

LE Magazine August 2005

## REPORT

### Super Oxide Dismutase (SOD)

Boosting your body's store of the enzyme SOD provides powerful protection against oxidative stress.

By John Colman

While everyone needs oxygen to stay alive, the same oxygen that sustains life also contributes to the generation of dangerous free radicals. Thousands of published studies implicate free radicals in the development of degenerative disease and accelerated aging.<sup>1</sup> Young people naturally produce the antioxidant enzymes superoxide dismutase (SOD), catalase, and glutathione peroxidase to help protect against free radicals produced during normal physiological processes.

Levels of SOD and other critical antioxidant enzymes decline with age, contributing to the scourge of age-related disease and decline. Fortunately, recent advances in nutritional science now allow adults to replenish their stores of these powerful antioxidant enzymes. Emerging research suggests that two novel SOD products—SODzyme™ and GliSODin®—help boost antioxidant status, reduce pain, quench free radicals, quell inflammation, and promote longevity.



#### DANGERS OF OXYGEN TOXICITY

Oxygen toxicity was first described in 1878, when laboratory animals were exposed to pure oxygen, and these deleterious effects were further established in 1899.<sup>1</sup> During the Battle of Britain in World War II, pilots breathing pure oxygen for several hours daily developed emphysema, scarred lungs, and the effects of greatly accelerated aging. In some cases, the pilots looked and acted like men who were more than three times their age. One of the most tragic episodes of oxygen toxicity occurred later in the 1940s, when newborn infants were placed in oxygen-rich incubators. Some of the newborns went blind because their eye tissue had not yet accumulated dietary antioxidant carotenoids to protect against the toxic effects of higher-than-normal oxygen concentrations.<sup>2</sup>

When placed in hyperbaric chambers of pure oxygen with several atmospheres of pressure, laboratory animals die within a matter of minutes. By contrast, when the atmospheric pressure is slowly increased over a period of days, the animals manage to survive, because their bodies have time to produce higher-than-normal levels of the antioxidant enzymes that protect against oxygen toxicity. The lungs of animals exposed to higher-than-normal oxygen concentrations reveal massive tissue damage caused by too much oxygen, a condition known as hyperoxia. Thus, at higher-than-normal concentrations, oxygen is a toxic element. Oxygen utilization by aerobic (that is, oxygen-requiring) organisms such as humans is associated with the generation of potent free radicals.<sup>1,3</sup>

#### OXYGEN AND ACCELERATED AGING

Numerous studies conducted over the last 60 years demonstrate that the by-products of normal oxygen utilization, including superoxide radicals and reactive oxygen species, may contribute to aging and degenerative diseases.<sup>4-6</sup> Antioxidant enzymes that naturally occur in the body—including SOD, catalase, and glutathione peroxidase—act to minimize this oxidative stress, thus protecting cell membranes, essential proteins, and DNA from damage. These endogenous (internally generated) antioxidants produced within our cells are more potent in preventing free radical damage than are dietary antioxidants. SOD, for example, may be up to 3,500 times more potent than vitamin C in quenching the dangerous superoxide radical.



As noted earlier, however, levels of these antioxidant enzymes decline with advancing age in humans and animals alike, leading to an accumulation of free radicals and oxidative damage.<sup>7,8</sup> In particular, SOD levels decline, correlating with an increased incidence of degenerative and inflammatory diseases.

Rheumatoid arthritis sufferers demonstrate lower SOD levels in their cartilage cells than do arthritis-free individuals. These lower levels of SOD may contribute to the destruction of cartilage in this inflammatory disease state.<sup>9,10</sup> Low SOD levels in humans have also been associated with a host of degenerative diseases, including fibromyalgia,<sup>11</sup> diabetes,<sup>12</sup> cancer,<sup>13-15</sup> multiple

SOD levels in humans vary by as much as 50% owing to genetic differences, which may help to explain why some people are more prone to degenerative diseases while others lead long, disease-free lives.<sup>19</sup>

## HOW SOD PROMOTES LONGEVITY

In research conducted in the early 1980s by Richard Cutler at the Gerontology Research Center at the National Institutes of Health, mammals that produced higher tissue and serum levels of SOD lived longer than those with lower SOD levels.<sup>20,21</sup> Cutler's research demonstrated that mice and rodents have the lowest SOD levels among mammals, and that SOD levels are highest among more highly evolved mammals, with humans displaying the highest relative SOD levels.<sup>20,21</sup>

Humans produce an average of 90 micrograms per milliliter (mcg/ml) of SOD and live an average of nearly 80 years. Our closest primate relatives, chimpanzees, produce 40 mcg/ml of SOD and live an average of only 40 years. Fruit flies that have been bred to produce twice as much SOD as normal live twice as long as ordinary fruit flies. Cutler's cross-species investigations strongly suggest that SOD is a primary determinant of longevity in mammals, and that increased SOD production played a key role in the higher order of mammals' evolution from shorter to longer life spans.<sup>20,21</sup>

Levels of vitamin E and glutathione transferases similarly increase at the higher rungs of the mammalian evolutionary ladder. Data on antioxidant levels in mammals have been compiled from zoo, veterinary, and medical records from around the world.<sup>20,21</sup>



## TWO STUDIES, STRIKING RESULTS

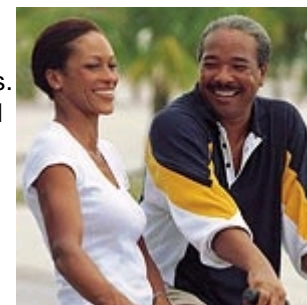
Although SOD's benefits are well established, an orally ingested supplement that can boost SOD levels has eluded scientists for decades. After initial research revealed impressive results, however, Life Extension conducted two pilot studies (one open-label trial, one placebo-controlled trial) to help determine whether a novel plant-based extract called SODzyme™ derived from the sprouts of corn, soy, and wheat—could boost the body's endogenous SOD levels and reduce chronic pain in aging adults.

Because free radicals are thought to contribute to chronic pain, it thus follows that antioxidants may offer pain relief. SOD activity in the blood lowers levels of the superoxide radical, which in turn

diminishes levels of the inflammatory agent, hydrogen peroxide.

In the first open-label Life Extension study, 12 middle-aged volunteers of both sexes took 2000 mg daily of SODzyme™ for two weeks. SODzyme™ boosted serum SOD levels by 30% on average while lowering blood levels of hydrogen peroxide by 47%. This is significant, because hydrogen peroxide may contribute to the inflammation of arthritis. While immune cells use bursts of hydrogen peroxide to kill viruses and bacteria, excess hydrogen peroxide may contribute to inflammation and arthritis.<sup>23,24</sup>

The 12 subjects in this study, whose average age was 58, did not suffer from arthritis but were beginning to experience normal age-related decline in their SOD levels. Two weeks of oral SODzyme™ supplementation restored their serum and blood levels of SOD to youthful parameters. Furthermore, supplementation with SODzyme™ boosted activity of blood catalase, another crucial antioxidant enzyme, by an impressive 47%.<sup>22</sup> If these subjects continue to use SODzyme™ and thus maintain or further boost their blood levels of SOD, they should remain well protected against arthritic diseases, as suggested by the numerous studies correlating low SOD levels with pain and arthritis.<sup>9-11</sup>



A second pilot study (placebo-controlled) conducted by Life Extension examined SODzyme™ effects on adults diagnosed with inflammatory conditions such as arthritis. This placebo-controlled, 3-arm study involving 30 subjects over 4 weeks tested placebo, probiotic SODzyme™ and nonprobiotic SODzyme™. A dramatic 71% response (clinically defined as a meaningful decrease in pain as measured by a validated pain assessment instrument) in the probiotic SODzyme™ group vs. a 30% response in the nonprobiotic group was observed. No differences were observed in the placebo group. One of the study's most remarkable findings was that those who were suffering the most pain at the study's onset experienced the greatest pain relief benefit from SODzyme™.

## CASE STUDIES CONFIRM BENEFITS

Case studies are a valuable means of gauging individual responses to SODzyme™ beneficial effects.

Thomas H., a 72-year-old man, had pain in both knees, as well as stiffness and arthritis in both hands. Within a week of

beginning the recommended daily 2000-mg dose of SODzyme™, he reported no noticeable pain in his knees or hands. A month after beginning supplementation, he reported no pain in his knees or hands, and had to be reminded that he had originally experienced pain in both knees. After three months of taking SODzyme™, he had no return of any pain. SODzyme™ effects did not diminish over the three-month course of use.<sup>25</sup>



Ursula A. was diagnosed with pain in both feet that prevented her from standing for more than 20 minutes at a time. After one week of supplementing with SODzyme™, she reported that not only could she stand for long periods, but she was able to stand in the kitchen for six to eight hours each day for three days in a row doing her holiday baking. After three months, she reported no return of pain in her feet or elsewhere. Despite numerous X-rays, her doctor had previously not been able to pinpoint the exact location of her arthritis.<sup>25</sup>

Thomas S., a 29-year-old man who had recently had surgery in both knees, re-injured one knee in a fall, further damaging the joint. He was in constant pain and had given up all sports, including rollerblading. After taking SODzyme™ for two weeks, he noticed a dramatic reduction in pain and inflammation in his knees. He has since returned to walking for exercise. During the three-month follow-up interview, he reported the same ongoing relief taking SODzyme™ that he had experienced initially.<sup>25</sup>

Marie R. reported a 90% improvement in her pain symptoms within two weeks of taking 2000 mg of SODzyme™ daily. She had developed severe inflammation in her right knee and had used crutches for two weeks at work and home. Within a week, she was able to discard the crutches, and at a three-month follow-up interview, she reported that she continued to experience a 90% reduction in pain.<sup>25</sup>

The two Life Extension pilot studies confirm that SODzyme™ helps to alleviate the discomfort and stiffness associated with arthritis and other painful conditions. As noted in the accompanying sidebar, this natural approach to pain relief utilizes a mechanism of action that differs from conventional therapies such as nonsteroidal anti-inflammatory drugs (NSAIDs).

## SODzyme™ VERSUS CONVENTIONAL PAINKILLER

Conventional pain medications such as aspirin and ibuprofen target the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes, thus decreasing levels of inflammation and pain.<sup>26</sup> However, these nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with stomach and gastrointestinal problems. This is because the COX-1 enzyme is required for production of the protective mucosa lining the stomach and intestine. Chronic use or misuse of these products for inflammation and pain can lead to gastrointestinal irritation, ulcerations, and erosion of the digestive tract.<sup>26-29</sup>

Newer prescription NSAIDs like Celebrex® inhibit only the COX-2 inflammatory enzyme and spare the stomach-protective COX-1 enzyme. While these drugs are associated with fewer gastrointestinal side effects than are medications that inhibit both COX-1 and COX-2,<sup>28</sup> these selective COX-2 inhibitors have been associated with increased incidence of heart attack and stroke. They may increase cardiovascular risk by upsetting the balance of vasoactive prostaglandins.<sup>30</sup> Two selective COX-2 inhibitors were recently taken off the market, and the last selective COX-2 inhibitor still on the market, Celebrex®, is currently under intense scrutiny.<sup>31,32</sup>

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#### ANOTHER POWERFUL SOD BOOSTER: GLISODIN®

Elevating serum and blood levels of endogenous antioxidants such as SOD and catalase is a safe, natural way to reduce inflammation and pain. Like SODzyme™, another recently developed natural product called GliSODin® raises serum and tissue levels of SOD. GliSODin® is derived from an extract of cantaloupe bred to produce more SOD than ordinary melons.<sup>33,34</sup>

In 1980, melon growers noticed that some varieties of cantaloupe had a shelf life of 15 days, or three to four times longer than the shelf life of the average fully ripened melon. Extensive research demonstrated that these non-rotting cantaloupes contained much higher levels of SOD and catalase than did standard melons. Years of additional research involving crushing, filtering, centrifuging, and freeze-drying extracts of the melons produced SOD in a concentrated granule form that, when bonded to wheat protein, made it highly absorbable in and bioavailable to the human body.<sup>33,34</sup>

GliSODin® is a natural, plant-derived SOD that has been bonded to a wheat protein called gliadin for better absorption. In fact, it has taken 40 years of research to make SOD orally bioavailable, since unbound SOD is broken down rapidly in the stomach into its separate amino acid components. Its high molecular weight of 25-40,000 units also makes it difficult or impossible to pass through cell membranes, even if directly injected into the bloodstream.<sup>33-35</sup>

Most of the early arthritis research with SOD was done with bovine SOD that was injected into the joints and bloodstreams of laboratory animals and humans. While the human studies produced some dramatic results, injecting SOD into arthritic joints posed a logistical challenge, especially since exogenously derived bovine SOD is rapidly broken down.<sup>35</sup>

#### EXTENSIVE RESEARCH ON GLISODIN®

Numerous scientific studies have examined the effects of GliSODin®. In one landmark study, 20 volunteers in a hyperbaric chamber breathed pure oxygen at 2.5 atmospheres of pressure for one hour. Hyperbaric oxygen treatment serves as an in-vivo model of oxidative stress in humans. Subjects exposed to oxygen in a high-pressure chamber typically demonstrate increased levels of free radicals and DNA damage in their white blood cells that cannot be prevented by oral antioxidants such as vitamin E or N-acetylcysteine.<sup>36</sup>

In this study, the group supplemented with GliSODin® capsules had less DNA damage than subjects who did not supplement. The scientists concluded that GliSODin® helped prevent breaks in DNA strands that are associated with exposure to high-pressure oxygen. The results also suggest GliSODin® is readily absorbed in the gastrointestinal tract and makes its way into the cells themselves, something that even injectible bovine SOD failed to do in previous studies.<sup>36</sup>



An emerging marker of oxidative stress in humans is isoprostanes, which are generated by the peroxidation of fatty acids in cell membranes or lipoproteins. Clinical data indicate that an increased level of isoprostane biosynthesis is correlated with certain disease states related to oxidative stress.<sup>37</sup> Human subjects who supplemented with GliSODin® capsules demonstrated lower baseline levels of isoprostanes—of 14.0 picograms per milliliter (pg/ml)—compared to an average level of 16.8 pg/ml in a control group.<sup>36</sup> After one hour in a hyperbaric oxygen chamber, isoprostane levels in the control group rose to 22.3 pg/ml, while the GliSODin®-supplemented group experienced no change in isoprostanes, demonstrating a sustained level of 14 pg/ml. Thus, GliSODin® appears to protect against cell membrane damage that occurs during normal oxygen exposure and in high-pressure oxygen environments. This study illustrates GliSODin®'s ability to limit daily oxidative damage from oxygen utilization, as well as to prevent the greater damage associated with conditions of severe oxidative stress.<sup>36</sup>

Another study found that small amounts of orally administered GliSODin® raised circulating blood levels of SOD by 89% in mice.<sup>33</sup> Blood levels of catalase, another antioxidant enzyme, also increased to almost three times the level seen in a control group.<sup>33</sup> Catalase is the enzyme that converts hydrogen peroxide to water, and high levels of hydrogen peroxide may contribute to inflammation and arthritis.<sup>34</sup> The liver cells of the mice also demonstrated greatly increased levels of SOD and catalase, indicating that GliSODin® stimulates production of these critical antioxidants inside the major organs and deep tissues.<sup>33</sup>

The potent antioxidant properties of GliSODin® were also studied in mouse macrophages taken from live, normal mice. Macrophages are a type of immune responder cell that is activated in inflammatory processes such as arthritis. When treated with GliSODin®, macrophage cells produced fewer of the free radicals superoxide, nitrites, and peroxynitrite than did macrophages taken from untreated animals.<sup>34</sup>



Researchers studied the interaction of GliSODin® with inflammatory cytokines that play a role in arthritis. They found that untreated immune responder cells produced high levels of the inflammatory cytokine, tumor necrosis factor-alpha (TNF-a), and normal levels of an anti-inflammatory cytokine, interleukin-10 (IL-10). When treated with GliSODin®, however, the immune responder cells produced very low levels of inflammatory TNF-a in combination with very high levels of anti-inflammatory IL-10. Previous studies have suggested that people who live to 90 or 100 years of age have high blood levels of IL-10, which may keep their inflammatory reactions in check during aging. GliSODin® may thus promote a protective anti-inflammatory profile similar to that of people who live to extreme old age.<sup>34,38</sup>

Lactic acid is a metabolic by-product generated during strenuous exercise. In some forms of arthritis, the lactic acid content of joints is increased.<sup>39</sup> Interventions that lower lactic acid levels in the blood and in joint fluids have been suggested to help modulate muscle and joint pain. Human studies demonstrated that four weeks of GliSODin® supplementation reduced lactic acid levels during strenuous cycling or treadmill exercise. The most strenuous exercise activity generated the highest levels of lactic acid. GliSODin® therapy exerted the most potent lactic acid-reducing effects in extreme cases of exercise-induced stress. GliSODin® may thus be indicated in reducing lactic acid levels related to exercise and certain pain-related conditions.<sup>40</sup>

A study of AIDS patients in Ivory Coast, Africa, found that GliSODin® supplementation minimized disease-related oxidative stress and helped restore immune cell function. Patients who received GliSODin® experienced a restoration of blood SOD levels and antioxidant status to values seen in uninfected controls. The AIDS patients demonstrated elevated levels of beta-2 microglobulin before taking GliSODin®, indicating an immune challenge. GliSODin® supplementation decreased beta-2 microglobulin levels, indicating a possible improvement in immune status that may correlate with strengthened antioxidant defense. Because these AIDS patients were not receiving anti-retroviral prescription therapy, their improvements were attributed to GliSODin®.<sup>41</sup>

## GliSODin® GUARDS AGAINST SUNBURN

GliSODin® offers powerful protection against the effects of ultraviolet (UV) light, thus reducing susceptibility to sunburn, according to study results presented at the Annual Congress for Dermatological Research in Brest, France, in May 2005.\*

Researchers at the Center Hospital University in Besançon, France, conducted a randomized, double-blind, placebo-controlled study of the effects of the SOD supplement GliSODin® in humans. The investigators used UV light to induce sunburn on the forearms of 50 subjects once a week for four weeks. The participants took a supplement containing either GliSODin® or placebo each day, beginning two to three days before the first irradiation. The researchers used chromometry to measure skin color and videocapillaroscopy to measure inflammatory changes in the skin.

The GliSODin®-supplemented group experienced a significant increase in the minimum amount of exposure necessary to produce sunburn. Even fair-skinned people required eight times more UV exposure to produce sunburn than did the placebo group. Once burning occurred, the redness decreased more rapidly in the GliSODin® group than in the placebo group. The supplemented group also demonstrated less skin inflammation. GliSODin® was extremely fast-acting, with just two to three days of supplementation before the first irradiation producing a noticeable difference compared to the placebo group.

“This study confirms the efficacy of GliSODin® in the prevention of the consequences of oxidative stress resulting from exposure to the sun. This efficacy is of particular interest for [fair-skinned individuals] that represent a major part of the consultations in dermatology,” said the researchers.

Previous human and laboratory studies have demonstrated GliSODin®’s effectiveness in protecting cells from oxidative stress by spurring the body’s production of endogenous antioxidants, including SOD, catalase, and glutathione peroxidase. These antioxidant enzymes are key elements of the “internal antioxidant defense system” that is so critical to countering free radicals produced by oxidative stress.

\*Available at: <http://www.npicenter.com/anm/templates/newsATemp.aspx?articleid=12601&zoneid=24>. Accessed June 5, 2005.

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#### CONCLUSION

Free radicals and oxidative stress are associated with accelerated aging and the onset of degenerative diseases. Internally generated anti-oxidants help protect against the effects of oxidative stress.

One of the most important antioxidant enzymes in humans is superoxide dismutase (SOD). Numerous studies correlate diminished SOD levels with disease, suggesting that abundant SOD promotes longer life. Two supplements in particular—SODzyme™ and GliSODin®—have been shown to boost levels of SOD and other antioxidant enzymes. SODzyme™ and GliSODin® offer promise in slowing aging, promoting longevity, relieving pain, modulating inflammation, and quenching free radicals. These powerful compounds may thus help promote good health and protect against many of the degenerative conditions associated with aging.

*Editor's note: People who are allergic to wheat, soy, corn, or gluten should consult their physician before using products containing SODzyme™ or GliSODin®.*

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