

## Hepatitis C

Up to 4 million Americans are chronically infected with the hepatitis C virus. About 20 percent of these people will develop cirrhosis of the liver, possibly followed by liver cancer. Hepatitis C is the most common cause of liver transplant in the United States.

Hepatitis C is an insidious viral disease because most people are unaware of their initial infection. Instead, the acute phase usually passes with minimal symptoms before turning into chronic hepatitis C infection. Many people have the disease for decades before it is diagnosed. Often people are diagnosed with chronic hepatitis C as a result of blood work performed for other medical conditions.

Chronic hepatitis C is dangerous because the virus causes high levels of free radicals to form in the liver. These free radicals put serious oxidative stress on the liver, which depletes protective antioxidants in the liver and eventually kills the liver cells. The disease is characterized by periods of fluctuating liver damage, with flare-ups of acute hepatitis over the course of the infection. Over time, this steady attack on the liver causes scar tissue (fibrosis), which can lead to cirrhosis if left untreated.

The value of antioxidant therapy in hepatitis C is supported by an extensive body of medical literature, yet antioxidant therapy is still not part of the standard care for people with chronic hepatitis C. It is imperative that people with chronic hepatitis C infection learn about nutrients that support a healthy liver and enhance the effectiveness of prescription drugs used to treat the disease.

### IRON'S ROLE IN HEPATITIS C INFECTION

Hepatitis C inflicts most of its damage by latching onto molecules of iron, resulting in free-radical damage to liver cells. In turn, the liver becomes inflamed, which can lead to the formation of scar tissue (fibrosis). If left unchecked, this steady damage will result in cirrhosis or liver cancer.

About 30 percent of people with hepatitis C have very high iron levels. Reduction of serum iron has been shown to normalize liver enzyme levels, which are elevated during periods of active liver damage (Fong TL et al 1998). Iron depletion therapy has also been shown to improve the response to conventional medicines used to treat hepatitis (Fargion S et al 1997). The only effective way to decrease serum iron is to have an iron loss, as occurs when donating blood. Hepatitis C patients cannot donate blood for common use, but their blood can still be removed, although it must be discarded.

Serum ferritin is a measure of the amount of stored iron and is used to guide therapy. A serum ferritin value between 30 and 80 ng/dL is optimal. Many hepatitis C patients have serum ferritin values in excess of 300 ng/dL.

Despite substantial scientific evidence, however, few physicians implement iron-depletion therapy before beginning antiviral therapy. This partially accounts for the high failure rate of conventional drugs in eradicating the virus (Boucher E et al 1997; Martin-Vivaldi R et al 1997; Tsai NC et al 1997).

### THE PHASES OF HEPATITIS C INFECTION

Hepatitis infection usually progresses in a predictable and slow fashion. About six weeks after exposure to the virus, people enter the acute phase of infection. This stage of illness is usually dismissed by the patient because it passes with very few, if any, signs or symptoms. At this point, the body has usually not even begun to manufacture antibodies to the virus, so a blood test may not reveal clues to infection.

If blood tests were to be done during the early stages of acute infection, they might show elevated serum alanine aminotransferase (ALT), a liver enzyme that rises in response to increased oxidative stress in the liver (Hoofnagle JH 1997; Iwasaki M et al 2002), or a slight elevation of bilirubin, but usually not enough to cause noticeable jaundice (yellowing of the skin). Approximately 75 percent of acute hepatitis C cases have no observable jaundice (Esteban JI et al 1990). If the illness is detected at this stage, it is usually during routine blood testing for some other condition or prior to a medical procedure. Elevated levels of ALT would alert a physician to a possible infection with hepatitis C.

After the acute phase is over, at least 70 percent of patients will develop chronic hepatitis C. This infection progresses very slowly and is marked by episodes of acute hepatitis characterized by liver inflammation and elevated ALT. Although the disease is transmittable at this time through blood, people may not recognize their infection for up to 20 years. Eventually, however, nonspecific symptoms such as fatigue usually prompt the patient to visit a physician. Symptoms even at this stage are often very mild, and laboratory findings consist of only mild elevations of the liver enzymes ALT and aspartate aminotransferase (AST).

If hepatitis C is suspected, a hepatitis screen should be ordered. The disease can be diagnosed by the presence of antibodies for hepatitis C or by the direct presence of the virus or viral products in the blood. If the screen is positive and ALT levels are elevated, a liver biopsy is indicated. The findings of the liver biopsy will be used to guide treatment; liver biopsy is not used to diagnose hepatitis C.

Once chronic hepatitis C is diagnosed, treatment will begin. The goal of conventional treatment is to prevent progression of the disease by reducing the viral load in the blood. It is also crucial to reduce oxidative stress in the liver by supporting healthy antioxidant levels and reducing iron. After the initial 20-year period, more advanced liver disease begins to develop, eventually possibly leading to cirrhosis and liver failure (Jankovic S 1999; Amarapurkar D 2000).

Two subsets of patients have a much more rapid course: people with alcoholic liver disease and those who have concomitant infection with HIV. Hepatitis C in the presence of alcoholic liver disease or HIV tends to be severe and progresses more rapidly than hepatitis C infection alone. Patients who use alcohol, which is toxic to the liver, may experience a particularly rapid progression of the disease. Because of this, it is imperative that all people with hepatitis C stop use of alcohol.

Even in the absence of ongoing alcohol use or HIV infection, hepatitis C may not follow its typically slow course. Why a more rapid progression occurs in some people is not known. The possibility of such rapid progression makes it especially important to monitor the disease on an ongoing basis and to obtain a liver biopsy at initial presentation.

Hepatitis C is a leading cause of liver cancer, which occurs in 1 to 6 percent of patients with chronic hepatitis C (Di Bisceglie AM 1997). Liver cancer occurs only in patients who have developed cirrhosis and have an ongoing inflammation. Liver cancer is to be suspected if the following symptoms develop in someone who has chronic hepatitis C: sudden worsening of the symptoms of cirrhosis, such as pronounced fatigue, jaundice, and ascites (accumulation of fluid in the abdomen), and possibly pain in the right upper quadrant of the abdomen.

Liver enzymes, including alkaline phosphatase, are usually very high when liver cancer occurs, and ultrasound or computed tomography scan of the abdomen reveals a mass within the liver. Liver biopsy of the mass confirms a diagnosis of liver cancer. Patients with liver cancer have a limited life span regardless of treatment.

## HOW HEPATITIS C VIRUS IS ACQUIRED AND TRANSMITTED

The virus is transmitted via exposure to blood or blood products infected with the hepatitis C virus. Blood transfusions occurring before 1992 are a known risk factor for the development of hepatitis C. By far the most common method of infection is the sharing of needles during intravenous (IV) drug abuse. The risk of transmission of hepatitis C in the United States from blood that has tested negative for hepatitis C antibodies is less than 1 in 103,000 transfused units (Lauer GM et al 2001).

In health-related professions, infected needle sticks are a possible exposure route. However, hepatitis C is no more frequent in healthcare workers than in the general population. The rate of transmission of the virus to healthcare workers from blood known to be infected with hepatitis C ranges between zero and 10 percent (Hernandez ME et al 1992; Mitsui T et al 1992). The CDC recommends frequent testing for hepatitis C in hospital personnel exposed via needle sticks (CDC 2003).

Perinatal transmission during birth is possible but rare and is thought to occur only in mothers having very high viral titers, such as those who also have HIV infection. The United States Public Health Service has estimated that perinatal transmission accounts for about 6 percent of cases of hepatitis C. Breastfeeding does not increase the risk of transmission (Dienstag JL 1997).

Other possible, although as yet unproven, risk factors for transmitting the hepatitis C virus include body piercing, tattooing, and sharing contaminated household items such as toothbrushes, razor blades, and nail clippers.

**Is hepatitis C a sexually transmitted disease?** Initially, it was thought that the virus might be sexually transmitted with a very low frequency because some people living in the same household were both found to be hepatitis C positive. These studies are difficult to interpret, however, because lifestyle factors, such as drug use and the possibility of multiple sexual partners confound the data. Perhaps the most reliable studies come from Saudi Arabia, where cultural behaviors are more restrictive. In one study (al-Faleh FZ et al 1995), no spouse of a participant with hepatitis C was infected.

An Italian study looked at women who had been infected with hepatitis C via blood transfusions (Sachithanandan S et al 1997). The authors concluded that their data suggested a “zero female to male sexual transmission rate of hepatitis C.” A similar study using blood products was conducted in Finland (Kolho E et al 1991). According to researchers, the results showed that “even though about 10 percent of people with reported cases of acute hepatitis C in the United States report a history of potential sexual exposure, sexual transmission is negligible in sex-partner studies” (Dienstag JL 1997).

However, epidemiological studies suggest that the rate of sexual transmission increases with traumatic intercourse or with the

presence of genital ulcers or breaks in the mucosal barrier. Sexual transmission of hepatitis C is thought to be the method of transmission in less than 3 percent of cases (Thomas DL 2001).

## CONVENTIONAL TREATMENT OF HEPATITIS C

The standard of care for chronic hepatitis C infection is combination therapy of pegylated interferon alfa-2b and ribavirin.

Pegylated interferon, given once weekly, is much more convenient to the patient than standard interferon, which was originally used to treat hepatitis C and is given three times a week. Pegylated interferon also offers the advantage of delivering the drug at a more even rate since it is absorbed slowly. Liver cancer is less common in patients who have been treated with interferon, even if the virus is not eradicated and they have a persistently positive hepatitis C-RNA count in their blood, which indicates the presence of high viral levels of hepatitis C (Bailon P et al 2001; Reddy KR et al 2001).

Interferon is typically administered in 24- or 48-week courses, once weekly, in combination therapy with ribavirin. Ribavirin, a broad-spectrum antiviral agent used against hepatitis C and other viral illnesses, has little effect against hepatitis C when used alone. However, when ribavirin is combined with interferon, the response rate is doubled. The standard dosage regimen for ribavirin is 800 to 1200 mg daily administered orally for six months (McHutchinson JG et al 1998; Christie JM et al 1999).

While these drugs have been shown to work, they nevertheless produce relatively low response rates. Pegylated interferon has about a 62 percent initial response (negative hepatitis C-RNA viral copy count) and about a 40 percent sustained response (negative hepatitis C-RNA after treatment).

Interferon should not be taken by patients who currently use alcohol or intravenous drugs or by patients with a current or previous severe psychiatric disorder, such as psychosis, bipolar disease, or major depression; low platelets or white blood cells; symptomatic heart disease; decompensated cirrhosis; uncontrolled seizures; or transplanted organ (other than the liver). Pregnancy should be prevented during treatment with any interferon drug. Interferon therapy should probably not be prescribed for anyone with an autoimmune disorder or uncontrolled diabetes.

Depression is fairly common in people taking interferon. It can usually be controlled with medicines such as selective serotonin reuptake inhibitors (e.g., Prozac® or Zoloft®). Flu-like symptoms of muscle aches and weight loss are also seen with interferon therapy, and some persons feel as though they have the flu the entire time they are taking interferon. Several studies state that side effects from pegylated interferon may be somewhat less severe than from regular interferon. Viral replication can occur during the repeated trough levels of drug in the bloodstream (Fried MW et al 2002; Sharieff KA et al 2002).

Ribavirin should not be taken by pregnant women or anyone with renal insufficiency, anemia, hemoglobinopathies, or severe heart disease. It should probably not be taken by people with uncontrolled hypertension and ischemic heart disease.

Ribavirin is teratogenic, meaning it causes fetal malformations. Therefore, contraception is mandatory for people taking ribavirin. Severe hemolytic anemia can also occur as a side effect of ribavirin. Blood counts will be monitored regularly during therapy. This type of anemia disappears after cessation of ribavirin. In particular, people with coronary artery disease, severe pulmonary disease, and kidney disorders must be closely monitored for ribavirin-induced anemia and kidney toxicity.

Throughout therapy, physicians will monitor the levels of liver enzymes, antibodies to the virus, and the virus itself in the bloodstream. These tests can help measure the effectiveness of treatment.

**Protecting against ribavirin-induced anemia.** Hemolytic anemia can result from the use of ribavirin in about 10 percent of cases. Folic acid and vitamin B12 (as methylcobalamin) may protect against ribavirin-induced anemia. The methylation-enhancing effects of both folic acid and vitamin B12 will also improve the liver-protecting effectiveness of S-adenosyl-L-methionine (SAME) (Bottiglieri T et al 1994; Swain RA et al 1997). Serum ferritin levels are closely monitored during interferon and ribavirin therapy to ensure that iron levels stay within the normal range. Iron supplements are to be taken only under direction of a healthcare provider.

**The presence of other liver disorders.** In patients with decompensating (end-stage) cirrhosis, who may not respond to interferon therapy, or who have not responded to standard hepatitis C therapy, liver transplantation is the next option. Patients with hepatitis C who have a liver transplant have about the same one-year and five-year rates of survival as patients with other diagnoses leading to liver transplants (Charlton M 2001).

Another viral infection of the liver in the presence of hepatitis C could be devastating. People with hepatitis C should be vaccinated against hepatitis A and hepatitis B so that they become immune—assuming, of course, that they have never had hepatitis A or B.

## NATURAL THERAPIES

Conventional hepatitis C therapy focuses on reducing the viral load through the use of pegylated interferon and ribavirin. While this mode of therapy may be effective in reducing the viral count, it does nothing to address the ongoing liver damage caused by the hepatitis C virus. During hepatitis C infection, the liver is besieged with free radicals that consume internal antioxidants and eventually kill liver cells. (These dead cells release liver enzymes into the blood, which explains why monitoring liver enzyme levels is valuable.)

There is some controversy surrounding therapies that are designed to lower liver enzyme levels. Levels of liver enzymes are not necessarily predictive of viral activity or viral load. However, reducing liver enzymes may provide a verifiable way of reducing liver damage.

**Ursodeoxycholic acid.** Ursodeoxycholic acid is a naturally occurring bile acid found in small quantities in the liver. A synthetic form known as ursodiol helps dissolve gallstones in those who cannot have gallbladder surgery or who do not need surgery. Ursodiol has low liver toxicity. When taken as a medication, it replaces some of the more toxic liver bile salts. In research related to hepatitis C, ursodiol in combination with licorice extract has helped normalize transaminase levels in hepatitis C patients who are resistant to interferon (Tsubota A et al 1999).

In an earlier study, researchers tested 91 patients (47 males and 44 females) with chronic hepatitis C liver disease. Patients were randomly assigned to receive ursodiol (450 mg) at bedtime for six months (44 patients) or no treatment (47 patients). No relevant side effects were reported. Researchers found that ursodiol was able to significantly reduce serum ALT and gamma-glutamyltransferase (GGT) levels. These results led researchers to hypothesize that ursodiol might be an alternative for patients who do not respond to interferon or who relapse once interferon is discontinued (Puoti C et al 1993).

**Polyenylphosphatidylcholine.** Polyenylphosphatidylcholine (PPC) is a naturally occurring phospholipid found throughout the body, particularly in cell membranes. It has been demonstrated that orally administered PPC can be incorporated into the liver cell membrane to enhance its integrity. PPC assists the cell membrane in determining what is safe to enter the cell as nutrients and what should be hampered from entry, such as toxins. Hepatocytes (liver cells) are prime examples of cells needing the protection of a vigilant cell membrane (Oneta CM et al 1999). In patients with hepatitis C and in animal models of hepatitis, PPC has been shown to reduce levels of liver enzymes (Lieber CS 2004).

Evidence of disease activity was also significantly reduced in chronic active hepatitis patients on phospholipid therapy (Holoman J et al 1998). Liver cell regeneration was greater in those receiving PPC. Because of its multifaceted nature, orally administered PPC, a constituent of lecithin, may have the potential of arresting and reversing liver damage (Abakumova OI et al 1996).

PPC can also enhance the bioavailability of various herbs, drugs, and nutrients, including silibinin, vitamin E, and interferon (Werner C et al 1990; Reizis AR et al 1992).

When PPC is administered in conjunction with interferon, there is an increase in both their therapeutic values. In one study, patients with hepatitis C were given interferon (3 million IU, three times a week for 24 weeks) and either placebo or PPC (1.8 g daily). Researchers measured ALT levels and defined a response as a reduction of at least 50 percent. They found 71 percent of study participants taking PPC experienced a 50 percent drop in ALT, compared to 51 percent on placebo (Niederau C et al 1998).

In another study, a complex of silymarin (milk thistle) and PPC was given to people with chronic active hepatitis. After seven days, 20 patients observed decreases in AST, ALT, and GGT. In addition, bilirubin and alkaline phosphatase levels dropped.

**Selenium.** Numerous studies have documented low levels of selenium in hepatitis C patients, and when used in conjunction with other antioxidants, it has been shown to reduce oxidative stress in the liver. The level of selenium depletion appears to correspond to disease severity: the more advanced the liver damage, the greater the degree of depletion. One study found that cirrhotic hepatitis C patients had significantly lower levels of selenium, glutathione, and vitamins A, C, and E than noncirrhotic patients and that all hepatitis C patients had lower levels of these antioxidants than age-matched healthy controls (Jain SK et al 2002). Another study examined untreated hepatitis C patients and found that levels of selenium and zinc were significantly reduced and overall antioxidant status was lower in hepatitis C patients than in healthy controls (Ko WS et al 2005).

## BOOSTING LIVER GLUTATHIONE LEVELS

Glutathione is the most important antioxidant used and manufactured by the liver. It kills bacterial invaders, acts as a cellular detoxifier, and helps prevent damage from free radicals. In patients with hepatitis C, particularly those who are HIV positive, a systemic depletion of glutathione is observed, especially in the liver. This depletion may be a factor underlying the resistance to interferon therapy and a biological basis for supplementing with the following nutrients that raise glutathione levels (Moriya K et al 2001):

- **N-acetyl-cysteine.** N-acetyl-cysteine (NAC) is derived from L-cysteine, a conditionally essential amino acid. NAC is more efficiently absorbed and also acts as an antioxidant.
- **S-adenosyl-L-methionine.** S-adenosyl-L-methionine (SAME) is an effective antidepressant that also helps regenerate normal liver function by increasing glutathione levels and decreasing the activity of free radicals. It is one of the most important liver-protecting substances in the body.
- **Lipoic acid.** This acid is used by almost every tissue in the body as a free-radical fighter. It also helps regenerate other essential antioxidants and acts as a metal chelator.
- **Whey protein isolate.** This protein boosts glutathione levels and improves the functioning of the immune system. The fact that hepatitis C often becomes active in people after they reach the age of 40 indicates that age-associated immune decline plays an important role in the progression of the disease.

## REDUCING DAMAGE FROM FREE RADICALS

In addition to supplements that boost glutathione, broad-spectrum antioxidant supplementation will help protect the liver against damage from free radicals. Recent trials have examined hepatitis C therapy with various antioxidants, including glycyrrhizin (from licorice extract), silymarin, vitamin C, lipoic acid, glutathione, and vitamin E. One study, which enrolled 50 hepatitis C patients, assigned patients randomly to one of these antioxidant groups for 20 weeks of treatment. Antioxidant therapy resulted in favorable scores for liver enzyme levels, virus RNA levels, or liver biopsy scores in almost half the patients. Normalization of liver enzymes occurred in 44 percent of patients who had elevated ALT levels before treatment. The treatment was well tolerated among all patients, leading the authors to conclude that multi-antioxidative treatment was beneficial in hepatitis C (Melhem A et al 2005).

In another study, a combination therapy of vitamin C and vitamin E was tested for its ability to protect the ratio of anti-inflammatory eicosapentaenoic acid (EPA) to pro-inflammatory arachidonic acid. Researchers found that these two vitamins protected EPA in the liver of people who were on combination interferon/ribavirin therapy, which suggested that these antioxidants might help boost the effectiveness of combination therapy (Murakami Y et al 2006).

Finally, in a study of patients who were candidates for liver transplant because of severe complications of hepatitis C, a research team examined the effectiveness of a combination treatment of lipoic acid, silymarin, and selenium. These nutrients were chosen because they protect the liver from oxidative damage, boost the levels of other antioxidants, and interfere with viral replication. At the end of the study, none of the three patients followed had undergone liver transplant. Instead, they had "recovered quickly and their laboratory values remarkably improved" (Berkson BM 1999).

## LIVER-PROTECTING NUTRIENTS

Silymarin and its chief active ingredient, silibinin, are derived from milk thistle, a member of the daisy family. Both substances help prevent toxic liver damage and help the liver regenerate after damage. Silymarin and silibinin actually accelerate the rate of protein synthesis in the liver, leading to faster cell regeneration (Sonnenbichler J et al 1984, 1986a, 1986b; Valenzuela A et al 1994). Silymarin has produced a reduction of liver enzyme levels in hepatitis C patients (Mayer KE et al 2005).

Some clinicians have found that a combination of silymarin and silibinin, PPC, SAME, selenium, and several glutathione-boosting supplements not only improves outcomes of hepatitis C patients who are treated, but because it produces fewer side effects than conventional antiviral therapy (interferon and ribavirin), also decreases the patient dropout rate.

Long-term use of licorice root extract (glycyrrhizin) has been shown to be helpful in preventing inflammation, liver cirrhosis, and hepatocellular carcinoma in Japanese hepatitis C patients (Guyton KZ et al 2002; Kumada H 2002). However, licorice flavoring is not effective. A possible side effect associated with ingestion of large amounts of licorice is hypertension. Therefore, blood pressure should be monitored regularly if one is taking licorice root.

## REDUCING IRON STORES

Elevated serum iron levels are often found in people with hepatitis C and cause further oxidative damage to the liver. Certain

nutritional supplements have evidence of reducing serum iron levels. To help keep serum iron levels in the low normal range of 30 to 80 ng/dL, high doses of green tea polyphenols and high-allylic garlic may be beneficial.

Lactoferrin, a subfraction of whey protein, may be especially beneficial as an adjunctive treatment for serum iron overload in hepatitis patients. Lactoferrin is a potent antioxidant, antiviral agent, and scavenger of free iron. In addition, lactoferrin is directly involved in the upregulation of natural killer cell activity, making it a natural modulator of immune function (Yi M et al 1997; Ikeda M et al 1998, 2000). As an immune booster, lactoferrin has been shown to work synergistically with interferon to reduce the viral load (Ishii K et al 2003).

Taking 300 mg of elemental calcium can reduce iron absorption by as much as 50 percent. When eating iron-rich foods, hepatitis C patients should consider taking a high-potency calcium supplement at the same time (Hallberg L et al 1991).

## LIFE EXTENSION FOUNDATION RECOMMENDATIONS

Some herbs are metabolized in the liver and can be toxic to it, especially in high doses. The following herbal products have demonstrated liver toxicity: germander, comfrey, chaparral leaf, ma huang, pennyroyal, skullcap, and mistletoe. If one desires to use any of these herbal products, it is advisable to do so under the care of a physician and with careful monitoring of liver enzymes and hepatitis C viral counts (Harvey J et al 1981; Gossrau R et al 1990).

Hepatitis C latches on to iron to inflict free-radical damage on liver cells. One way of reducing these toxic free radicals is to lower the amount of iron in the liver. Serum iron levels should be maintained at the lowest possible tolerable levels (ideally below 60 mcg/dL of blood), and serum ferritin levels should be maintained in the low normal range of 30 to 80 ng/dL.

Another way of protecting the liver is to consume the proper antioxidant nutrients to protect cells against the damaging effects of free radicals. A healthy immune system may keep hepatitis C in check. Supplements that help maintain youthful immune function are of particular importance.

The following supplements have been shown to reduce liver oxidative damage, lower iron, and boost the effectiveness of conventional drugs:

- **Calcium citrate**—1000 to 2000 milligrams (mg) daily with iron-containing foods to block iron absorption
- **Lactoferrin**—900 mg daily, to block iron, in divided doses
- **Lipoic acid**—750 mg in three divided doses daily
- **NAC**—600 mg daily
- **Whey protein isolate**—20 to 40 grams (g) daily
- **Glutathione**—500 mg daily, on an empty stomach
- **Silibinin extract**—900 mg daily, in two divided doses
- **SAME**—1200 mg daily, in three divided doses
- **PPC**—1800 to 3600 mg daily
- **Green tea extract** (93 percent polyphenols)—750 mg daily
- **Garlic (high allylic)**—900 mg daily
- **Aged garlic extract** (Kyolic®)—1200 mg daily
- **Selenium**—200 to 600 micrograms (mcg) daily
- **Vitamin E**—400 international units (IU) daily with at least 200 mg gamma tocopherol
- **Vitamin C**—2000 mg daily (on an empty stomach to minimize the increased iron absorption caused by vitamin C)

## HEPATITIS C SAFETY CAVEATS

An aggressive program of dietary supplementation should not be launched without the supervision of a qualified physician. Several of the nutrients suggested in this protocol may have adverse effects. These include:

### Calcium

- Do not take calcium if you have hypercalcemia.
- Do not take calcium if you form calcium-containing kidney stones.
- Ingesting calcium without food can increase the risk of kidney stones in women and possibly men.
- Calcium can cause gastrointestinal symptoms such as constipation, bloating, gas, and flatulence.
- Large doses of calcium carbonate (12 grams or more daily or 5 grams or more of elemental calcium daily) can cause milk-

alkali syndrome, nephrocalcinosis, or renal insufficiency.

## **Garlic**

- Garlic has blood-thinning, anticlotting properties.
- Discontinue using garlic before any surgical procedure.
- Garlic can cause headache, muscle pain, fatigue, vertigo, watery eyes, asthma, and gastrointestinal symptoms such as nausea and diarrhea.
- Ingesting large amounts of garlic can cause bad breath and body odor.

## **Green Tea**

- Consult your doctor before taking green tea extract if you take aspirin or warfarin (Coumadin). Taking green tea extract and aspirin or warfarin can increase the risk of bleeding.
- Discontinue using green tea extract 2 weeks before any surgical procedure. Green tea extract may decrease platelet aggregation.
- Green tea extract contains caffeine, which may produce a variety of symptoms including restlessness, nausea, headache, muscle tension, sleep disturbances, and rapid heartbeat.

## **Lipoic Acid**

- Consult your doctor before taking lipoic acid if you have diabetes and glucose intolerance. Monitor your blood glucose level frequently. Lipoic acid may lower blood glucose levels.

## **NAC**

- NAC clearance is reduced in people who have chronic liver disease.
- Do not take NAC if you have a history of kidney stones (particularly cystine stones).
- NAC can produce a false-positive result in the nitroprusside test for ketone bodies used to detect diabetes.
- Consult your doctor before taking NAC if you have a history of peptic ulcer disease. Mucolytic agents may disrupt the gastric mucosal barrier.
- NAC can cause headache (especially when used along with nitrates) and gastrointestinal symptoms such as nausea and diarrhea.

## **Milk Thistle**

- Consult your doctor before taking milk thistle with tranquilizers such as Haldol, Serentil, Stelazine, and Thorazine. Milk thistle combats the effect of tranquilizers.
- Do not combine milk thistle with the blood pressure medication Regitine. Milk thistle combats the effect of Regitine.

## **Phosphatidylcholine**

- Phosphatidylcholine can cause increased salivation, a metallic taste, headache, drowsiness, and gastrointestinal symptoms such as nausea and diarrhea.

## **SAMe**

- Consult your doctor before taking SAMe if you have bipolar disorder. See your doctor frequently if you take SAMe and you have bipolar disorder.
- Consult your doctor before taking SAMe if you take antidepressants. See your doctor frequently if you take SAMe in place of or in addition to antidepressants.
- Consult your doctor before taking SAMe if you have cancer. Nucleic acid methylation patterns may change in people who have cancer and take SAMe.
- Do not take SAMe if you are undergoing gene therapy.
- SAMe can cause anxiety, hyperactive muscle movement, insomnia, hypomania, and gastrointestinal symptoms such as nausea and diarrhea.

## **Selenium**

- High doses of selenium (1000 micrograms or more daily) for prolonged periods may cause adverse reactions.
- High doses of selenium taken for prolonged periods may cause chronic selenium poisoning. Symptoms include loss of hair and nails or brittle hair and nails.
- Selenium can cause rash, breath that smells like garlic, fatigue, irritability, and nausea and vomiting.

## Vitamin C

- Do not take vitamin C if you have a history of kidney stones or of kidney insufficiency (defined as having a serum creatine level greater than 2 milligrams per deciliter and/or a creatinine clearance less than 30 milliliters per minute).
- Consult your doctor before taking large amounts of vitamin C if you have hemochromatosis, thalassemia, sideroblastic anemia, sickle cell anemia, or erythrocyte glucose-6-phosphate dehydrogenase (G6PD) deficiency. You can experience iron overload if you have one of these conditions and use large amounts of vitamin C.

## Vitamin E

- Consult your doctor before taking vitamin E if you take warfarin (Coumadin).
- Consult your doctor before taking high doses of vitamin E if you have a vitamin K deficiency or a history of liver failure.
- Consult your doctor before taking vitamin E if you have a history of any bleeding disorder such as peptic ulcers, hemorrhagic stroke, or hemophilia.
- Discontinue using vitamin E 1 month before any surgical procedure.

For more information see the Safety Appendix

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