

Cirrhosis and Liver Disease

The liver is the largest organ in the body, weighing up to 2.5 percent of total lean body mass. Located in the upper right quadrant of the abdomen, the liver varies in size and shape, depending on each person's anatomy. Its main function is to metabolize substances in the blood in preparation for excretion, although it has many other important functions, including synthesis of most essential proteins, production of bile, and regulation of nutrients such as glucose, cholesterol, and amino acids.

The main kind of liver cell is called a hepatocyte. These cells comprise about two thirds of the liver's mass. The liver's blood supply comes from the hepatic artery, which supplies oxygen-rich blood. The liver also receives blood from the portal vein, which filters blood from the stomach, intestines, pancreas, and spleen.

The most common liver function tests are enzyme, bilirubin, albumin, and prothrombin time tests. The liver contains thousands of enzymes, only a few of which are routinely measured as indicators of liver function. These enzymes include the following:

- **Alkaline phosphatase.** Abnormal levels may indicate bile obstruction, liver injury, or some forms of cancer.
- **Alanine transaminase.** Abnormal levels may indicate hepatitis or other liver cell injury.
- **Aspartate transaminase.** Abnormal levels may indicate injury to liver, heart, muscle, or brain.
- **Gamma-glutamyl transpeptidase.** Abnormal levels may indicate organ damage, drug toxicity, alcohol abuse, or pancreatic disease.
- **Lactic dehydrogenase.** Abnormal levels may indicate damage to liver, heart, or lung, and excessive breakdown of red blood cells.
- **5'-nucleotidase.** Abnormal levels may indicate impaired bile flow.

The other major liver tests include the serum bilirubin test, which measures bile excretion, and the albumin test, which can indicate liver damage. Finally, the prothrombin time test measures the time needed for blood to clot. Because most blood clotting factors are produced in the liver, and they have rapid turnover, this test can help measure the liver's ability to synthesize cells. Prothrombin may be elevated in hepatitis and cirrhosis as well as in disorders related to vitamin K deficiency.

Taken together, these tests provide physicians with a relatively complete picture of liver function and can help diagnose liver disease.

FORMS OF LIVER DISEASE

The many possible liver diseases can be grouped loosely into three categories: hepatocellular diseases, cholestatic diseases, and mixed forms. In hepatocellular diseases, the liver is typically inflamed and shows signs of injury. Over time, liver cells may begin to die. Causes of hepatocellular liver disease include alcoholic cirrhosis and viral hepatitis, both of which attack liver cells directly. In cholestatic diseases, the flow of fluid through the liver is blocked by such things as gall stones, liver cancer, or biliary cirrhosis. In mixed forms of liver disease, both conditions are present.

The pattern and onset of symptoms can help physicians determine what kind of liver disease is present. Symptoms of liver disease include jaundice, fatigue, itching, pain in the upper abdomen, distention of the abdomen, and intestinal bleeding. However, many forms of liver disease have no symptoms and are diagnosed only during routine blood tests that detect abnormalities in the markers of liver function.

Cirrhosis is an end-stage liver disease. It is characterized by chronic injury to the liver cells, fibrosis (scarring) within the liver, and the formation of regenerative nodules. The causes of cirrhosis include the following:

Alcohol consumption. Excess alcohol consumption is a primary cause of cirrhosis. However, only 10 percent to 20 percent of alcoholics develop cirrhosis (Beers MH et al 2004–2005).

Alcohol lowers the liver's levels of antioxidants, including vitamin E (Kawase T et al 1989; Leo MA et al 1993) and S-adenosyl-L-methionine (SAME) (Lieber CS 1997), making the liver vulnerable. In addition, alcohol lowers glutathione, an important internal antioxidant (Speisky H et al 1985; Hirano T et al 1992).

Because heavy drinkers consume a substantial number of calories as alcohol, they consume less vitamin- and mineral-rich food

than they otherwise might, exacerbating alcohol-induced nutritional deficiencies. Virtually all individuals with alcoholic hepatitis suffer from malnutrition to a degree more or less proportional to the severity of their disease (Mendenhall CL et al 1984).

Indeed, survival in alcoholics with moderate or severe hepatitis is directly proportional to how much food they consume. Mortality drops to zero in those consuming 3000 or more calories during treatment (Mendenhall C et al 1995). Similar results were seen with alcoholic cirrhosis patients, except for the most severely malnourished, who may have been too compromised to recover (Hirsch S et al 1993,1999; Gopalan S et al 2000).

In addition to antioxidant depletion, alcoholics tend to have a number of other nutritional deficiencies. These include low levels of vitamin C, riboflavin, zinc, pyridoxine (vitamin B6), and vitamin A (Gruchow HW et al 1985; Rosenthal WS et al 1973; Ijuin H 1998; Fonda ML et al 1989; Lumeng LJ 1978; Lieber CS 2000).

Hepatitis. Hepatitis, another common cause of liver cirrhosis, is caused by infection with the hepatitis B or C virus. Because the symptoms of infection are mild and flulike, viral hepatitis often goes undiagnosed. Blood donors sometimes find out they are infected when their donated blood undergoes routine screening. Viral hepatitis causes chronic liver inflammation, which results in cirrhosis in the majority of those infected.

Nonalcoholic fatty liver disease. The most common cause of fatty liver disease is alcohol consumption, but it can also be caused by a number of other conditions, including obesity, diabetes, and elevated triglyceride levels. If the condition is associated with obesity, it is sometimes called nonalcoholic fatty liver disease, or NAFLD. Up to one-third of patients with NAFLD also have type 2 diabetes, high cholesterol levels, or both. NAFLD is closely associated with metabolic syndrome, which is a related cluster of conditions, including obesity, diabetes, elevated triglycerides, and high blood pressure, that is considered a major risk factor for heart attack. Fatty liver disease is exacerbated by inflammation within the liver, which may hasten its progression to cirrhosis.

Biliary cirrhosis. Biliary cirrhosis results from prolonged obstruction of or injury to the biliary system. One of the liver's functions is to secrete bile, which is used in the gut in the normal breakdown and absorption of fats from the diet, among other things. Primary biliary cirrhosis, which has no known cause, is characterized by inflammation of the liver and the destruction of the liver bile ducts by scar tissue. It is associated with various autoimmune diseases, such as Raynaud's phenomenon.

Cardiac cirrhosis. Cardiac cirrhosis occurs when prolonged, severe right-sided congestive heart failure leads to chronic liver injury and inflammation and the formation of scar tissue in the liver (fibrosis). A heart in this condition cannot handle the venous circulation, causing blood to back up in the body's major veins. Eventually, the liver becomes engorged and swollen.

Inherited disorders. Various inherited disorders can cause cirrhosis.

Whatever the cause of cirrhosis, it is a difficult disease to manage in its advanced stages, in part because of the complications that it causes. For example, people suffering from cirrhosis also frequently suffer from portal hypertension, or elevated blood pressure in the vein that drains into the liver. This, in turn, can cause complications in the stomach and esophagus, such as ascites (see below). Portal hypertension occurs in about 60 percent of cases of cirrhosis in the United States (Kasper DL et al 2005). The treatment of portal hypertension often focuses on relieving the underlying liver disease. In serious cases, drugs such as diuretics might be prescribed to reduce blood pressure.

Cirrhosis may entail other complications:

- **Esophageal varices.** Portal hypertension can cause varicose veins in the esophagus. They can rupture, requiring emergency surgery.
- **Ascites.** The pressure created by portal hypertension can also cause the liver and intestines to exude fluid into the abdominal cavity, which can become swollen and distended, a condition known as ascites.
- **Hepatoma.** Not surprisingly, a compromised liver is more susceptible to cancer. Hepatocellular carcinoma occurs in about 10 percent to 20 percent of cirrhotic patients (Wolf DC 2001). Liver cancer is relatively asymptomatic. It is usually not detected until it has progressed significantly. Consequently, the patient's prognosis is usually poor.
- **Hepatic encephalopathy.** This is a complex condition characterized by psychological and personality disturbances. Its specific cause is unknown; in serious cases, it can result in coma or death.

While cirrhosis is irreversible, it is usually the result of a chronic condition and thus takes a long time to develop. In fact, many people with developing liver disease (e.g., fibrotic livers) have no symptoms, and their condition is detected only by routine blood tests. If the condition is detected early enough, the patient may have an opportunity to arrest the cirrhotic process before it goes too far.

As is the case with many other diseases, cirrhosis is characterized by inflammation (hepatitis literally means "inflammation of the liver"). This liver inflammation is often caused by a rise in free radicals within the liver. Under normal circumstances, the liver

maintains a supply of internal antioxidants to neutralize the free radicals generated by the toxins processed in the liver. However, when the liver antioxidants are low, or when the liver is overwhelmed by continued toxic insults (e.g., alcohol or chronic drug use), damage from free radicals increases, resulting in inflammation and the formation of scar tissue (fibrosis). Thus, it is important to maintain a healthy supply of antioxidants and to make positive lifestyle changes, such as abstaining from all alcohol and avoiding environmental toxins whenever possible, to reduce the strain on the liver.

If cirrhosis is allowed to progress and the liver's function is compromised beyond repair, the only solution is a liver transplant. This is a complicated medical procedure with a significant risk of organ rejection, and even in successful cases, lifelong follow-up therapy with immunosuppressant drugs will be necessary.

DIAGNOSIS OF LIVER DISEASE AND CIRRHOSIS

The symptoms of cirrhosis may be insidious, or there may be no symptoms at all for many years. If symptoms are present, they can include jaundice (yellowing of the eyes and skin), lethargy, bleeding from varices, and spider veins under the skin.

While it can be difficult to diagnose liver disease by its symptoms alone, early liver damage is often apparent from blood test results. Standard blood tests of liver enzymes or bilirubin may show a suspicious elevation and alert the clinician to the possibility of liver dysfunction.

The deposition of fat in the liver (such as in fatty liver disease) can also be detected by diagnostic imaging techniques, such as computed tomography scanning, ultrasound, and magnetic resonance imaging.

TREATMENT OF LIVER DISEASE

The goal of medicine with regard to the liver is to prevent liver disease and, if it is diagnosed, to stop its progression toward cirrhosis. Cirrhosis is an end-stage disease with a poor prognosis and can require a liver transplant if liver failure occurs. Thus, lifestyle changes that support liver health, especially abstention from alcohol, are the cornerstone of treatment for liver disease. No matter the cause of cirrhosis, alcohol aggravates the condition and should be avoided.

In addition, physicians will attempt to treat the complications of cirrhosis, including portal hypertension and ascites, with various medications. In general, however, the use of medications must be approached with caution in people with liver disease because the liver metabolizes many of these substances. For example, aspirin should be avoided in patients with cirrhosis because of its effects on coagulation and the gastric mucosa (Kasper DL et al 2005). The following conventional medicines are often prescribed to treat cirrhosis or fibrotic liver disease:

- **Corticosteroids.** These drugs have been shown to reduce the inflammation that characterizes liver disease. While they may be helpful to patients with alcoholic hepatitis and encephalopathy, they are less helpful to patients with alcoholic cirrhosis (Kasper DL et al 2005; Glanze WD 1996; Mathurin P et al 2002).
- **Ursodiol.** Among people with biliary cirrhosis, this drug replaces lost biliary acids. Side effects are rare. This drug may not halt progression of the disease (Kasper DL et al 2005).

What You Have Learned So Far

- The liver is the largest internal organ. It filters the blood from the digestive system, metabolizing toxins and monitoring nutrients such as glucose and cholesterol.
- Liver disease often develops over years, without obvious symptoms. Many people are diagnosed with liver disease after abnormalities are detected during routine blood tests.
- Cirrhosis occurs when the liver is inflamed and scar tissue forms. It is irreversible; thus prevention of liver disease is the ideal. Cirrhosis can be caused by alcohol consumption, hepatitis, right-sided heart failure, and other conditions.
- Antioxidants, which neutralize the toxins processed by the liver, are an important element in liver health.
- Treatment of liver disease is limited because many drugs are metabolized by the liver; thus only a few drugs, including corticosteroids, which have significant side effects, are used routinely to treat liver disease.

NUTRITIONAL AND SUPPLEMENTAL SUPPORT

The same rule that applies to conventional pharmaceuticals applies to nutritional supplements: they should be used with caution by people with liver diseases because they are often metabolized in the liver. It is important that people with liver disease work in close cooperation with a knowledgeable and qualified physician to design a program of nutritional support.

Nevertheless, there are numerous nutritional approaches that have been studied in liver disease that can help slow the inflammation associated with advancing liver disease and support healthy liver function. For more detailed information on Life Extension's anti-inflammatory recommendations, please see the Inflammation chapter. It is also critical that alcohol be strictly avoided.

The following nutrients have been shown to enhance liver function and reduce inflammation:

Fish oil. Omega-3 fatty acids and sesame lignans have been shown to reduce inflammation, which is a distinctive feature of liver disease and cirrhosis (Barham JB et al 2000; Dias VC et al 1995; Gronn M et al 1992; Shimizu S et al 1991; Chavali SR et al 1999; Utsunomiya T et al 2000).

Studies have shown that reducing the ratio of omega-6 to omega-3 fatty acids prevents liver damage induced by total parenteral (intravenous) nutrition in newborn piglets, rats, and humans (Van Aerde JE et al 1999; Yeh SL et al 1997; Chen WJ et al 2003; Alwayn IP et al 2005). Thus, it may be prudent for patients with cirrhosis to take fish oil supplements and lower their consumption of omega-6 fats, such as those found in corn oil.

It is important that any increase in fatty acids be accompanied by an increase in vitamin E. Without supplemental vitamin E, even fish oil can be detrimental. Diets containing 35 percent of calories from fish oil are likely to exacerbate liver damage due to alcohol and other toxins because fish oil's polyunsaturated bonds are so readily oxidized by free radicals (Nanji AA et al 1989a, 1989b, 1994).

Monounsaturated oils, such as olive oil, should be the major source of fat calories for those with cirrhotic liver disease. Monounsaturated oils are preferable since saturated fats from animal sources usually contain considerable amounts of arachidonic acid, the precursor to inflammatory prostaglandins. For those whose main source of fat calories is animal fat, supplementation with eicosapentaenoic acid (EPA) may help to reduce the buildup of pro-inflammatory arachidonic acid and reduce levels of inflammatory mediators (Barham JB et al 2000).

In addition to using olive oil in preference to corn oil or animal fats, people with liver disease would most likely benefit from supplementation with a dose of fish oil high enough to inhibit inflammatory prostaglandin synthesis without providing a significant target for reactive oxygen species. While more work is needed to determine how much fish oil is too much, the nutrition studies cited above suggest that supplementation with fish oil should be limited to about 10 percent of total calories (Nanji AA et al 2001). Also, maintaining high levels of antioxidant nutrients such as vitamin E will help limit oxidant damage from polyunsaturated fats.

SAMe. By increasing oxidative stress, many liver toxins, such as alcohol and acetaminophen, deplete glutathione and other important antioxidant molecules. As a result, SAMe, a glutathione precursor, is also decreased (Lieber CS 2002). In both rodents and nonhuman primates, depletion of antioxidants occurs at early stages of liver disease. Supplementation with SAMe restores levels of glutathione and decreases liver damage in animals and it has been recommended as an area of study for humans with early liver disease or with chronic exposure to liver toxins, including alcohol (Lieber CS 2002; Vendemiale G et al 1989).

In one clinical trial, 123 patients with alcoholic liver cirrhosis were given either a placebo or 1200 mg daily of oral SAMe. At the end of the two-year trial, 30 percent of the placebo-treated patients had died, compared with 16 percent of people in the SAMe group. When the patients with the most severe disease were excluded from the calculation, these numbers became 29 percent in the placebo group and only 12 percent in the SAMe-supplemented group (Mato JM 1999). The livers in the patients with the most advanced cirrhosis may have been too damaged to respond to the SAMe.

PPC. Phosphatidylcholines are produced in the liver through a process involving SAMe. Supplementing alcohol-treated rats or baboons with polyenylphosphatidylcholine (PPC) during alcohol feeding prevents the depletion of SAMe (Aleynik SI et al 2003).

In rats, PPC treatment accelerated regression of preexisting fibrosis (Ma X et al 1996). In a baboon study, none of the animals fed 2.8 g PPC per 1000 calories (about 2 g daily per 20 kg body weight) developed fibrosis or cirrhosis, even after 6.5 years of alcohol feeding, whereas 10 out of 12 untreated baboons developed fibrosis or cirrhosis (Lieber CS et al 1994). In addition to preventing alcohol-induced oxidative stress, PPC stimulates the enzyme responsible for the breakdown of liver collagen (Lieber CS et al 1994).

Among humans, two years of treatment of alcoholic cirrhosis patients with 4.5 g daily of PPC resulted in favorable changes in two blood parameters of liver damage, bilirubin and liver transaminases, among certain subgroups. Fibrosis, however, continued to

progress, leading the authors to conclude that while PPC is effective in preventing liver damage among animals, it is less effective among humans with long histories of drinking (Lieber CS et al 2003a).

Silymarin. A standardized plant extract from milk thistle, silymarin contains about 60 percent silibinin (Boigk G et al 1997). Silymarin appears to inhibit the formation of mediators of inflammation, such as leukotrienes (Dehmlow C et al 1996). In animal studies, silymarin protected the liver from carbon tetrachloride damage and slowed the accumulation of scar tissue in the biliary tract (Kravchenko LV et al 2000; Batakov EA 2001; Boigk G et al 1997). In baboons, silymarin slowed the progression of alcohol-induced liver fibrosis (Lieber CS et al 2003b).

Some placebo-controlled human trials have shown promising results. For example, in one study of patients with alcoholic cirrhosis, mortality was 39 percent among the patients treated with Legalon, a proprietary standardized product containing 70 percent to 80 percent silymarin, after 24 to 41 months of treatment. Mortality in placebo-treated patients was significantly higher, 58 percent (Ferenci P et al 1989). In another clinical study, this same silymarin preparation normalized blood levels of bilirubin and other markers of liver disease after six months (Feher J et al 1989). Favorable changes in blood chemistry were noticed in as little as four weeks (Salmi HA et al 1982).

Improvements were also observed with a silymarin-phospholipid complex in patients with chronic active hepatitis (Buzzelli G et al 1993). Recently, an Italian firm has developed a proprietary preparation of silibinin complexed with both vitamin E and phospholipids. The complex successfully protected rat livers against necrosis and inhibited collagen formation in rats after bile duct obstruction (Di Sario A et al 2005).

Antioxidants. Since cirrhosis is the result of chronic injury to the liver from free radicals, antioxidant therapy may slow the progression of the disease. Studies have found that people with cirrhosis have low levels of vitamin C and vitamin E (Prakash S et al 2004).

In one remarkable study, patients with hepatitis C were given seven oral antioxidants, glycyrrhizin (500 mg twice daily), schisandra (500 mg three times daily), silymarin (250 mg three times daily), ascorbate (2 g three times daily), lipoic acid (150 mg twice daily), L-glutathione (150 mg twice daily), and alpha-tocopherol (800 IU daily) for 20 weeks. Four different intravenous antioxidant preparations, including glycyrrhizin (120 mg), ascorbic acid (10 g), L-glutathione (750 mg), and B-complex (1 mL; composition not specified), were also administered twice weekly for the first 10 weeks. No significant side effects were observed. Normalization of liver enzymes, which indicated reduced liver injury, occurred in 44 percent of patients. One-fourth of the patients showed viral load decreases of 90 percent or more. Histologic improvement was noted in 36 percent of patients (Melhem A et al 2005).

Consistent with these findings, an Italian study demonstrated that eating foods high in antioxidants (fruits and vegetables) decreased the progression of cirrhosis, while a high level of fatty animal products and sugar from nonfruit sources increased it (Corrao G et al 2004).

Animal products are high in arachidonic acid, a precursor to inflammatory mediators such as prostaglandins and leukotrienes, and sugars from nonfruit sources are more likely to increase insulin levels because fiber is not present to slow the absorption of sugar. High insulin levels stimulate the conversion of arachidonic acid into inflammatory prostaglandins. The resulting inflammation generates high levels of reactive oxygen species. Thus, cirrhotic patients should avoid nonfruit sources of sugar or consume additional fiber when nonfruit sugars are consumed.

Selenium, a potent antioxidant, appears to protect against hepatic cancers. In a four-year trial, selenium-enhanced table salt reduced primary liver cancer 35 percent in study participants compared with controls. In a study involving hepatitis B patients, one 200-mcg tablet of selenium daily reduced the incidence of primary liver cancer to zero. When selenium supplementation ceased, primary liver cancer incidence began to rise, indicating that hepatic carcinoma risk may be minimized with selenium supplementation (Yu SY et al 1997).

Branched-chain amino acids. The branched-chain amino acids (BCAAs) include leucine, isoleucine, and valine. They must be obtained in the diet because the human body cannot make them. Cirrhotic patients have an increased energy requirement that BCAAs seem to fill better than glucose or amino acids (Kato M et al 1998). Supplementing the diet with these amino acids lowers hospital admission rates and improves nutritional parameters, liver function tests, and overall quality of life in patients with liver disease (Marchesini G et al 2003). In addition, supplementing with BCAAs after surgery for hepatic carcinoma shortens hospital stays and improves the return of liver function (Meng WC et al 1999). Encephalopathy is also alleviated after treatment with BCAAs (Marchesini G et al 1990).

LIFE EXTENSION FOUNDATION RECOMMENDATIONS

Liver cirrhosis is a life-threatening condition that requires close supervision by a qualified physician. Because the liver metabolizes many nutrients and drugs, it is important that liver patients not add any substances to their regimen without cooperation and close monitoring by a qualified physician. The goal of therapy is threefold:

1. Eliminate the toxins or conditions that cause liver damage. Among patients with alcoholic liver disease, this means the total elimination of alcohol. Cirrhotic patients should also limit exposure to environmental toxins, decrease consumption of omega-6 fatty acids (corn oil especially), and use monounsaturated fats such as olive oil instead.
2. Provide the liver with appropriate nutritional and pharmaceutical support so that it may heal itself.
3. Maintain health sufficient to undergo liver transplantation should other measures fail.

The following supplements have been shown to boost liver health and help manage cirrhosis:

- **PPC**—2 to 4 900-milligram (mg) capsules daily. Each capsule contains phosphatidylcholine 900 mg.
- **BCAAs**:—L-leucine 1200 mg, L-isoleucine 600 mg, and L-valine 600 mg
- **Silymarin (milk thistle extract)**—900 mg
- **L-glutathione**—250 mg, in two divided doses
- **SAME**—1200 mg daily, in three divided doses
- **Vitamin B complex**—1 capsule 3 times daily. Each capsule contains thiamin (B1) 100 mg, riboflavin (B2) 50 mg, niacin 200 mg, vitamin B6 75 mg, folic acid 800 mcg, vitamin B12 1000 mcg, biotin 600 mcg, pantothenic acid 1000 mg, betaine free base 50 mg, choline 45 mg, inositol 250 mg, and para-aminobenzoic acid 100 mg
- **Vitamin B6 (as pyridoxine HCl)**—100 mg
- **Vitamin C (ascorbic acid)**—6000 mg daily
- **Vitamin E**—800 international units (IU) daily
- **EPA/docosahexaenoic acid (DHA)**—fish oil supplement supplying EPA 700 mg and DHA 500 mg, and ideally providing 100 mg of Polyphen-Oil™ Olive Fruit Extract 265 mg along with sesame seed (*Sesamum indicum*) lignans.
 - **PGX fiber**—2 capsules with every meal or snack that includes nonfruit carbohydrates. Two capsules contain 1000 mg proprietary blend of Konjac root extract, sodium alginate, xanthan gum, mulberry powdered extract (leaf) 50 mg

LIVER CIRRHOSIS 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:

EPA/DHA

- Consult your doctor before taking EPA/DHA if you take warfarin (Coumadin). Taking EPA/DHA with warfarin may increase the risk of bleeding.
- Discontinue using EPA/DHA 2 weeks before any surgical procedure.

Fiber

- Take fiber supplements with a full 8-ounce glass of water.
- Drink eight 8-ounce glasses of water daily while taking fiber.

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.

Niacin (nicotinic acid)

- Do not take high doses of nicotinic acid (1.5 to 5 grams daily or more) if you have liver dysfunction, an unexplained elevation in your serum aminotransferase (transaminase) level, active peptic ulcer disease, arterial bleeding, or if you consume large amounts of alcohol.
- Consult your doctor before taking high doses of nicotinic acid if you have a history of jaundice, peptic ulcer disease, gastritis, disease of the liver or bile ducts, gout, kidney dysfunction, or cardiovascular disease (especially acute myocardial infarction or unstable angina).
- Consult your doctor before taking high doses of nicotinic acid if you have diabetes. High doses of nicotinic acid can negatively affect glucose tolerance. Monitor your serum glucose level frequently if you take nicotinic acid and have diabetes.
- Have your doctor monitor your serum aminotransferase level if you take high-doses of nicotinic acid.

- Nicotinic acid may cause flushing, principally of the face, neck, and chest. This flushing is thought to be prostaglandin-prostacyclin mediated. Histamine may also play a role in the flushing.
- Nicotinic acid can cause dizziness, palpitations, rapid heartbeat, shortness of breath, sweating, chills, insomnia, nausea, vomiting, abdominal pain, and muscle pain.
- High doses of nicotinic acid can cause blurred vision, macular edema, toxic amblyopia, and cystic maculopathy.

PABA (Para-aminobenzoic Acid)

- Do not take PABA if you are taking sulfonamides or have a kidney disease.
- PABA can cause anorexia, nausea, vomiting, fever, and rash.

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.

Vitamin B1 (Thiamin)

- Consult your doctor before taking vitamin B1 for a thiamin deficiency, lactic acidosis secondary to thiamin deficiency, Wernicke-Korsakoff syndrome, Wernicke's encephalopathy, or Korsakoff's psychosis.

Vitamin B2 (riboflavin)

- High doses of vitamin B2 (riboflavin) may interfere with the Abbott TDx drugs-of-abuse assay.
- Riboflavin absorption is increased in hypothyroidism and decreased in hyperthyroidism.
- If you are taking nucleoside reverse-transcriptase inhibitors, even a mild riboflavin deficiency can increase your risk of lactic acidosis.

Vitamin B6

- Individuals who are being treated with levodopa without taking carbidopa at the same time should avoid doses of 5 milligrams or greater daily of vitamin B6.

Vitamin B12 (cyanocobalamin)

- Do not take cyanocobalamin if you have Leber's optic atrophy.

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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