

Muscular Dystrophy

Muscular dystrophy (MD) is a family of genetic disorders characterized by progressive muscle weakness, loss of muscle function, and wasting. Despite many years of intensive research—and heavy publicity—aimed at conquering this tragic disease, patients rarely survive past 30 years of age.

The many forms of MD are distinguished on the basis of their chief characteristics. They may be categorized according to the ways symptoms manifest, such as where, precisely, muscle weakness occurs primarily, or at what age symptoms commence, or in what manner the disorder is inherited. For instance, the most common form, Duchenne muscular dystrophy (DMD), is passed only from a female parent to her son(s). In addition to being the most common form of MD, DMD (also known as Meryon's disease) is the second most common childhood genetic disease, afflicting one of every 3330 to 3500 boys born worldwide (Tidball JG 2004 et al).

DMD is also defined by the specific genes it affects. There are many other varieties of MD, characterized by the muscular groups involved, the age of onset, and other criteria. Most forms of MD result from mutations in genes that ordinarily code for a variety of proteins and enzymes associated with the structure and function of muscle cells. DMD and Becker MD, for example, are associated with a deficiency of the protein dystrophin. Other MDs are associated with deficiencies in additional proteins (Guglieri M et al 2005). Half of congenital MD cases, for instance, involve a deficiency of merosin (Nieto-Ceron S et al 2005).

Unless otherwise noted, in this discussion DMD will be considered representative of the general MD family of diseases and referred to in particular. Although specifics may not apply to all forms of MD, the general principles involved are similar. It should be noted, however, that there is wide variability among specific subtypes of muscular dystrophies in terms of the age of onset, patterns of skeletal muscle involvement, rate of complications such as heart damage, rate of progression, and mode of inheritance (Guglieri M et al 2005).

UNDERSTANDING MD

To understand MD, it is necessary to delve into the molecular realm of genes and cells, where an inheritable mutation of a specific gene results in failure to produce a viable protein. Dystrophin, the protein affected in DMD, is a minor, yet crucial, component of every muscle cell. It forms part of the flexible framework of filaments, tubules, and other structures within the cell. This network, called the cytoskeleton, provides every cell with structure, shape, and function. Communications within the cell depend on the compounds of the cytoskeleton to work properly, so when dystrophin or any other component fails to function, there is serious disruption of the cell's ability to operate.

Among patients suffering from any of the muscular dystrophies, serum levels of creatine kinase, an enzyme involved in energy storage and expenditure, rise. It has been proposed that the absence of dystrophin in MD patients' muscle may lead to damage of the muscle cell membranes. Cell membranes are responsible for the selective passage of various nutrients, gases, and wastes. Damage to muscle membranes is believed to allow creatine kinase to escape from the cells into the bloodstream (Leighton S 2003). There is some indication that supplementation with creatine may delay or alleviate some of the muscle deterioration associated with MD (Louis M et al 2003; Felber S et al 2000).

DMD is associated with a notable loss of muscle mass. As muscle cell membranes degrade, fibers are replaced at first by connective tissue and then by fat. In time, only residual areas of muscle fibers remain, adrift in a pool of fat. Usually beginning with the upper thigh and buttocks muscles, and eventually including the muscles associated with breathing and the specialized muscle cells of the heart, the progressive loss of muscle function ultimately forces patients to rely on wheelchairs and ventilators until death comes at approximately 20 years of age. Death is usually due to respiratory failure, although heart problems may also contribute (Leighton S 2003).

Dystrophin has also been identified in the brain, although its function in that organ remains unclear. In any event, its absence appears to also affect neurological function in patients with DMD, as they are known to experience cognitive and intellectual deficits, as well as occasional emotional problems and a reading disability similar to a common type of dyslexia (Leighton S 2003; Anderson JL et al 2002; Billard C et al 1998; Dubowitz V 1995).

TREATMENT OPTIONS

Numerous treatments for MD have been proposed and investigated, but results have been largely disappointing. Few approaches offer even marginal improvements in prognosis. But there is some cause for hope. Recent research suggests that certain

approaches may delay degeneration, prolonging life and providing a more comfortable existence. In the long run, it is likely that gene therapy offers the best hope for an actual cure. But this line of inquiry is in its infancy, and many obstacles remain to be overcome before a true cure for this deadly genetic disease is achieved (Tidball JG et al 2004). Other future treatments may include transplantation of stem cells or muscle precursor cells that will proliferate and replace defective, dystrophin-deficient muscle cells (Tidball JG et al 2004).

The lack of a true cure renders the development of palliative treatments—intended to improve quality of life and reduce symptoms—all the more important. Scientists are still learning about dystrophin deficiency and how to minimize its effects. Currently, several approaches promise some modest benefits.

STEROID THERAPIES

The normal growth and maintenance of muscle mass is accompanied by some degradation and regeneration of muscle tissue, but this process is grossly imbalanced in MD. Regeneration fails to keep pace with inflammation and disintegration. By definition, anabolic steroids enhance muscle building, so steroids have been investigated for their potential in MD. But anabolic steroids, such as the male hormone testosterone, also tend to be androgenizing; they trigger masculinization effects, which, in addition to beefing up muscle, include promotion of beard and body hair growth, maturation of genitalia, and development of acne, among others.

Early attempts to harness the potential of testosterone were only partially successful. While they initially improved muscle mass, they failed to increase strength, and the numerous side effects became problematic (Griggs RC et al 1989). Later attempts with synthetic anabolic steroids, such as those abused by body builders and some unscrupulous professional athletes, have yielded mixed results. Synthetics such as norethandrolone and methandrostenolone provided some initial benefits, but young boys contended with premature development of secondary sex characteristics, and far worse, when treatment was halted, rapid and severe deterioration in muscle mass and function ensued (Tidball JG et al 2004).

Newer synthetic steroids, such as oxandrolone, offer fewer side effects and the promise of decreased muscle degeneration (Balagopal P et al 2006; Orr R et al 2004). Oxandrolone is considered particularly promising because it provides benefits on two fronts. While it enhances muscle building, like other anabolic steroids, it also interferes with the binding of the hormone cortisol to glucocorticoid receptors on muscle, thus preventing muscle breakdown. Among burn victims who have received this treatment, increases in lean body mass (largely muscle) continued for up to six months after treatment ceased. This bodes well for MD patients, for whom withdrawal of anabolic steroids is often accompanied by rapid decline in muscle mass.

Glucocorticoid drugs, including corticosteroids such as prednisone and deflazacort, have become fairly standard treatment for MD (Balaban B et al 2005; Manzur AY et al 2004). Among other things, they have been shown to delay degeneration of heart function. At best, they improve motor function and delay breakdown of existing muscle (Beenakker EA et al 2005). Studies show that these drugs may prolong the time a patient remains capable of walking and delay the onset of spinal curvature (scoliosis), which is a common development in the progression of the disease (Yilmaz O et al 2004). But improvements tend to be short lived, lasting on average from six months to two years. And side effects range from growth suppression and excessive weight gain to osteoporosis. Like all existing treatments for the various forms of MD, glucocorticoids are ultimately powerless to halt the eventual progression of the disease.

NUTRITIONAL SUPPORT

Nutritional support, although often overlooked, is especially important in order to improve quality of life. Antioxidants and anti-inflammatories offer some benefit. So does exercise, especially early in life. But studies have shown that the ability of affected muscle to regenerate and repair itself may quickly become overwhelmed, at which point further exercise becomes counterproductive.

Creatine supplementation. Long used as a supplement by bodybuilders to enhance strength and endurance, creatine may also benefit MD patients. Creatine is an “energy precursor” that is naturally produced by the body (Passaquin AC et al 2002). Transformed by the body into phosphocreatine, it enters muscle cells and promotes protein synthesis while reducing protein breakdown. In healthy individuals, creatine has been shown to enhance endurance and increase energy levels by preventing depletion of the body’s primary energy-storage compound, adenosine triphosphate (Persky AM et al 2001). Among MD patients, studies have suggested that supplemental creatine can improve muscle performance and strength, decrease fatigue, and slightly improve bone mineral density.

A small, randomized, double-blind, placebo-controlled crossover study in Belgium assessed the effects of creatine supplementation on 12 boys afflicted with DMD and three with Becker MD (Louis M et al 2003). Participants received either 3 g creatine or placebo daily for three months, followed by a two-month washout period. They then received the opposite substance for another three months. After each phase of the study, doctors assessed the boys’ strength, bone and joint health, and fatigue levels.

When the boys were given placebo, they exhibited no change in maximum voluntary muscle contraction (a quantitative measure of

strength). Likewise, resistance to fatigue remained unchanged, while joint stiffness worsened by 25 percent. But after taking creatine for three months, the boys' strength increased by 15 percent, and resistance to fatigue actually doubled. Joint stiffness remained unchanged. Furthermore, a biochemical marker of bone tissue degradation decreased by an impressive two-thirds.

Among the five boys who were able to walk at the beginning of the study, bone mineral density increased by 3 percent after the creatine supplementation phase of the study. MD patients frequently suffer from osteoporosis, in which bone mineral density declines, rendering bones fragile.

A somewhat larger study conducted in Ontario, Canada, assessed the effects of creatine supplementation (100 mcg daily per kilogram of body weight) on 30 participants for four months. Again, researchers found that bone degradation decreased when participants were taking creatine, and strength (measured by dominant hand grip strength) increased. The same was not true during the placebo phase. Researchers noted that creatine was well tolerated, and fat-free mass increased (Tarnopolsky MA et al 2004).

Other studies on patients with myotonic dystrophy have been somewhat less encouraging, although creatine may still be of some benefit for them. In one German study, scientists randomly assigned 34 myotonic patients to receive either 10.6 g creatine daily or placebo. After eight weeks, "creatine supplementation was well tolerated, without relevant side effects," the researchers concluded. But, disappointingly, there was no statistically significant improvement in muscle strength or daily-life activities (Walter MC et al 2002).

Another double-blind crossover study considered creatine's effects on a variety of MD types, including 12 facioscapulohumeral patients, 10 Becker and eight DMD boys, and six limb-girdle MD patients. After eight weeks, patients who received creatine exhibited "mild but significant improvement in muscle strength and daily-life activities." Creatine was well tolerated throughout the study (Walter MC et al 2000).

In another study, Austrian researchers administered creatine to one 9-year-old boy with DMD for more than five months. The patient subsequently demonstrated "improved muscle performance." Magnetic resonance imaging of calf muscle function supported this finding (Felber S et al 2000).

Another study examined the effects of creatine supplementation alone and in combination with the corticosteroid drug prednisolone on mouse models of MD. The study also investigated the effects of conjugated linoleic acid, alpha-lipoic acid, and hydroxyl-beta-methylbutyrate, alone and in combination with creatine and prednisolone. Each of the supplements showed some benefit when given alone, but the combination of all four with the corticosteroid "provided the most consistent evidence of efficacy." Efficacy, or effectiveness of therapy, was assessed in terms of increased strength and decreased fatigue, among other parameters (Payne ET et al 2006).

Green tea. Green tea has been credited with diverse benefits, ranging from protection of the skin from the damaging rays of the sun (Morley N et al 2005; Katiyar SK 2003; Katiyar SK et al 2001) to protection against numerous cancers, to improvements in cardiovascular health and protection against neurological decline (Zaveri NT 2006; Cooper R et al 2005).

Recently, scientists in Switzerland published the results of a study conducted on mouse models of MD. These "mdx" mice were fed ordinary chow, chow containing green tea extract, or green tea's major bioactive polyphenol compound, epigallocatechin gallate (EGCG). After feeding the animals for either one or five weeks, the researchers examined the rodents' muscle tissue microscopically for signs of the damage associated with the progression of their MD-like disease. "Diet supplementation . . . with green tea extract or [EGCG] protected muscle against the first massive wave of necrosis and stimulated muscle adaptation toward a stronger and more resistant phenotype," concluded the Swiss researchers (Dorchies OM et al 2006).

Green tea polyphenols, such as EGCG, are known to be powerful antioxidants. Because inflammation is involved in the degradation of muscle tissue in MD, oxidative stress is believed to play a role in this process. Green tea and its active constituents may improve MD prognosis by reducing this oxidative stress (Buetler TM et al 2002). In an earlier experiment with mdx mice, the same Swiss team gave varying concentrations of green tea extract to mice for four weeks, beginning at birth. On examining various muscles, they determined that the extract significantly reduced the degradation of certain muscles and noted that higher doses correlated with greater inhibition of decline. There was also biochemical evidence that green tea extract reduced oxidative stress in muscle cells. The effective dosage of extract used in this study corresponds to about seven cups of brewed green tea per day in humans, rendering its use in DMD patients feasible (Buetler TM et al 2002).

Coenzyme Q10. Coenzyme Q10 (CoQ10; also called *ubiquitin*) is a powerful antioxidant and mitochondrial respiratory chain cofactor. It possesses membrane-stabilizing properties and is capable of penetrating cell membranes and mitochondria. Mitochondria serve as cellular powerhouses, generating energy to power life's many processes. Muscle cells expend a great deal of energy and are rich in mitochondria. As an essential cofactor, CoQ10 acts to facilitate a complex series of reactions that occur within the mitochondria. Known as the respiratory chain, these chemical reactions ultimately supply energy, which may be stored for later use or readily expended.

Given its importance in this process, scientists wondered if supplemental CoQ10 might improve the prognosis of MD patients, who suffer from declining muscle strength and deficient energy metabolism within muscle cells. Scientists at the University of Texas conducted double-blind investigative trials of daily CoQ10 supplementation in a dozen patients with a variety of muscular dystrophies, including DMD and Becker, limb-girdle, and myotonic dystrophy. Participants received either 100 mg CoQ10 daily for three months or placebo. A second trial, with a comparable treatment protocol, enrolled 15 patients with a similar mix of MD. The scientists concluded that participants' physical performance was "definitely improved" and added, "Patients suffering from these muscle dystrophies and the like, should be treated with [Coenzyme] Q10 indefinitely." Although patients received 100 mg CoQ10 daily and the treatment was considered effective and safe, the researchers noted that the most effective dose is probably larger (Folkers K et al 1995).

Further evidence of the link between MD and CoQ10 deficiency was reported by Italian researchers who investigated CoQ10 levels in myotonic dystrophy patients. "Serum CoQ10 appeared significantly reduced with respect to normal controls," they reported. In subsequent experiments on patients with Steinert's myotonic dystrophy, they discovered that patients with the greatest degree of genetic mutation tended to have the lowest levels of CoQ10, a finding that at least suggests that CoQ10 deficiency is indeed related to the deficient energy metabolism of muscle cells in MD patients (Siciliano G et al 2001; Tedeschi D et al 2000)

Calcium and vitamin D. By the time they reach 10 years of age, many boys with MD will have lost the ability to walk. Confined to a wheelchair, they inevitably develop bone-weakening osteoporosis, although the process often begins before patients become wheelchair bound (Aparicio LF et al 2002; Larson CM et al 2000). In fact, although bone density in MD has received relatively little attention, one study investigated bone health in 32 DMD patients and found that bone mineral density in all patients was lower than normal for children of comparable ages. This indicator of declining bone health was especially advanced in patients on corticosteroid therapy. The scientists also found that patients had lower-than-normal levels of a form of bioactive vitamin D (Bianchi ML et al 2003). Although no formal clinical trials have been conducted on providing supplemental vitamin D and calcium to MD patients, the practice has been recommended by at least one MD researcher (Leighton S 2003).

In normal individuals, vitamin D and calcium are known to play a crucial role in the maintenance of healthy bone mineralization and density. Although vitamin D is generated within the body in response to adequate sunlight, exposure to sunlight sufficient to guarantee an adequate supply of vitamin D may be problematic. This is especially true in the northern latitudes during winter months. Research shows that winter sunlight is simply too weak in such areas for the body to generate adequate vitamin D (Webb AR et al 1988). Even in southern latitudes, vitamin D levels may drop sufficiently during winter to contribute to osteoporosis among otherwise healthy aging men and women (Levis S 2005).

Glutamine. Glutamine is involved in many metabolic processes. It is an important energy source for many cells.

Some researchers have suggested that glutamine may be "conditionally essential" in DMD because the ability to synthesize glutamine is impaired in MD patients (Hankard R et al 1999). Scientists in Florida administered oral glutamine to six boys with DMD and monitored indicators of protein synthesis and degradation. They concluded, "Acute oral glutamine administration might have a protein-sparing effect" in the boys (Hankard RG et al 1998).

More recently, a larger, double-blind, placebo-controlled clinical trial looked at the effects of six months of supplementation with oral glutamine and creatine on 50 boys with MD. Results were tantalizing but ultimately inconclusive. "Although there was no statistically significant effect of either therapy based on manual and quantitative measurements of muscle strength," wrote researchers, "a disease-modifying effect of creatine in older Duchenne muscular dystrophy, and creatine and glutamine in younger Duchenne muscular dystrophy cannot be excluded." Both treatments were well tolerated (Escobar DM et al 2005).

Arginine and utrophin. The most prevalent forms of MD are caused by lack or inadequacy of the cytoskeletal protein dystrophin. A related protein, utrophin, is not affected by the MD mutations responsible for dystrophin deficiency. Because utrophin is 80 percent similar to dystrophin, and evidence suggests that it may fulfill many of the same functions as dystrophin, scientists have proposed that utrophin may serve as an effective substitute for dystrophin in the muscle cells of MD patients. Therefore, any substance that promotes an increase in production of utrophin may be of benefit in treating MD.

In the late 1990s, French scientists showed that feeding supplemental arginine to mdx mice enhanced production of utrophin (Chaubourt E et al 1999). They also showed that this increase was likely mediated by arginine-fueled production of nitric oxide (NO), which plays an important role in blood vessel function and is generally lower in people with MD (Kasai T et al 2004). In subsequent experiments, the same team demonstrated that both healthy and MD-model muscle cells can be prompted to produce greater amounts of utrophin by supplying the NO substrate, arginine, or an NO donor compound (Chaubourt E et al 2002).

A team of scientists in the United States investigated this effect and came to similar conclusions. They administered L-arginine (the bioactive form of the amino acid) to both normal and mdx mice. Muscle cells from treated mdx mice were less susceptible to exercise-induced damage, and the animals exhibited decreased muscle cell death. An increase in utrophin was also noted in muscle cells of treated mice, which contributed to a decrease in muscle degradation (Barton ER et al 2005).

Aside from stimulating production of utrophin, arginine and other chemicals that increase NO may also benefit MD patients by stimulating muscle regeneration. Brazilian scientists administered mdx mice a drug that serves as an NO donor, while other mice received placebo or other drug treatment, for 20 days. Muscle fiber regeneration was increased by 20 percent only in the mice given the NO-donor drug, isosorbide dinitrate (ISD). "These results suggested that NO derived from ISD stimulated and/or recruited satellite cells," wrote the researchers. "Pharmacological treatment with ISD could be clinically useful for improving muscle regeneration in Duchenne muscular dystrophy" (Marques MJ et al 2005).

Canadian scientists published the results of a study recently suggesting that the combination of arginine and deflazacort (a standard corticosteroid drug used in the treatment of MD) is more beneficial than deflazacort alone. Mdx mice were treated for three weeks with deflazacort, placebo, or deflazacort plus arginine. They were subsequently assessed for evidence of muscle degeneration and regeneration initiated by 24 hours of voluntary exercise. Although deflazacort alone prevented the progressive loss of function that ordinarily occurs in such mice, the deflazacort/arginine combination yielded still more impressive protection from exercise-induced muscle damage and "induced a persistent functional improvement in distance run." According to the scientists, these results offer a new treatment option that might improve quality of life (Archer JD et al 2006).

Taurine. There is some evidence that the amino acid taurine may be of benefit in the symptomatic treatment of MD. Taurine is abundant in normal skeletal muscle and is believed to exert both long- and short-term control over the functionality of ion channels (Conte Camarino D et al 2004). These channels serve as passageways between the interior of a cell and the cell's external environment. An excessive influx of calcium ions into MD muscle cells is believed to play a significant role in the inflammation and pathology associated with the disease (Ruegg UT et al 2002). Accordingly, regulation of ion channel function would appear to play an especially important role in the management of MD.

In ordinary laboratory rodents, it has been shown that aging is associated with biochemical changes that decrease muscles' ability to contract. These changes are accompanied by a decrease in muscle cell taurine content. When taurine becomes depleted in adult rat muscle cells, biochemical changes similar to those seen in aged rats occur. When aged rats are fed supplemental taurine, these changes may be reversed (Pierno S et al 1998).

Building on this preliminary research, Italian scientists investigated taurine's potential to influence muscle status in mdx mice. To test taurine's effects in MD, the researchers treated mdx mice with taurine or other substances for four to eight weeks. The animals were subjected to chronic exercise on a treadmill, an activity known to worsen symptoms of MD. Afterwards, animals were evaluated for various indicators of declining or improving muscle functionality. "Exercise produced a significant weakness," researchers reported. But taurine "counteracted the exercise-induced weakness." Among the substances tested, this counteraction effect was strongest for taurine. "The results predict a potential benefit of taurine . . . for treating human dystrophy," the researchers concluded (De Luca A 2001, 2003).

ANTI-INFLAMMATORY THERAPY

Inflammation is playing an increasingly large role in the research regarding MD. Physicians are steadily gaining knowledge and insight into the inflammatory changes that are responsible for much of the actual damage associated with many diseases, including MD. This progress opens up the possibility for new, targeted treatment that would interfere with the inflammatory cascade, thus limiting muscle damage and slowing the disease. Although most of this research remains speculative, there appears to be great promise in anti-inflammatory therapies for MD (Tidball JG et al 2005).

Scientists have shown that chronic inflammation in DMD results from the coordinated activity of numerous components, including cytokine and chemokine signaling, white blood cell adhesion, and complement system activation, among others (Porter JD et al 2002).

The omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), primarily obtained from fish oil, have repeatedly been shown to exert anti-inflammatory effects when consumed in sufficient quantities (Ferrucci L et al 2006; La Guardia M et al 2005). Omega-3s are crucial components of cell membranes, where they contribute to stabilization and healthy function (Zamaria N 2004). Accordingly, at least one scientist has proposed that supplemental omega-3 fatty acids may be of some benefit in the nutritional support of MD patients (Leighton S 2003).

LIFE EXTENSION FOUNDATION RECOMMENDATIONS

Although advances in molecular biology, genetics, pharmacology, and stem cell research represent the best hope for an eventual cure, at present the muscular dystrophies remain a family of genetic disorders that are debilitating and ultimately fatal. Advances in palliative care have extended life span somewhat, however, and nutritional approaches to patient support should not be dismissed. They offer a potential means of delaying degeneration, promoting muscle regeneration, and thwarting destructive inflammation, thus improving quality of life.

The following supplements may be beneficial to MD patients:

- **Creatine**—1000 to 3000 milligrams (mg) daily on an empty stomach
- **Green tea extract**—725 mg daily (at least 93 percent polyphenols)
- **CoQ10**—100 mg or more daily
- **Vitamin D**—400 to 1000 international units (IU) daily
- **Calcium**—1000 to 2000 mg daily
- **Glutamine**—1000 mg daily
- **Arginine**—900 to 2700 mg daily
- **Taurine**—1000 to 3000 mg daily
- **EPA/DHA**—1400 mg EPA and 1000 mg DHA daily

PRODUCT AVAILABILITY

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.

MUSCULAR DYSTROPHY SAFETY CAVEATS

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

Calcium

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

Coenzyme Q10

- See your doctor and monitor your blood glucose level frequently if you take CoQ10 and have diabetes. Several clinical reports suggest that taking CoQ10 may improve glycemic control and the function of beta cells in people who have type 2 diabetes.
- Statin drugs (such as lovastatin, simvastatin, and pravastatin) are known to decrease CoQ10 levels.

Creatine

- Do not take creatine if you have diabetes, kidney failure, a kidney disorder such as nephrotic syndrome, or are otherwise at risk of having a kidney disorder.
- If you take creatine, have your serum creatinine level monitored frequently.
- Creatine can cause muscle cramping, muscle strains, and 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.

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.

L-Arginine

- Do not take L-arginine if you have the rare genetic disorder argininemia.
- Consult your doctor before taking L-arginine if you have cancer. L-arginine can stimulate growth hormone.
- Consult your doctor before taking L-arginine if you have kidney failure or liver failure.
- Consult your doctor before taking L-arginine if you have herpes simplex. L-arginine may increase the possibility of recurrence.

L-Glutamine

- Consult your doctor before taking L-glutamine if you have kidney failure or liver failure.

- L-glutamine can cause gastrointestinal symptoms such as nausea and diarrhea.

Vitamin D

- Do not take vitamin D if you have hypercalcemia.
- Consult your doctor before taking vitamin D if you are taking digoxin or any cardiac glycoside.
- Only take large doses of vitamin D (2000 international units or 50 micrograms or more daily) if prescribed by your doctor.
- See your doctor frequently if you take vitamin D and thiazides or if you take large doses of vitamin D. You may develop hypercalcemia.
- Chronic large doses (95 micrograms or 3800 international units or more daily) of vitamin D can cause hypercalcemia.

For more information see the Safety Appendix

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