Int J Clin Exp Med 2015;8(7):10284-10303
www.ijcem.com /ISSN:1940-5901/IJCEM0007955

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 Refaat[1], Adel Galal El-Shemi[1,2], Ahmed Ashshi[1], Esam Azhar[3,4]

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

Received March 13, 2015; Accepted July 1, 2015; Epub July 15, 2015; Published July 30, 2015

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-INF-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

'PubMed' and 'EMBASE' databases were searched using the terms 'hepatitis C virus', 'chronic hepatitis C', 'pegylated interferon-α', 'ribavirin', 'risk factors', 'prevalence', 'complications', 'adverse effect', 'side effect', 'response rate' and 'sustained viral response' in combination with 'hematology', 'anemia', 'endocrinology', 'thyroid' and 'vitamin D' for studies published between 2004 and 2014.

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].

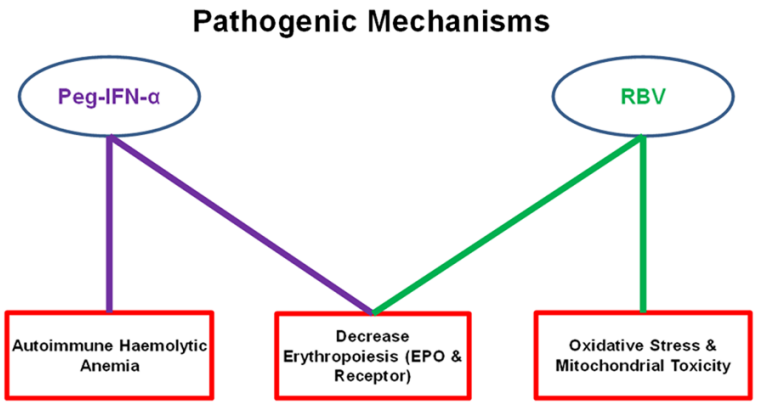

Figure 1. Summary of pathogenic mechanisms by which pegylated interferon-α (Peg-IFN-α) and ribavirin (RBV) induce anemia during the treatment of chronic hepatitis C infection.

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 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,

60]. 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.

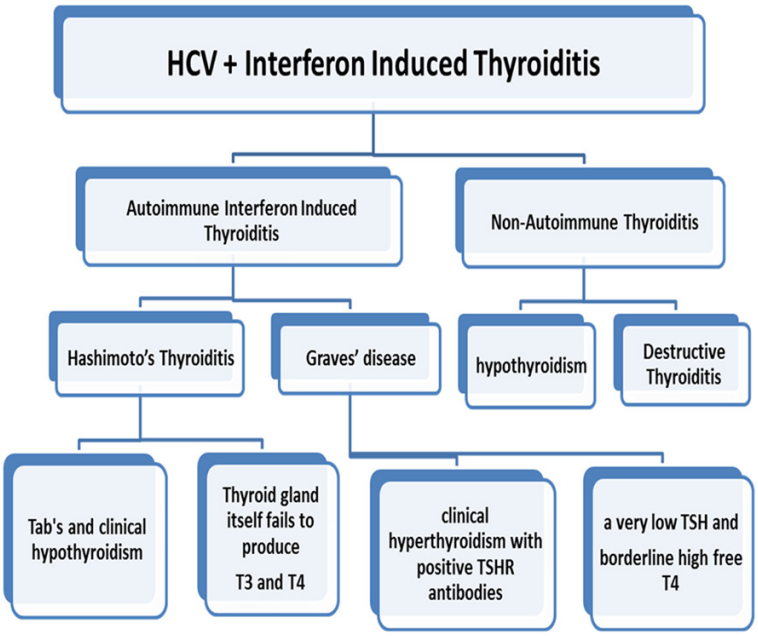

Figure 2. Types of thyroid disorders associated with chronic hepatitis C infections and its treatment with pegylated interferon-α based therapy.

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 TAbs 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-

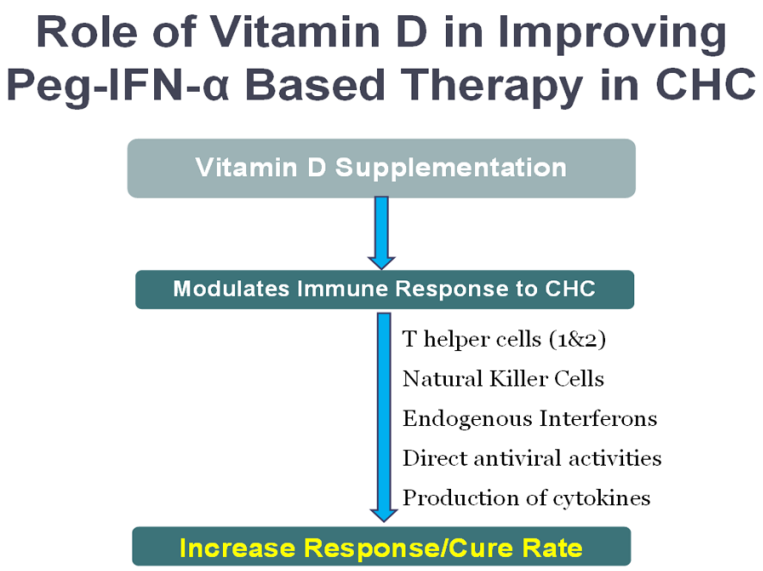

Figure 3. Mechanisms by which vitamin D supplementation could increase the response rate during the treatment of chronic hepatitis C with pegylated interferon-α based therapy.

plementation 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]. 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-

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

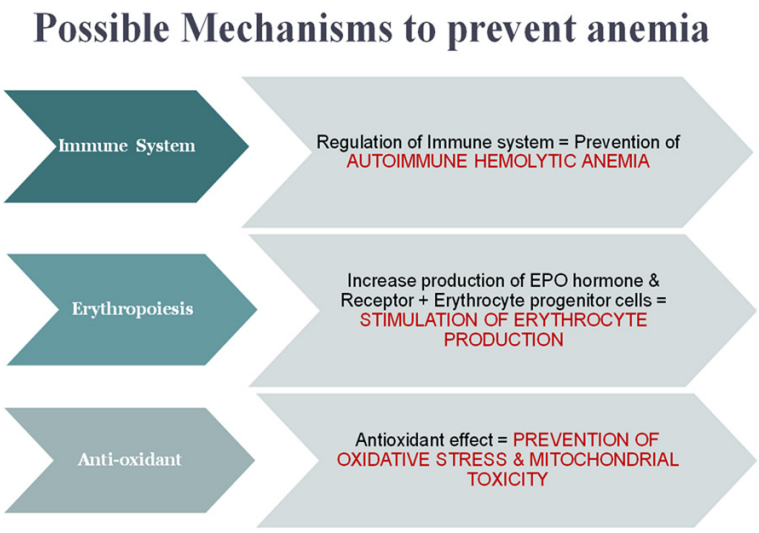

Figure 4. Possible mechanisms by which vitamin D supplementation could prevent the development of anemia during the treatment of chronic hepatitis C with pegylated interferon-α based therapy.

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 D_3 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].

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-Dihyroxyvitamin 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.

Acknowledgements

This study was funded by the National Science, Technology and Innovation Plan (MARRIFAH)-King Abdul Aziz City for Science and Technology (KACST), the Kingdom of Saudi Arabia, Award Number (12-MED2302-10).

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

References

[1] Averhoff FM, Glass N and Holtzman D. Global burden of hepatitis C: considerations for healthcare providers in the United States. Clin Infect Dis 2012; 55 Suppl 1: S10-15.

[2] Ghany MG, Strader DB, Thomas DL and Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009; 49: 1335-1374.

[3] Metts J, Carmichael L, Kokor W and Scharffenberg R. Hepatitis C: Existing and New Treatments. FP Essent 2014; 427: 18-24.

[4] Metts J, Carmichael L, Kokor W and Scharffenberg R. Hepatitis C: Extrahepatic Manifestations. FP Essent 2014; 427: 32-35.

[5] Metts J, Carmichael L, Kokor W and Scharffenberg R. Hepatitis C: Liver Transplantation. FP Essent 2014; 427: 25-31.
[6] Lee C. Daclatasvir: potential role in hepatitis C. Drug Des Devel Ther 2013; 7: 1223-1233.
[7] EASL. EASL Recommendations on Treatment of Hepatitis C 2014. J Hepatol 2014; 61: 373-395.
[8] Afdhal NH, Zeuzem S, Schooley RT, Thomas DL, Ward JW, Litwin AH, Razavi H, Castera L, Poynard T, Muir A, Mehta SH, Dee L, Graham C, Church DR, Talal AH, Sulkowski MS and Jacobson IM. The new paradigm of hepatitis C therapy: integration of oral therapies into best practices. J Viral Hepat 2013; 20: 745-760.
[9] Chan K, Lai MN, Groessl EJ, Hanchate AD, Wong JB, Clark JA, Asch SM, Gifford AL and Ho SB. Cost effectiveness of direct-acting antiviral therapy for treatment-naive patients with chronic HCV genotype 1 infection in the veterans health administration. Clin Gastroenterol Hepatol 2013; 11: 1503-1510.
[10] Cure S, Bianic F, Gavart S, Curtis S, Lee S and Dusheiko G. Cost-effectiveness of telaprevir in combination with pegylated interferon alpha and ribavirin in previously untreated chronic hepatitis C genotype 1 patients. J Med Econ 2014; 17: 65-76.
[11] Refaat B, Ashshi AM, El-Shemi AG and AlZanbagi A. Effects of chronic hepatitis C genotype 1 and 4 on serum activins and follistatin in treatment naive patients and their correlations with interleukin-6, tumour necrosis factor-alpha, viral load and liver damage. Clin Exp Med 2014; [Epub ahead of print].
[12] Refaat B, El-Shemi AG, Ashshi AM and Alzanbagi A. Serum Activins and Follistatin during the Treatment of Chronic Hepatitis C Genotypes 1 and 4 and Their Correlations with Viral Load and Liver Enzymes: A Preliminary Report. Gastroenterol Res Pract 2014; 2014: 628683.
[13] Alexopoulou A and Papatheodoridis GV. Current progress in the treatment of chronic hepatitis C. World J Gastroenterol 2012; 18: 6060-6069.
[14] Gatselis NK, Zachou K, Saitis A, Samara M and Dalekos GN. Individualization of chronic hepatitis C treatment according to the host characteristics. World J Gastroenterol 2014; 20: 2839-2853.
[15] Tran TT. A review of standard and newer treatment strategies in hepatitis C. Am J Manag Care 2012; 18: S340-349.
[16] Poordad F, Lawitz E, Reddy KR, Afdhal NH, Hezode C, Zeuzem S, Lee SS, Calleja JL, Brown RS Jr, Craxi A, Wedemeyer H, Nyberg L, Nelson DR, Rossaro L, Balart L, Morgan TR, Bacon BR, Flamm SL, Kowdley KV, Deng W, Koury KJ, Pedicone LD, Dutko FJ, Burroughs MH, Alves K, Wahl J, Brass CA, Albrecht JK and Sulkowski MS. Effects of ribavirin dose reduction vs erythropoietin for boceprevir-related anemia in patients with chronic hepatitis C virus genotype 1 infection--a randomized trial. Gastroenterology 2013; 145: 1035-1044 e1035.
[17] Refaat B, Ashour TH and El-Shemi AG. Ribavirin induced anaemia: the effect of vitamin D supplementation on erythropoietin and erythrocyte indices in normal Wistar rat. Int J Clin Exp Med 2014; 7: 2667-2676.
[18] Refaat B, Ashour TH and El-Shemi AG. Ribavirin induced anaemia: the effect of vitamin D supplementation on erythropoietin and erythrocyte indices in normal Wistar rat. Int J Clin Exp Med 2014; 7: 2667.
[19] Atsukawa M, Tsubota A, Shimada N, Kondo C, Itokawa N, Nakagawa A, Hashimoto S, Fukuda T, Matsushita Y, Kidokoro H, Narahara Y, Nakatsuka K, Iwakiri K, Kawamoto C and Sakamoto C. Efficacy of Alfacalcidol on PEG-IFN/ Ribavirin Combination Therapy for Elderly Patients With Chronic Hepatitis C: A Pilot Study. Hepat Mon 2013; 13: e14872.
[20] Atsukawa M, Tsubota A, Shimada N, Abe H, Kondo C, Itokawa N, Nakagawa A, Iwakiri K, Kawamoto C, Aizawa Y and Sakamoto C. Serum 25(OH)D3 levels affect treatment outcomes for telaprevir/peg-interferon/ribavirin combination therapy in genotype 1b chronic hepatitis C. Dig Liver Dis 2014; 46: 738-743.
[21] Atsukawa M, Tsubota A, Shimada N, Kondo C, Itokawa N, Nakagawa A, Hashimoto S, Fukuda T, Matsushita Y, Narahara Y, Iwakiri K, Nakatsuka K, Kawamoto C and Sakamoto C. Serum 25-hydroxyvitamin D levels affect treatment outcome in pegylated interferon/ribavirin combination therapy for compensated cirrhotic patients with hepatitis C virus genotype 1b and high viral load. Hepatol Res 2014; 44: 1277-1285.
[22] Bitetto D, Fattovich G, Fabris C, Ceriani E, Falleti E, Fornasiere E, Pasino M, Ieluzzi D, Cussigh A, Cmet S, Pirisi M and Toniutto P. Complementary role of vitamin D deficiency and the interleukin-28B rs12979860 C/T polymorphism in predicting antiviral response in chronic hepatitis C. Hepatology 2011; 53: 1118-1126.
[23] Bitetto D, Fabris C, Fornasiere E, Pipan C, Fumolo E, Cussigh A, Bignulin S, Cmet S, Fontanini E, Falleti E, Martinella R, Pirisi M and Toniutto P. Vitamin D supplementation improves response to antiviral treatment for recurrent hepatitis C. Transpl Int 2011; 24: 43-50.

[24] Bizzaro G and Shoenfeld Y. Vitamin D and autoimmune thyroid diseases: facts and unresolved questions. Immunol Res 2014; 61: 46-52.
[25] Bizzaro G and Shoenfeld Y. Vitamin D and thyroid autoimmune diseases: the known and the obscure. Immunol Res 2014; 61: 107-9.
[26] Abdel-Moneim AS, Bamaga MS, Shehab GM, Abu-Elsaad AA and Farahat FM. HCV infection among Saudi population: high prevalence of genotype 4 and increased viral clearance rate. PLoS One 2012; 7: e29781.
[27] Al Ashgar HI, Khan MQ, Al-Ahdal M, Al Thawadi S, Helmy AS, Al Qahtani A and Sanai FM. Hepatitis C genotype 4: genotypic diversity, epidemiological profile, and clinical relevance of subtypes in Saudi Arabia. Saudi J Gastroenterol 2013; 19: 28-33.
[28] Fallahian F and Najafi A. Epidemiology of hepatitis C in the Middle East. Saudi J Kidney Dis Transpl 2011; 22: 1-9.
[29] Madani TA. Hepatitis C virus infections reported over 11 years of surveillance in Saudi Arabia. Trans R Soc Trop Med Hyg 2009; 103: 132-136.
[30] Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M and Albrecht JK. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001; 358: 958-965.
[31] Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL Jr, Haussinger D, Diago M, Carosi G, Dhumeaux D, Craxi A, Lin A, Hoffman J and Yu J. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002; 347: 975-982.
[32] Hadziyannis SJ, Sette H Jr, Morgan TR, Balan V, Diago M, Marcellin P, Ramadori G, Bodenheimer H Jr, Bernstein D, Rizzetto M, Zeuzem S, Pockros PJ, Lin A and Ackrill AM. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med 2004; 140: 346-355.
[33] Lee SS and Ferenci P. Optimizing outcomes in patients with hepatitis C virus genotype 1 or 4. Antivir Ther 2008; 13 Suppl 1: 9-16.
[34] Dahlan Y, Ather HM, Al-ahmadi M, Batwa F and Al-hamoudi W. Sustained virological response in a predominantly hepatitis C virus genotype 4 infected population. World J Gastroenterol 2009; 15: 4429-4433.
[35] Abenavoli L, Mazza M and Almasio PL. The optimal dose of ribavirin for chronic hepatitis C: From literature evidence to clinical practice: The optimal dose of ribavirin for chronic hepatitis C. Hepat Mon 2011; 11: 240-246.
[36] Chukkapalli V, Berger KL, Kelly SM, Thomas M, Deiters A and Randall G. Daclatasvir inhibits hepatitis C virus NS5A motility and hyper-accumulation of phosphoinositides. Virology 2014; 476C: 168-179.
[37] Yau AH and Yoshida EM. Hepatitis C drugs: the end of the pegylated interferon era and the emergence of all-oral interferon-free antiviral regimens: a concise review. Can J Gastroenterol Hepatol 2014; 28: 445-451.
[38] Lange CM and Zeuzem S. Perspectives and challenges of interferon-free therapy for chronic hepatitis C. J Hepatol 2013; 58: 583-592.
[39] Younossi ZM, Singer ME, Mir HM, Henry L and Hunt S. Impact of Interferon Free Regimens on Clinical and Cost Outcomes for Chronic Hepatitis C Genotype 1 Patients. J Hepatol 2013;
[40] Ferrante SA, Chhatwal J, Brass CA, El Khoury AC, Poordad F, Bronowicki JP and Elbasha EH. Boceprevir for previously untreated patients with chronic hepatitis C Genotype 1 infection: a US-based cost-effectiveness modeling study. BMC Infect Dis 2013; 13: 190.
[41] Blackard JT, Kong L, Huber AK and Tomer Y. Hepatitis C virus infection of a thyroid cell line: implications for pathogenesis of hepatitis C virus and thyroiditis. Thyroid 2013; 23: 863-870.
[42] Menconi F, Hasham A and Tomer Y. Environmental triggers of thyroiditis: hepatitis C and interferon-alpha. J Endocrinol Invest 2011; 34: 78-84.
[43] Tomer Y. Hepatitis C and interferon induced thyroiditis. J Autoimmun 2010; 34: J322-326.
[44] Oliveira TL, Caetano AZ, Belem JM, Klemz BC and Pinheiro MM. Interferon-alpha induced psoriatic arthritis and autoimmune hemolytic anemia during chronic hepatitis C treatment. Acta Reumatol Port 2014; 39: 327-30.
[45] Ennaifer R, Cheikh M, Romdhane H, Hefaiedh R, Ben Nejma H and Bel Hadj N. Severe autoimmune hemolytic anemia in a patient with chronic hepatitis C during treatment with Peg interferon alfa-2a and ribavirin. Tunis Med 2014; 92: 42-43.
[46] Keeffe EB and Kowdley KV. Hematologic side effects of PEG interferon and ribavirin. Management with growth factors. J Clin Gastroenterol 2005; 39: S1-2.
[47] Martin P and Jensen DM. Ribavirin in the treatment of chronic hepatitis C. J Gastroenterol Hepatol 2008; 23: 844-855.
[48] McHutchison JG, Manns MP, Brown RS Jr, Reddy KR, Shiffman ML and Wong JB. Strategies for managing anemia in hepatitis C patients undergoing antiviral therapy. Am J Gastroenterol 2007; 102: 880-889.
[49] McHutchison JG, Manns MP and Longo DL. Definition and management of anemia in pa-

tients infected with hepatitis C virus. Liver Int 2006; 26: 389-398.
[50] Sulkowski MS, Poordad F, Manns MP, Bronowicki JP, Rajender Reddy K, Harrison SA, Afdhal NH, Sings HL, Pedicone LD, Koury KJ, Sniukiene V, Burroughs MH, Albrecht JK, Brass CA and Jacobson IM. Anemia during treatment with peginterferon Alfa-2b/ribavirin and boceprevir: Analysis from the serine protease inhibitor therapy 2 (SPRINT-2) trial. Hepatology 2013; 57: 974-984.
[51] Sulkowski MS. Anemia in the treatment of hepatitis C virus infection. Clin Infect Dis 2003; 37 Suppl 4: S315-322.
[52] Tarumi T, Sawada K, Sato N, Kobayashi S, Takano H, Yasukouchi T, Takashashi T, Sekiguchi S and Koike T. Interferon-alpha-induced apoptosis in human erythroid progenitors. Exp Hematol 1995; 23: 1310-1318.
[53] Van Vlierbergh H, Delanghe JR, De Vos M and Leroux-Roel G. Factors influencing ribavirin-induced hemolysis. J Hepatol 2001; 34: 911-916.
[54] Morello J, Rodriguez-Novoa S, Jimenez-Nacher I and Soriano V. Usefulness of monitoring ribavirin plasma concentrations to improve treatment response in patients with chronic hepatitis C. J Antimicrob Chemother 2008; 62: 1174-1180.
[55] Sulkowski MS, Wasserman R, Brooks L, Ball L and Gish R. Changes in haemoglobin during interferon alpha-2b plus ribavirin combination therapy for chronic hepatitis C virus infection. J Viral Hepat 2004; 11: 243-250.
[56] Tanaka H, Miyano M, Ueda H, Fukui K and Ichinose M. Changes in serum and red blood cell membrane lipids in patients treated with interferon ribavirin for chronic hepatitis C. Clin Exp Med 2005; 5: 190-195.
[57] Kato K, Kamezaki K, Shimoda K, Numata A, Haro T, Aoki K, Ishikawa F, Takase K, Ariyama H, Matsuda T, Miyamoto T, Nagafuji K, Gondo H, Nakayama K and Harada M. Intracellular signal transduction of interferon on the suppression of haematopoietic progenitor cell growth. Br J Haematol 2003; 123: 528-535.
[58] Kurschel E, Metz-Kurschel U, Niederle N and Aulbert E. Investigations on the subclinical and clinical nephrotoxicity of interferon alpha-2B in patients with myeloproliferative syndromes. Ren Fail 1991; 13: 87-93.
[59] Sacchi S, Kantarjian H, O'Brien S, Cohen PR, Pierce S and Talpaz M. Immune-mediated and unusual complications during interferon alfa therapy in chronic myelogenous leukemia. J Clin Oncol 1995; 13: 2401-2407.
[60] De Franceschi L, Fattovich G, Turrini F, Ayi K, Brugnara C, Manzato F, Noventa F, Stanzial AM, Solero P and Corrocher R. Hemolytic anemia induced by ribavirin therapy in patients with chronic hepatitis C virus infection: role of membrane oxidative damage. Hepatology 2000; 31: 997-1004.
[61] Canonico PG, Kastello MD, Spears CT, Brown JR, Jackson EA and Jenkins DE. Effects of ribavirin on red blood cells. Toxicol Appl Pharmacol 1984; 74: 155-162.
[62] Canonico PG, Kastello MD, Cosgriff TM, Donovan JC, Ross PE, Spears CT and Stephen EL. Hematological and bone marrow effects of ribavirin in rhesus monkeys. Toxicol Appl Pharmacol 1984; 74: 163-172.
[63] Cosgriff TM, Hodgson LA, Canonico PG, White JD, Kastello MD, Donovan JC and Ross PE. Morphological alterations in blood and bone marrow of ribavirin-treated monkeys. Acta Haematol 1984; 72: 195-200.
[64] Balan V, Schwartz D, Wu GY, Muir AJ, Ghalib R, Jackson J, Keeffe EB, Rossaro L, Burnett A, Goon BL, Bowers PJ and Leitz GJ. Erythropoietic response to anemia in chronic hepatitis C patients receiving combination pegylated interferon/ribavirin. Am J Gastroenterol 2005; 100: 299-307.
[65] D'Souza UJ and Narayana K. Mechanism of cytotoxicity of ribavirin in the rat bone marrow and testis. Indian J Physiol Pharmacol 2002; 46: 468-474.
[66] Narayana K, D'Souza UJ and Seetharama Rao KP. The genotoxic and cytotoxic effects of ribavirin in rat bone marrow. Mutat Res 2002; 521: 179-185.
[67] Mao XR, Zhang LT, Chen H, Xiao P and Zhang YC. Possible factors affecting thyroid dysfunction in hepatitis C virus-infected untreated patients. Exp Ther Med 2014; 8: 133-140.
[68] Ashshi AM, El-Shemi AG, AlZanbagi A and Refaat B. Prevalence of thyroid disorders and the correlation of thyroid profile with liver enzymes, serum activin-A and follistatin during the treatment of patients with chronic hepatitis C genotype 1 and 4. J Clin Exp Invest www.jceionline. org Vol 2014; 5.
[69] Chung HS, Cho SJ and Park CS. Effects of liver function on ionized hypocalcaemia following rapid blood transfusion. J Int Med Res 2012; 40: 572-582.
[70] El-Kabbany ZA, Hamza RT, Abd El Hakim AS and Tawfik LM. Thyroid and Hepatic Haemodynamic Alterations among Egyptian Children with Liver Cirrhosis. ISRN Gastroenterol 2012; 2012: 595734.
[71] Khan TM, Malik S and Diju IU. Correlation between plasma thyroid hormones and liver enzymes level in thyrotoxic cases and controls in Hazara Division. J Ayub Med Coll Abbottabad 2010; 22: 176-179.

[72] Ittermann T, Haring R, Wallaschofski H, Baumeister SE, Nauck M, Dorr M, Lerch M, Meyer zu Schwabedissen HE, Rosskopf D and Volzke H. Inverse association between serum free thyroxine levels and hepatic steatosis: results from the Study of Health in Pomerania. Thyroid 2012; 22: 568-574.
[73] Tas A, Koklu S, Beyazit Y, Kurt M, Sayilir A, Yesil Y and Celik H. Thyroid hormone levels predict mortality in intensive care patients with cirrhosis. Am J Med Sci 2012; 344: 175-179.
[74] Andrade LJ, Atta AM, Atta ML, Mangabeira CN and Parana R. Thyroid disorders in patients with chronic hepatitis C using interferon-alpha and ribavirin therapy. Braz J Infect Dis 2011; 15: 377-381.
[75] Carella C, Mazziotti G, Amato G, Braverman LE and Roti E. Clinical review 169: Interferon-alpha-related thyroid disease: pathophysiological, epidemiological, and clinical aspects. J Clin Endocrinol Metab 2004; 89: 3656-3661.
[76] Vezali E, Elefsiniotis I, Mihas C, Konstantinou E and Saroglou G. Thyroid dysfunction in patients with chronic hepatitis C: virus-or therapy-related? J Gastroenterol Hepatol 2009; 24: 1024-1029.
[77] Tomer Y. Genetic susceptibility to autoimmune thyroid disease: past, present, and future. Thyroid 2010; 20: 715-725.
[78] Soppi E. [Concurrent subacute thyroiditis and Graves disease]. Duodecim 2012; 128: 1808-1810.
[79] Costelloe SJ, Wassef N, Schulz J, Vaghijiani T, Morris C, Whiting S, Thomas M, Dusheiko G, Jacobs M and Vanderpump MP. Thyroid dysfunction in a UK hepatitis C population treated with interferon-alpha and ribavirin combination therapy. Clin Endocrinol (Oxf) 2010; 73: 249-256.
[80] Andrade LJ, D'Oliveira A Jr, Silva CA, Nunes P, Franca LS, Malta AM and Parana R. A meta-analysis of patients with chronic hepatitis C treated with interferon-alpha to determine the risk of autoimmune thyroiditis. Acta Gastroenterol Latinoam 2011; 41: 104-110.
[81] Mandac JC, Chaudhry S, Sherman KE and Tomer Y. The clinical and physiological spectrum of interferon-alpha induced thyroiditis: toward a new classification. Hepatology 2006; 43: 661-672.
[82] Zantut-Wittmann DE, Pavan MH, Pavin EJ and Goncales FL Jr. Central hypothyroidism in patients with chronic hepatitis C and relation with interferon-alpha treatment. Endocr Regul 2011; 45: 157-161.
[83] Nadeem A and Aslam M. Association of interferon-alpha and ribavirin-induced thyroid dysfunction with severity of disease and response to treatment in pakistani asian patients of chronic hepatitis C. Hepat Res Treat 2012; 2012: 864315.
[84] Yan Z, Fan K, Fan Y, Wang X, Mao Q, Deng G and Wang Y. Thyroid dysfunction in chinese patients with chronic hepatitis C treated with interferon alpha: incidence, long-term outcome and predictive factors. Hepat Mon 2012; 12: e6390.
[85] Tomer Y, Sarapura V and Kahaly GJ. Thyroid disorders: it's very personal. Thyroid 2010; 20: 677-679.
[86] Song RH, Yu ZY, Qin Q, Wang X, Muhali FS, Shi LF, Jiang WJ, Xiao L, Li DF and Zhang JA. Different levels of circulating Th22 cell and its related molecules in Graves' disease and Hashimoto's thyroiditis. Int J Clin Exp Pathol 2014; 7: 4024-4031.
[87] Oppenheim Y, Ban Y and Tomer Y. Interferon induced Autoimmune Thyroid Disease (AITD): a model for human autoimmunity. Autoimmun Rev 2004; 3: 388-393.
[88] Giovanella L, Toffalori E, Tozzoli R, Caputo M, Ceriani L and Verburg FA. Multiplexed immunoassay of thyroglobulin autoantibodies in patients with differentiated thyroid carcinoma. Head Neck 2012; 34: 1369-1371.
[89] Jadali Z. Autoimmune thyroid disorders in hepatitis C virus infection: Effect of interferon therapy. Indian J Endocrinol Metab 2013; 17: 69-75.
[90] Joffe RT, Pearce EN, Hennessey JV, Ryan JJ and Stern RA. Subclinical hypothyroidism, mood, and cognition in older adults: a review. Int J Geriatr Psychiatry 2013; 28: 111-118.
[91] Chen EQ, Shi Y and Tang H. New insight of vitamin D in chronic liver diseases. Hepatobiliary Pancreat Dis Int 2014; 13: 580-585.
[92] Cholongitas E, Theocharidou E, Goulis J, Tsochatzis E, Akriviadis E and Burroughs K. Review article: the extra-skeletal effects of vitamin D in chronic hepatitis C infection. Aliment Pharmacol Ther 2012; 35: 634-646.
[93] Fitzpatrick TB, Basset GJ, Borel P, Carrari F, DellaPenna D, Fraser PD, Hellmann H, Osorio S, Rothan C, Valpuesta V, Caris-Veyrat C and Fernie AR. Vitamin deficiencies in humans: can plant science help? Plant Cell 2012; 24: 395-414.
[94] Rosen CJ. Clinical practice. Vitamin D insufficiency. N Engl J Med 2011; 364: 248-254.
[95] Rosen CJ, Adams JS, Bikle DD, Black DM, Demay MB, Manson JE, Murad MH and Kovacs CS. The nonskeletal effects of vitamin D: an Endocrine Society scientific statement. Endocr Rev 2012; 33: 456-492.
[96] Chaplin G and Jablonski NG. The human environment and the vitamin D compromise: Scotland as a case study in human biocultural

adaptation and disease susceptibility. Hum Biol 2013; 85: 529-552.
[97] Assa A, Vong L, Pinnell LJ, Avitzur N, Johnson-Henry KC and Sherman PM. Vitamin D deficiency promotes epithelial barrier dysfunction and intestinal inflammation. J Infect Dis 2014; 210: 1296-1305.
[98] Falleti E, Bitetto D, Fabris C, Cussigh A, Fontanini E, Fornasiere E, Fumolo E, Bignulin S, Cmet S, Minisini R, Pirisi M and Toniutto P. Vitamin D receptor gene polymorphisms and hepatocellular carcinoma in alcoholic cirrhosis. World J Gastroenterol 2010; 16: 3016-3024.
[99] Gagnon C, Lu ZX, Magliano DJ, Dunstan DW, Shaw JE, Zimmet PZ, Sikaris K, Ebeling PR and Daly RM. Low serum 25-hydroxyvitamin D is associated with increased risk of the development of the metabolic syndrome at five years: results from a national, population-based prospective study (The Australian Diabetes, Obesity and Lifestyle Study: AusDiab). J Clin Endocrinol Metab 2012; 97: 1953-1961.
[100] Schoindre Y, Terrier B, Kahn JE, Saadoun D, Souberbielle JC, Benveniste O, Amoura Z, Piette JC, Cacoub P and Costedoat-Chalumeau N. [Vitamin D and autoimmunity. Second part: Clinical aspects]. Rev Med Interne 2012; 33: 87-93.
[101] Schoindre Y, Terrier B, Kahn JE, Saadoun D, Souberbielle JC, Benveniste O, Amoura Z, Piette JC, Cacoub P and Costedoat-Chalumeau N. [Vitamin D and autoimmunity. First part: Fundamental aspects]. Rev Med Interne 2012; 33: 80-86.
[102] Terrier B, Carrat F, Geri G, Pol S, Piroth L, Halfon P, Poynard T, Souberbielle JC and Cacoub P. Low 25-OH vitamin D serum levels correlate with severe fibrosis in HIV-HCV co-infected patients with chronic hepatitis. J Hepatol 2011; 55: 756-761.
[103] Petta S, Camma C, Scazzone C, Tripodo C, Di Marco V, Bono A, Cabibi D, Licata G, Porcasi R, Marchesini G and Craxi A. Low vitamin D serum level is related to severe fibrosis and low responsiveness to interferon-based therapy in genotype 1 chronic hepatitis C. Hepatology 2010; 51: 1158-1167.
[104] Lange CM, Bojunga J, Ramos-Lopez E, von Wagner M, Hassler A, Vermehren J, Herrmann E, Badenhoop K, Zeuzem S and Sarrazin C. Vitamin D deficiency and a CYP27B1-1260 promoter polymorphism are associated with chronic hepatitis C and poor response to interferon-alfa based therapy. J Hepatol 2011; 54: 887-893.
[105] Jablonski KL, Jovanovich A, Holmen J, Targher G, McFann K, Kendrick J and Chonchol M. Low 25-hydroxyvitamin D level is independently associated with non-alcoholic fatty liver disease. Nutr Metab Cardiovasc Dis 2013; 23: 792-798.
[106] Petta S, Grimaudo S, Marco VD, Scazzone C, Macaluso FS, Camma C, Cabibi D, Pipitone R and Craxi A. Association of vitamin D serum levels and its common genetic determinants, with severity of liver fibrosis in genotype 1 chronic hepatitis C patients. J Viral Hepat 2013; 20: 486-493.
[107] Gerova DI, Galunska BT, Ivanova, II, Kotzev IA, Tchervenkov TG, Balev SP and Svinarov DA. Prevalence of vitamin D deficiency and insufficiency in Bulgarian patients with chronic hepatitis C viral infection. Scand J Clin Lab Invest 2014; 74: 665-672.
[108] Garcia-Alvarez M, Pineda-Tenor D, Jimenez-Sousa MA, Fernandez-Rodriguez A, Guzman-Fulgencio M and Resino S. Relationship of vitamin D status with advanced liver fibrosis and response to hepatitis C virus therapy: a meta-analysis. Hepatology 2014; 60: 1541-1550.
[109] Baur K, Mertens JC, Schmitt J, Iwata R, Stieger B, Frei P, Seifert B, Bischoff Ferrari HA, von Eckardstein A, Mullhaupt B and Geier A. The vitamin D receptor gene bAt (CCA) haplotype impairs the response to pegylated-interferon/ribavirin-based therapy in chronic hepatitis C patients. Antivir Ther 2012; 17: 541-547.
[110] Baur K, Mertens JC, Schmitt J, Iwata R, Stieger B, Eloranta JJ, Frei P, Stickel F, Dill MT, Seifert B, Ferrari HA, von Eckardstein A, Bochud PY, Mullhaupt B and Geier A. Combined effect of 25-OH vitamin D plasma levels and genetic vitamin D receptor (NR 1I1) variants on fibrosis progression rate in HCV patients. Liver Int 2012; 32: 635-643.
[111] Falleti E, Bitetto D, Fabris C, Fattovich G, Cussigh A, Cmet S, Ceriani E, Fornasiere E, Pasino M, Ieluzzi D, Pirisi M and Toniutto P. Vitamin D binding protein gene polymorphisms and baseline vitamin D levels as predictors of antiviral response in chronic hepatitis C. Hepatology 2012; 56: 1641-1650.
[112] Falleti E, Cmet S, Fabris C, Fattovich G, Cussigh A, Bitetto D, Ceriani E, Lenisa I, Dissegna D, Ieluzzi D, Rostello A, Pirisi M and Toniutto P. Genetic polymorphisms of vitamin D pathway predict antiviral treatment outcome in slow responder naive patients with chronic hepatitis C. PLoS One 2013; 8: e80764.
[113] Garcia-Martin E, Agundez JA, Maestro ML, Suarez A, Vidaurreta M, Martinez C, Fernandez-Perez C, Ortega L and Ladero JM. Influence of vitamin D-related gene polymorphisms (CYP27B and VDR) on the response to interferon/ribavirin therapy in chronic hepatitis C. PLoS One 2013; 8: e74764.
[114] Barchetta I, Carotti S, Labbadia G, Gentilucci UV, Muda AO, Angelico F, Silecchia G, Leonetti F, Fraioli A, Picardi A, Morini S and Cavallo MG.

Liver vitamin D receptor, CYP2R1, and CYP27A1 expression: relationship with liver histology and vitamin D3 levels in patients with nonalcoholic steatohepatitis or hepatitis C virus. Hepatology 2012; 56: 2180-2187.
[115] Lange CM, Miki D, Ochi H, Nischalke HD, Bojunga J, Bibert S, Morikawa K, Gouttenoire J, Cerny A, Dufour JF, Gorgievski-Hrisoho M, Heim MH, Malinverni R, Mullhaupt B, Negro F, Semela D, Kutalik Z, Muller T, Spengler U, Berg T, Chayama K, Moradpour D and Bochud PY. Genetic analyses reveal a role for vitamin D insufficiency in HCV-associated hepatocellular carcinoma development. PLoS One 2013; 8: e64053.
[116] Hung CH, Chiu YC, Hu TH, Chen CH, Lu SN, Huang CM, Wang JH and Lee CM. Significance of vitamin d receptor gene polymorphisms for risk of hepatocellular carcinoma in chronic hepatitis C. Transl Oncol 2014; 7: 503-507.
[117] Abu-Mouch S, Fireman Z, Jarchovsky J, Zeina AR and Assy N. Vitamin D supplementation improves sustained virologic response in chronic hepatitis C (genotype 1)-naive patients. World J Gastroenterol 2011; 17: 5184-5190.
[118] Nimer A and Mouch A. Vitamin D improves viral response in hepatitis C genotype 2-3 naive patients. World J Gastroenterol 2012; 18: 800-805.
[119] Amanzada A, Goralczyk AD, Moriconi F, van Thiel DH, Ramadori G and Mihm S. Vitamin D status and serum ferritin concentration in chronic hepatitis C virus type 1 infection. J Med Virol 2013; 85: 1534-1541.
[120] Mandorfer M, Reiberger T, Payer BA, Ferlitsch A, Breitenecker F, Aichelburg MC, Obermayer-Pietsch B, Rieger A, Trauner M and Peck-Radosavljevic M. Low vitamin D levels are associated with impaired virologic response to PEGIFN + RBV therapy in HIV-hepatitis C virus coinfected patients. AIDS 2013; 27: 227-232.
[121] Yokoyama S, Takahashi S, Kawakami Y, Hayes CN, Kohno H, Tsuji K, Aisaka Y, Kira S, Yamashina K, Nonaka M, Moriya T, Kitamoto M, Aimitsu S, Nakanishi T, Kawakami H and Chayama K. Effect of vitamin D supplementation on pegylated interferon/ribavirin therapy for chronic hepatitis C genotype 1b: a randomized controlled trial. J Viral Hepat 2014; 21: 348-356.
[122] Gal-Tanamy M, Bachmetov L, Ravid A, Koren R, Erman A, Tur-Kaspa R and Zemel R. Vitamin D: an innate antiviral agent suppressing hepatitis C virus in human hepatocytes. Hepatology 2011; 54: 1570-1579.
[123] Matsumura T, Kato T, Sugiyama N, Tasaka-Fujita M, Murayama A, Masaki T, Wakita T and Imawari M. 25-Hydroxyvitamin D3 suppresses hepatitis C virus production. Hepatology 2012; 56: 1231-1239.
[124] Villar LM, Del Campo JA, Ranchal I, Lampe E and Romero-Gomez M. Association between vitamin D and hepatitis C virus infection: a meta-analysis. World J Gastroenterol 2013; 19: 5917-5924.
[125] Borella E, Nesher G, Israeli E and Shoenfeld Y. Vitamin D: a new anti-infective agent? Ann N Y Acad Sci 2014; 1317: 76-83.
[126] Kitson MT, Dore GJ, George J, Button P, McCaughan GW, Crawford DH, Sievert W, Weltman MD, Cheng WS and Roberts SK. Vitamin D status does not predict sustained virologic response or fibrosis stage in chronic hepatitis C genotype 1 infection. J Hepatol 2013; 58: 467-472.
[127] Ladero JM, Torrejon MJ, Sanchez-Pobre P, Suarez A, Cuenca F, de la Orden V, Devesa MJ, Rodrigo M, Estrada V, Lopez-Alonso G and Agundez JA. Vitamin D deficiency and vitamin D therapy in chronic hepatitis C. Ann Hepatol 2013; 12: 199-204.
[128] Esmat G, El Raziky M, Elsharkawy A, Sabry D, Hassany M, Ahmed A, Assem N, El Kassas M and Doss W. Impact of Vitamin D Supplementation on Sustained Virological Response in Chronic Hepatitis C Genotype 4 Patients Treated by Pegylated Interferon/Ribavirin. J Interferon Cytokine Res 2014; 35: 49-54.
[129] Kitson MT, Sarrazin C, Toniutto P, Eslick GD and Roberts SK. Vitamin D level and sustained virologic response to interferon-based antiviral therapy in chronic hepatitis C: A systematic review and meta-analysis. J Hepatol 2014; 61: 1247-1252.
[130] Grammatikos G, Lange C, Susser S, Schwendy S, Dikopoulos N, Buggisch P, Encke J, Teuber G, Goeser T, Thimme R, Klinker H, Boecher WO, Schulte-Frohlinde E, Penna-Martinez M, Badenhoop K, Zeuzem S, Berg T and Sarrazin C. Vitamin D levels vary during antiviral treatment but are unable to predict treatment outcome in HCV genotype 1 infected patients. PLoS One 2014; 9: e87974.
[131] Zerwekh JE. Blood biomarkers of vitamin D status. Am J Clin Nutr 2008; 87: 1087S-1091S.
[132] Schwartz JB, Lai J, Lizaola B, Kane L, Markova S, Weyland P, Terrault NA, Stotland N and Bikle D. A comparison of measured and calculated free 25(OH) vitamin D levels in clinical populations. J Clin Endocrinol Metab 2014; 99: 1631-1637.
[133] Schwartz JB, Lai J, Lizaola B, Kane L, Weyland P, Terrault NA, Stotland N and Bikle D. Variability in free 25(OH) vitamin D levels in clinical populations. J Steroid Biochem Mol Biol 2014; 144 Pt A: 156-158.
[134] Lauer GM and Walker BD. Hepatitis C virus infection. N Engl J Med 2001; 345: 41-52.

[135] Fallahi P, Ferri C, Ferrari SM, Corrado A, Sansonno D and Antonelli A. Cytokines and HCV-related disorders. Clin Dev Immunol 2012; 2012: 468107.
[136] Lanford RE, Guerra B, Chavez D, Bigger C, Brasky KM, Wang XH, Ray SC and Thomas DL. Cross-genotype immunity to hepatitis C virus. J Virol 2004; 78: 1575-1581.
[137] Heim MH and Thimme R. Innate and adaptive immune responses in HCV infections. J Hepatol 2014; 61: S14-S25.
[138] Wong M and Chen SS. Emerging roles of interferon-stimulated genes in the innate immune response to hepatitis C virus infection. Cell Mol Immunol 2014; [Epub ahead of print].
[139] Ibrahim MA, Mostafa AA, El-Said HW, Mohab AM and Hebah HA. Study of peripheral blood natural killer cells, T-cell helper/T-cell suppressor ratio and intercurrent infection frequency in hepatitis C seropositive prevalent hemodialysis patients. Hemodial Int 2014; 18 Suppl 1: S23-31.
[140] Dill MT, Makowska Z, Duong FH, Merkofer F, Filipowicz M, Baumert TF, Tornillo L, Terracciano L and Heim MH. Interferon-gamma-stimulated genes, but not USP18, are expressed in livers of patients with acute hepatitis C. Gastroenterology 2012; 143: 777-786, e771-776.
[141] Jinushi M, Takehara T, Kanto T, Tatsumi T, Groh V, Spies T, Miyagi T, Suzuki T, Sasaki Y and Hayashi N. Critical role of MHC class I-related chain A and B expression on IFN-alpha-stimulated dendritic cells in NK cell activation: impairment in chronic hepatitis C virus infection. J Immunol 2003; 170: 1249-1256.
[142] Barth H, Klein R, Berg PA, Wiedenmann B, Hopf U and Berg T. Analysis of the effect of IL-12 therapy on immunoregulatory T-cell subsets in patients with chronic hepatitis C infection. Hepatogastroenterology 2003; 50: 201-206.
[143] Makowska Z, Duong FH, Trincucci G, Tough DF and Heim MH. Interferon-beta and interferon-lambda signaling is not affected by interferon-induced refractoriness to interferon-alpha in vivo. Hepatology 2011; 53: 1154-1163.
[144] Thomas E, Gonzalez VD, Li Q, Modi AA, Chen W, Noureddin M, Rotman Y and Liang TJ. HCV infection induces a unique hepatic innate immune response associated with robust production of type III interferons. Gastroenterology 2012; 142: 978-988.
[145] Golden-Mason L, Hahn YS, Strong M, Cheng L and Rosen HR. Extracellular HCV-core protein induces an immature regulatory phenotype in NK cells: implications for outcome of acute infection. PLoS One 2014; 9: e103219.
[146] Tseng CT and Klimpel GR. Binding of the hepatitis C virus envelope protein E2 to CD81 inhibits natural killer cell functions. J Exp Med 2002; 195: 43-49.
[147] Weber F and Thimme R. [Viral anti-interferon strategies: mechanisms and clinical impact]. Dtsch Med Wochenschr 2003; 128: 323-325.
[148] Murata K, Sugiyama M, Kimura T, Yoshio S, Kanto T, Kirikae I, Saito H, Aoki Y, Hiramine S, Matsui T, Ito K, Korenaga M, Imamura M, Masaki N and Mizokami M. Ex vivo induction of IFN-lambda3 by a TLR7 agonist determines response to Peg-IFN/ribavirin therapy in chronic hepatitis C patients. J Gastroenterol 2014; 49: 126-137.
[149] Pelletier S, Bedard N, Said E, Ancuta P, Bruneau J and Shoukry NH. Sustained hyperresponsiveness of dendritic cells is associated with spontaneous resolution of acute hepatitis C. J Virol 2013; 87: 6769-6781.
[150] Liu BS, Janssen HL and Boonstra A. Type I and III interferons enhance IL-10R expression on human monocytes and macrophages, resulting in IL-10-mediated suppression of TLR-induced IL-12. Eur J Immunol 2012; 42: 2431-2440.
[151] Liu BS, Groothuismink ZM, Janssen HL and Boonstra A. Role for IL-10 in inducing functional impairment of monocytes upon TLR4 ligation in patients with chronic HCV infections. J Leukoc Biol 2011; 89: 981-988.
[152] Pelletier S, Drouin C, Bedard N, Khakoo SI, Bruneau J and Shoukry NH. Increased degranulation of natural killer cells during acute HCV correlates with the magnitude of virus-specific T cell responses. J Hepatol 2010; 53: 805-816.
[153] Charo IF and Ransohoff RM. The many roles of chemokines and chemokine receptors in inflammation. N Engl J Med 2006; 354: 610-621.
[154] Ouaguia L, Mrizak D, Renaud S, Morales O and Delhem N. Control of the Inflammatory Response Mechanisms Mediated by Natural and Induced Regulatory T-Cells in HCV-, HTLV-1-, and EBV-Associated Cancers. Mediators Inflamm 2014; 2014: 564296.
[155] Li J, Men K, Yang Y and Li D. Dynamical analysis on a chronic hepatitis C virus infection model with immune response. J Theor Biol 2015; 365: 337-346.
[156] Larrubia JR, Benito-Martinez S, Calvino M, Sanz-de-Villalobos E and Parra-Cid T. Role of chemokines and their receptors in viral persistence and liver damage during chronic hepatitis C virus infection. World J Gastroenterol 2008; 14: 7149-7159.
[157] Zhang L, Hao CQ, Miao L and Dou XG. Role of Th1/Th2 cytokines in serum on the pathogenesis of chronic hepatitis C and the outcome of

interferon therapy. Genet Mol Res 2014; 13: 9747-9755.
[158] Bitetto D, Fabris C, Falleti E, Fornasiere E, Fumolo E, Fontanini E, Cussigh A, Occhino G, Baccarani U, Pirisi M and Toniutto P. Vitamin D and the risk of acute allograft rejection following human liver transplantation. Liver Int 2010; 30: 417-444.
[159] Mangin M, Sinha R and Fincher K. Inflammation and vitamin D: the infection connection. Inflamm Res 2014; 63: 803-819.
[160] Mirzakhani H, Al-Garawi A, Weiss ST and Litonjua AA. Vitamin D and the development of allergic disease: how important is it? Clin Exp Allergy 2014; 45: 114-25.
[161] Kongsbak M, von Essen M, Levring T, Schjerling P, Woetmann A, Odum N, Bonefeld C and Geisler C. Vitamin D-binding protein controls T cell responses to vitamin D. BMC Immunol 2014; 15: 35.
[162] Kongsbak M, Levring TB, Geisler C and von Essen MR. The vitamin d receptor and T cell function. Front Immunol 2013; 4: 148.
[163] von Essen MR, Kongsbak M, Schjerling P, Olgaard K, Odum N and Geisler C. Vitamin D controls T cell antigen receptor signaling and activation of human T cells. Nat Immunol 2010; 11: 344-349.
[164] Almerighi C, Bergamini A, Lionetti R, Sinistro A, Lenci I, Tariciotti L, Tisone G and Angelico M. Vitamin D3 modulates T lymphocyte responses in hepatitis C virus-infected liver transplant recipients. Dig Liver Dis 2012; 44: 67-73.
[165] Kitson MT and Roberts SK. D-livering the message: the importance of vitamin D status in chronic liver disease. J Hepatol 2012; 57: 897-909.
[166] Terrier B, Derian N, Schoindre Y, Chaara W, Geri G, Zahr N, Mariampillai K, Rosenzwajg M, Carpentier W, Musset L, Piette JC, Six A, Klatzmann D, Saadoun D, Patrice C and Costedoat-Chalumeau N. Restoration of regulatory and effector T cell balance and B cell homeostasis in systemic lupus erythematosus patients through vitamin D supplementation. Arthritis Res Ther 2012; 14: R221.
[167] Zhan Y and Jiang L. Status of vitamin D, antimicrobial peptide cathelicidin and T helper-associated cytokines in patients with diabetes mellitus and pulmonary tuberculosis. Exp Ther Med 2015; 9: 11-16.
[168] Kondo Y, Kato T, Kimura O, Iwata T, Ninomiya M, Kakazu E, Miura M, Akahane T, Miyazaki Y, Kobayashi T, Ishii M, Kisara N, Sasaki K, Nakayama H, Igarashi T, Obara N, Ueno Y, Morosawa T and Shimosegawa T. 1(OH) vitamin D3 supplementation improves the sensitivity of the immune-response during Peg-IFN/RBV therapy in chronic hepatitis C patients-case controlled trial. PLoS One 2013; 8: e63672.
[169] Schaalan MF, Mohamed WA and Amin HH. Vitamin D deficiency: correlation to interleukin-17, interleukin-23 and PIIINP in hepatitis C virus genotype 4. World J Gastroenterol 2012; 18: 3738-3744.
[170] El Husseiny NM, Fahmy HM, Mohamed WA and Amin HH. Relationship between vitamin D and IL-23, IL-17 and macrophage chemoattractant protein-1 as markers of fibrosis in hepatitis C virus Egyptians. World J Hepatol 2012; 4: 242-247.
[171] Heim MH. Interferons and hepatitis C virus. Swiss Med Wkly 2012; 142: w13586.
[172] Ahlenstiel G, Edlich B, Hogdal LJ, Rotman Y, Noureddin M, Feld JJ, Holz LE, Titerence RH, Liang TJ and Rehermann B. Early changes in natural killer cell function indicate virologic response to interferon therapy for hepatitis C. Gastroenterology 2011; 141: 1231-1239, 1239, e1231-1232.
[173] Pavon-Castillero EJ, Munoz-de-Rueda P, Lopez-Segura R, Gila A, Quiles R, Munoz-Gamez JA, Carazo A, Martinez P, Ruiz-Extremera A and Salmeron J. Importance of IL-10 and IL-6 during chronic hepatitis c genotype-1 treatment and their relation with IL28B. Cytokine 2013; 61: 595-601.
[174] O'Connor KS, George J, Booth D and Ahlenstiel G. Dendritic cells in hepatitis C virus infection: Key players in the -genotype response. World J Gastroenterol 2014; 20: 17830-17838.
[175] Jimenez-Sousa MA, Almansa R, de la Fuente C, Caro-Paton A, Ruiz L, Sanchez-Antolin G, Gonzalez JM, Aller R, Alcaide N, Largo P, Resino S, de Lejarazu RO and Bermejo-Martin JF. Increased Th1, Th17 and pro-fibrotic responses in hepatitis C-infected patients are down-regulated after 12 weeks of treatment with pegylated interferon plus ribavirin. Eur Cytokine Netw 2010; 21: 84-91.
[176] Pavon-Castillero EJ, Munoz-de-Rueda P, Lopez-Segura R, Gila A, Quiles R, Munoz-Gamez JA, Carazo A, Martinez P, Ruiz-Extremera A and Salmeron J. Importance of IL-10 and IL-6 during chronic hepatitis C genotype-1 treatment and their relation with IL28B. Cytokine 2013; 61: 595-601.
[177] Ueyama M, Nakagawa M, Sakamoto N, Onozuka I, Funaoka Y, Watanabe T, Nitta S, Kiyohashi K, Kitazume A, Murakawa M, Nishimura-Sakurai Y, Sekine-Osajima Y, Itsui Y, Azuma S, Kakinuma S and Watanabe M. Serum interleukin-6 levels correlate with resistance to treatment of chronic hepatitis C infection with pegylated-interferon-alpha2b plus ribavirin. Antivir Ther 2011; 16: 1081-1091.

[178] Krause I, Valesini G, Scrivo R and Shoenfeld Y. Autoimmune aspects of cytokine and anticytokine therapies. Am J Med 2003; 115: 390-397.
[179] Weeres MA, Robien K, Ahn YO, Neulen ML, Bergerson R, Miller JS and Verneris MR. The effects of 1,25-dihydroxyvitamin D3 on in vitro human NK cell development from hematopoietic stem cells. J Immunol 2014; 193: 3456-3462.
[180] Yu S, Zhao J and Cantorna MT. Invariant NKT cell defects in vitamin D receptor knockout mice prevents experimental lung inflammation. J Immunol 2011; 187: 4907-4912.
[181] Yu S and Cantorna MT. Epigenetic reduction in invariant NKT cells following in utero vitamin D deficiency in mice. J Immunol 2011; 186: 1384-1390.
[182] Min D, Lv XB, Wang X, Zhang B, Meng W, Yu F and Hu H. Downregulation of miR-302c and miR-520c by 1,25(OH)2D3 treatment enhances the susceptibility of tumour cells to natural killer cell-mediated cytotoxicity. Br J Cancer 2013; 109: 723-730.
[183] Al-Jaderi Z and Maghazachi AA. Effects of vitamin D3, calcipotriol and FTY720 on the expression of surface molecules and cytolytic activities of human natural killer cells and dendritic cells. Toxins (Basel) 2013; 5: 1932-1947.
[184] van der Does AM, Kenne E, Koppelaar E, Agerberth B and Lindbom L. Vitamin D(3) and phenylbutyrate promote development of a human dendritic cell subset displaying enhanced antimicrobial properties. J Leukoc Biol 2014; 95: 883-891.
[185] Brosbol-Ravnborg A, Bundgaard B and Hollsberg P. Synergy between vitamin D(3) and Toll-like receptor agonists regulates human dendritic cell response during maturation. Clin Dev Immunol 2013; 2013: 807971.
[186] Bakdash G, van Capel TM, Mason LM, Kapsenberg ML and de Jong EC. Vitamin D3 metabolite calcidiol primes human dendritic cells to promote the development of immunomodulatory IL-10-producing T cells. Vaccine 2014; 32: 6294-6302.
[187] Ferreira GB, Vanherwegen AS, Eelen G, Gutierrez AC, Van Lommel L, Marchal K, Verlinden L, Verstuyf A, Nogueira T, Georgiadou M, Schuit F, Eizirik DL, Gysemans C, Carmeliet P, Overbergh L and Mathieu C. Vitamin D3 Induces Tolerance in Human Dendritic Cells by Activation of Intracellular Metabolic Pathways. Cell Rep 2015; [Epub ahead of print].
[188] Huang Y, Zhao Y, Ran X and Wang C. Increased expression of herpesvirus entry mediator in 1,25-dihydroxyvitamin D3-treated mouse bone marrow-derived dendritic cells promotes the generation of CD4(+)CD25(+)Foxp3(+) regulatory T cells. Mol Med Rep 2014; 9: 813-818.
[189] Hidaka M, Wakabayashi I, Takeda Y and Fukuzawa K. Vitamin D(3) derivatives increase soluble CD14 release through ERK1/2 activation and decrease IL-8 production in intestinal epithelial cells. Eur J Pharmacol 2013; 721: 305-312.
[190] Akbarzadeh M, Eftekhari MH, Dabbaghmanesh MH, Hasanzadeh J and Bakhshayeshkaram M. Serum IL-18 and hsCRP correlate with insulin resistance without effect of calcitriol treatment on type 2 diabetes. Iran J Immunol 2013; 10: 167-176.
[191] Ryynanen J and Carlberg C. Primary 1,25-dihydroxyvitamin D3 response of the interleukin 8 gene cluster in human monocyte-and macrophage-like cells. PLoS One 2013; 8: e78170.
[192] Andrukhov O, Andrukhova O, Hulan U, Tang Y, Bantleon HP and Rausch-Fan X. Both 25-hydroxyvitamin-D3 and 1,25-dihydroxyvitamin-D3 reduces inflammatory response in human periodontal ligament cells. PLoS One 2014; 9: e90301.
[193] Jamali Z, Ararabadi MK and Asadikaram G. Serum levels of IL-6, IL-10, IL-12, IL-17 and IFN-gamma and their association with markers of bone metabolism in vitamin D-deficient female students. Inflammation 2013; 36: 164-168.
[194] Izquierdo MJ, Cavia M, Muniz P, de Francisco AL, Arias M, Santos J and Abaigar P. Paricalcitol reduces oxidative stress and inflammation in hemodialysis patients. BMC Nephrol 2012; 13: 159.
[195] Karatayli SC, Ulger ZE, Ergul AA, Keskin O, Karatayli E, Albayrak R, Ozkan M, Idilman R, Yalcin K, Bozkaya H, Uzunalimoglu O, Yurdaydin C and Bozdayi AM. Tumour necrosis factor-alpha, interleukin-10, interferon-gamma and vitamin D receptor gene polymorphisms in patients with chronic hepatitis delta. J Viral Hepat 2014; 21: 297-304.
[196] Niino M, Fukazawa T, Miyazaki Y, Takahashi E, Minami N, Amino I, Fujiki N, Doi S and Kikuchi S. Suppression of IL-10 production by calcitriol in patients with multiple sclerosis. J Neuroimmunol 2014; 270: 86-94.
[197] Sabry D, Al-Ghussein MA, Hamdy G, Abul-Fotouh A, Motawi T, El Kazaz AY, Eldemery A and Shaker M. Effect of vitamin D therapy on interleukin-6, visfatin, and hyaluronic acid levels in chronic hepatitis C Egyptian patients. Ther Clin Risk Manag 2015; 11: 279-288.
[198] Alon DB, Chaimovitz C, Dvilansky A, Lugassy G, Douvdevani A, Shany S and Nathan I. Novel role of 1,25(OH)(2)D(3) in induction of erythroid progenitor cell proliferation. Exp Hematol 2002; 30: 403-409.

[199] Deicher R and Horl WH. Hormonal adjuvants for the treatment of renal anaemia. Eur J Clin Invest 2005; 35 Suppl 3: 75-84.
[200] Sim JJ, Lac PT, Liu IL, Meguerditchian SO, Kumar VA, Kujubu DA and Rasgon SA. Vitamin D deficiency and anemia: a cross-sectional study. Ann Hematol 2010; 89: 447-452.
[201] Albitar S, Genin R, Fen-Chong M, Serveaux MO, Schohn D and Chuet C. High-dose alfacalcidol improves anaemia in patients on haemodialysis. Nephrol Dial Transplant 1997; 12: 514-518.
[202] Saab G, Young DO, Gincherman Y, Giles K, Norwood K and Coyne DW. Prevalence of vitamin D deficiency and the safety and effectiveness of monthly ergocalciferol in hemodialysis patients. Nephron Clin Pract 2007; 105: c132-138.
[203] Zughaier SM, Alvarez JA, Sloan JH, Konrad RJ and Tangpricha V. The role of vitamin D in regulating the iron-hepcidin-ferroportin axis in monocytes. J Clin Transl Endocrinol 2014; 1: 19-25.
[204] Aljohani NJ, Al-Daghri NM, Al-Attas OS, Alokail MS, Alkhrafy KM, Al-Othman A, Yakout S, Alkabba AF, Al-Ghamdi AS, Almalki M, Buhary BM and Sabico S. Differences and associations of metabolic and vitamin D status among patients with and without sub-clinical hypothyroid dysfunction. BMC Endocr Disord 2013; 13: 31.
[205] Zhang Q, Wang Z, Sun M, Cao M, Zhu Z, Fu Q, Gao Y, Mao J, Li Y, Shi Y, Yang F, Zheng S, Tang W, Duan Y, Huang X, He W and Yang T. Association of high vitamin d status with low circulating thyroid-stimulating hormone independent of thyroid hormone levels in middle-aged and elderly males. Int J Endocrinol 2014; 2014: 631819.
[206] Kivity S, Agmon-Levin N, Zisappl M, Shapira Y, Nagy EV, Danko K, Szekanecz Z, Langevitz P and Shoenfeld Y. Vitamin D and autoimmune thyroid diseases. Cell Mol Immunol 2011; 8: 243-247.