

Osteoarthritis

Osteoarthritis is a distressingly common joint disease that causes localized inflammation with possibly crippling consequences. By age 70, most people (up to 70 percent) will be affected to some degree by osteoarthritis (Kasper DL et al 2004). In the elderly, osteoarthritis of the knee is the leading cause of disability; it is estimated that 100,000 Americans are unable to walk independently, even from the bedroom to the bathroom, because of osteoarthritis in their knees or hips (Kasper DL et al 2004).

In most cases, the cause of osteoarthritis is not known, although it can be secondary to injury, repetitive joint use, or conditions such as obesity. Contrary to what many people believe, however, osteoarthritis is not a normal part of aging. It is a disease that should be treated aggressively at the earliest symptoms.

Unfortunately, conventional medicine has never developed an effective approach to treating osteoarthritis. Many people with a mild case of osteoarthritis are simply told to ignore the condition and to avoid doing any activities that may cause pain or discomfort. People who have a more severe case of osteoarthritis are in an even worse position. The drugs most often used to combat osteoarthritis are nonsteroidal anti-inflammatory drugs (NSAIDs). Over-the-counter NSAIDs, such as ibuprofen, can cause gastrointestinal upset, while prescription NSAIDs, such as rofecoxib and valdecoxib, were recently discovered to raise the risk of heart attack and stroke and were removed from the market by their manufacturers.

While the search for a drug that is a “magic bullet” continues, there is a wealth of data on the value of natural therapies to treat osteoarthritis. Natural anti-inflammatory agents have been found to reduce the swelling and pain associated with osteoarthritis, while other nutrients supply the underlying building blocks of joints and reduces the oxidative damage caused by the loss of joint cartilage.

The Life Extension Foundation’s osteoarthritis program can be summed up simply—take early, aggressive action. Because osteoarthritis is the rule rather than the exception, all adults should consider instituting a joint-supporting, anti-inflammatory nutrient program as soon as possible.

THE DANGERS OF OSTEOARTHRITIS

Unlike rheumatoid arthritis, which is characterized by systemic inflammation, osteoarthritis is a localized disease that occurs only in the affected joints.

With osteoarthritis, the thin layer of cartilage between the joints gradually erodes and wears away. As the protective layer of cartilage vanishes, the bone beneath becomes pitted and uneven, and the structural integrity of the joint is destroyed. Movement can become extremely painful and, in the worst cases, people who have severe osteoarthritis can no longer take care of themselves on a day-to-day basis.

In a normal joint, the ends of adjoining bones are covered by smooth cartilage that offers little friction. The whole joint is covered with special tissue called synovial tissue, which secretes synovial fluid to lubricate the cartilage and ensure that the joint continues to function smoothly. Cartilage is a firm, gel-like substance that acts as a shock absorber. Joints can withstand enormous pressure by releasing water from the cartilage.

During osteoarthritis, it is thought that the cells that synthesize collagen (and the proteoglycans that comprise cartilage) cease to function correctly. Over time, the cartilage begins to retain water and swell, becoming soft and eventually cracking. Next, tiny cavities form in the bone beneath the cartilage. The bone may overgrow the edges of the joint, resulting in bumps (osteophytes) that restrict movement. In the final stages, the cartilage becomes rough and pitted.

The symptoms of osteoarthritis include aching joint pain that is aggravated by use. In advanced osteoarthritis, pain may interfere with sleep. In some patients, synovitis, or inflammation of the synovial membrane, may be caused by shards of bone in the joint.

To diagnose osteoarthritis, physicians typically rely on symptoms. It is important that a physician differentiate osteoarthritis from other joint diseases. X-rays may be taken to make sure the diagnosis is correct. Osteoarthritis may be characterized by bone enlargement and narrowing of the joint space. Otherwise, laboratory studies are rarely helpful in diagnosing osteoarthritis.

NUTRITION: AN EARLY APPROACH TO OSTEOARTHRITIS

The value of nutrients is well known to come to arthritis. Even conventional textbooks recommend that people with osteoarthritis consume a diet rich in natural anti-inflammatory, antioxidant, and joint-supporting nutrients, and avoid eating pro-inflammatory foods that are high in sugar, saturated fats, and trans fatty acids.

Omega-3 Fatty Acids. The benefit of omega-3 fatty acids is well known in the treatment of people who have osteoarthritis. Clinical studies over the past two decades have proved again and again the value of omega-3 fatty acids in treating inflammatory conditions ranging from atherosclerosis to osteoarthritis. In people who have osteoarthritis, increased consumption of omega-3 fatty acids and adequate intake of monounsaturated fatty acids such as those found in olive oil (and decreased consumption of omega-6 fatty acids) can improve symptoms and even sometimes allow a reduction in the use of NSAIDs (Miggiano GA et al 2005). These fatty acids have many positive effects, including influencing cellular metabolic functions, supporting cell membrane structure, and directly reducing the expression of pro-inflammatory cytokines (Zak A et al 2005). The most potent of the omega-3 fatty acids containing oils are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are found in abundance in cold-water fish (Mori TA et al 2004).

Soybean and Avocado Oil. In Europe, avocado and soybean oil unsaponifiable (ASU) is sold as a drug for osteoarthritis. In the United States, ASU is available as a dietary supplement. Studies have shown that ASU inhibits interleukin-1 (IL-1) and stimulates collagen synthesis (Mauviel A et al 1991). It also reduces the production of other inflammatory cytokines, such as interleukin-6 (IL-6), interleukin-8 (IL-8), and prostaglandin E2 (Henrotin YE et al 1998). In a 3-month study of 260 people, aged 45 to 80 years, who had osteoarthritis of the knee, ASU was shown to yield significant improvements compared to placebo (Appelboom T et al 2001). Another 3-month human trial of ASU versus placebo found a reduced need for NSAIDs among study subjects who took 300 milligrams per day (mg/day) of ASU (Blotman F et al 1997).

Curcumin. Curcumin is a component of turmeric and is an anti-inflammatory compound that inhibits both COX-2 and lipoygenase enzyme activity, along with decreasing levels of IL-1 beta (IL-1b) (Banerjee M et al 2003; Plummer SM et al 1999). A study investigating capsaicin from red pepper and curcumin found that these two nutrients decrease the production of pro-inflammatory cytokines. Curcumin and capsaicin also inhibited the secretion of collagenase, hyaluronidase, and elastase, which are linked to the breakdown of cartilage that characterizes osteoarthritis. Researchers concluded that curcumin and capsaicin can influence inflammatory mediators (Joe B et al 1997).

Some studies revealed that users of curcumin supplements were not getting optimal benefits from the extract. The reason is that, for curcumin to be effectively assimilated into the bloodstream, it must be combined with small amounts of piperine (a component of black pepper). Piperine has been shown to enhance the serum concentration, the bioavailability, and the extent of absorption of curcumin in humans without any adverse effects.

Ginger. Ginger is an anti-inflammatory and antirheumatic agent used in ayurveda, a form of holistic medicine traditional to India (Srivastava KC et al 1992). Ginger extract blocks activation of proinflammatory mediators (Fronzoza CG et al 2004). In a 3-month to 2.5-year study that investigated the effects of powdered ginger on patients who had either rheumatoid arthritis or osteoarthritis, approximately 75 percent of the patients experienced pain relief and decreased swelling, and there were no reports of adverse effects (Srivastava KC et al 1992). A similar study of more than 240 patients who had osteoarthritis of the knee demonstrated a significant reduction in osteoarthritis symptoms (Altman RD et al 2001). A study examining the mechanism of action of ginger extract demonstrated that 100 micrograms per milliliter (mcg/mL) significantly inhibited the activation of COX-2 and tumor necrosis factor (TNF), in addition to suppressing prostaglandin-E2 production (Fronzoza CG et al 2004).

Nobiletin. Flavonoids are natural compounds found in a wide variety of fruits and vegetables. Bioflavonoids from citrus fruits such as oranges, tangerines, and grapefruits have been found to exert anti-inflammatory effects (Manthey JA et al 2001; O'Leary KA et al 2004).

The bioflavonoid nobiletin was first isolated from orange peel in 1938. Nobiletin has been shown to be a powerful anti-inflammatory agent (Lin N et al 2003; Murakami A et al 2000a; Tanaka S et al 2004). Early studies revealed that nobiletin significantly inhibits production of nitric oxide and superoxide, two powerful free radicals involved in promoting inflammation.

The flavonoid nobiletin has been found to selectively down-regulate COX-2 without interfering with COX-1 (O'Leary KA et al 2004). In mouse macrophages, nobiletin was also shown to suppress production of prostaglandin E2 while interfering with pro-inflammatory cytokines such as IL-1(b), TNF-alpha, and IL-6 (Ishiwa J et al 2000).

In addition, nobiletin demonstrated great anti-inflammatory activity (Murakami A et al 2000b). Through its effects in reducing inflammation, nobiletin may help to protect against a host of age-related problems, including joint discomfort, cardiovascular problems, and other inflammation-induced disorders.

Nettle Leaf. A study investigating the effects of nettle leaf extract demonstrated that the stinging nettle leaf extract Hox alpha significantly suppressed IL-1(b)-induced expression of matrix metalloproteinase, which is linked to cartilage degradation (Schulze-Tanzil G et al 2002). An extract of nettle leaf is well known for its positive effects in the treatment of rheumatic diseases and its

capacity for partial inhibition of leukotriene and prostaglandin. A laboratory study examining the effects of 5 mg/mL of nettle leaf extract on TNF and IL-1 in human whole blood demonstrated significant reductions in these cytokines. After 24 hours, they decreased by 50 percent and 100 percent, respectively. After 60 hours, inhibition rates were 40 percent and 100 percent, respectively (Obertreis B et al 1996).

S-Adenosylmethionine. S-adenosylmethionine (SAME) is the activated form of the amino acid methionine. It is naturally converted to cysteine in the body. SAME protects synovial cells by reversing glutathione depletion, thus supporting levels of an important internal antioxidant (Lieber CS et al 2002). In addition to its antioxidant protection, it may protect synovial cells by blocking the enzymes that degrade cartilage. It may also protect the important cartilage proteins and proteoglycans in the joint lining.

In the laboratory, SAME increases the number of cartilage cells and proteoglycans (protein). This suggests that SAME treatment may help reverse the underlying process of osteoarthritis by stimulating cartilage to grow (Barcelo HA et al 1990; Kalbhen DA et al 1990). The other main component of the joint is synovial fluid, which acts as a lubricant. In two studies comparing SAME to NSAIDs, test results demonstrated that SAME was generally more effective and better tolerated than the NSAIDs (Glorioso S et al 1985; Vetter G 1987). SAME alleviates the pain and functional limitation of osteoarthritis, in addition to rebuilding joint cartilage (Soeken KL et al 2002).

JOINT-PROTECTIVE AGENTS

Effective treatment of osteoarthritis includes the protection of the cartilage and synovial fluid in the joint against further destruction. In addition, it is important to stimulate anabolic restoration of joint cartilage and synovial fluid. Chondroprotective agents are compounds the body produces to regenerate cartilage and maintain healthy joint function. Chondroprotective agents protect and restore joint cartilage by a variety of mechanisms. They enhance development of chondrocytes, enhance the synthesis of synovial fluid, and inhibit free-radical damage to proteins and joint cartilage degradation by autoimmune processes.

Hyaluronic Acid. Hyaluronic acid is a joint lubricant. Several randomized clinical studies have examined the role of hyaluronic acid in relieving osteoarthritis symptoms, especially in patients who have osteoarthritis of the knee. In one study, four groups of patients with osteoarthritis of the knee were randomly assigned to treatment. One group performed exercises; one group performed exercises and received pulse ultrasound therapy (for pain); and one group performed exercises, received pulse ultrasound therapy, and received injections of hyaluronic acid. The fourth group was the control group. All three treatment groups showed progress, but the group receiving hyaluronic acid showed the greatest progress, measured by walking speed and decrease in disability (Huang MH et al 2005). Other studies have found that intra-articular hyaluronic acid injections are well tolerated in patients who have osteoarthritis of the knee and confer benefits that last up to 19 weeks after the last injection (Theiler R et al 2005). This treatment is effective in mild to severe cases of osteoarthritis of the knee (Neustadt D et al 2005). Hyaluronic acid injections have also been shown to relieve pain and disability in other arthritic joints, including the ankle (Salk R et al 2005).

Glucosamine. Glucosamine is a naturally occurring substance. It is synthesized by chondrocytes for the purpose of producing joint cartilage. In osteoarthritis, glucosamine synthesis is defective, and supplementation with glucosamine has proven to be beneficial. The body uses the supplemental glucosamine to synthesize the proteoglycans and the water-binding glycosaminoglycans in the cartilage matrix. In addition to providing raw material, the presence of glucosamine seems to stimulate the chondrocytes to produce more proteoglycans and glycosaminoglycans. Glucosamine also inhibits certain enzymes such as collagenase and phospholipase, which destroy cartilage. By blocking pathogenic mechanisms that lead to articular degeneration, glucosamine delays the progression of the disease and relieves symptoms, even for weeks after termination of the treatment. Among the natural therapies for osteoarthritis, glucosamine sulfate is probably the best known. Commercial sources of glucosamine are from the exoskeleton of certain shellfish and are available as glucosamine sulfate and N-acetylglucosamine.

Glucosamine has been shown to be almost totally free of adverse effects, particularly when compared to NSAIDs. A 4-week study of more than 170 patients who had osteoarthritis of the knee compared the effects of glucosamine sulfate at a dose of 1500 mg/day to 1200 mg/day of ibuprofen. Glucosamine relieved the symptoms as effectively as ibuprofen and was significantly better tolerated than ibuprofen. The safety and tolerability of glucosamine is because of its specific actions on the pathogenic structural and biochemical mechanisms of osteoarthritis without inhibition of the cyclooxygenases. Glucosamine sulfate is a good alternative therapy for osteoarthritis (Qiu GX et al 1998).

As with most natural remedies, the therapeutic effect of glucosamine is not immediate. It usually takes from 1 to 8 weeks to appear. Once achieved, it tends to persist for a notable time even after discontinuation of the treatment. The probable reason is that glucosamine is incorporated into rebuilding the cartilage itself.

Chondroitin Sulfate. Chondroitin sulfate is a major structural component of articular cartilage. It is a very large molecule, composed of repeated units of glucosamine sulfate. Like glucosamine, chondroitin sulfate stimulates the production of cartilage. Likewise, it has the ability to prevent enzymes from dissolving cartilage. Chondroitin sulfate inhibits free radicals that degrade joint cartilage and collagen. It improves blood circulation to joints, which enables antioxidants and glucosamine to enter inflamed joints to stimulate the repair process required for the regression of osteoarthritis. Although the intestinal absorption of chondroitin sulfate is

much lower than that of glucosamine (10 to 15 percent versus 90 to 98 percent), a few studies have shown very good results (reducing pain and increasing range of motion) from long-term treatment with chondroitin sulfate.

A 3-year study investigated the effects of 800 mg of chondroitin sulfate on a group of people with osteoarthritis of finger joints. The results indicated that the chondroitin sulfate was well tolerated, significantly reduced pain, and increased joint mobility. In addition, the joints were protected from further erosive osteoarthritis (Verbruggen G et al 1998).

Improvement in walking time was studied in 80 patients with osteoarthritis of the knee. In this 6-month, double-blind study, the chondroitin sulfate dosage was 400 mg twice daily. The minimum time to perform a 20-meter walk showed a constant reduction of time only in the group who took chondroitin. Lower consumption of pain-killing drugs and excellent tolerability was also observed (Bucsi L et al 1998).

Sulfur. Animal studies have shown that joints affected by osteoarthritis have lower sulfur content (Rizzo R et al 1995). Arthritic mice given the sulfur-containing nutrient methylsulfonylmethane (MSM) experience less joint degeneration (Murav'ev I et al 1991). In a double-blind trial in people with osteoarthritis, study participants who received MSM by itself experienced significant pain relief (Lawrence RM 1998).

In a 2004 study, a combination of glucosamine and MSM was found to be more effective in improving the signs and symptoms of osteoarthritis than either agent alone (Usha PR et al 2004). After 12 weeks of treatment, the average pain score in the group that took only the glucosamine dropped from 1.74 to 0.65—a 63 percent reduction. In the group that took only MSM, the average pain score fell from 1.53 to 0.74—a 52 percent reduction. However, in the group that took both glucosamine and MSM, the average pain score dropped from 1.7 to 0.36—an astounding reduction of 79 percent! The researchers also found that the combination therapy had a faster effect on pain and inflammation than either glucosamine or MSM alone.

In another study, 50 patients with osteoarthritis, aged 40 to 76 years, were given 3 grams (g) of MSM or placebo twice daily for 12 weeks. At the end of the study, researchers concluded that the patients taking MSM experienced significant declines in pain and disease status (Kim LS et al 2006).

Green Tea Extracts. There is ample evidence to suggest that compounds found in green tea, including the polyphenol epigallocatechin gallate (EGCG), can interfere with the progression of osteoarthritis. During osteoarthritis, IL-1(b) causes an inflammatory response that enhances the expression and activity of matrix metalloproteinases, which are known to degrade cartilage. Studies have already shown that green tea extracts inhibited the expression of inflammatory cytokines in arthritic joints. Now newer studies are suggesting that EGCG can also inhibit the expression of IL-1(b) and matrix metalloproteinases (Ahmed S et al 2004). In a study of osteoarthritis, researchers found that EGCG was a potent inhibitor of IL-1(b)-induced cartilage damage (Singh R et al 2003). Additional studies have found that EGCG from green tea inhibits both IL-1(b) and the inflammatory cytokines COX-2 and inducible nitric oxide synthase, which are induced by IL-1(b) (Ahmed S et al 2002). Overall, laboratory studies have found that EGCG was nontoxic and that green tea consumption was effective at preventing osteoarthritis and may benefit patients who have osteoarthritis by reducing inflammation and slowing the breakdown of cartilage (Adcocks C et al 2002).

ANTIOXIDANTS AND OSTEOARTHRITIS

According to the newest research, oxidative stress seems to play a role in osteoarthritis (and rheumatoid arthritis) (Podoprigrorova VG et al 2005; Regan E et al 2005). Researchers found that human cartilage in patients with osteoarthritis was significantly deficient in superoxide dismutase, a major free-radical scavenger (Regan E et al 2005).

Because this research is so new, however, few studies have been conducted on the effectiveness of antioxidant supplementation in relieving symptoms and in slowing the progression of the disease. Nevertheless, because of the clear connection between oxidative stress and both rheumatoid arthritis and osteoarthritis, the Life Extension Foundation believes that people with either form of arthritis should maintain a healthy intake of antioxidants by taking vitamin E and vitamin C and other supplements that support glutathione levels such as N-acetylcysteine (NAC).

THE PROBLEM WITH CONVENTIONAL TREATMENT

Although nutritional approaches are the best option, millions of people still rely on prescription medications to manage their arthritis. Unfortunately, there just isn't a good solution when it comes to the standard prescription drugs. Even the best of them have serious drawbacks. Drugs used to treat arthritis include:

- **NSAIDs.** These drugs represent the mainstay of conventional treatment for arthritis. Over-the-counter NSAIDs, such as naproxen, ibuprofen, and others, operate by inhibiting the cyclooxygenase enzymes (COX-1 and COX-2), which convert arachidonic acid to pro-inflammatory prostaglandins. Adverse effects of over-the-counter NSAIDs include gastrointestinal upset, since the COX-1 enzyme is also partly responsible for protecting the lining of the stomach by maintaining its mucosal lining. In an attempt to reduce this side effect, prescription selective COX-2 inhibitors were introduced. These drugs, including

rofecoxib, valdecoxib, and celecoxib, were equally as effective as the older NSAIDs, without the side effects. In 2004, however, rofecoxib was linked to an increased risk of heart attack and cerebrovascular events. Rofecoxib was subsequently removed from the market by its manufacturer. Not long after, valdecoxib was also voluntarily removed because of the increased risk of cardiovascular events. Celecoxib is still on the market, but the Food and Drug Administration demanded that a strong black-box warning be added to its label, warning people who take this drug of the increased potential for heart attack.

- **Corticosteroids.** Prednisone, a corticosteroid, is used mainly as a treatment for rheumatoid arthritis. In severe cases of osteoarthritis, prednisone will be injected directly into the affected joints. Corticosteroids have significant adverse effects, and great caution should be used when taking them. Injections should be spaced months apart to avoid joint degeneration. Long-term systemic corticosteroid use is associated with a wide range of metabolic abnormalities, including weight gain, osteoporosis, stress fractures, stretch marks, and adrenal gland failure.
- **Narcotics.** Narcotics such as codeine and morphine are sometimes used to control pain in acute flare-ups of osteoarthritis. These drugs must be used in the short term because of the risk of dependency.
- **Acetaminophen.** Acetaminophen is a painkiller, as opposed to an anti-inflammatory. This drug is widely available over the counter, yet few people are aware of the significant danger of long-term acetaminophen use, which can cause liver toxicity. The Life Extension Foundation does not recommend acetaminophen.

In addition to these medications, physicians may recommend surgery for patients with severely damaged joints who have not responded to aggressive treatment. In this case, joint replacement may be recommended as a last resort.

LIFE EXTENSION FOUNDATION RECOMMENDATIONS

People who have osteoarthritis often benefit from exercise, including stretching and strength exercises. These exercises help to build the muscles around affected joints. Muscle weakness is a major cause of disability in people who have osteoarthritis.

It is extremely important that people with osteoarthritis launch their nutritional program as early in the disease process as possible. The goal is to provide nutrients to help rebuild damaged bone and cartilage. The following nutrients are recommended:

- **EPA and DHA**—1400 milligrams (mg)/day of EPA and 1000 mg/day of DHA
- **ASU**—300 to 600 mg/day
- **Curcumin**—900 mg/day, with 5 mg of piperine
- **Ginger**—60 mg/day
- **Bioflavonoids**—300 mg/day, including nobiletin
- **Nettle leaf extract**—375 to 500 mg/day
- **SAME**—400 to 1200 mg/day
- **Glucosamine**—1500 mg/day
- **Chondroitin**—1000 mg/day
- **MSM**—1000 to 3000 mg/day
- **Green tea extract**—725 mg/day of green tea powder, yielding at least 246 mg of EGCG
- **Vitamin C**—1 to 3 grams (g)/day
- **Vitamin E**—400 International Units (IU)/day, with 200 mg of gamma-tocopherol
- **NAC**—600 mg/day
- **Hyaluronic acid**—Most published studies have examined the benefits of intra-articular injections of hyaluronic acid. This treatment is effective in treating osteoarthritis of major joints. Discuss hyaluronic acid therapy with your physician.

OSTEOARTHRITIS 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:

Chondroitin Sulfate

- Consult your doctor before taking chondroitin if you are taking warfarin sodium or if you have hemophilia. Chondroitin can have antithrombotic activity.
- Use a salt-free chondroitin preparation if you need to restrict your salt intake.
- Chondroitin can cause gastrointestinal symptoms such as epigastric distress, nausea, and diarrhea.

Curcumin

- Do not take curcumin if you have a bile duct obstruction or a history of gallstones. Taking curcumin can stimulate bile production.
- Consult your doctor before taking curcumin if you have gastroesophageal reflux disease (GERD) or a history of peptic ulcer disease.
- Consult your doctor before taking curcumin if you take warfarin or antiplatelet drugs. Curcumin can have antithrombotic activity.
- Always take curcumin with food. Curcumin may cause gastric irritation, ulceration, gastritis, and peptic ulcer disease if taken on an empty stomach.
- Curcumin can cause gastrointestinal symptoms such as nausea and diarrhea.

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.

Ginger

- Do not take ginger if you have a bile duct obstruction or gallstones. Ginger may stimulate bile production.
- High doses of ginger (6 grams or more) can cause damage to the stomach lining and ulcers.
- Ginger can cause allergic skin reactions.
- Consult your doctor before taking ginger if you take blood thinners such as warfarin (Coumadin). Ginger can increase the risk of bleeding.

Glucosamine

- Consult your doctor before taking glucosamine if you have diabetes. It is unknown if glucosamine will increase insulin resistance in humans but glucosamine has been shown to increase insulin resistance in healthy animals and in animals with diabetes. Animals given intravenous glucosamine were found to have a significantly decreased rate of glucose uptake in their skeletal muscle (this effect was not observed, however, in animals given oral glucosamine).
- If you have diabetes, are overweight, or have difficulty with glucose tolerance and take glucosamine under medical advisement, monitor your blood glucose level frequently. Your doctor will need to adjust your medication levels accordingly.
- Glucosamine can cause gastrointestinal symptoms such as nausea and diarrhea.

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.

MSM

- MSM can cause headache or gastrointestinal symptoms such as nausea and diarrhea.

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.

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 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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