

## Rheumatoid Arthritis Arthritis Treatment

Rheumatoid arthritis (RA) is a degenerative autoimmune disease in which the joints are attacked by an abnormal immune response and slowly destroyed. RA is much less common than osteoarthritis (OA), occurring in about 1 percent of the population and affecting women two to three times more frequently than men. The first symptoms typically appear between the ages of 25 and 50, although it can occur at any age, even childhood (juvenile RA). Unlike OA, RA is a systemic disease. It can affect organ systems throughout the body, not just the joints. Problems associated with RA include inflamed blood vessels, heart attack, neuropathy, lung complications, and others.

Although about 10 percent of people with RA have a first-degree relative with the disease, genetic factors do not fully explain the incidence of RA. Some researchers have suggested that RA is a response to an infectious agent in a genetically susceptible person. If this is the case, the disease may be caused by persistent infection in the synovial tissues, which protect joints, or by microbial by-products that remain in the synovial tissues after infection. This theory would explain the immune system activation that targets synovial tissue. Other theories propose that such an infectious agent would involve proteins that trigger an immune response or that the infectious microorganism might prime the immune system to attack synovial tissue through “molecular mimicry,” in which proteins in the synovial fluid are mistaken for the infectious agent.

The earliest signs of RA are tiny injuries to the synovial membrane and an increase in the number of synovial cells. At this point, long before symptoms are experienced, there is evidence of immune cell penetration into the synovial membrane. Over time, the immune response continues to gain momentum and inflict damage on the synovial membrane.

This entire process is characterized by inflammation. Mast cells, which secrete pro-inflammatory cytokines, migrate into the synovium, along with by-products of other immune cells, including lymphocytes, macrophages, and fibroblasts. The result is an increase in cytokines, which is responsible for the symptoms of RA. The exact mechanism of bone and cartilage destruction during RA is not completely understood. One theory suggests that the pro-inflammatory cytokines interleukin-1 and tumor necrosis factor-alpha (TNF-alpha) stimulate the production of enzymes that degrade cartilage and inhibit the production of new cartilage and also contribute to the local demineralization of bone by activating osteoclasts (cells that break down bone) (Kasper DL et al 2005).

RA symptoms are caused by chemical messengers called cytokines. It is thought that the release of interleukin-1, TNF-alpha, and interleukin-6 into the circulation system may account for systemic symptoms such as malaise and fatigue. In fact, these symptoms, along with weakness and vague musculoskeletal symptoms, are often the first indication of any disease. They may last for weeks or months, during which time a diagnosis may be difficult to make. It is not until specific, joint-related symptoms appear that RA is diagnosed.

The joint-related symptoms of RA are different from those of OA in that they are generally symmetrical. Specific symptoms may begin to appear in joints of the hands, wrists, knees, and feet. These symptoms include pain that is aggravated by movement. Stiffness is also common, with morning stiffness that lasts longer than one hour occurring frequently. Infrequently, the joints may also be warm to the touch. Motion may be limited by inflammation of the joints.

No specific tests are used to diagnose RA. However, more than 65 percent of people with RA will have rheumatoid factors, or autoantibodies that are produced during the disease, in their blood. The results of testing for rheumatoid factors are not always correct, because up to 20 percent of people over age 65 have rheumatoid factors but do not suffer from RA. Also, a number of other diseases, such as systemic lupus erythematosus, Sjogren's syndrome, liver disease, hepatitis B, tuberculosis, and syphilis, are characterized by rheumatoid factors. Other tests that might help guide a physician, but will not confirm a diagnosis, include an examination of synovial joint fluid, biopsy of rheumatoid nodules, and increased erythrocyte sedimentation rate, which simply indicates that inflammation is present.

A definitive diagnosis of RA is usually made by identifying the characteristic symptoms of the disease. The disease is usually obvious within one to two years of its onset. To diagnose the disease, four of the following seven criteria are required:

- Morning stiffness lasting one hour before improvement
- Swelling and joint effusion in at least three different joints out of 14 specifically identified joints
- Swelling of wrist or finger joints specifically
- Symmetric swelling involving the same joint on both sides of the body
- Rheumatoid nodules

- Rheumatoid factors in the blood
- Typical changes seen in x-rays, including erosions or decalcification in involved joints.

## UNDERSTANDING AND TRACKING INFLAMMATION

Arthritis is not the only inflammatory disease that plagues aging humans. In fact, many degenerative diseases of aging are caused by inflammation, including atherosclerosis, Alzheimer's disease, heart failure, and cancer. Life Extension has devoted considerable resources to studying the inflammatory cascade and developing ways to inhibit it. But first it is important to understand what triggers the kind of inflammation that causes arthritis.

Aging results in an increase of inflammatory cytokines that contribute to diseases such as arthritis. In RA, inflammation is caused by cytokines such as TNF-alpha, interleukin-6, interleukin-1(b), and leukotriene B(4). These inflammatory cytokines have been shown to destroy joint cartilage and bone. In addition, the amount of inflammatory marker C-reactive protein is usually sharply elevated.

One of the persistent problems with arthritis therapy had been a lack of measurement tools, but it is now possible to track therapy by measuring the levels of these various cytokines in the blood, which give an accurate picture of the level of inflammatory stress caused by the disease.

### ***Inflammatory Cytokine Blood Reference Ranges***

There are at least three different methods of testing blood levels of pro-inflammatory cytokines. The table below shows the standard reference ranges for each type of test. Ideally, arthritis patients should strive to be at or below these cytokine ranges.

<b>Cytokine</b>	<b>Ideal Reference Range LabCorp</b>	<b>ISI</b>	<b>DPC</b>
TNF-alpha	Less than 8.1 pg/mL	10–50 pg/mL	0–8.1 pg/mL
Interleukin-6	Less than 12.0 pg/mL	2–29 ng/mL	0–9.7 pg/mL
Interleukin-1(b)	Less than 15 pg/mL	0–150 pg/mL	0–5 pg/mL
Leukotriene B(4)	N/A	300–750 pg/mL	N/A

C-reactive protein should also be measured regularly to track levels of inflammation. Levels more than 1.3–2.0 mg/L indicate that your body is under inflammatory stress.

## ANTICYTOKINE DRUGS AND ARTHRITIS TREATMENT

The Food and Drug Administration has approved three drugs that neutralize TNF-alpha for the treatment of RA: etanercept (Enbrel®), which binds to TNF-alpha; infliximad (Remicade®), which is a mouse/human antibody to TNF-alpha; and adalimumab (Humira®), which is a fully human antibody to TNF-alpha.

In early clinical trials, these drugs showed a remarkable ability to suppress signs and symptoms of RA in patients who experienced no relief with other drugs. The three drugs have been shown not only to reduce symptoms but to slow the progression of joint damage and relieve disability (Kasper DL et al 2005). Side effects include increased risk of serious infections and certain types of cancers.

Unfortunately, while these drugs are uniquely effective and hold out the promise of revolutionizing treatment for RA, they are prohibitively expensive and must be administered by injection. Because of their expense and side effects, researchers are looking for other ways to suppress TNF-alpha.

## NUTRITIONAL THERAPY FOR RA

The value of nutrients is well known when it comes to arthritis. Even conventional textbooks recommend that people with arthritis consume a diet rich in natural anti-inflammatories, antioxidants, and joint-supporting nutrients while avoiding pro-inflammatory foods that are high in sugar and saturated and trans-fatty acids. Some people also find relief by avoiding foods that contain gluten, such as wheat, rye, oats, and barley. Antiglutin antibodies have been found in many people with RA.

**Omega-3 fatty acids.** The omega-3 fatty acids are well-known anti-inflammatories that interfere with the underlying disease progression in RA. Studies have found that fish oil supplements, which are high in the omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), can reduce TNF-alpha and interleukin-6. In one human study with 60 patients, groups were randomly assigned to take fish oil supplements or placebo. No other dietary modifications were made. At the end of the study, there were significant differences in the levels of pro-inflammatory cytokines in the patients taking fish oil (Sundrarjun T et al 2004). Another study compared the value of a diet high in omega-3 fatty acids and low in pro-inflammatory arachidonic acid with a normal

Western diet (which tends to be pro-inflammatory). At the end of the study, patients on the anti-inflammatory diet experienced a 14 percent decrease in the number of swollen joints, while the patients on the Western diet experienced no change (Adam O et al 2003). These results have been supported by many other human studies demonstrating profound benefits of omega-3 fatty acids, including studies showing that some people can discontinue nonsteroidal anti-inflammatory drug (NSAID) treatment after beginning therapy with fish oil supplements (Kremer JM et al 1995).

**Gamma-linolenic acid.** Gamma-linoleic acid (GLA) is an omega-6 fatty acid that can be found in borage oil, evening primrose oil, and black currant seed oil. GLA is a precursor of anti-inflammatory prostaglandins such as prostaglandin E1 (PGE1), which has known anti-inflammatory and anti-autoimmune effects, and it decreases the activity of pro-inflammatory cytokines. Studies have shown that GLA decreases production of interleukin-beta, interleukin-6, and TNF-alpha in RA patients (Watson J et al 1993; Kast RE 2001). A study examining the effects of borage oil in RA patients demonstrated significantly decreased production of leukotriene B4, leukotriene C4, and prostaglandin E2 (PGE2) after 12 weeks of taking 1.1 g GLA daily (Pullman-Mooar S et al 1990).

**Boswellic acid (5-loxin).** Several chronic inflammatory disorders are thought to be perpetuated by leukotrienes (Ammon HP 2002). In Ayurvedic medicine, preparations from the gum resin of *Boswellia serrata* have been commonly used to treat inflammatory diseases such as RA. Boswellic acids act by binding to 5-lipoxygenase and inhibiting the synthesis of leukotriene (Ammon HP 2002). In addition, boswellic acid demonstrates the ability to reduce pro-inflammatory human leukocyte elastase activity (Safayhi H et al 1997)

**Curcumin.** Curcumin is a component of turmeric and is an anti-inflammatory compound that inhibits both COX-2 and lipoxygenase enzyme activity, along with decreasing levels of interleukin-beta (Plummer SM et al 1999; Banerjee M et al 2003). 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 arthritis. Researchers concluded 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. 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/antirheumatic agent used in Ayurvedic medicine (Srivastava KC et al 1992). Ginger extract blocks activation of pro-inflammatory mediators (Fronzoza CG et al 2004). In a study investigating the effects of powdered ginger in RA and OA patients over a 3-month to 2.5-year period, approximately 75 percent experienced pain relief and decreased swelling, and there were no reports of adverse effects (Srivastava KC et al 1992). A study examining the mechanism of action of ginger extract demonstrated that 100 mcg/mL significantly inhibited the activation of COX-2 and TNF-alpha, in addition to suppressing PGE2 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 grapefruit have been found to exert anti-inflammatory effects (O'Leary KA et al 2004; Manthey JA et al 2001).

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; Tanaka S et al 2004; Murakami A et al 2000b). 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 downregulate COX-2 without interfering with COX-1 (O'Leary KA et al 2004). In mouse macrophages, nobiletin was also shown to suppress production of PGE2 while interfering with pro-inflammatory cytokines such as interleukin-1 beta, TNF-alpha, and interleukin-6 (Ishiwa J et al 2000).

In addition, nobiletin demonstrated great anti-inflammatory activity (Murakami A et al 2000a). Through its effects in reducing inflammation, nobiletin may help 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 interleukin-beta-induced expression of matrix metalloproteinase (MMP), 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 capacity for partial inhibition of leukotriene and prostaglandin. A laboratory study examining the effects of 5 mg/mL nettle leaf extract on TNF-alpha and interleukin-1 in human whole blood demonstrated significant reductions in these cytokines. After 24 hours they decreased by 50 percent and 100 percent, respectively, and after 65 hours, inhibition rates were 40 percent and 100 percent, respectively (Obertreis B et al 1996).

**S-adenosyl-L-methionine.** S-adenosyl-L-methionine (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 also protect synovial cells by blocking the enzymes that degrade cartilage. It may also protect the important cartilage proteins and proteoglycans in the joint lining.

The pro-inflammatory cytokine TNF-alpha has been found in the synovial fluid of people with RA, and it plays a role in bone and cartilage destruction (Bertolini DR et al 1986). It has been demonstrated in synovial cells of rabbits in vitro that SAME reverses the effects of damage caused by TNF (Gutierrez S et al 1997).

## JOINT-PROTECTIVE AGENTS AND ARTHRITIS TREATMENT

Effective arthritis treatment 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.

**Glucosamine.** Glucosamine is a naturally occurring substance that is used to help build joints. While it is normally thought of in the context of OA, animal studies have indicated that it may also be a novel anti-inflammatory and joint-protective agent for people with RA. In one study, arthritic rats given glucosamine experienced a significant decrease in the progression of their disease (Hua J et al 2005). Glucosamine comes from the exoskeleton of certain shellfish and is available as glucosamine sulfate and N-acetyl-glucosamine. Glucosamine is almost totally free of side effects, particularly when compared with nonsteroidal anti-inflammatory drugs (NSAIDs), discussed below.

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

**Green tea extracts.** There is ample evidence to suggest that compounds found in green tea, including the polyphenol epigallocatechin-3-gallate (EGCG), can interfere with the progression of arthritis. During arthritis, interleukin-beta causes an inflammatory response that enhances the expression and activity of MMPs, which are known to degrade cartilage. Studies have already shown that green tea extracts inhibit the expression of inflammatory cytokines in arthritic joints, and newer studies suggest that EGCG can also inhibit the expression of interleukin-beta and MMPs. Studies have suggested that EGCG from green tea also inhibits the inflammatory cytokines COX-2 and inducible nitric oxide synthase, which are induced by interleukin-beta (Ahmed S et al 2002, 2004). Overall, laboratory studies found that EGCG was nontoxic and that green tea consumption was effective at preventing arthritis and may benefit arthritis patients by reducing inflammation and slowing the breakdown of cartilage (Adcocks C et al 2002).

## ANTIOXIDANTS AND ARTHRITIS

According to recent research, oxidative stress seems to play a role in causing both RA and OA (Popoprigrorova VG et al 2005; Regan E et al 2005). Researchers have found that patients with RA have significantly elevated levels of oxidative products in their blood, leading the researchers to propose that the effectiveness of RA therapy could in part be measured by the level of oxidative stress (Cai WC et al 2005; Sarban S et al 2005). Another study demonstrated that levels of important antioxidants, including vitamin E, glutathione, and beta-carotene, were all reduced in RA, leading researchers to conclude that oxidant stress "plays a very important role in the pathogenesis of RA" (Kamanli A et al 2004).

Also, studies have documented that adequate intake of antioxidants including vitamin C and vitamin E, as well as the minerals copper and zinc, may help reduce older women's risk of developing RA (Cerhan JR et al 2003; Goggs R et al 2005).

Because this research is so new, however, few studies have been conducted on the effectiveness of antioxidant supplementation in existing cases of RA to relieve symptoms and possibly slow progression of the disease. Nevertheless, because of the clear connection between oxidative stress and both RA and OA, Life Extension believes that patients with either form of arthritis should maintain a healthy supply of antioxidants by supplementing with vitamin E, vitamin C, and supplements such as N-acetylcysteine, which support glutathione levels.

## THE HORMONE CONNECTION

It is well known that hormone levels are affected by arthritis, especially RA. Studies have shown that women with RA have lower levels of testosterone and DHEA, while they have normal or elevated levels of estrogen (Straub RH et al 2005). These altered levels may be due to the effects of TNF-alpha, which alters production of androgen hormones (Straub RH et al 2005). This elevated estrogen in RA patients is thought to be connected to the enzyme aromatase, which converts androgens into estrogens, including pro-inflammatory estrogens such as 17 beta-estradiol (Capellino S et al 2005). In fact, in women with RA, the entire balance of estrogen, including the ratio between 16-hydroxylated estrogen and 2-hydroxylated estrogen, seems to be upset in favor of pro-inflammatory estrogens (Cappellino S et al 2005). Finally, local levels of hormones such as insulin, aldosterone, and growth hormone, are elevated in arthritis, suggesting that these hormones also play a pro-inflammatory role (Rovensky J et al 2005).

Because of the variability in hormone levels, researchers have examined the role of DHEA in various forms of arthritis. In the body, DHEA can be converted to both estrogen and testosterone. Hoping to learn whether DHEA can help normalize hormone levels among women with arthritis, researchers have conducted human studies, giving women DHEA and carefully following their hormone levels. In one study of 26 OA patients and 24 RA patients, hormone conversion rates were analyzed. Researchers found that DHEA was converted into a variety of hormones, including anti- and pro-inflammatory estrogens and testosterone, which were further converted into anti-inflammatory metabolites (Schmidt M et al 2005).

DHEA is also known to directly suppress pro-inflammatory cytokines, including interleukin-6 and TNF-alpha, both of which contribute to the joint inflammation that characterizes RA. Research is also shedding new light on the relationship between anti-TNF-alpha drugs, such as Enbrel®, and DHEA. Studies have shown that levels of active DHEA are reduced in the synovial cells of patients with RA. After therapy with anti-TNF drugs, however, the conversion of DHEA into its active form is increased, which would help explain why these drugs have an anti-inflammatory effect (Weidler C et al 2005; Imrich R et al 2005).

## THE PROBLEM WITH CONVENTIONAL DRUGS

Although nutritional approaches are the best option, many 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 among them have serious drawbacks that should give pause. The following drugs are used to treat arthritis:

- **NSAIDs.** These drugs represent the mainstay of conventional treatment for arthritis. Over-the-counter NSAIDs, such as naproxen (Aleve®), ibuprofen, and others, operate by inhibiting the cyclooxygenase enzymes (COX-1 and COX-2), which convert arachidonic acid to pro-inflammatory PGE2. Side effects of over-the-counter NSAIDs include gastrointestinal upset because the COX-1 enzyme is also partly responsible for maintaining the mucosal lining of the stomach. In an attempt to reduce this side effect, prescription-selective COX-2 inhibitors were introduced. These drugs, including Vioxx®, Bextra®, and Celebrex®, were as effective as the older NSAIDs and did not produce the side effects. In 2004, however, Vioxx® was linked to increased risk of heart attack and cerebrovascular events. It was subsequently removed from the market by its manufacturer. Not long after, Bextra® was also voluntarily removed because of increased risk of cardiovascular events. Celebrex® is still on the market, but the Food and Drug Administration has demanded that a strong "black box" be added to its label, warning people who take this drug of the increased potential for heart attack.
- **Slow-acting drugs.** This type of drug includes gold compounds, penicillamine, hydroxychloroquine, and sulfasalazine. These drugs slow the progression of RA by interfering with the disease process. For example, gold compounds and penicillamine slow the formation of bone deformities. All these drugs can cause liver and kidney toxicity. Other side effects include rashes, stomach upset, and itching. They are sometimes recommended for patients who cannot tolerate NSAIDs.
- **Corticosteroids.** Prednisone, a corticosteroid, is used mainly as a treatment for RA, although in severe cases of OA, it will be injected directly into the affected joints. Corticosteroids work by reducing inflammation, and some evidence suggests that prednisone may slow bone erosion in RA (Kasper DL et al 2005). Whether these drugs are used as a systemic treatment (for RA), or injected directly into joints (for OA), corticosteroids have significant side effects and should be used with great caution. 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.
- **Immunosuppressive drugs.** These drugs are sometimes used in RA to suppress the immune response that causes disease progression. Common immunosuppressive drugs used in RA include azathioprine, leflunomide, cyclosporine, and cyclophosphamide. These drugs are not considered first-line therapy. Studies have shown they are no more effective than slow-acting drugs (Kasper DL et al 2005), and they have a variety of toxic side effects, including liver damage and the increased risk of opportunistic infection because of a depressed immune system.
- **Narcotics.** Narcotics such as codeine and morphine are sometimes used to control pain in acute flare-ups. These drugs must be used only 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.

Life Extension does not recommend acetaminophen.

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

## LIFE EXTENSION FOUNDATION RECOMMENDATIONS

As with any disease, it is important to regularly track your progress and begin treatment early. People who suffer from arthritis should consider a cytokine profile and C-reactive protein blood test to measure the levels of inflammation throughout their body. These initial measurements provide a baseline for tracking disease therapy. Both of these tests are available through the Life Extension by calling 1-800-208-3444.

Exercise is not very effective with RA because of the underlying nature of the disease. Many people with RA find that regular resting periods for their joints helps to relieve symptoms.

- **EPA and DHA**—2100 milligrams (mg) EPA and 1500 mg DHA daily
- **GLA**—900 to 1800 mg daily
- **Boswellic acid**—300 mg daily
- **Curcumin**—900 mg daily, with 5 mg Bioperine® piperine
- **Ginger**—60 mg daily
- **Bioflavonoids, including nobiletin**—300 mg daily
- **Nettle leaf extract**—375 to 500 mg daily
- **SAME**—400 to 1200 mg daily
- **Glucosamine**—500 mg daily
- **Green tea extract**—725 mg green tea powder daily, yielding at least 246 mg of EGCG
- **Vitamin C**—1 to 3 grams (g) daily
- **Vitamin E**—400 international units (IU) daily (with at least 200 mg gamma tocopherol)
- **N-acetylcysteine**—600 mg daily
- **DHEA**—15 to 75 mg daily, with blood testing after 3 to 6 weeks to determine optimal levels

In addition, a hormone blood test may reveal a testosterone deficiency and high levels of pro-inflammatory estrogen metabolites. In this case, bioidentical hormone therapy may be recommended. For more information, call 1-800-544-4440.

## PRODUCT AVAILABILITY

All the nutrients and supplements discussed in this section are available through the Life Extension Foundation Buyers Club, Inc. For ordering information, call anytime toll-free 1-800-544-4440, or visit us online at [www.LifeExtension.com](http://www.LifeExtension.com).

The blood tests discussed in this section are available through Life Extension National Diagnostics, Inc. For ordering information, call anytime toll-free 1-800-208-3444, or visit us online at [www.LifeExtension.com](http://www.LifeExtension.com).

## RHEUMATOID ARTHRITIS 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:

### 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.

### DHEA

- Do not take DHEA if you could be pregnant, are breastfeeding, or could have prostate, breast, uterine, or ovarian cancer.
- DHEA can cause androgenic effects in woman such as acne, deepening of the voice, facial hair growth and hair loss.

## **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.

## **GLA**

- Consult your doctor before taking GLA if you take warfarin (Coumadin). Taking GLA with warfarin may increase the risk of bleeding.
- Discontinue using GLA 2 weeks before any surgical procedure.
- GLA can cause gastrointestinal symptoms such as nausea and diarrhea.

## **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.

## **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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