have important immunomodulatory properties [100, 101]. The most active natural vitamin D metabolite, 1,25-Dihydroxyvitamin D3, effectively prevents the development of autoimmune thyroiditis. 1,25(OH)2D3 exerts its immunomodulatory actions by inhibiting HLA class II expression on endocrine cells, proliferation of T cell and secretion of inflammatory cytokines [24, 25, 204, 205].

Deficiency of vitamin D was also found to correlate with an increased incidence of autoimmune diseases [206]. Vitamin D supplementation enhances innate immunity and reduces the severity of autoimmunity [94, 100, 101]. Vitamin D levels were found to be lower in patients with AITDs than in healthy people [24, 25, 206]. Deficiency of vitamin D was also linked to the presence of anti-thyroid antibodies and abnormal thyroid functions [95, 206]. Hence vitamin D supplementation during the treatment of CHC with Peg-IFN-α based therapy could be beneficial in the prevention/elimination of the associated thyroid disorders; especially that VitD is inexpensive and carries minimal side effects [24, 25, 95, 206].

Conclusions

Infection with HCV is a worldwide health problem and it is one of the most common causes of end stage liver diseases. The conventional treatment of chronic hepatitis C consists of a weekly injection of Peg-IFN-α and a daily oral dose of ribavirin. Although new directly acting antiviral agents have been introduced and they achieve better cure rates, these medications are expensive and a large proportion of patients may not have access to them. The recent findings that vitamin D supplementation could have a potential role in improving the success rate of Peg-IFN-α during the treatment of CHC merit further research especially that it is widely available and inexpensive, and it could provide an alternative option to treat those patients who have limited financial support and/or access to the new antiviral treatment.

Besides its long duration and low response rate, Peg-IFN-α based therapy is also associated with several extrahepatic adverse effects and the most common are the development of anemia and thyroid disorders during the course of treatment, which could lead to termination of CHC treatment. Vitamin D has recently been reported to play significant roles in the regulation of immune system, the process of erythropoiesis and thyroid functions. Several studies have indicated that VitD supplementation is useful for the prevention/treatment of anemia and thyroid disorders. However, little is known about the potential effect(s) for vitamin D as a prophylactic/treatment agent against these side effects during the treatment of CHC with Peg-IFN-α based therapy. Further studies with large number of patients are required to determine whether supplementation with vitamin D during the treatment of CHC with Peg-IFN-α based therapy is useful in increasing the rates of SVR and preventing the development of associated adverse effects.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Bassem Refaat, Laboratory Medicine Department, Faculty of Applied Medical Sciences, Umm Al-Qura University, Makkah, PO Box 7607, KSA. Tel: +966 541162707; Fax: +966 12 52700004242; E-mail: Bassem.refaat@yahoo.co.uk

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