The Impact of Exercise and Nutrition on the Outcome of Patients with Chronic Hepatitis C

INTRODUCTION

The addition of a protease inhibitor, either Incivek (telaprevir) or Victrelis (boceprevir) to pegylated interferon (PI) and ribavirin (RBV) increases sustained virological response (SVR) rates in both treatment naïve and treatment experienced patients, and decreases length of treatment in many patients with genotype 1 (G1) chronic hepatitis C (HCV). Despite this major advance in therapy, many patients such as null responders, cirrhotics, and Black/African Americans, continue to have suboptimal response rates. Furthermore, some patients and clinicians have opted to postpone treatment until less-complicated regimens, interferon-free regimens, and/or less costly regimens become available, which is still many years away. While the impact of lifestyle on this new standard of care (SOC) treatment has yet to be evaluated, numerous lifestyle factors have previously been shown to influence SVR rates, disease progression and side effects associated with therapy (Table 1). This article addresses the impact of lifestyle interventions—specifically exercise and nutrition, on the outcome of patients with chronic HCV.
EXERCISE

A regular exercise regimen including both aerobics and weight-bearing exercises has numerous health benefits for individuals with HCV, such as improving energy levels, weight reduction in overweight patients resulting in a decreased percentage body fat, improving cardiovascular function and reducing the risk for comorbidities such as type 2 diabetes, hypertension, and osteopenia/osteoporosis (1).

Hickman and colleagues (2,3) found that when overweight patients with chronic liver disease, such as HCV, continued a regular exercise routine and maintained their weight loss over time, a sustained improvement in liver enzyme elevations, insulin levels, and QOL resulted. Lifestyle interventions such as regular physical activity and dietary modifications has been demonstrated to improve health-related quality of life (HRQOL), including enhanced exercise capacity and a healthier body composition in HCV patients after liver transplantation, independent of other comorbidities (4,5,6). A Mexican study found that HCV patients who followed a regular routine of walking, synchronized breathing and focused attention, known as breathwalk, for a time period of 6 months, had a healthier body composition, improved emotional state, lower liver enzyme elevations and better lipid profiles, compared with these indices prior to starting this exercise regimen (7).

Results from a small study of seventeen HCV patients found that those patients who walked more than 8000 steps/day a had lower alanine aminotransferase (ALT) elevation, body fat content, body mass index (BMI), leptin level and Homeostasis Model of Assessment-Insulin Resistance (HOMA-IR) at the end of the trial period which included 6 months of pedometer monitoring (8). A study conducted in France found that HCV patients on who maintained a regular exercise routine throughout treatment with PI plus RBV reported improved QOL indicators compared to those patients not complying with an exercise regimen (9).

Patients with chronic liver disease have an increased likelihood of developing bone disorders including osteoporosis (10). In addition, ribavirin may be causally related to reduced bone mineral density (11,12,13). Since it is well known that a lack of physical exercise is associated with poor bone health (14), routine exercise program incorporating both weight-training and aerobic exercises should be encouraged in all patients with HCV. More research addressing the impact of exercise in patients with chronic HCV is needed.

ALCOHOL

Alcohol is a known hepatotoxin. And, when consumed by a person who has HCV, the hepatotoxicity of alcohol is additive. HCV has been found frequently in people with alcoholic liver disease (ALD), especially in those people who have severe liver damage or cirrhosis, suggesting a causative relationship (15). Thus, alcohol ingestion is considered to be an independent risk factor for progression to cirrhosis in patients with HCV.

Consumption of <50 grams/day (approximately 48 ounces of beer, 4.5 ounces of 80 proof or 15 ounces of wine) of alcohol has been found to stimulate HCV replication, resulting in increased viral loads (16). However, quantities of alcohol even less than this amount may also be detrimental. Many studies have confirmed that patients who drink alcohol while on...
HCV treatment are less likely to achieve an SVR when compared to patients who do not drink alcohol while on treatment. And, those HCV patients with recent alcohol use were found to be less compliant with treatment and less likely to achieve SVR compared with their nondrinking cohorts (17,18). The precise amount of alcohol use that is considered to be safe for patients with HCV is still a subject of debate. Furthermore, this dose is dependent upon numerous individualized factors—such as gender, genetic predisposition, BMI, and duration of alcohol use. However, advising people with chronic hepatitis C to refrain from drinking any alcohol is a reasonable recommendation.

RESVERATROL

Resveratrol, a polyphenol antioxidant found in the skin of red grapes, is a component of red wine. Moderate red wine consumption has been associated with decreased insulin resistance, improved lipid profiles, and a reduced risk of cardiovascular disease (19,20). Animal studies have shown that resveratrol decreases steatosis in rats fed a high-calorie diet (21). In patients with HCV, the purported protective properties of resveratrol are not seen. In fact, viral replication increases upon resveratrol supplementation, thus negating the antiviral effects of pegylated interferon plus ribavirin (22). Therefore, patients with HCV should be discouraged from using resveratrol, especially during antiviral therapy.

OBESITY

The presence of obesity in patients with chronic HCV is associated with accelerated progression to cirrhosis (23,24), and a reduced likelihood of achieving a SVR rate (25). While originally felt to be associated with BMI, it is now known that the development of hepatic steatosis, which is a risk factor for HCV disease progression, instead correlates with visceral (central) obesity. (26) Steatosis occurs in over 50% of patients with HCV and may be divided into 2 types—metabolic and viral (Table 2). Viral steatosis is due to the direct cytopathic nature of the hepatitis C virus and develops in the absence of other steatogenic cofactors. It is characteristic of patients with genotype 3a. Metabolic steatosis is associated with insulin resistance, and most commonly occurs in patients with G1. Both increased central adiposity and the presence of steatosis hasten disease progression and decrease the likelihood of achieving SVR. Weight reduction in overweight patients with HCV can result in a reduction of liver enzyme elevations, a decrease in hepatic steatosis (27), a reversal of fibrosis (28), and higher SVR rates (29). The deleterious consequence of obesity on disease outcome was demonstrated in the HALT-C TRIAL, (Hepatitis C Antiviral Long-Term Treatment against Cirrhosis) a large multicenter study which randomized 985 patients with advanced fibrosis and prior nonresponse to HCV SOC treatment to receive either peginterferon alfa-2a 90 μg/wk. maintenance monotherapy or no treatment at all. During the 4-year follow-up period, it was found that a significant number of overweight HCV patients who gained additional weight during this time period were more likely to experience worsening hepatic fibrosis, hepatic decompensation, or liver-related death, compared to overweight HCV patients who lost weight during this time period. Most

<table>
<thead>
<tr>
<th>Metabolic Steatosis</th>
<th>Viral Steatosis</th>
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<tr>
<td>Typically associated with G1</td>
<td>Typically associated with G 3a</td>
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<tr>
<td>Not due to the direct cytopathic effect of HCV</td>
<td>Direct cytopathic effect of HCV</td>
</tr>
<tr>
<td>Associated with insulin resistance and its clinical components</td>
<td>Absence of other steatogenic cofactors</td>
</tr>
<tr>
<td>Both increased adiposity and the presence of steatosis hastens disease progression</td>
<td>Degree of steatosis correlates with HCVRNA</td>
</tr>
<tr>
<td>Both increased adiposity and the presence of steatosis decreases the likelihood of achieving SVR with SOC therapy</td>
<td>Viral eradication results in steatosis resolution</td>
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<tr>
<td>Weight reduction decreases steatosis and improves fibrosis severity</td>
<td>HCV recurrence is associated with steatosis return</td>
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Table 2: Comparison of Hepatitis C-Related Steatosis
HEPATITIS C: A NEW ERA OF TREATMENT

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importantly, it was found that patients who lost weight during the trial had improvements in hepatic inflammation that was comparable to those patients who received pegylated interferon (30,31). Thus, overweight HCV patients, particularly those with central adiposity, should be encouraged to adhere to a healthy diet geared toward weight reduction.

GRAPEFRUIT

HCV-associated steatosis may in part be due to the interaction of the virus with cholesterol and fatty acid metabolism (32,33). One step in the HCV life cycle involves attachment of the virus to very low density lipoprotein (vLDL) prior to secretion. The grapefruit flavonoid naringenin has been found to inhibit secretion of HCV from hepatocytes in cell culture in part by inhibiting vLDL secretion. While dosages of naringenin up to 1000 μM have been found to be nontoxic to hepatocytes in cell culture (34). While it is unclear how many grapefruits per day a patient with HCV would need to consume in order to achieve benefit, it is unlikely the amount is realistic for daily consumption. It is important to remember that grapefruit contains furanocoumarins and flavonoids which can inhibit components of the cytochrome P450 drug metabolism pathway, such as CYP3A4, causing potentially toxic drug levels (35,36). Thus, patients should consider avoiding the consumption of excessive amounts of grapefruits and grapefruit juice during treatment with either telaprevir or boceprevir, as this may result in increased systemic exposure with the potential for worsening adverse events such as anemia, rash and rectal symptoms. Table 3 lists some commonly used medications that may interact with grapefruit.

POLYUNSATURATED FATTY ACIDS (PUFAS)

Arachidonic acid (AA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) are polyunsaturated fatty acids (PUFAs) that can inhibit hepatitis C replication in vitro (37). Takaki et al found that patients supplemented with eicosapentaenoic acid (EPA), an omega-3 polyunsaturated fatty acid, required less ribavirin dose reduction due to anemia during the first 12 weeks of therapy with pegylated interferon plus ribavirin (38). Avoidance of ribavirin dose reductions during the first weeks of therapy is known to correlate with diminished HCV relapse rates and improved SVR rates (39). Thus, it may be beneficial to encourage patients with HCV to incorporate corn oil, safflower oil, soybean oil, sunflower oil, walnuts, and oily fish (salmon, herring, tuna and mackerel) into their diets.

BLUEBERRIES

Blueberry leaves have been found to contain a potent inhibitor of HCV replication known as proanthocyanidin (40). Rats fed diets high in blueberries were protected from acute hepatic injury (41) and CCl4-induced hepatic fibrosis. (42) Clinical trials will need to be conducted on humans in order to elucidate the effect of this fruit component in patients with HCV.

Table 3

<table>
<thead>
<tr>
<th>Potential Medication—Grapefruit Interactions*</th>
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<tbody>
<tr>
<td>1. Statins: lovastatin, atorvastatin, simvastatin, simvastatin/ezetimibe</td>
</tr>
<tr>
<td>2. Immunosuppressants: cyclosporine, tacrolimus, sirolimus</td>
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<tr>
<td>3. HIV medication: saquinavir, ritonavir, indinavir, sustiva</td>
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<tr>
<td>4. Mood altering medications: buspirone, sertraline, ziprasidone, carbamazepine, aripiprazole, bupropion, fluvoxamine</td>
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<tr>
<td>5. Sedative/hypnotic: triazolam, diazepam, midazolam, eszopiclone</td>
</tr>
<tr>
<td>6. Erectile dysfunction: sildenafil</td>
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<tr>
<td>7. Antiarrhythmics: amiodarone, disopyramide, quinidine</td>
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<tr>
<td>8. Antihistamines: fexofenadine</td>
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<tr>
<td>9. Methadone</td>
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<tr>
<td>10. Colchicine</td>
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<tr>
<td>11. Steroids: Budesonide, methylprednisolone</td>
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<tr>
<td>12. Calcium channel blocker: Verapamil</td>
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<tr>
<td>13. DAAs—Telaprevir/Boceprevir</td>
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*This table provides a partial list of commonly used medications which may interact with grapefruit resulting in supratherapeutic toxic levels

(continued on page 48)
CAFFEINE/COFFEE

The hepatoprotective effect of caffeine, particularly caffeinated coffee, on patients with chronic liver disease has been demonstrated in many studies. Analysis of the baseline characteristics of 766 patients in the HALT-C trial concluded that higher coffee consumption was associated with less hepatic steatosis, lower serum aspartate (AST)/alanine aminotransferase (ALT) ratio and lower alpha-feto protein (AFP) levels. Follow-up evaluation approximately 4 years later revealed that patients who drank three or more cups of coffee/day had a lower incidence of disease progression compared to those who ingested less than three cups of coffee/day (43). This finding was confirmed in a study by Modi and colleagues who found that HCV patients consuming between 2–3 cups of regular coffee/day had less fibrosis on histologic evaluation, compared to patients who drank less than this daily amount (44). Similar results were not seen in patients who consumed caffeine from other sources or who consumed decaffeinated coffee. Costentin and colleagues in France found that HCV patients who consumed more than 408 mg of caffeine/day—approximately 3 cups of a caffeinated beverage/day, had less histologic inflammation compared with those HCV patients who drank less than this daily amount of caffeinated beverages/day, although no correlation with degree of fibrosis was found (45).

While the exact amount of coffee consumption necessary to obtain beneficial results is unclear, it appears reasonable for patients with HCV to drink two-to-four cups of caffeinated coffee/day. Caffeine may also reduce fatigue that is often associated with HCV, although higher amounts of caffeine may cause irritability, restlessness, and insomnia. This should be taken into consideration for people undergoing HCV treatment, as side effects of PI plus RBV may also include anxiety and insomnia. Finally, it should also be kept in mind that coffee is also risk factor for the development of osteoporosis, which as noted above occurs, with increased frequency in people with chronic liver disease.

IRON OVERLOAD

The liver is the primary storage organ for iron and is intricately involved in iron homeostasis through the secretion of the amino acid peptide hepcidin. Low hepcidin levels result in iron overload (46). It is well established that iron overload can accelerate liver damage. Approximately 40% of people with HCV have elevated iron indices (47). This is consistent with the finding of low hepcidin levels in many patients with HCV (48). Iron overload has been associated with increased hepatitis C viral replication, more advanced liver disease and an increased incidence of HCC in patients with HCV. Low plasma prohepcidin levels have been found to correlate with fibrosis score in patients with HCV, and may represent a surrogate marker of fibrosis (49). While some researchers have linked the presence of the hemochromatosis gene mutation with both increased liver iron concentrations and fibrosis (50,51), others have not found such a relationship (52). Some studies have shown a lower likelihood of achieving a SVR when HCV patients with iron overload are treated with alfa-interferon monotherapy compared to treated HCV patients who lack an iron overload (53). Retreatment with interferon plus phlebotomy has been shown to improve SVR in some non-responders to interferon monotherapy (54). Others have suggested that elevated serum ferritin levels are

<table>
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<th>Table 4</th>
<th>Factors Which May Impact Iron Absorption</th>
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<tr>
<td>Factors which may increase iron absorption or increase serum iron levels</td>
<td>Factors which may decrease iron absorption</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Tea—especially black tea</td>
</tr>
<tr>
<td>Alcohol</td>
<td>PPIs</td>
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<tr>
<td>Red Meat</td>
<td>Non-citrus fruits (polyphenols)</td>
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<tr>
<td>Poultry</td>
<td>Coffee</td>
</tr>
<tr>
<td>Fish</td>
<td>Cocoa</td>
</tr>
<tr>
<td>Cooking with cast-iron laden cookware and utensils</td>
<td>Calcium</td>
</tr>
<tr>
<td>Cereals and other foods fortified with iron</td>
<td>Egg yolks</td>
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</tbody>
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*Raw Shellfish
*Does not increase iron absorption but increases the risk of morbidity and mortality when raw shellfish is contaminated with V. Vulnificus
predictive of non-response to interferon and ribavirin treatment (55). Hofer and colleagues failed to find a correlation between elevated liver iron stores and non-response to standard or pegylated-IFN/ribavirin therapy in patients with chronic hepatitis C (56). Kato et al found the likelihood HCC development to be lower in HCV phlebotomized patients who consumed low-iron diets compared to non-phlebotomized normal-diet consuming HCV patients (57). Finally, male HCV patients with mild iron overload who were either non-responders to SOC or who had contraindications to treatment, achieved histologic improvement when treated with mild iron depletion (58).

Phlebotomy is not currently advised for mild secondary iron overload—defined as a hepatic iron concentration (HIC) <2500 µg/g dry weight, in patients with HCV (59). Nutritional factors that may impact iron absorption are summarized in Table 4. The potential benefit of iron-reduction therapy for people with chronic hepatitis C in the era of DAAs has yet to be evaluated.

**THIAMINE**

Thiamine deficiency has been found in patients with HCV and cirrhosis, but not in non-cirrhotic HCV patients. This suggests that the virus per se does not affect thiamine levels (60). Thus, it may be prudent to check thiamine levels in cirrhotic patients of any etiology, especially if suffering from symptoms suggestive of deficiency, such as peripheral neuropathy, and in patients with coexistent alcoholic liver disease.

**VITAMIN A DEFICIENCY**

In a study conducted in Brazil more than half of the 140 HCV patients evaluated were found to be deficient in Vitamin A (61). Furthermore, vitamin A levels, as assessed by a combination of dietetic and functional indicators, as well as serum retinol levels, inversely correlated with the severity of liver disease. Thus, it was concluded that vitamin A supplementation may be beneficial for some patients with HCV. However, it must be remembered that activation of hepatic stellate cells, which store vitamin A, may cause an excessive amount of extracellular matrix production which can result in perisinusoidal fibrosis (62), and that excessive intake of vitamin A—approximately 25,000–50,000 IU per day, may cause hypervitaminosis A, which may lead to cirrhosis. Therefore, assessment of serum retinol levels is crucial prior to Vitamin A supplementation.

**VITAMIN D**

HCV G1 patients typically have lower serum levels of 25 hydroxy (OH) vitamin D compared to individuals without HCV, with a severe vitamin D deficiency occurring in approximately one third of patients (63). Decreased 25 (OH) Vitamin D serum levels independently correlate with both increased extent of histologic inflammation and fibrosis, in addition to a reduced likelihood of achieving SVR to therapy with pegylated interferon PI plus RBV (64). Additional findings have suggested that supplementation with vitamin D 1000–4000 IU/day to achieve a serum level >32ng/mL, may improve SVR rates to SOC antiviral therapy in G1 HCV patients. In fact, 96% of HCV patients treated PI plus RBV plus vitamin D supplementation achieved HCVRNA negativity by week 12 of therapy compared with 48% of the HCV control group receiving PI plus RBV without vitamin D supplementation. Thus, the immunomodulatory properties of vitamin D may act in synergy with PI plus RBV. Indeed, further evaluation has revealed that tissue expression of cytochrome P 450 25-hydroxylating liver enzymes CYP27A1 paralleled with vitamin D levels and inversely correlated with hepatic necroinflammatory activity. A study evaluating the benefits of vitamin D supplementation in combination with DAAs is anticipated. In the meantime, since population-based studies have concluded that up to 75% of Americans have a vitamin D deficiency, (65) it seems reasonable for all patients with HCV to add Vitamin D to their antiviral regimens, unless otherwise contraindicated.

**VITAMIN E AND VITAMIN C**

Vitamin E supplementation may be a beneficial adjunct to the treatment of HCV, and vitamin C improves the antioxidant properties of Vitamin E (66). When used in combination, vitamin E (800 IU/day) with vitamin C (1000 IU/day) have been shown to prevent, delay the onset of, and/or reduce the degree of,
Lifestyle interventions with attention to appropriate dietary intake, correction of nutritional derangements and maintenance of a routine exercise regimen, provide an important therapeutic adjunct in the care of patients with chronic hepatitis C—whether on or off antiviral therapy. This article underscores the need for the clinician to be aware of the potential beneficial and/or detrimental impact that the HCV patients’ lifestyle may have on the progression of disease, QOL issues, and the response to antiviral therapy. Studies addressing the influence of nutrition and exercise in the new era of antiviral treatment with DAAs are eagerly anticipated.

**CONCLUSIONS**

Lifestyle interventions with attention to appropriate dietary intake, correction of nutritional derangements

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**ZINC**

Serum zinc levels have been shown to inversely correlate with progression of chronic HCV. Furthermore, zinc deficiency is often present in patients with HCV complicated by HCC and/or cirrhosis (69). Oral zinc supplementation (150 mg/day) may slow HCV disease progression, reduce the incidence of HCV-related HCC (70) and may improve response to antiviral treatment (72,73). While daily dosages up to 100 mg of zinc may boost the immune system and improve response to interferon, an excess of this amount may be immunosuppressive. It should also be kept in mind that excessive zinc consumption may lead to nausea, vomiting, and diarrhea, which are potential side effects associated with HCV antiviral therapy.

**S-ADENOSYL METHIONINE (SAME)**

SAMe functions as a methyl group donor. In a mouse model SAMe has been shown to enhance interferon’s antiviral properties. (73). In a small pilot study performed on genotype 1 HCV nonresponders to pegylated interferon plus ribavirin, it was demonstrated that those patients who were retreated with the same regimen but supplemented with 400 mg SAMe tablets per day, displayed both improved early viral kinetics and interferon signaling. This lead to enhanced interferon responsiveness and resulted in a higher percentage of patients achieving SVR (74). Further studies are required to confirm these intriguing results.

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