Role of Nutrition in the Progression and Treatment of Hepatitis C Virus-Related Chronic Liver Disease: A Review

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Abstract

The hepatitis C virus (HCV) is associated with oxidative stress and metabolic abnormalities. Research efforts have shown that excess macro-components and deficiencies in micro-components in the diet are linked to increases in the severity of liver disease. Studies have demonstrated a high prevalence of overweight and obesity in HCV patients, which has been linked to high viral load, liver damage, hepatic inflammation, insulin resistance and hepatocellular (HCC) occurrence, so a balanced diet restricted in calories is required for such patients. Supplementation with L-carnitine, soybean, vitamins E and C, and zinc has been shown to have promising results where the quality of life, as well as antioxidant and inflammatory profile of patients with HCV-related chronic liver disease is concerned. Nutrition management includes regular coffee consumption above the equivalent of two cups per day; dietary iron restricted to under 7 mg/d, increased consumption of fatty acid omega-3, curcumin and ingestion of micronutrients according to recommended dietary allowances. Nutritional management presents an important adjunct role in improving pharmacological response in patients under anti-HCV treatment. In this review, we provide an overview of existing evidence regarding nutrient intake and its impact on the outcomes of HCV patients, and some mechanisms of action.

Keywords: Hepatitis C; HCV; Hepatitis C Management; Diet; Nutrients; Lifestyle Changes; Obesity

Abbreviations

HCV: Hepatitis C Virus; HCC: Hepatocellular; CLD: Chronic Liver Disease; CHC: Chronic Hepatitis C; HSC: Hepatic Stellate Cell; ALT: Alanine Aminotransferase; BMI: Body Mass Index; CRP: C-Reactive Protein; IR: Insulin Resistance; PKC: Protein Kinase C; VAD: Vitamin A Deficiency; ROS: Reactive Oxygen Species; AO: Antioxidant; RDAs: Recommended Dietary Allowances; BC01: Carotene 15, 15’ oxygenase-1; BC02: β-carotene 9’,10’ oxygenase-2; RA: Retinoic Acid; RXRα: retinoid X receptor; RARα: retinoic acid receptor; RBP: Retinol-Binding Protein; IRES: Internal Ribosome Entry Site; TIMP-1: Tissue Inhibitor of Metallopeptinase 1; IFN-alpha: Interferon-Alpha; w3-PUFAs: Omega-3 Polyunsaturated Fatty Acids; EPA: Eicosapentenoic Acid; DHA: Docosahexaenoic Acid; AA: Arachidonic Acids; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; HO-1: Hemeoxigenase 1.

Introduction

The hepatitis C virus (HCV) is a major causative agent for chronic liver disease (CLD) and is the leading cause of end-stage liver disease, liver-related death and liver transplants in the Western world. Chronic hepatitis C (CHC) is primarily characterized by inflammation and progressive fibrosis, which often leads to cirrhosis and hepatocellular carcinoma (HCC) [1]. Furthermore, HCV infection is associated with the development of insulin resistance, diabetes mellitus, and hepatic steatosis [2].

The mechanisms of liver pathogenesis in HCV infection are not yet completely understood. The primary cell associated with liver fibrosis in HCV infection is the hepatic stellate cell (HSC), which when activated becomes the greatest collagen-producing cell in the injured liver. It is known that fibrosis progression rates vary according to viral, host, environmental and lifestyle factors [3,4].

Knowledge regarding the influence of dietary components in liver health is continuously improving. Dietary habits influence nutritional status, liver enzymes, insulin secretion and liver metabolism. Additionally, some foods have been described to exert hepatoprotective or hepatotoxic effects in humans [5-9]. In a study carried out by Loguercio et al. [10] on a large number of HCV patients and controls, it was noted that a high intake of calories, carbohydrates and lipids was associated with more-advanced fibrosis, and that in the multivariate analysis BMI was an independent predictor of the outcome to antiviral therapy, negatively affecting the response to pharmacotherapy. Hence, dietary modulation based on balanced macronutrient and micronutrient consumption is an important issue in the clinical management of HCV patients. The aim of this review is to provide an overview of existing evidence regarding nutrient intake and its impact in HCV patients, and to present some proposed mechanisms of action of some nutrients on HCV replication and infection.

Nutrition Management in HCV Patients

Dietary Management: Evidence regarding the influence diet has on HCV-related-chronic disease progression and outcomes are accumulating. Findings collected from past clinical studies [11-14] have led to the estimation of the ideal macronutrient intake for patients with chronic hepatitis C (CHC), as shown in Table 1. Moreover, vegetable fruits and grains should be prioritized apriority should be made of including grains, vegetable and fruits in the diet. Furthermore, the consumption of processed foods containing fructose should be avoided altogether, since the ingestion of industrialized fructose, not fruit fructose, has been linked with increases in the severity of liver fibrosis in HCV patients with genotype 1 [15].

Supplementation in HCV Patients: Few studies have assessed the effects supplementation has on antioxidant protection, insulin resistance, fatty liver, alanine amino transferase (ALT) and health-related quality of life in patients with chronic hepatitis C. In a prospective, randomized, open-label trial it was demonstrated that L-carnitine supplementation at a dose of 2 g twice a day for 12 months modulate erythropoiesis, leucopoiesis and thrombocytopoiesis in patients under treatment for HCV [16]. In 2012, daily antioxidant supplementation (vitamin E 800mg/day, vitamin C 500 mg/day and zinc 40 mg/day) was administered to HCV patients for a period of 24 weeks. The antioxidant supplementation was effective in antioxidant protection in untreated patients and those undergoing standard therapy [17].
Some studies have shown that soy protein might be able to lower insulin resistance and modulate hepatic lipid metabolism [18,19]. In a previous study [20] it was observed that soy supplementation with 32 g of protein/day was effective in reducing ALT levels in HCV patients, compared to isonitrogenous casein supplementation, and nutritional therapy with either soybean or casein supplementation was able to improve quality of life in HCV patients [21].

Impact of Obesity on HCV-Patient Outcomes

The prevalence of obesity has grown markedly over the past two decades. In obese state, adipocytokines released from adipocytes play an important role in controlling hepatic inflammation and fibrosis that can result in cirrhosis. The secretion of leptin and adiponectin is thought to contribute to a low grade inflammation and hepatic fibrosis and its resolution, since leptin acts as a profibrogenic molecule, while adiponectin presents relevant antifibrotic properties [3,22]. Visceral obesity has been linked to high viral load and liver damage in elderly genotype 1-chronic hepatitis C sufferers with low adiponectin levels. Therefore, patterns of adipose tissue distribution should be taken into consideration when assessing the nutritional status of these patients [23,24]. In 2012, a meta-analysis of prospective studies [25] found that excess weight increases the risk of primary liver cancer (PLC), suggesting that a five-unit increase in body mass index (BMI) related to a 39% increase in the risk of PLC, and the most pronounced in increase in PLC risk was observed at a BMI > 32 Kg/m². Furthermore, patients with chronic hepatitis C or cirrhosis are at greater risk of PLC, compared to the general population.

Obesity and fatty liver are commonly found among patients with chronic HCV and may potentiate this pro-inflammatory state in HCV patients, consisting in risk factors for increased hepatic fibrosis in patients with CHC [26]. In fact, a previous study [27] found a prevalence of 32% overweight and 17% obesity in HCV patients, and 30% had mild steatosis while 19% had moderate or severe steatosis. The authors observed that HCV patients who are overweight and obese had higher circulating and hepatic C-reactive protein (CRP) levels and an increased expression of inflammatory markers.

HCV infection also leads to changes in glucose metabolism and insulin resistance or diabetes in susceptible patients, contributing to the progression of HCV [28,29]. Moreover, visceral adiposity enhances HCV-induced whole-body insulin resistance. Free fatty acids (FFAs) secreted by visceral adipocytes induce insulin resistance (IR), probably by intracellular accumulation of fatty acid metabolites that appear to initiate activation of the lipid-activated protein kinase C (PKC) family, resulting in impairment of insulin signaling in skeletal muscle and the liver [30].

Gradual weight loss is recommended as a first step in the treatment of patients with obesity and CHC. Hickman et al. [31] observed in CHC patients a mean BMI decrease of 2 Kg/m² over a 12-week period, which was achieved by reducing total energy and fat intake, with a diet composed of 50% carbohydrate, 20% protein, and 30% fat along with an increase in daily activity. Weight loss in these patients may be associated with a reduction in hepatic steatosis and abnormal liver enzymes, besides an improvement in fibrosis. In 2004, a study [5] demonstrated that lifestyle intervention involving weight loss of only 4-5% body weight, without necessarily normalizing BMI, and physical activity were linked to sustained improvement in alanine amino transferase, insulin levels and quality of life in overweight patients with chronic liver disease.

More recently, a randomized controlled trial compared a normogluclid low-caloric diet with a low-fat diet and demonstrated the benefits of both diets and physical activity in the management of patients with CHC over a one-year period. During this period, there were improvements in weight loss, insulin resistance, steatosis, fibrosis, lipid and hepatic profile [13] as well as, lifestyle modifications that included a 33% reduction in median caloric intake and physical activity for 24 weeks, a drop in BMI and reversal of IR in a significant proportion of obese patients with CHC [8]. This indicates that lifestyle intervention in CHC patients may reduce the progression of HCV infection to HCC [32] and improve serum α-fetoprotein and insulin resistance in patients with CHC [33].

Vitamin Deficiency in HCV Patients

Vitamin A: Vitamin A deficiency (VAD) is a major malnutrition problem around the world. In a normal liver, hepatic stellate cells (HSCs) account for 80-90% of total body vitamin A stores. In the human diet, vitamin A comprises two forms: the preformed vitamin A from animal sources and pro-vitamin carotenoids present in plant pigments: β-carotene, α-carotene and β-cryptoxanthin, which can be deaved and metabolized into retinol with varying degrees of efficiency [34-35]. Canthaxanthin, lutein, lycopene and zeaxanthin are carotenoids that are not able to convert vitamin A [34]. Vitamin A and its retinoid derivatives are essential for normal cell growth, cell differentiation, visual acuity, immune system activity and have been shown to have antioxidant properties in animal studies [35].

HCV infection is associated with steatosis and oxidative stress, which are characterized by an increase in the levels of reactive oxygen species (ROS) from the decrease in antioxidant (AO) defense levels and can result in lipid peroxidation [36]. Oxidative stress plays an important role in the onset and progression of liver disease and adaptation to oxidative stress is a key to surviving the virus [37]. In 2002 a study [38] demonstrated increased oxidative stress and severe depletion of serum levels of retinol, lutein, beta-cryptoxanthin, lycopene, alpha- and beta-carotene, alpha- and gamma-tocopherol in HCV patients. Furthermore, the levels of all

The mean conversion rate of carotenoids to retinol is, approximately, 12 μg for β-carotene and 24 μg for other carotenoids to 1 μg in healthy adults and is dependent upon two known carotenoid-cleavage enzymes expressed in a healthy human liver known as Carotene 15, 15’ oxygenase-1 (BCO1) and β-carotene 9',10' oxygenase-2 (BCO2). BCO1 is highly expressed in HSCs and portal endothelial cells in the liver [42], so, it can be speculated that this conversion may be compromised in liver disease [43]. Besides, this low intake from animal sources may be due to dietary beliefs, taboos and constraints associated with liver disease resulting in a reduced intake of protein and fat that compromises the intake and absorption of preformed vitamin A [39,44].

An insufficient vitamin A intake during the early stage may contribute to the progression of HCV-related chronic disease, considering the powerful ability vitamin A has to modulate the redox status and the fact that the increase in viral load has been associated with increased consumption of antioxidants [45,46]. Furthermore, vitamin A deficiency is associated with nonresponse to antiviral therapy, since it is suggested that vitamin A modulates the expression of the type I interferon receptor, enhancing the pharmacological action of interferon-α on HCV [47].

The hepatitis C virus is the leading cause of HCC in Western countries since it may be caused by the direct or indirect effects of HCV core protein. Vitamin A deficiency may create a predisposition to the development of HCC, and retinoic acid (RA) plays an important role in preventing the occurrence of HCC [49-50]. Retinoic acid is a major oxidative metabolite for vitamin A and is responsible for important biological effects when bound to the retinoic acid receptor α, β or γ (RARs) and the retinoid X receptor α, β or γ (RXRs), activating the transcription of many target genes [51]. A previous study [52] assessed the contribution of RA signaling to immune-driven liver damage using two in vivo models of hepatitis and proposed that RA is strongly implicated in the control of NKT-cell cytokine by down regulating IFN-γ and IL-4 production by MAPK-dependent mechanisms. These findings highlight the importance of adequate dietary vitamin A intake in the immune regulation of T-cell subpopulations.

Vitamin A supplementation for HCV patients should be evaluated with caution. In a recent study [53] we found that a reduction in retinol-binding protein (RBP) synthesis interfered with the mobilization of hepatic retinol in 178 patients with cirrhosis, wherein 82.6% had viral etiology, suggesting that vitamin A supplementation may have deleterious effects in HCV patients. In fact, free retinol, whether non-esterified or bound to carrier proteins, and its retinoic acid metabolite are fat soluble and can interpose between the lipids in the cell membrane, thereby destroying the membrane and leading to cell lysis. Moreover, there have been reports of increases in hepatic retinal esters in patients with chronic hepatitis associated with depletion of plasma and hepatic alpha-tocopherol in rats supplemented with vitamin A, signifying a reduction in antioxidant defense [6].

**Vitamin B:** The B complex consists of nine water-soluble vitamins that play important roles in cell metabolism. Findings from an earlier study [54] has described B-vitamin status in HCV patients and found them to suffer a significant reduction in their levels of red blood cell and plasma vitamins B2, B6 and folates. A high concentration of cyanocobalamin (vitamin B12) is stored in hepatocytes and could interfere with HCV replication. In vitro, vitamin B12 has been shown to inhibit the HCV internal ribosome entry site (IRES)-dependent translator in a dose-dependent manner [55]. Research in recent years has found that serum B12 is significantly and independently correlates to on-treatment viral response, with patients with higher levels of pre-treatment serum B12 showing greater improvement in response to treatment with interferon and ribavirin [56].

**Vitamin D:** Vitamin D has a pleiotropic role in immune regulation, as it decreases the levels of pro-inflammatory cytokines and promotes innate immune response. Humans derive most vitamin D from the action of solar ultraviolet radiation on their skin. However, diet plays an increasingly important role when decreases in outdoor activities limit the exposure to sunlight. Very few foods naturally contain vitamin D, and those that do are mainly of animal origin. These include oily fish such as salmon, sardine, mackerel and trout, as well as liver, egg yolk and dairy products [57-58]. The active metabolite of vitamin D is obtained through two hydroxylations. The first hydroxylations occurs in the liver, where vitamin D, generated in the skin or obtained through the diet, is hydroxylated to form the intermediate metabolite 25-hydroxyvitamin D [25(OH)D], 25(OH)D, the major circulating form of vitamin D, is transported to the kidney, where it undergoes a second hydroxylation into the active form of the hormone, 1a,25-dihydroxyvitamin D [1a,25(OH)2D or calcitriol] by 25-hydroxyvitamin-D 1a-hydroxylase (1a-hydroxylase) [57-59].

The effect of vitamin D on HCV replication was observed in in vitro models and can be explained by its immunomodulatory effect. It was shown that vitamin D had a direct inhibitory effect on viral production, at least in part attributed to the increase of innate immune response up regulating the expression of interferon-beta (INF-β) [57]. Indeed, chronic HCV infection is associated with intrahepatic inflammation and increased circulating levels of several inflammatory cytokines and chemokines closely related to disease progression.

Some studies have demonstrated that high levels of serum vitamin D are closely related to higher SVR (sustained virological response). Petta et al. [60] evaluated chronic HCV genotype 1 patients and found that these patients had low serum levels of 25(OH)D, possibly because of lower expression of liver CYP27A1, a mediator of vitamin D liver hydroxilation. Vitamin D levels inversely associated with severe fibrosis and low SVR in interferon (IFN)-based therapy. Another study [61] also found in a cohort of genotype 1-3 HCV patients that vitamin D levels associated with failure to achieve SVR.

Vitamin D supplementation increases VR (virological response) and its effect seems to depend on HCV genotype. An earlier study [62] found that vitamin D supplementation enhanced the VR...
rate at week 24 in HCV genotype 1 patients being treated with PEG-IFN/RBV. Data from a study [63] revealed that vitamin D supplementation improved the rate of SVR in naive patients with HCV genotype 2-3. However, no significant impact on SVR was observed in HCV genotype 4 patients after receiving vitamin D supplementation combined with Peg-INF/RBV therapy [64]. A meta-analysis showed that high rates of SVR were found in HCV patients with higher basal serum vitamin D levels or receiving vitamin D supplementation regardless of genotype [65]. However, a different meta-analysis and systematic review comprising a greater number of participants, which proposed to evaluate the association between baseline vitamin D and SVR and combined PEG-INF plus RBV therapy, showed that baseline vitamin D levels had no impact on SVR [66]. Although the findings of these two meta-analyses conflict, they both agree on the importance of early detection of vitamin D deficiency in order to introduce supplementation.

On the other hand, vitamin D deficiency is common in chronic liver disease patients. It is expected in cholestatic liver disease, such as primary biliary cirrhosis, since the absorption of this fat-soluble vitamin is compromised. However, a study has shown [67] vitamin D deficiency in 92% of patients with chronic liver disease including hepatitis C cirrhosis, hepatitis C but not cirrhosis or non-hepatitis C-related cirrhosis.

The causes of vitamin D deficiency in chronic liver disease, regardless the aetiology, seems to be multifactorial and may include lower production of vitamin D binding protein and albumin by the liver; impaired liver hydroxylation, although liver function must be severely compromised before this impairment happens; lower exposure to sunlight and/or fewer vitamin D food sources in chronic III patients; reduced intestinal absorption due to intestinal edema complicating portal hypertension [68-71]. It has been suggested that vitamin D deficiency in cirrhosis is influenced more by the degree of liver dysfunction than by etiology [72].

Vitamin D plays an important role in slowing the progression of HCV hepatitis to liver fibrosis, since it has anti-proliferative and antifibrotic effects on hepatic stellate cells [73]. An earlier study observed in vitro that the addition of vitamin D to activated HSCs stimulated the vitamin D receptor (VDR) expression, suppressed HSC proliferation, reduced cyclin D1, tissue inhibitor of metalloproteinase 1 (TIMP-1), collagen Iα1 and increased MMP-9 activity [74]. The authors confirmed in a TAA-induced liver fibrosis model that treatment with vitamin D significantly reduced extracellular matrix deposition and lowered the fibrotic score. More recently, the authors showed that when vitamin D was administered simultaneously with TAA in rats for 10 weeks, it suppressed liver fibrosis and reduced PDGF, TGF-β, collagen Iα1, TIMP-1, and alpha-smooth muscle actine. However, vitamin D was not efficient when administered after liver fibrosis was established [75].

Vitamin D, beta-carotene and linoleic acid, out of 46 nutrients assessed, were found to inhibit HCV RNA replication in vitro, which was reversed by Vitamin E. Other vitamins (A, C, E, K) enhanced HCV replication. These findings may contribute to the development of a nutritional supplement specifically for the treatment of people with chronic hepatitis C [76].

The volume of evidence suggests that vitamin D status should be measured in all HCV patients as early as possible at the beginning of treatment. Vitamin D serum levels should be monitored and patients should be questioned and advised about their exposure to sunlight and their consumption of vitamin D food sources. The duration of contact with the sun a person needs depends on season, skin pigmentation and geographic location. There is no single recommendation for everyone. A brief period, about 10 to 15 minutes, is enough for most lighter-skinned people. The darker the skin, the longer their exposure should be. Moreover, the larger the area of skin exposed to sunlight, the greater the chance of producing enough vitamin D. The goal for all patients with chronic liver disease should be a 25-OH vitamin D level of 30 ng/mL. Anything less than 15-20 ng/mL is considered deficient [68]. There is a dearth of evidence as to the optimal dose of vitamin D supplementation in case of deficiency.

Vitamin E: Vitamin E is a fat-soluble vitamin which comprises eight structurally related compounds known as tocopherol and tocotrienol and functions primarily as a lipid antioxidant. Alpha tocopherol has the highest biological activity. In a 1997 pilot study [77] carried out on six HCV patients who were refractory to interferon treatment, it was found that eight weeks of 1200 IU of alpha tocopherol supplementation prevented the fibrogenesis cascade from resulting from the activation of stellate cells, in addition to reducing oxidative stress in the plasma. These findings suggest the potential role of vitamin E supplementation in preventing the development of liver fibrosis, but it does not affect serum ALT levels, hepatitis C virus titer, or the histologically-determined degree of hepatic cellular inflammation or fibrosis, suggesting that supplementation may need to be extended for a period greater than eight weeks. That same year, another study [78] was conducted on 23 HCV patients refractory to alpha-interferon therapy whom were treated with vitamin E doses of 800 IU/day over a 12-week period. The authors reported drops in serum AST and ALT levels in 48% of these patients during treatment, although cessation of vitamin E treatment was followed by a rapid rebound in ALT and AST elevation.

In a previous study [79] HCV patients were treated with 500mg/day vitamin E for three months and noted a reduction in oxidative stress and serum ALT levels, particularly in those HCV patients with initial ALT levels > 70 IU/L. A recent randomized, double-blind, placebo-controlled study [80] assessed the effect of vitamin E on HCV genotype 3 in patients who were ineligible for or non-respondent to standard therapy. The HCV patients were treated with vitamin E at doses of 400 IU twice daily or placebo for 12 weeks and serum ALT levels were markedly lower in the vitamin E group when compared to the placebo group. The authors point out that vitamin E treatment was well-tolerated with no serious adverse events during the study and suggests that vitamin E may be a valuable support therapy for patients with HCV.

A recent meta-analysis [81] supported the theory that vitamin E supplementation can reduce AST and ALT levels in HCV patients and mentioned that vitamin E supplementation of less than 400 IU/day in combination with vitamin C for regenerating oxidized vitamin E should be evaluated in better-designed, large-scale clinical trials.

Hypozincemia in HCV Patients

Zinc serves important functions in the body, with the daily requirement for adults being 10-15 mg and overall content in a healthy human body being approximately two grams. Zinc is an important trace element that regulates immunological and cellular functions, metabolism of nucleic acid and protein, participates in wound healing and the sense of taste, and is involved as cofactor in several enzymes [82]. The liver is the main site for zinc metabolism. Hypozincemia has been associated with the pathogenesis of liver disease, since zinc participates in the redox process and zinc deficiency may promote cell-damaging oxidative stress in the liver. In HCV patients, blood zinc concentrations decrease as the liver disease progresses, and it has been noted that liver damage can be reduced through zinc supplementation [83,84].

A study conducted in 1997 [85] found that zinc nutritional
Role of Fatty Acid Omega-3 in Hepatitis C

The omega-3 polyunsaturated fatty acids (w3-PUFAs), eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA), have shown health benefits related mainly to their modulatory effect on inflammatory pathways. The main sources of omega-3 fatty acids are oily fish including salmon, mackerel, herring and sardine [88].

Hepatitis C virus (HCV) utilizes host lipidic metabolic pathways for its replication and infectivity [89]. Based on this, inhibitors of cholesterol and fatty acid biosynthetic pathways have been used to inhibit HCV replication. Kapadia et al. [90] verified in an in vitro model that PUFAs inhibited HCV RNA replication. In concordance, another study too found that several PUFAs including arachidonic acids (AA), EPA and DHA have anti-HCV properties [91]. Kohjima et al. [92] showed that the addition of pitavastatin and in EPA to peg-IFN/ribavirin therapy improved sustained virological response in genotype 1b HCV patients. However, no effect of omega-3 supplementation (fish oil containing EPA and DHA) and/or statin on HCV-RNA viral load was noted in a pilot study involving chronic hepatitis C patients who were unresponsive to prior antiviral therapy [93].

The link between HCV infection and hepatic cell lipid metabolism favors a strong association between HCV and hepatosteatosis. In this scenario, omega-3 supplementation may protect against HCV-induced hepatosteatosis [94]. A meta-analysis of nine studies comprising 355 NAFLD patients demonstrated that omega-3 supplementation lowered the degree of hepatic steatosis, decreased aspartateamino transferase (AST) levels and showed an insignificant trend for decreasing alanineamino transferase (ALT). However, the optimal dose is not currently established [95]. Besides its effects on HCV replication, it is well known that long-chain omega-3 fatty acids EPA and DHA and their COX and LOX metabolites have anti-inflammatory properties and may be significant in preventing the progression of hepatitis C [93].

Lotrich et al. [96] assessed plasma fatty acids in 138 patients prior to INF-a therapy. The authors found that AA/EPA +DHA ratio was associated with increased vulnerability to depression induced by systemic inflammation. The authors suggest that n3 supplementation can reduce depression in this population. While there is a lack of studies concerning optimal omega-3 supplementation for HCV patients and clinical evidence regarding its incorporation into drug therapy is still scarce, HCV patients might be encouraged to regularly consume n-3 food sources. This recommendation seems to be a feasible strategy for improving HCV treatment.

Additional Dietary Factors in HCV Infection

Lycopene: Lycopene is a carotenoid pigment found in red fruits and vegetables, with tomatoes and their processed derivatives being a significant dietary source. The process of cooking and factors such as dietary fats enhance the bioavailability of lycopene and a high singlet oxygen- and peroxyl radicals-quenching capacity make lycopene a powerful antioxidant [97]. A prior study has demonstrated that an accumulation of lycopene in the liver and blood plasma brought on an increase in total plasma antioxidant activity in rats treated with lycopene, demonstrating its action at the hepatic level [98].

The effectiveness of lycopene has been demonstrated in two studies carried out on HCV patients. In one study conducted to verify whether supplementation with an antioxidant-rich tomato-based functional food reduces anemia during pegylated interferon and ribavirin therapy demonstrated that this functional food reduces the severity of ribavirin-related anemia and improves tolerance to pharmacotherapy [99]. In 2007, Vitagliano developed a food rich in lycopene for special medical purposes and observed that it was not effective as an adjuvant treatment to pharmacological therapy in HCV patients, although it was effective in improving the oxidative status [100].

Coffee: Coffee contains a variety of bioactive compounds with potentially healthful effects, including the alkalioids caffeine and trigonelline, the antioxidants chlorogenic acid and melanoids, and such diterpenes ascafestol and kahweol. Such biological activities as antioxidant, antimicrobial, anticariogenic, anti-inflammatory, antihypertensive, and antiinflammatory have been attributed to coffee [101,102]. Several studies have reported the benefits of coffee on liver disease; however, the mechanism of action or which compound is more effective are not yet fully understood.

Caffeic acid is a metabolite of chlorogenic acid, a polyphenolin coffee. Following absorption chlorogenic acid is metabolically decomposed into caffeic and quinic acids. In an in vitro naïve HCV particle-infection model, treatment of HCV-infected cells with caffeic acid resulted in decreased release of HCV particles [103].

Caffeine is the most studied compound in coffee. In an in vitro model, caffeine inhibited HCV genotype 2 replication in a dose-dependent manner. The mechanism suggested by the authors is the alteration of Cox-2 expression, which is associated with HCV replication [104]. Cardin et al. [105] demonstrated in a study carried out on chronic hepatitis C patients that daily coffee consumption at a dose of four coffee cups/day for one month reduced oxidative DNA damage, increased apoptosis, promoted telomere elongation and consequently DNA stabilization. Indeed, coffee consumption reduced pro-collagen III plasma levels, indicating less collagen deposited in the liver.

Modi et al. [106] asked that a caffeine questionnaire was filled out by patients undergoing liver biopsy, most of them with chronic hepatitis C. Caffeine consumption, mainly from coffee, associated with a lower risk of advanced liver fibrosis, particularly in patients with HCV infection. The data suggest that achieving a beneficial effect requires caffeine consumption above a threshold of approximately two coffee-cup equivalents per day.

Another study [107] too assessed daily caffeine consumption in the treatment of naïve patients with histologically-proven chronic hepatitis C. They found that caffeine consumption greater than 408 mg/day (three cups or more) inversely associated with histological activity. This study, however, only focused on caffeine intake, not on coffee intake. In a cross sectional study [108] involving patients with chronic HCV infection, it was found that an average daily intake ≥ 100 mg of caffeine associated with a lower risk of hepatic fibrosis. The study also found that this amount of caffeine from sodas and teas does not produce the same protective effect as the same amount of caffeine from coffee. This finding suggests that other components of coffee may contribute to its effect on liver disease. The optimal hepatoprotective dose of caffeine in HCV...
patients remains unclear.

Sasaki et al. [109] carried out a study to evaluate the association between baseline coffee consumption and subsequent ALT levels in chronic HCV patients over a 12-month period. The authors also investigated the brewing method (whether filtered, unfiltered or decaffeinated). The authors found that filtered coffee consumption associated significantly with ALT reduction or sustained levels in those patients with higher or normal baseline ALT levels, respectively. A meta-analysis showed that the risk of HCC is reduced by 40% for any level of coffee consumption compared to non-consumption in the studies assayed. An inverse relationship was also noted when individuals were categorized according to history of HBV/HCV, liver disease and consumption of alcohol [110].

Considering that chronic hepatitis C is one of the main cause of HCC worldwide, the findings suggest that daily coffee consumption is an important adjuvant in antiviral therapy and should be recommended (two to four cups) to patients with hepatitis C in order to prevent progression to liver fibrosis and/or to HCC. Filtered coffee is preferable to other types.

**Curcumin:** Curcumin, a polyphenolic compound is the most active component of *Curcuma longa* (turmeric or curcuma), an herbaceous plant member of the ginger family. Curcumin is a major component in curry powder and is responsible for its characteristic yellow color. Curcumin has been found to be very beneficial for its antioxidant, anti-inflammatory, anticarcinogenic, thrombospresive, neuroprotective, renoprotective, cardioprotective, and antiarthritic properties [111,112].

One of the well-established roles curcumin serves is as an activator of the Nrf-2 pathway. Nrf-2, under basal conditions, is located in the cytoplasm as an inactive complex bound to the kelch-like ECH-associating protein 1 (Keap-1), which is degraded by the ubiquitition-proteosome pathway. Once exposed to oxidative stress or to activators, Nrf-2 is dissociated from Keap-1 and translocated to the nucleus, where it up regulates the expression of cytoprotective and antioxidant proteins, and down regulates inflammatory and fibrogenic transcriptional factors [113]. Oxidative stress occurs as a direct result of HCV core-protein expression both in *vitro* and *in vivo*, which in turn is able to increase HCV replication [114]. In this way, curcumin may decrease HCV replication by up regulating antioxidant enzymes.

There is some evidence suggesting that curcumin may also have antiviral bioactivity. Kim et al. [115] showed in an *in vitro* model that curcumin suppressed HCV RNA replication via PI3K/AKT. This pathway is known to contribute to cell survival. A previous study [116] confirmed the curcumin inhibition of HCV replication through suppression of PI3K-AKT signaling but also via induction of the hemoxigenase 1 (HO-1) expression. HO-1 has cytoprotective properties and is induced by Nrf-2 transcription factor.

A recent study demonstrated that curcumin affects the fluidity of the HCV envelope, resulting in impairment of viral binding and fusion of all major HCV genotypes [117]. Curcumin has also been found to inhibit cell-to-cell transmission. So, curcumin, with its pan genotype antiviral action, could be associated with multiple HCV therapies. Activation of hepatic stellate cells, either by HCV or HBV virus, alcohol- and toxin-induced oxidative stress, is the cornerstone of liver fibrosis. The antifibrotic effect of curcumin by suppressing inflammation, decreasing oxidative stress and inhibiting hepatic stellate cell activation, may play an important role in hampering the progression of HCV to chronic liver disease [118,119].

However, despite all the properties of curcumin, there is no clinical evidence of its efficacy in any type of liver disease. This may be due to its poor availability due to water insolubility and high instability at the intestinal pH. Some strategies for improving the bioavailability of curcumin have been studied. One of these is a patented phytosome complex, combining it with soy lecithin, but there is no clinical study using it for HCV patients or those with chronic liver disease. Considering the promising effects of curcumin in HCV patients-its safety, tolerability, the lack of toxicity in experimental model and low cost--its use as a regular kitchen spice should be encouraged, especially associated with piperine, which is known to improve its bioavailability. There is a need for clinical studies using higher bioavailability formulations in these patients.

**Iron Overload in HCV Patients**

HCV infection is associated with hepatic iron overload, which is known to exacerbate oxidative stress. These conditions have been implicated in diminished sustained response to antiviral therapy, liver damage and HCC in HCV-related chronic liver diseases [120,121]. The heaptic peptide hormone hepcidin controls iron distribution. Usually, in a systemic inflammatory state, hepcidin excludes iron from serum by sequestering it in macrophages and preventing dietary uptake. However, HCV infection suppresses hepcidin in HCV patients, contributing to liver iron overload [122]. Moreover, transgenic mice that express HCV core protein develop HCC, since the HCV core protein inhibits mitochondrial complex I and generates reactive oxygen species [123].

Therefore, it is recommended that HCV-patients reduce their iron intake. Reduced intake of dietary iron with appropriate nutritional counseling has been demonstrated to decrease serum ferrit in and ALT levels in CHC. As observed in previous studies, iron intake of less than 7 mg/d for a prolonged period is desirable in HCV patients [124,125]. A previous study [124] found that a therapeutic iron reduction, including phlebotomy and low-iron diet, with a long-term follow-up of six years may potentially lower the risk of progression to HCC. Further, a low-iron diet has an important additional effect in iron reduction therapy for HCV patients, since phlebotomy alone is not enough to completely remove iron-induced oxidative stress [12]. Supplementation with branched-chain amino acids has been shown to reduce oxidative stress and improve iron metabolism by increasing hepcidin-25 in both mice and patients with HCV-related advanced fibrosis, which may partially account for their inhibitory effects on the development of HCC in HCV patients [123].

**Conclusion**

A substantial body of data exists clearly showing that HCV patients as a group are at risk of ingesting inadequate amounts of micronutrients and that excessive caloric, carbohydrate and fat intake seems to be associated with poor outcomes and increased obesity prevalence for these patients. Moreover, deficiencies in retinol and vitamin D consumption have been associated with the progression of the liver disease in HCV patients. It is noteworthy that most of the studies regarding the impact these nutrients have on improving HCV treatment involve the standard therapy with pegylated interferon plus ribavirin; however, a new era of anti-HCV treatment is overshadowing this conventional therapy. Nevertheless, these natural nutrients must be regarded as adjuvant therapy regardless of pharmacotherapy. Modifications to lifestyle and regular ingestion and/or supplementation of these nutrients may inhibit HCV replication, optimize the new therapy, and hamper disease progression. The introduction of new recipes to the daily diet may help increase micronutrient intake and facilitate the inclusion of curcumin as a seasoning.
References


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