

Counseling Persons with Chronic HCV Infection

This is a PDF version of the following document:

Module 2: <u>Evaluation, Staging, and Monitoring of Chronic Hepatitis C</u>

Lesson 3: <u>Counseling Persons with Chronic HCV Infection</u>

You can always find the most up-to-date version of this document at https://www.hepatitisC.uw.edu/go/evaluation-staging-monitoring/counseling-liver-health/core-concept/all.

Background

The following section provides guidance on how to counsel persons with chronic hepatitis C virus (HCV) infection on the use of over-the-counter pain medications, iron and vitamins, and complementary and alternative therapies. This section also provides guidance on diet and weight management, as well as the use of alcohol, cannabis, and tobacco.



Over-the-Counter Pain Medications

Because many medications are metabolized through the liver, it is important for the medical provider to know all the medications a person with chronic HCV is taking, including over-the-counter medications. A current medication list should be solicited frequently.

Acetaminophen

Acetaminophen can cause clinically important hepatotoxicity, either through an acute overdose or when taken on a regular basis (even at lower doses).[1,2,3] In one large study that examined acetaminophen-related acute liver failure, individuals taking less than 4 grams per day of acetaminophen accounted for 7% of the cases.[3] Among healthy adults taking 4 grams per day for 14 days, 38% developed alanine aminotransferase (ALT) values in excess of 3 times the upper limit of normal.[2] In contrast, healthy adults who took 1 gram of acetaminophen twice daily for 12 weeks had only minor elevations in aminotransferase levels.[5] Studies involving persons with chronic HCV have shown an increased risk of acute liver injury among individuals with chronic HCV following acetaminophen overdose.[6,7] Concurrent alcohol use further increases the chance of acute or chronic acetaminophen-induced hepatotoxicity in persons with chronic HCV infection.[7] Formal guidelines for the safe use of acetaminophen in persons with HCV infection do not exist, but some experts have issued general recommendations.[8,9,10]

Recommendations

- Low dosages of acetaminophen (up to 2 grams per day) can safely be used in most persons with chronic HCV infection without cirrhosis
- Individuals with chronic HCV infection and cirrhosis should limit their intake of acetaminophen to 1 gram per day.
- Persons with chronic HCV who drink excess alcohol should avoid taking acetaminophen.
- Clinicians should inform persons with chronic HCV infection that many narcotic combination pills and over-the-counter cold and flu medications may contain acetaminophen.
- Individuals with chronic HCV who frequently take acetaminophen should have laboratory monitoring for hepatotoxicity every 3 to 6 months.

Aspirin and Nonsteroidal Anti-inflammatory Medications

Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) are generally safe for persons who have chronic HCV without cirrhosis, when taken at standard doses. For persons with cirrhosis, NSAIDs and aspirin are best avoided, especially for those with decompensated cirrhosis.[13] The American Association for the Study of Liver Disease (AASLD) recommends persons with cirrhosis and ascites avoid taking NSAIDs, except in special circumstances.[14] In persons with decompensated cirrhosis, the use of NSAIDs and aspirin may further increase the inherent risk these patients have for developing nephrotoxicity and gastrointestinal bleeding.[15]

Recommendation

- Individuals with chronic HCV who do not have cirrhosis can take aspirin or NSAIDs at low or standard recommended dosages.
- Persons with chronic HCV infection and cirrhosis should, in general, avoid taking NSAIDs or aspirin.
- Individuals with cirrhosis who have short-term, minor pain should take acetaminophen in this setting as long as the acetaminophen dose does not exceed 1 gram per day. If a person with cirrhosis has joint or musculoskeletal pain unresponsive to acetaminophen, NSAIDs can be used for a very brief period of time (less than 3 days), if given at the lowest daily dose possible.
- Persons with chronic HCV and decompensated cirrhosis should not take aspirin or NSAIDs.



Iron and Vitamins

Iron

In persons with chronic hepatitis C infection, mild to moderate hepatic iron overload is common.[16,17] In some studies, excess hepatic iron in persons with chronic HCV has been associated with accelerated fibrosis, whereas other studies have not shown a correlation of iron and hepatic fibrosis progression in persons with chronic HCV.[18,19,20]

Recommendation

• Based on the potential negative impact of iron in persons with chronic HCV, many experts have recommended these individuals avoid taking iron supplements or a daily multivitamin that contains iron, unless a compelling reason exists to regularly take iron, such as iron deficiency anemia from gastrointestinal bleeding.[15]

Vitamin A

Vitamin A is a fat-soluble vitamin that can be obtained in the diet as provitamin A (mostly plant sources) and preformed vitamin A (animal sources or supplements). Intake of vitamin A at levels contained in a multivitamin does not cause hepatotoxicity. Vitamin A deficiency is often made on a clinical basis, but is supported by either a serum retinol level less than 20 micrograms/dL or a molar ratio of retinol to retinol-binding protein less than 0.8.[22] Vitamin A deficiency is uncommon in the United States. Chronic ingestion of mega-doses of vitamin A, especially in excess of 25,000 international units per day, can potentially cause severe hepatotoxicity.[23,24,25,26]

Recommendations

- Vitamin A is a fat-soluble vitamin and should only be taken at standard doses of less than 5,000 international units per day.
- Intake of high-doses of vitamin A, such as a dose greater than 25,000 international units per day, is not recommended.

Vitamin D

Vitamin D deficiency is common in persons with chronic HCV infection, particularly those individuals with cirrhosis.[27,28] Some experts have suggested that vitamin D has antiinflammatory and antifibrotic properties in persons with chronic HCV infection.[29,30] In one study that examined 25-hydroxyvitamin D levels in 218 persons receiving direct-acting antiviral (DAA) therapy, investigators found no correlation of vitamin D levels and sustained virologic response (SVR) rates.[28] The Institute of Medicine defines vitamin D deficiency as a serum 25-hydroxyvitamin D level less than 20 ng/mL, but other societies, including the Endocrine Society, the National Osteoporosis Foundation, the International Osteoporosis Foundation, and the American Geriatric Society recommend using less than 30 ng/mL as the cutoff for vitamin D deficiency.[32,33,34,35]

Recommendations

- There are no liver-specific reasons to take vitamin D supplementation, but persons with chronic HCV infection who are deficient in vitamin D should have vitamin D replacement therapy.
- For otherwise healthy adults, the Institute of Medicine has a recommended vitamin D dietary allowance of 600 IU per day, with an upper level of intake of 4,000 IU/day.[32] Some experts recommend that persons who do not have regular sun exposure take 800 IU per day of vitamin D. There are no known hepatotoxic effects of excess vitamin D dosing.[36]



• For individuals with more severe vitamin deficiency (e.g. serum 25-hydroxyvitamin D level less than 10 ng/mL), many experts recommend initial replacement therapy consisting of 50,000 IU of vitamin D once weekly for 8 weeks, followed by a maintenance dose of 800 to 1000 IU per day. For milder vitamin D deficiency, a daily dose of 1000 IU per day may be sufficient.



Complementary and Alternative Therapies

Complementary and alternative therapies are frequently used among adults in the United States, including persons with chronic HCV.[37,38,39] Some of these complementary and alternative therapies, however, may have harmful effects on the liver or cause serious interactions with medications used for HCV therapy.[40,41] At the initial visit for HCV care and at regular intervals thereafter, clinicians should obtain a complete list of the individual's prescription medications, over-the-counter medications, complementary and alternative therapies, and dietary and herbal supplements. For patients taking complementary or alternative therapies, clinicians should discuss whether it is wise for them to continue taking these alternative and complementary therapies. The list of complementary and alternative therapies should be reviewed again during HCV, since some individuals may seek out these options for relief of treatment-related side effects. The National Center for Complementary and Alternative Medicine (NCCAM) resource LiverTox has information on the safety and efficacy of dietary and herbal supplements.[42] The following summarizes several common complementary and alternative therapies that have been used by persons living with chronic HCV infection.

General Recommendation

• Given the extremely high SVR rates with current DAA therapy, it is unlikely that any of the complementary and alternative therapies listed below would provide any significant benefit for HCV treatment. In addition, complementary and alternative medications may cause drug interactions with DAA medications. Accordingly, we do not recommend the use of any complementary or alternative therapies for persons with HCV infection.

Ginseng

Ginseng includes Asian ginseng (*Panax ginseng*) and American ginseng (*Panax quinquefolius*). Asian ginseng is purported to have hepatoprotective effects.[43,44] There are insufficient data with ginseng in persons with HCV to make any recommendations on its use. Ginseng can cause varying degrees of herb-drug interactions.[43] In addition, Asian ginseng may lower blood glucose, so it should be used cautiously in persons with a history of hypoglycemia.[43]

Lactoferrin

Lactoferrin, also known as apolactoferrin or lactotransferrin, is a protein found in milk and other body fluids that binds and transports iron. The highest concentration of lactoferrin is in colostrum. Bovine lactoferrin is the formulation of lactoferrin most often used when taken as a dietary supplement, with a typical dose of 1.8 to 3.6 grams per day; lactoferrin can also be produced via recombinant technology. Several small studies suggested that lactoferrin may lower HCV RNA levels.[45,46,47] In a placebo-controlled trial in persons with chronic HCV, orally administered bovine lactoferrin at a dose of 1.8 g daily for 12 weeks had no greater impact on HCV RNA levels than placebo.[49] In a randomized placebo-controlled trial of interferon alpha-2b plus ribavirin, with and without lactoferrin, for treatment of chronic HCV, lactoferrin did not increase SVR rates.[50] Although lactoferrin appears to be safe, there is no compelling reason to use it in persons with HCV infection.

Licorice Root (Glycyrrhiza glabra)

Licorice root contains a compound called glycyrrhizin (or glycyrrhizic acid). Several preliminary studies suggested intravenous glycyrrhizin had some beneficial effects for persons with HCV.[52,53] The intravenous formulation, however, is not available outside a research setting. Since there are minimal reliable data on oral licorice root for treatment of HCV, no specific recommendations can be made regarding its use. When taken in large amounts, however, licorice root containing glycyrrhizin can cause high blood pressure, salt and water retention, low potassium levels, and alterations in serum cortisol levels.[54,55] Because of lack of convincing benefit and potential adverse effects, it is not recommended for individuals taking diuretics or those with



cirrhosis or cardiovascular problems.

Red Yeast Rice Extract

Red yeast rice extract is a dietary supplement commonly used in Asia to lower blood cholesterol.[57,58,59] It contains a compound (monacolin K) that is biochemically similar to the HMG-CoA-reductase inhibitor lovastatin. Some red yeast rice extract contains citrinin, a chemical that can cause nephrotoxicity. In addition, red yeast rice extract can potentially cause the same adverse effects that occur with statins, such as acute hepatitis, myopathy, and rhabdomyolysis. For these reasons, we recommend strongly against using red yeast rice extracts in persons with chronic HCV infection.

S-Adenosyl-L-Methionine (SAMe)

S-adenosyl-L-methionine (also called S-adenosyl methionine, S-adenosylmethionine, SAMe, or SAM-e) is a molecule involved in multiple cellular reactions, acting as the principal methyl donor.[60] Animal models have shown that SAMe depletion may favorably impact liver function.[61] *In vitro* models of HCV demonstrated that SAMe enhances the antiviral effect of interferon, although SAMe does not have any direct antiviral activity. Persons with HCV who took SAMe in conjunction with peginterferon and ribavirin had improved viral kinetics (improved early response), but this did not translate into better sustained virologic response rates.[62,63] Most often, SAMe is taken at a dose of 1200 mg per day. There are no large, high-quality studies to date demonstrating a treatment outcome benefit of taking SAMe for persons with chronic HCV.[64] A meta-analysis of SAMe concluded that it is superior to placebo in controlling pruritus in persons with chronic liver disease.

Sho-Saiko-To/Dai-Saiko-To/TJ-9/Xiao-Chai-Hu-Tang

Sho-saiko-to, is a mixture of at least seven different herbs that is widely used in parts of Asia, including China and Japan, to treat persons with hepatitis.[65] Sho-saiko-to is often referred to interchangeably as TJ-9 and Dai-saiko-to and Xiao-chai-hu-tang, but these products may have slightly different herbal mixtures. Although the mechanism for Sho-saiko-to remains unclear, there are limited data suggesting it lowers serum aminotransferase levels in persons with chronic hepatitis and may reduce the risk of hepatocellular carcinoma in patients with cirrhosis.[66,67,68] Sho-saiko-to is generally described as having little to no side effects,[68] but there have been several case reports suggesting Sho-saiko-to and Dai-saiko-to can cause acute liver injury (without liver failure).[65,69,70,71] The mechanism of acute liver injury and the responsible ingredients are not well understood, but Skullcap (*Scutellaria lateriflora*), which is often used with Sho-saiko-to, is felt to be a likely culprit.[65] Persons taking Sho-saiko-to or Dai-saiko-to should be counseled on the rare but real risk of acute liver injury with this herbal supplement.

Silymarin

The alternative medication silymarin is an extract produced from the seeds of the flowering milk thistle plant (*Silybum marianum*). In vitro and animal studies suggest silymarin and its derivatives protect liver cells from injury and have antiviral activity.[73,74,75] Although oral silymarin is a frequently taken supplement by persons living with chronic HCV infection, clinical studies have not shown a convincing benefit.[73,76,77,78] A randomized study with high-dose oral silymarin found no significant improvement in ALT or decreases in HCV RNA levels.[76] There are data that suggest intravenous silymarin may produce antiviral effects in persons with chronic HCV who receive a liver transplant.[73] Oral milk thistle can be purchased in health food stores without a prescription; the most frequently studied dose is 420 mg per day. The intravenous form of silymarin is available only in a research setting. The most common side effects with oral silymarin are gastrointestinal (laxative effect, nausea, and epigastric discomfort) and arthralgias.[74] Silymarin may also rarely cause hypoglycemia. Individuals who have allergies to ragweed, chrysanthemum, marigold, or daisy may have a similar reaction to silymarin. Oral preparations of silymarin do not appear to cause hepatotoxicity, but it can decrease bilirubin conjugation and inhibit the cytochrome P450 enzyme system.[79,80] In summary, milk thistle taken orally does not appear to have any beneficial or toxic effects on the liver, and it does not



significantly alter HCV RNA levels.

St. John's Wort (Hypericum perforatum)

The St. John's wort plant (*Hypericum perforatum*), and its derivative hypericin and hyperforin, are commonly used herbal medicines for the treatment of depression.[81] The evidence for its effectiveness in depression is mixed, with several large studies showing no benefit over placebo for major depression.[82,83] Although sometimes taken by persons living with chronic HCV infection, St. John's wort does not have anti-HCV activity. In a small phase 1 study that examined the safety and efficacy of oral St. John's wort in persons with chronic HCV, investigators reported no detectable antiviral activity, but significant problems with phototoxicity.[84] St. John's wort is a strong CYP3A inducer and thus can significantly lower the levels of medications that are substrates of CYP3A.[83,85] This effect on CYP3A can potentially impact all recommended DAA regimens used to treat HCV. Thus, it is very important that persons receiving HCV DAA therapy avoid concomitantly taking St. John's wort. Other significant drug interactions with St. John's wort include digoxin, warfarin, oral contraceptives, and anti-epileptics. Due to lack of antiviral activity, potential adverse effects, and major problematic drug interactions, persons with chronic HCV infection should not take St. John's wort.

Thymus Extract

Produced from the thymus gland of cows, thymus extract contains lymphocytopoietic factors, referred to as thymosins, some of which have pleiotropic immunomodulatory effects, including augmentation of T-cell activity.[87] One member in the family of thymosins, thymosin alpha-1, is a 28-amino acid peptide that stimulates T-cell maturation, antigen recognition, and stimulation of native interferons.[88] Studies involving thymosin alpha-1 in persons with chronic HCV have primarily focused on its use as an adjunctive immune modulatory with interferon-based therapy.[88,89,90] Overall, these studies suggested that thymosin alpha-1 might improve SVR rates in interferon-based therapy, but thymosin alpha-1 was never recommended as part of the standard of care for HCV treatment.[91] Since current HCV therapy has moved completely away from interferon-based therapy, there is no longer significant need or interest in using thymosin alpha-1 to augment HCV treatment. Further, some have raised concerns of contamination of thymus extract products as well as the potential for zoonotic disease transmission given its bovine source.



Coffee, Diet, and Sodium Intake

Coffee

Coffee consumption may provide a benefit to persons with chronic HCV infection by slowing fibrosis progression, decreasing the risk of developing hepatocellular carcinoma, and increasing the rates of sustained virologic responses with therapy.[92,93,94,95] A large, NIH-sponsored study (referred to as the HALT-C Trial) found that individuals who consumed 3 or more cups of coffee per day were half as likely to have progression of their liver disease and twice as likely to respond to peginterferon and ribavirin therapy.[98] In addition, a subsequent meta-analysis of 16 studies concluded that coffee consumption can significantly reduce the risk for hepatic fibrosis and cirrhosis.[97]

Recommendation

• Persons with chronic HCV infection should be advised that consuming 3 cups of coffee per day may have a beneficial effect on their liver.

Diet

In general, persons with HCV should choose nutritious foods from each food group: fruits, vegetables, dairy, meat, and grains. A well-balanced diet can help persons receive appropriate amounts of all the vitamins, minerals, and other nutrients. All persons receiving HCV therapy should drink an adequate amount of water (at least 2 liters per day) to prevent dehydration. It is important to emphasize that protein restriction has not been shown to reduce the risk of hepatic encephalopathy in persons with advanced liver disease and is associated with increased mortality. Individuals living with chronic HCV, especially those with cirrhosis, should consume enough protein (1.2 gm of protein per kg weight per day) to avoid muscle wasting and to promote tissue healing. In particular, persons with cirrhosis are often malnourished and should be encouraged to optimize their protein intake. Examples of high-quality protein include chicken, fish, lean beef, pork, tofu, nuts, beans, milk, yogurt, and eggs.

Recommendations

- Persons living with chronic HCV infection should have a balanced diet and choose nutritious foods from each major food group.
- Individuals with cirrhosis should not have protein restriction; we recommend a protein intake of approximately 1.2-1.5 g/kg/day.
- For persons with cirrhosis and hepatic encephalopathy, the 2014 AASLD-EASL Practice Guideline on Hepatic Encephalopathy recommends a protein intake of 1.2-1.5 g/kg/day.[103]

Sodium Intake

Individuals with cirrhosis and ascites should limit sodium intake to less than 2,000 mg per day (88 mEq per day) because excessive sodium intake can lead to fluid retention in the form of lower extremity edema and ascites.[14] As a rough guide, one teaspoon of table salt contains about 2,000 mg of sodium. Persons with cirrhosis should not add salt to their food, but instead should replace salt with herbs or spices that can add flavor to the food, without the sodium load. Advise persons with cirrhosis to choose fresh, unprocessed foods instead of salted, smoked, cured, canned, or dried meats, since these processed meats often contain large amounts of sodium.

Recommendation

• Persons with chronic HCV, cirrhosis, and ascites should limit sodium intake to less than 2,000 mg per day.



Modifying Obesity

In the United States and other Western nations, obesity is a growing epidemic. Obesity is defined as a body mass index (BMI) of 30 or greater and overweight as a BMI of 25 or greater (see BMI Calculator).[104] Concurrent with the obesity epidemic, the prevalence of nonalcoholic fatty liver disease (NAFLD) has risen substantially, as has the more severe form of NAFLD, known as nonalcoholic steatohepatitis (NASH).[112] The prevalence of NAFLD and NASH in the United States population is estimated at 30% and 5%, respectively.[] Even in the absence of HCV infection, NASH can cause cirrhosis, liver cancer, and end-stage liver disease. In persons with chronic HCV, hepatic fibrosis is accelerated by NAFLD, particularly when the HCV infection is with genotype 3.[110] In addition, among persons with chronic HCV and cirrhosis, the presence of hepatic steatosis is an independent risk factor for developing hepatocellular carcinoma.[111,112] Further, in HCV treatment clinical trials using interferon-based therapy, obesity, insulin resistance, and hepatic steatosis consistently predicted a poorer response to therapy.[115,116,117] In contrast, with DAA therapy for HCV, individuals with obesity and hepatic steatosis appear to have responses similar to non-obese persons who receive the same therapy.[118] There are, however, concerns that persons successfully treated for HCV, but who have continued NAFLD or NASH, could develop further liver disease and liver complications.

Recommendations

- Persons with steatosis who undergo HCV treatment and achieve an SVR should have their liver monitored with liver function tests every 6 to 12 months to ascertain ongoing liver inflammation.
- Any person with a BMI greater than 30 should be referred to a nutritionist for diet and weight loss counseling, with a goal of decreasing their BMI to less than 25.
- Obese persons should limit total caloric intake from fat to less than 30% (about 50 to 60 grams of fat per day) and they should receive counseling that any kind of weight loss can benefit them, even if they lose as little as 3 to 5% of their baseline weight.
- A combination of exercise and diet often produces the best long-term results.



Alcohol, Cannabis, and Tobacco

Alcohol

In the United States, excessive alcohol consumption is one of the most common causes of cirrhosis and liver failure. The combination of excessive alcohol use with hepatitis C infection causes accelerated fibrosis progression, thereby significantly increasing the risk of developing cirrhosis and liver complications, including hepatocellular carcinoma.[119,120,121,122] Available data show that consumption in excess of 30 grams of alcohol per day is hazardous to liver health.[124,125] Note that one alcoholic beverage typically contains about 14 grams of alcohol. In addition, an exact "safe" level of alcohol consumption has never been clearly established for persons with chronic HCV. The Alcohol Use Disorders Identification Test Consumption questionnaire (AUDIT-C) is a useful screening test for estimating a person's alcohol consumption.[126] Data on the impact of alcohol on DAA HCV treatment are limited, but a large study from the Veterans Affairs health care system suggested excellent SVR rates with DAA therapy, regardless of alcohol use.[127] Individuals who clear HCV with treatment, but continue to drink excessive amounts of alcohol, will continue to be at risk of long-term hepatic complications related to alcohol consumption.[128]

Recommendations

- Ideally, persons with chronic HCV infection should abstain from alcohol. The highest priority is in persons with a history of excessive alcohol use (including alcohol use associated with legal, working, or relationship problems); these individuals should abstain completely from alcohol.
- Women who have never had an alcohol problem should have no more than one alcoholic drink per day, and men with no history of alcohol problems should have no more than two alcoholic drinks per day.
- Individuals with past or present alcohol use should not be excluded from consideration of HCV
 treatment. Nevertheless, those with ongoing alcohol use should be encouraged to discontinue alcohol
 prior to, during, and after therapy for HCV, since continued alcohol use will place them at ongoing risk
 for long-term hepatic complications and liver-induced mortality. In addition, these individuals should
 be considered for medical therapy, such as naltrexone, to treat alcohol use disorder.

Cannabis

Data evaluating the impact of cannabis on liver fibrosis are mixed. Several studies in persons with chronic HCV monoinfection have shown that individuals who frequently smoked cannabis had an increased risk of developing cirrhosis, even after controlling for other factors, such as alcohol use and obesity.[129,130,131] A more recent meta-analysis showed that marijuana use in persons with chronic HCV was not associated with increased prevalence of hepatic fibrosis.[132] Several studies involving persons with HIV and HCV coinfection have not shown any adverse effect of cannabis or cannabidiol (CBD) on hepatic fibrosis.[132,133,134] There are insufficient data on the impact of cannabis or cannabidiol (CBD) on HCV treatment outcomes.

Recommendations

- Clinicians should inform all persons with chronic HCV about potential hazards of cannabis, but abstinence is not a requirement for HCV treatment.
- Use of cannabis in persons with chronic liver disease is preferable to alcohol or opioids.
- Past or present cannabis use should not exclude a person with chronic HCV from receiving HCV treatment.

Tobacco

The effects of tobacco smoking on the liver are controversial.[135,136,137,138] In a study involving 244 adults with chronic HCV infection, smokers had increased hepatic inflammation when compared with



nonsmokers, but the two groups had similar rates of hepatic fibrosis.[137] In addition, other studies involving persons with chronic liver disease have shown increased rates of steatosis and advanced fibrosis, but those studies were retrospective and difficult to control for concurrent alcohol use and obesity.[136,139,140] One study involving adults with HIV and HCV coinfection did not show any adverse effect of smoking.[135] It is clear, however, that tobacco use significantly increases the risk of hepatocellular carcinoma, irrespective of HCV status.[141,142,143]

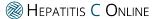
Recommendation

• Clinicians should counsel all tobacco smokers with chronic HCV infection to quit tobacco completely for the following three reasons: (1) smoking may potentially accelerate hepatic fibrosis, (2) smoking clearly increases the risk of developing hepatocellular cancer, and (3) smoking is associated with numerous serious adverse health outcomes that are not related to liver disease.



Summary Points

- Persons with chronic HCV infection without cirrhosis may take up to 2 grams per day of acetaminophen, but individuals with cirrhosis should limit daily intake of acetaminophen to 1 gram per day. Those with excessive alcohol intake should not take acetaminophen.
- In general, NSAIDs are safe for persons with chronic HCV, except for those with cirrhosis, in which case they should be avoided.
- Individuals with chronic HCV can take a multivitamin without iron, but excess iron intake in the absence of iron deficiency can promote hepatic injury.
- Vitamin D levels should be checked and if less than 20 ng/mL vitamin D supplementation should be administered.
- No complementary or alternative medications have shown a definite benefit for persons with HCV and St. John's wort should be avoided in persons receiving treatment for HCV, given its potential to interact with DAA medications.
- Drinking 3 or more cups of coffee per day may have beneficial effects for the liver.
- A balanced, low-fat (less than 30% of total calories) diet is recommended. Individuals with cirrhosis should limit sodium intake to less than 2 grams per day and consume at least 1.2 to 1.5 grams of protein per kilogram per day.
- Obese persons are encouraged to lose at least 3 to 5% of their body weight, with a goal body mass index of less than 25, primarily to reduce the risk of fatty liver disease, but also for general health benefits.
- Ideally, persons with chronic HCV infection should abstain from alcohol for liver health, but persons with past or present alcohol use should not be excluded from consideration of HCV treatment.



Citations

1. Khandelwal N, James LP, Sanders C, Larson AM, Lee WM; Acute Liver Failure Study Group. Unrecognized acetaminophen toxicity as a cause of indeterminate acute liver failure. Hepatology. 2011;53:567-76.

- 2. Watkins PB, Kaplowitz N, Slattery JT, Colonese CR, Colucci SV, Stewart PW, Harris SC. Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily: a randomized controlled trial. JAMA. 2006; 296:87-93.

 [PubMed Abstract] -
- 3. Larson AM, Polson J, Fontana RJ, Davern TJ, Lalani E, Hynan LS, Reisch JS, Schiødt FV, Ostapowicz G, Shakil AO, Lee WM; Acute Liver Failure Study Group. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology. 2005; 42:1364-72. [PubMed Abstract] -
- Wohlrab P, Boehme S, Kaun C, et al. Ropivacaine Activates Multiple Proapoptotic and Inflammatory Signaling Pathways That Might Subsume to Trigger Epidural-Related Maternal Fever. Anesth Analg. 2020;130:321-31.
 [PubMed Abstract] -
- 5. loannides SJ, Siebers R, Perrin K, et al. The effect of 1g of acetaminophen twice daily for 12 weeks on alanine transaminase levels--A randomized placebo-controlled trial. Clin Biochem. 2015;48:713-5. [PubMed Abstract] -
- Nguyen GC, Sam J, Thuluvath PJ. Hepatitis C is a predictor of acute liver injury among hospitalizations for acetaminophen overdose in the United States: a nationwide analysis. Hepatology. 2008;48:1336-41.
 [PubMed Abstract] -
- 7. Myers RP, Shaheen AA, Li B, Dean S, Quan H. Impact of liver disease, alcohol abuse, and unintentional ingestions on the outcomes of acetaminophen overdose. Clin Gastroenterol Hepatol. 2008;6:918-25. [PubMed Abstract] -
- 8. Dwyer JP, Jayasekera C, Nicoll A. Analgesia for the cirrhotic patient: a literature review and recommendations. J Gastroenterol Hepatol. 2014;29:1356-60.

 [PubMed Abstract] -
- Chandok N, Watt KD. Pain management in the cirrhotic patient: the clinical challenge. Mayo Clin Proc. 2010;85:451-8.
 [PubMed Abstract] -
- Bosilkovska M, Walder B, Besson M, Daali Y, Desmeules J. Analgesics in patients with hepatic impairment: pharmacology and clinical implications. Drugs. 2012;72:1645-69.
 [PubMed Abstract] -
- 11. Bauerlein DK, Williams AP, John PR. Optimizing Acetaminophen Use in Patients with Risk Factors for Hepatotoxicity: Reviewing Dosing Recommendations in Adults. Pain Med. 2021;22:1469-72. [PubMed Abstract] -
- 12. Rakoski M, Goyal P, Spencer-Safier M, Weissman J, Mohr G, Volk M. Pain management in patients with cirrhosis. Clin Liver Dis (Hoboken). 2018;11:135-140.



[PubMed Abstract] -

13. Risser A, Donovan D, Heintzman J, Page T. NSAID prescribing precautions. Am Fam Physician. 2009;80:1371-8.

[PubMed Abstract] -

14. Runyon BA. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. Hepatology. 2013;57:1651-3.

- 15. Riley TR, Smith JP. Preventive care in chronic liver disease. J Gen Intern Med. 1999;14:699-704. [PubMed Abstract] -
- 16. Piperno A, Vergani A, Malosio I, et al. Hepatic iron overload in patients with chronic viral hepatitis: role of HFE gene mutations. Hepatology. 1998;28:1105-9.

 [PubMed Abstract] -
- 17. Hézode C, Cazeneuve C, Coué O, et al. Liver iron accumulation in patients with chronic active hepatitis C: prevalence and role of hemochromatosis gene mutations and relationship with hepatic histological lesions. J Hepatol. 1999;31:979-84.

 [PubMed Abstract] -
- 18. D'Souza RF, Feakins R, Mears L, Sabin CA, Foster GR. Relationship between serum ferritin, hepatic iron staining, diabetes mellitus and fibrosis progression in patients with chronic hepatitis C. Aliment Pharmacol Ther. 2005;21:519-24.

 [PubMed Abstract] -
- 19. Metwally MA, Zein CO, Zein NN. Clinical significance of hepatic iron deposition and serum iron values in patients with chronic hepatitis C infection. Am J Gastroenterol. 2004;99:286-91. [PubMed Abstract] -
- 20. Riggio O, Montagnese F, Fiore P, et al. Iron overload in patients with chronic viral hepatitis: how common is it? Am J Gastroenterol. 1997;92:1298-1301.

 [PubMed Abstract] -
- 21. Martín-González C, Pelazas-González R, Fernández-Rodríguez C, et al. Ferritin and liver fibrosis among patients with chronic hepatitis C virus infection. J Trace Elem Med Biol. 2020;61:126542.

 [PubMed Abstract] -
- 22. de Pee S, Dary O. Biochemical indicators of vitamin A deficiency: serum retinol and serum retinol binding protein. J Nutr. 2002;132:2895S-2901S.

 [PubMed Abstract] -
- 23. Fallon MB, Boyer JL. Hepatic toxicity of vitamin A and synthetic retinoids. J Gastroenterol Hepatol. 1990;5:334-42.

 [PubMed Abstract] -
- 24. Kowalski TE, Falestiny M, Furth E, Malet PF. Vitamin A hepatotoxicity: a cautionary note regarding 25,000 IU supplements. Am J Med. 1994;97:523-8.

 [PubMed Abstract] -
- 25. Minuk GY, Kelly JK, Hwang WS. Vitamin A hepatotoxicity in multiple family members. Hepatology. 1988;8:272-5.



[PubMed Abstract] -

- 26. Weber FL Jr, Mitchell GE Jr, Powell DE, Reiser BJ, Banwell JG. Reversible hepatotoxicity associated with hepatic vitamin A accumulation in a protein-deficient patient. Gastroenterology. 1982;82:118-23. [PubMed Abstract] -
- 27. Stokes CS, Volmer DA, Grünhage F, Lammert F. Vitamin D in chronic liver disease. Liver Int. 2013; 33:338-52.

[PubMed Abstract] -

- 28. Backstedt D, Pedersen M, Choi M, Seetharam A. 25-Vitamin D levels in chronic hepatitis C infection: association with cirrhosis and sustained virologic response. Ann Gastroenterol. 2017;30:344-348. [PubMed Abstract] -
- 29. Rahman AH, Branch AD. Vitamin D for your patients with chronic hepatitis C? J Hepatol. 2013;58:184-9.

- 30. Gutierrez JA, Parikh N, Branch AD. Classical and emerging roles of vitamin D in hepatitis C virus infection. Semin Liver Dis. 2011;31:387-98.

 [PubMed Abstract] -
- 31. Bjelakovic M, Nikolova D, Bjelakovic G, Gluud C. Vitamin D supplementation for chronic liver diseases in adults. Cochrane Database Syst Rev. 2021;8:CD011564.

 [PubMed Abstract] -
- 32. Institute of Medicine of the National Academies. Report at a Glance, Report Brief: Dietary Feference Intakes for Calcium and Vitamin D. November 2010.

 [Institute of Medicine] -
- 33. Dawson-Hughes B, Mithal A, Bonjour JP, et al. IOF position statement: vitamin D recommendations for older adults. Osteoporos Int. 2010;21:1151-4.

 [PubMed Abstract] -
- 34. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96:1911-30. [PubMed Abstract] -
- 35. Recommendations abstracted from the American Geriatrics Society Consensus Statement on vitamin D for Prevention of Falls and Their Consequences. J Am Geriatr Soc. 2014;62:147-52. [PubMed Abstract] -
- 36. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357:266-81. [PubMed Abstract] -
- 37. Coon JT, Ernst E. Complementary and alternative therapies in the treatment of chronic hepatitis C: a systematic review. J Hepatol. 2004;40:491-500.

 [PubMed Abstract] -
- 38. Seeff LB, Curto TM, Szabo G, et al. Herbal product use by persons enrolled in the hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) Trial. Hepatology. 2008;47:605-12. [PubMed Abstract] -
- 39. Barnes PM, Powell-Griner E, McFann K, Nahin RL. Complementary and alternative medicine use among

HEPATITIS C ONLINE

adults: United States, 2002. Adv Data. 2004:1-19. [PubMed Abstract] -

40. Marzio DL, Fenkel JM. Complementary and alternative medications in hepatitis C infection. World J Hepatol. 2014;6:9-16.

[PubMed Abstract] -

41. Seeff LB. Herbal hepatotoxicity. Clin Liver Dis. 2007;11:577-96, vii. [PubMed Abstract] -

- 42. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012.

 [LiverTox] -
- 43. Ginseng. In: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet].

 Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012. [Last Updated Mar 14, 2018].

 [LiverTox] -
- 44. Park TY, Hong M, Sung H, Kim S, Suk KT. Effect of Korean Red Ginseng in chronic liver disease. J Ginseng Res. 2017;41:450-455.

 [PubMed Abstract] -
- 45. Tanaka K, Ikeda M, Nozaki A, et al. Lactoferrin inhibits hepatitis C virus viremia in patients with chronic hepatitis C: a pilot study. Jpn J Cancer Res. 1999;90:367-71.

 [PubMed Abstract] -
- 46. Okada S, Tanaka K, Sato T, et al. Dose-response trial of lactoferrin in patients with chronic hepatitis C. Jpn J Cancer Res. 2002;93:1063-9. [PubMed Abstract] -
- 47. Redwan el-RM, Tabll A. Camel lactoferrin markedly inhibits hepatitis C virus genotype 4 infection of human peripheral blood leukocytes. J Immunoassay Immunochem. 2007;28:267-77. [PubMed Abstract] -
- 48. Picard-Jean F, Bouchard S, Larivée G, Bisaillon M. The intracellular inhibition of HCV replication represents a novel mechanism of action by the innate immune Lactoferrin protein. Antiviral Res. 2014;111:13-22.

 [PubMed Abstract] -
- 49. Ueno H, Sato T, Yamamoto S, et al. Randomized, double-blind, placebo-controlled trial of bovine lactoferrin in patients with chronic hepatitis C. Cancer Sci. 2006;97:1105-10. [PubMed Abstract] -
- 50. Ishibashi Y, Takeda K, Tsukidate N, Miyazaki H, Ohira K, Dosaka-Akita H, Nishimura M. Randomized placebo-controlled trial of interferon alpha-2b plus ribavirin with and without lactoferrin for chronic hepatitis C. Hepatol Res. 2005;32:218-23.

 [PubMed Abstract] -
- 51. Sinopoli A, Isonne C, Santoro MM, Baccolini V. The effects of orally administered lactoferrin in the prevention and management of viral infections: A systematic review. Rev Med Virol. 2022;32:e2261. [PubMed Abstract] -
- 52. Fiore C, Eisenhut M, Krausse R, Ragazzi E, Pellati D, Armanini D, Bielenberg J. Antiviral effects of



Glycyrrhiza species. Phytother Res. 2008;22:141-8. [PubMed Abstract] -

53. Matsumoto Y, Matsuura T, Aoyagi H, et al. Antiviral activity of glycyrrhizin against hepatitis C virus in vitro. PLoS One. 2013;8:e68992.

[PubMed Abstract] -

54. Mumoli N, Cei M. Licorice-induced hypokalemia. Int J Cardiol. 2008;124:e42-4. [PubMed Abstract] -

55. Ottenbacher R, Blehm I. An Unusual Case of Licorice-Induced Hypertensive Crisis. S D Med. 2015;68:346-7, 349.

[PubMed Abstract] -

56. Licorice. In: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012. [Last Updated March 20, 2023].

[LiverTox] -

57. Verhoeven V, Lopez Hartmann M, Remmen R, Wens J, Apers S, Van Royen P. Red yeast rice lowers cholesterol in physicians - a double blind, placebo controlled randomized trial. BMC Complement Altern Med. 2013;13:178.

[PubMed Abstract] -

58. Gerards MC, Terlou RJ, Yu H, Koks CH, Gerdes VE. Traditional Chinese lipid-lowering agent red yeast rice results in significant LDL reduction but safety is uncertain - a systematic review and metaanalysis. Atherosclerosis. 2015;240:415-23.

[PubMed Abstract] -

59. Red Yeast Rice. In: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012. [Last Updated March 20, 2023].

[LiverTox] -

60. Bottiglieri T. S-Adenosyl-L-methionine (SAMe): from the bench to the bedside--molecular basis of a pleiotrophic molecule. Am J Clin Nutr. 2002;76:1151S-7S. [PubMed Abstract] -

- 61. Mora SI, García-Román I, Gómez-Ñañez I, García-Román R. Chronic liver diseases and the potential use of S-adenosyl-L-methionine as a hepatoprotector. Eur | Gastroenterol Hepatol. 2018;30:893-900. [PubMed Abstract] -
- 62. Feld JJ, Modi AA, El-Diwany R, et al. S-adenosyl methionine improves early viral responses and interferon-stimulated gene induction in hepatitis C nonresponders. Gastroenterology. 2011;140:830-9. [PubMed Abstract] -
- 63. Filipowicz M, Bernsmeier C, Terracciano L, Duong FH, Heim MH. S-adenosyl-methionine and betaine improve early virological response in chronic hepatitis C patients with previous nonresponse. PLoS One. 2010;5:e15492.

[PubMed Abstract] -

64. Anstee QM, Day CP. S-adenosylmethionine (SAMe) therapy in liver disease: A review of current evidence and clinical utility. J Hepatol 2012; 57:1097-1109. [PubMed Abstract] -



- 65. Sho Saiko To and Dai Saiko To. In: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012. Last Update Aug 15, 2020.

 [LiverTox] -
- 66. Hirayama C, Okumura M, Tanikawa K, Yano M, Mizuta M, Ogawa N. A multicenter randomized controlled clinical trial of Shosaiko-to in chronic active hepatitis. Gastroenterol Jpn. 1989;24:715-9. [PubMed Abstract] -
- 67. Oka H, Yamamoto S, Kuroki T, et al. Prospective study of chemoprevention of hepatocellular carcinoma with Sho-saiko-to (TJ-9). Cancer. 1995;76:743-9.

 [PubMed Abstract] -
- 68. Shimizu I. Sho-saiko-to: Japanese herbal medicine for protection against hepatic fibrosis and carcinoma. J Gastroenterol Hepatol. 2000;15 Suppl:D84-90.

 [PubMed Abstract] -
- 69. Itoh S, Marutani K, Nishijima T, Matsuo S, Itabashi M. Liver injuries induced by herbal medicine, syosaiko-to (xiao-chai-hu-tang). Dig Dis Sci. 1995;40:1845-8.

 [PubMed Abstract] -
- 70. Kamiyama T, Nouchi T, Kojima S, Murata N, Ikeda T, Sato C. Autoimmune hepatitis triggered by administration of an herbal medicine. Am J Gastroenterol. 1997;92:703-4. [PubMed Abstract] -
- 71. Matsuda R, Takahashi D, Chiba E, et al. [A case of drug induced hepatitis and interstitial pneumonia caused by a herbal drug, Dai-saiko-to]. Nihon Shokakibyo Gakkai Zasshi. 1997;94:787-91. [PubMed Abstract] -
- 72. Milk Thistle. In: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet].

 Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012. [Last Updated January 21, 2020].

 [LiverTox] -
- 73. Yang Z, Zhuang L, Lu Y, Xu Q, Chen X. Effects and tolerance of silymarin (milk thistle) in chronic hepatitis C virus infection patients: a meta-analysis of randomized controlled trials. Biomed Res Int. 2014;2014:941085.

 [PubMed Abstract] -
- 74. Polyak SJ, Oberlies NH, Pécheur EI, Dahari H, Ferenci P, Pawlotsky JM. Silymarin for HCV infection. Antivir Ther. 2013;18:141-7.

 [PubMed Abstract] -
- 75. Polyak S, Ferenci P, Pawlotsky JM. Hepatoprotective and antiviral functions of silymarin components in hepatitis C virus infection. Hepatology. 2013;57:1262-71.

 [PubMed Abstract] -
- 76. Fried MW, Navarro VJ, Afdhal N, et al. Effect of silymarin (milk thistle) on liver disease in patients with chronic hepatitis C unsuccessfully treated with interferon therapy: a randomized controlled trial. JAMA. 2012;308:274-82.

 [PubMed Abstract] -
- 77. Hawke RL, Schrieber SJ, Soule TA, et al. Silymarin ascending multiple oral dosing phase I study in

HEPATITIS C ONLINE

noncirrhotic patients with chronic hepatitis C. J Clin Pharmacol. 2010;50:434-49. [PubMed Abstract] -

- 78. Parés A, Planas R, Torres M, et al. Effects of silymarin in alcoholic patients with cirrhosis of the liver: results of a controlled, double-blind, randomized and multicenter trial. J Hepatol. 1998;28:615-21. [PubMed Abstract] -
- 79. Rainone F. Milk thistle. Am Fam Physician. 2005;72:1285-8. [PubMed Abstract] -
- 80. Venkataramanan R, Ramachandran V, Komoroski BJ, Zhang S, Schiff PL, Strom SC. Milk thistle, a herbal supplement, decreases the activity of CYP3A4 and uridine diphosphoglucuronosyl transferase in human hepatocyte cultures. Drug Metab Dispos. 2000;28:1270-3.

 [PubMed Abstract] -
- 81. St. John's Wort. In: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012. [Last Updated March 28, 2020].

 [LiverTox] -
- 82. Hypericum Depression Trial Study Group. Effect of Hypericum perforatum (St John's wort) in major depressive disorder: a randomized controlled trial. JAMA. 2002;287:1807-14. [PubMed Abstract] -
- 83. Lawvere S, Mahoney MC. St. John's wort. Am Fam Physician. 2005;72:2249-54. [PubMed Abstract] -
- 84. Jacobson JM, Feinman L, Liebes L, et al. Pharmacokinetics, safety, and antiviral effects of hypericin, a derivative of St. John's wort plant, in patients with chronic hepatitis C virus infection. Antimicrob Agents Chemother. 2001;45:517-24.

 [PubMed Abstract] -
- 85. Chrubasik-Hausmann S, Vlachojannis J, McLachlan AJ. Understanding drug interactions with St John's wort (Hypericum perforatum L.): impact of hyperforin content. J Pharm Pharmacol. 2019;71:129-38. [PubMed Abstract] -
- 86. Soleymani S, Bahramsoltani R, Rahimi R, Abdollahi M. Clinical risks of St John's Wort (Hypericum perforatum) co-administration. Expert Opin Drug Metab Toxicol. 2017;13:1047-62.

 [PubMed Abstract] -
- 87. Goldstein AL, Goldstein AL. From lab to bedside: emerging clinical applications of thymosin alpha 1. Expert Opin Biol Ther. 2009;9:593-608. [PubMed Abstract] -
- 88. Sherman KE, Sjogren M, Creager RL, et al. Combination therapy with thymosin alpha1 and interferon for the treatment of chronic hepatitis C infection: a randomized, placebo-controlled double-blind trial. Hepatology. 1998;27:1128-35.

 [PubMed Abstract] -
- 89. Andreone P, Gramenzi A, Cursaro C, et al. Thymosin-alpha 1 plus interferon-alpha for naive patients with chronic hepatitis C: results of a randomized controlled pilot trial. J Viral Hepat. 2004;11:69-73. [PubMed Abstract] -
- 90. Raymond RS, Fallon MB, Abrams GA. Oral thymic extract for chronic hepatitis C in patients previously



treated with interferon. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 1998;129:797-800.

[PubMed Abstract] -

91. Sherman KE. Thymosin alpha 1 for treatment of hepatitis C virus: promise and proof. Ann N Y Acad Sci. 2010;1194:136-40.

[PubMed Abstract] -

- 92. Setiawan VW, Wilkens LR, Lu SC, Hernandez BY, Le Marchand L, Henderson BE. Association of coffee intake with reduced incidence of liver cancer and death from chronic liver disease in the US multiethnic cohort. Gastroenterology. 2015;148:118-25; quiz e15.

 [PubMed Abstract] -
- 93. Hodge A, Lim S, Goh E, et al. Coffee Intake Is Associated with a Lower Liver Stiffness in Patients with Non-Alcoholic Fatty Liver Disease, Hepatitis C, and Hepatitis B. Nutrients. 2017;9:56.

 [PubMed Abstract] -
- 94. Freedman ND, Everhart JE, Lindsay KL, et al. Coffee intake is associated with lower rates of liver disease progression in chronic hepatitis C. Hepatology. 2009;50:1360-9.

 [PubMed Abstract] -
- 95. Khalaf N, White D, Kanwal F, et al. Coffee and Caffeine Are Associated With Decreased Risk of Advanced Hepatic Fibrosis Among Patients With Hepatitis C. Clin Gastroenterol Hepatol. 2015;13:1521-31.e3.

[PubMed Abstract] -

96. Jaruvongvanich V, Sanguankeo A, Klomjit N, Upala S. Effects of caffeine consumption in patients with chronic hepatitis C: A systematic review and meta-analysis. Clin Res Hepatol Gastroenterol. 2017 Feb:41:46-55.

[PubMed Abstract] -

- 97. Liu F, Wang X, Wu G, et al. Coffee Consumption Decreases Risks for Hepatic Fibrosis and Cirrhosis: A Meta-Analysis. PLoS One. 2015;10:e0142457.

 [PubMed Abstract] -
- 98. Freedman ND, Curto TM, Lindsay KL, Wright EC, Sinha R, Everhart JE; HALT-C TRIAL GROUP. Coffee consumption is associated with response to peginterferon and ribavirin therapy in patients with chronic hepatitis C. Gastroenterology. 2011;140:1961-9.

 [PubMed Abstract] -
- 99. Iqbal U, Jadeja RN, Khara HS, Khurana S. A Comprehensive Review Evaluating the Impact of Protein Source (Vegetarian vs. Meat Based) in Hepatic Encephalopathy. Nutrients. 2021;13:370. [PubMed Abstract] -
- 100. Milke García MP. Nutritional support in the treatment of chronic hepatic encephalopathy. Ann Hepatol. 2011;10 Suppl 2:S45-9. [PubMed Abstract] -
- 101. Ramírez MJ, Titos E, Clària J, Navasa M, Fernández J, Rodés J. Increased apoptosis dependent on caspase-3 activity in polymorphonuclear leukocytes from patients with cirrhosis and ascites. J Hepatol. 2004;41:44-8.

[PubMed Abstract] -

102. European Association for the Study of the Liver.. EASL Clinical Practice Guidelines on nutrition in



chronic liver disease. J Hepatol. 2019;70:172-93. [PubMed Abstract] -

- 103. Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology. 2014;60:715-35.

 [PubMed Abstract] -
- 104. Heymsfield SB, Wadden TA. Mechanisms, Pathophysiology, and Management of Obesity. N Engl J Med. 2017;376:254-266.

 [PubMed Abstract] -
- 105. Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol. 2018;15:11-20.

 [PubMed Abstract] -
- 106. Wang T, Xi Y, Raji A, et al. Overall and subgroup prevalence of non-alcoholic fatty liver disease and prevalence of advanced fibrosis in the United States: An updated national estimate in National Health and Nutrition Examination Survey (NHANES) 2011-2018. Ann Hepatol. 2024;29:101154.

 [PubMed Abstract] -
- 107. Rinella ME, Lazarus JV, Ratziu V, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. J Hepatol. 2023;79:1542-56.

 [PubMed Abstract] -
- 108. Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol. 2020;73:202-9. [PubMed Abstract] -
- 109. Phoolchund AGS, Khakoo SI. MASLD and the Development of HCC: Pathogenesis and Therapeutic Challenges. Cancers (Basel). 2024;16:259.

 [PubMed Abstract] -
- 110. Adinolfi LE, Gambardella M, Andreana A, Tripodi MF, Utili R, Ruggiero G. Steatosis accelerates the liver damage of chronic hepatitis C patients and correlates with specific genotypes and visceral adiposity. Hepatology. 2001;33:1358-64.

 [PubMed Abstract] -
- 111. Pekow JR, Bhan AK, Zheng H, Chung RT. Hepatic steatosis is associated with increased frequency of hepatocellular carcinoma in patients with hepatitis C-related cirrhosis. Cancer. 2007;109:2490-6. [PubMed Abstract] -
- 112. Diehl AM, Day C. Cause, Pathogenesis, and Treatment of Nonalcoholic Steatohepatitis. N Engl J Med. 2017;377:2063-2072. [PubMed Abstract] -
- 113. Kim MN, Han K, Yoo J, Hwang SG, Ahn SH. Increased risk of hepatocellular carcinoma and mortality in chronic viral hepatitis with concurrent fatty liver. Aliment Pharmacol Ther. 2022;55:97-107. [PubMed Abstract] -
- 114. Kim MN, Han K, Yoo J, Hwang SG, Zhang X, Ahn SH. Diabetic MAFLD is associated with increased risk of hepatocellular carcinoma and mortality in chronic viral hepatitis patients. Int J Cancer. 2023;153:1448-58.

 [PubMed Abstract] -



115. Eslam M, Aparcero R, Kawaguchi T, Del Campo JA, Sata M, Khattab MA, Romero-Gomez M. Metaanalysis: insulin resistance and sustained virological response in hepatitis C. Aliment Pharmacol Ther. 2011;34:297-305.

- 116. Bressler BL, Guindi M, Tomlinson G, Heathcote J. High body mass index Is an independent risk factor for nonresponse to antiviral treatment in chronic hepatitis C. Hepatology. 2003;38:639-44. [PubMed Abstract] -
- 117. Thomopoulos KC, Theocharis GJ, Tsamantas AC, et al. Liver steatosis is an independent risk factor for treatment failure in patients with chronic hepatitis C. Eur J Gastroenterol Hepatol. 2005;17:149-53. [PubMed Abstract] -
- 118. Fox DS, McGinnis JJ, Tonnu-Mihara IQ, McCombs JS. Comparative treatment effectiveness of direct acting antiviral regimens for hepatitis C: Data from the Veterans administration. J Gastroenterol Hepatol. 2017;32:1136-1142.

 [PubMed Abstract] -
- 119. Rigamonti C, Mottaran E, Reale E, et al. Moderate alcohol consumption increases oxidative stress in patients with chronic hepatitis C. Hepatology. 2003;38:42-9.

 [PubMed Abstract] -
- 120. Poynard T, Bedossa P, Opolon P. Lancet. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet. 1997;349:825-32. [PubMed Abstract] -
- 121. Hézode C, Lonjon I, Roudot-Thoraval F, Pawlotsky JM, Zafrani ES, Dhumeaux D. Impact of moderate alcohol consumption on histological activity and fibrosis in patients with chronic hepatitis C, and specific influence of steatosis: a prospective study. Aliment Pharmacol Ther. 2003;17:1031-7. [PubMed Abstract] -
- 122. Ikeda K, Saitoh S, Koida I, et al. A multivariate analysis of risk factors for hepatocellular carcinogenesis: a prospective observation of 795 patients with viral and alcoholic cirrhosis. Hepatology. 1993;18:47-53.

 [PubMed Abstract] -
- 123. Trickey A, Ingle SM, Boyd A, et al. Contribution of alcohol use in HIV/hepatitis C virus co-infection to all-cause and cause-specific mortality: A collaboration of cohort studies. J Viral Hepat. 2023;30:775-86. [PubMed Abstract] -
- 124. Hsu CC, Kowdley KV. The Effects of Alcohol on Other Chronic Liver Diseases. Clin Liver Dis. 2016;20:581-94. [PubMed Abstract] -
- 125. Monto A, Patel K, Bostrom A, Pianko S, Pockros P, McHutchison JG, Wright TL.Risks of a range of alcohol intake on hepatitis C-related fibrosis. Hepatology. 2004;39(3):826-34. [PubMed Abstract] -
- 126. Dawson DA, Grant BF, Stinson FS, Zhou Y. Effectiveness of the derived Alcohol Use Disorders Identification Test (AUDIT-C) in screening for alcohol use disorders and risk drinking in the US general population. Alcohol Clin Exp Res. 2005;29:844-54.

 [PubMed Abstract] -



- 127. Tsui JI, Williams EC, Green PK, Berry K, Su F, Ioannou GN. Alcohol use and hepatitis C virus treatment outcomes among patients receiving direct antiviral agents. Drug Alcohol Depend. 2016;169:101-9. [PubMed Abstract] -
- 128. McMahon BJ, Bruden D, Bruce MG, et al. Adverse outcomes in Alaska Natives who recovered from or have chronic hepatitis C infection. Gastroenterology. 2010;138:922-31.

 [PubMed Abstract] -
- 129. Hézode C, Roudot-Thoraval F, Nguyen S, et al. Daily cannabis smoking as a risk factor for progression of fibrosis in chronic hepatitis C. Hepatology. 2005;42:63-71.

 [PubMed Abstract] -
- 130. Hézode C, Zafrani ES, Roudot-Thoraval F, et al. Daily cannabis use: a novel risk factor of steatosis severity in patients with chronic hepatitis C. Gastroenterology. 2008;134(2):432-9. [PubMed Abstract] -
- 131. Ishida JH, Peters MG, Jin C, Louie K, Tan V, Bacchetti P, Terrault NA. Influence of cannabis use on severity of hepatitis C disease. Clin Gastroenterol Hepatol. 2008;6:69-75.

 [PubMed Abstract] -
- 132. Farooqui MT, Khan MA, Cholankeril G, et al. Marijuana is not associated with progression of hepatic fibrosis in liver disease: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2019;31:149-56.

 [PubMed Abstract] -
- 133. Brunet L, Moodie EE, Rollet K, et al. Marijuana smoking does not accelerate progression of liver disease in HIV-hepatitis C coinfection: A longitudinal cohort analysis. Clin Infect Dis. 2013;57:663-70. [PubMed Abstract] -
- 134. Carrieri MP, Serfaty L, Vilotitch A, et al. Cannabis Use and Reduced Risk of Insulin Resistance in HIV-HCV Infected Patients: A Longitudinal Analysis (ANRS CO13 HEPAVIH). Clin Infect Dis. 2015;61:40-8. [PubMed Abstract] -
- 135. Costiniuk CT, Brunet L, Rollet-Kurhajec KC, et al. Tobacco Smoking Is Not Associated With Accelerated Liver Disease in Human Immunodeficiency Virus-Hepatitis C Coinfection: A Longitudinal Cohort Analysis. Open Forum Infect Dis. 2016;3:ofw050.

 [PubMed Abstract] -
- 136. Dev A, Patel K, Conrad A, Blatt LM, McHutchison JG. Relationship of smoking and fibrosis in patients with chronic hepatitis C. Clin Gastroenterol Hepatol. 2006;4:797-801.

 [PubMed Abstract] -
- 137. Hézode C, Lonjon I, Roudot-Thoraval F, Mavier JP, Pawlotsky JM, Zafrani ES, Dhumeaux D. Impact of smoking on histological liver lesions in chronic hepatitis C. Gut. 2003;52:126-9.

 [PubMed Abstract] -
- 138. Pessione F, Degos F, Marcellin P, et al. Effect of alcohol consumption on serum hepatitis C virus RNA and histological lesions in chronic hepatitis C. Hepatology. 1998;27:1717-22. [PubMed Abstract] -
- 139. Pessione F, Ramond MJ, Njapoum C, et al. Cigarette smoking and hepatic lesions in patients with chronic hepatitis C. Hepatology. 2001;34:121-5.

 [PubMed Abstract] -



140. Tsochatzis E, Papatheodoridis GV, Manolakopoulos S, Tiniakos DG, Manesis EK, Archimandritis AJ. Smoking is associated with steatosis and severe fibrosis in chronic hepatitis C but not B. Scand J Gastroenterol. 2009;44:752-9.

[PubMed Abstract] -

141. Abdel-Rahman O, Helbling D, Schöb O, et al. Cigarette smoking as a risk factor for the development of and mortality from hepatocellular carcinoma: An updated systematic review of 81 epidemiological studies. J Evid Based Med. 2017;10:245-254.

[PubMed Abstract] -

142. Koh WP, Robien K, Wang R, Govindarajan S, Yuan JM, Yu MC. Smoking as an independent risk factor for hepatocellular carcinoma: the Singapore Chinese Health Study. Br J Cancer. 2011 Oct 25;105:1430-5.

[PubMed Abstract] -

143. Marrero JA, Fontana RJ, Fu S, Conjeevaram HS, Su GL, Lok AS. Alcohol, tobacco and obesity are synergistic risk factors for hepatocellular carcinoma. J Hepatol 2005; 42:218-24. [PubMed Abstract] -

References

Bruggmann P, Dampz M, Gerlach T, Kravecz L, Falcato L. Treatment outcome in relation to alcohol consumption during hepatitis C therapy: an analysis of the Swiss Hepatitis C Cohort Study. Drug Alcohol Depend. 2010;110:167-71.
 [PubMed Abstract] -

 Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018;67:328-57.

[PubMed Abstract] -

- De Luca L, De Angelis C, Fagoonee S, Di Bella S, Rizzetto M, Pellicano R. Is smoking a prognostic factor in patients with chronic hepatitis C? Minerva Gastroeterol Dietol 2009; 55:139-43.
 [PubMed Abstract] -
- García-Álvarez M, Pineda-Tenor D, Jiménez-Sousa MA, Fernández-Rodríguez A, Guzmán-Fulgencio M, Resino S. Relationship of vitamin D status with advanced liver fibrosis and response to hepatitis C virus therapy: A meta-analysis. Hepatology. 2014;60:1541-50.
 [PubMed Abstract] -
- Kitson MT, Dore GJ, George J, et al. Vitamin D status does not predict sustained virologic response or fibrosis stage in chronic hepatitis C genotype 1 infection. J Hepatol. 2013;58:467-72.
 [PubMed Abstract] -
- Patsenker E, Sachse P, Chicca A, et al. Elevated levels of endocannabinoids in chronic hepatitis C may modulate cellular immune response and hepatic stellate cell activation. Int J Mol Sci. 2015;16:7057-76.
 [PubMed Abstract] -
- Pattullo V, Duarte-Rojo A, Soliman W, V, et al. A 24-week dietary and physical activity lifestyle intervention reduces hepatic insulin resistance in the obese with chronic hepatitis C. Liver Int. 2013;33:410-9.



- Riley TR 3rd, Smith JP. Ibuprofen-induced hepatotoxicity in patients with chronic hepatitis C: a case series. Am J Gastroenterol. 1998;93:1563-5.
 [PubMed Abstract] -
- Rinella ME. Nonalcoholic fatty liver disease: a systematic review. JAMA. 2015;313:2263-73. [PubMed Abstract] -
- Ruhl CE, Everhart JE. Coffee and tea consumption are associated with a lower incidence of chronic liver disease in the United States. Gastroenterology. 2005;129:1928-36.
 [PubMed Abstract] -
- Russell M, Pauly MP, Moore CD, et al. The impact of lifetime alcohol use on hepatitis C treatment outcomes in privately insured members of an integrated health care plan. Hepatology. 2012;56:1223-30.