

LE Magazine October 2002

## REPORT

### Newly Discovered Benefits of Gamma Tocopherol

Vitamin E was discovered in 1922. It is only in the last decade, however, that the public began to be educated about the critical fact that "vitamin E" is not a single compound. Instead, it is a general name for a whole family of compounds. Eight forms of vitamin E have been identified as existing in nature. These belong either to the tocopherol sub-family, consisting of alpha tocopherol, beta tocopherol, gamma tocopherol and delta tocopherol, or to the tocotrienol sub-family, consisting of alpha tocotrienol, beta tocotrienol, gamma tocotrienol and delta tocotrienol. The scientific focus is slowly shifting away from "vitamin E" to specific tocopherols and tocotrienols.

It turns out that the heretofore neglected beta, gamma and delta tocopherols and tocotrienols seem to have important health benefits, including anti-inflammatory, cardioprotective and anticancer activity. Gamma tocopherol in particular also has the ability to protect against nitrogen-based free radicals, which alpha tocopherol cannot do. Nitrogen free radicals play an important role in diseases associated with chronic inflammation, including cancer, heart disease and degenerative brain disorders such as Alzheimer's disease.

The latest research places special emphasis on the newly discovered benefits of gamma tocopherol. Since taking large doses of alpha tocopherol depletes plasma levels of gamma tocopherol, the health-conscious consumer who takes only alpha tocopherol supplements needs to seriously reconsider this practice. Likewise, most vitamin E supplements provide only alpha tocopherol. New evidence strongly suggests that this is inadequate supplementation.

A thorough review of recent findings about gamma tocopherol has appeared in a recent issue of the American Journal of Clinical Nutrition.[1] The authors include Bruce Ames, Qing Jiang and their colleagues at the University of California, Berkeley. After reviewing scores of studies, the authors conclude that it is high time to abandon the outdated view that only alpha tocopherol is important, and to conduct more research on gamma tocopherol, the especially promising "other" vitamin E.

For many decades only alpha tocopherol was considered to be biologically important mainly because of the "dirty" test used to measure vitamin E activity[2]-the so-called "rat fetal resorption assay." First, pregnant rats are depleted of vitamin E. Unless the vitamin is then adequately supplemented, the embryos will die. Alpha tocopherol was established as the most active tocopherol in preventing the death of rat embryos. gamma tocopherol was only 10% to 30% as potent in this assay. Thus, early researchers prematurely concluded that only alpha tocopherol was important. This conclusion was reinforced by the finding that in human plasma the levels of alpha tocopherol tend to be four to 10 times as high as the levels of gamma tocopherol, even though gamma tocopherol is the dominant tocopherol in the diet. This difference in plasma levels is even more pronounced in rodents.

The total inadequacy of the rat fetal resorption assay for investigating the properties of various tocopherols and tocotrienols has been exposed only in the last decade or so. While tissue levels of gamma tocopherol have not been extensively studied, one study that did a broader survey discovered that 30% to 50% of vitamin E found in human muscle, skin, vein and body fat is in fact gamma tocopherol. In addition, the levels of gamma tocopherol in human muscle and skin are 20 to 50 times higher than those found in rodent muscle and skin. In humans, dietary intake of gamma tocopherol strongly correlates with its concentrations in these tissues.

#### Anti-inflammatory properties of gamma tocopherol

The authors of the American Journal of Clinical Nutrition study found that both gamma tocopherol and its water-soluble metabolite inhibit cyclooxygenase (COX-2) activity and the production of pro-inflammatory prostaglandin E2. Alpha tocopherol showed no anti-inflammatory activity at the same concentrations.



Many serious degenerative conditions, including atherosclerosis, various types of cancer and Alzheimer's disease, appear to be promoted by chronic inflammation. COX-2 inhibitors show great promise in the prevention and sometimes adjunct treatment of these diseases. Fewer people know that COX-2 inhibitors have also been found to protect against the autoimmune destruction of beta cells in the pancreas. Thus, gamma tocopherol may help prevent Type I diabetes.

Aging and chronic inflammation go hand in hand. Anti-inflammatory agents have been drawing more and more attention in regard to their antiaging effects. Aging is associated with a decline in plasma levels of gamma tocopherol, but not of alpha tocopherol.

On the other hand, a fuller picture of the anti-inflammatory activity of various tocopherols and tocotrienols remains to be clarified by further research. Of special interest is the recently discovered synergy between aspirin and vitamin E.

#### Protection against prostate and other cancers

Let us look at the most striking finding first. In a prospective study, men with the highest plasma levels of gamma tocopherol (the top quintile) had only one-fifth the risk of prostate cancer compared with the men with the lowest plasma levels.[3] Moreover, the protective effects of selenium and alpha tocopherol were found only in the presence of high levels of gamma tocopherol.

Though the authors did not mention findings related to breast cancer, an early study found that women who consumed most vitamin E from food sources only had a 60% reduction in the risk of breast cancer, compared to women with the lowest consumption. The form of vitamin E that strongly predominates in food sources is gamma tocopherol. When total vitamin E intake was considered, including supplements (presumably supplying solely alpha tocopherol), the risk of breast cancer was reduced by 30%.[4] More research is needed to test the supposition that depletion of gamma tocopherol may have been involved in this lesser degree of protection.

Colon cancer may be another type of cancer that gamma tocopherol helps prevent. One obvious mechanism is the inhibition of COX-2; colon cancer is highly dependent on COX-2 and the resulting prostaglandin E2. There is yet another possible interesting mechanism, however. One way that the human body eliminates excess gamma tocopherol is by using the biliary route. It turns out that in bile the ratio of gamma tocopherol to alpha tocopherol is several times higher than the plasma ratio. "Excess gamma tocopherol secreted into feces during supplementation may play a role in eliminating fecal mutagens and thus reduce colon cancer," the authors suggest.

Another possible mechanism through which gamma tocopherol helps prevent cancer may be its ability to inhibit protein kinase C activity. gamma tocopherol shares this antiproliferative property with alpha tocopherol and delta-tocopherol.

But the overall picture is still far from clear. For instance, a Japanese study reported that the levels of total carotenoids and gamma tocopherol, but not alpha tocopherol, were significantly lower in patients with cancers of the upper aerodigestive tract, i.e., cancer involving either the upper respiratory pathways or the upper digestive tract.[5] At the same time, however, higher gamma tocopherol levels were found to be associated with certain cancers, such as invasive cervical cancer. There may be several reasons for this, including possible excess consumption of commercial vegetable oils and slower degradation of gamma tocopherol in the presence of inflammatory cytokines. The impact of inflammatory cytokines on tocopherol metabolism makes it probable that the higher plasma gamma tocopherol levels found in some cancer patients are likely to be the effect, not the cause, of the disease.

Smoking is another confounding variable whose impact on the levels of tocopherols remains to be clarified. Only further research is going to give us a more complete picture of the role of gamma tocopherol in cancer prevention. The authors emphasize that future studies should be controlled for dietary fat and other confounding factors.

#### Gamma tocopherol's role in cardiovascular disease

Just as dietary vitamin E, which is mainly gamma tocopherol, has been found to offer significant protection against breast cancer, high dietary intake of vitamin E, but not of alpha tocopherol supplements, has been found to be associated with lower stroke and cardiovascular mortality in a seven-year study of a large (close to 35,000) cohort of postmenopausal women.[6] It is also known that regular consumption of nuts, a particularly rich source of gamma tocopherol, reduces cardiovascular mortality.



Aging and chronic inflammation go hand in hand. Anti-inflammatory agents have been drawing more and more attention in regard to their antiaging effects. Aging is associated with a decline in plasma levels of gamma tocopherol.



Smoking is another confounding variable whose impact on the levels of tocopherols remains to be clarified. Only further research is going to give us a more complete picture of the role of gamma tocopherol in cancer prevention.

Likewise, several studies found that high plasma levels of gamma tocopherol are correlated with a reduced incidence of cardiovascular disease and cardiovascular mortality. One study reported that plasma levels of gamma tocopherol, but not alpha tocopherol, were lower in cardiovascular patients than in healthy controls. Another study found that middle-aged Swedish men had twice the plasma gamma tocopherol as middle-aged Lithuanian men; the Swedish men also had a 25% lower cardiovascular mortality. No such inverse correlation was found with alpha tocopherol levels.

Animal studies have also provided further fascinating data on the probable role of gamma tocopherol in cardiovascular protection. In rats, gamma tocopherol supplementation led to a more potent decrease in platelet clumping and clot formation than supplementation with alpha tocopherol (but it should be remembered that supplementing with gamma tocopherol raises the levels of both gamma and alpha tocopherol). Gamma tocopherol was also a more effective inhibitor of ex-vivo lipid peroxidation, LDL oxidation and superoxide generation. Likewise, gamma tocopherol more effectively enhanced the superoxide dismutase (SOD) expression and activity.[7]

Both alpha and gamma tocopherol increased the generation of nitric oxide, or NO, (NO causes the dilation of blood vessels) by increasing the activity of endothelial nitric oxide synthase. However, only gamma tocopherol supplements led to enhanced protein expression of this crucial enzyme.

#### Other benefits

Gamma tocopherol lacks one of the electron-donating methyl groups on its chromanol ring, and thus is a somewhat less potent antioxidant than alpha tocopherol. However, gamma tocopherol is better able to trap nitrogen-based free radicals, technically called reactive nitrogen oxide species (RNOS). RNOS such as peroxynitrite and nitrogen dioxide are formed in excess in the process of inflammation. The chemical structure of alpha tocopherol does not allow it to bind nitrogen compounds; the structure of gamma tocopherol, on the other hand, makes it a good nitro trap. For instance, gamma tocopherol can trap nitrogen dioxide to form 5-nitro-gamma tocopherol. gamma tocopherol also traps peroxynitrite in a similar manner.

The protection against nitrogen free radicals is extremely important in the prevention of heart disease, brain disease and cancer.

In unsupplemented humans, an estimated 50% of gamma tocopherol is converted to a water-soluble metabolite called gamma-CEHC. Like the equivalent water-soluble alpha tocopherol metabolite, alpha-CEHC, gamma-CEHC is excreted into urine. By inhibiting potassium channels in certain specialized kidney cells, gamma-CEHC, but not alpha-CEHC, promotes the excretion of excess sodium (natriuretic activity).

Science has recently provided a compelling answer to the puzzle as to why levels of alpha tocopherol in the body are higher than the levels of gamma tocopherol, considering that diet provides mainly gamma tocopherol. While both gamma- and alpha tocopherol are equally absorbed through the intestines, the liver possesses the tocopherol transfer protein. This protein preferentially binds alpha tocopherol to very low-density lipoproteins (VLDLs). It is likely that supplementation with large doses of alpha tocopherol further reduces the incorporation of gamma tocopherol into VLDLs.

At the same time, the presence of sufficient concentrations of gamma tocopherol appears to have a sparing effect on alpha tocopherol. This is probably due to the lower degradation of alpha tocopherol by the cytochrome P450 system, which also degrades gamma tocopherol. Thus, supplementation with gamma tocopherol increases the levels of both gamma- and alpha tocopherol.

Readers should not conclude that supplementation with alpha tocopherol is harmful. There are many studies confirming the health benefits of alpha tocopherol. However, there is also strong reason to believe that taking high doses of alpha tocopherol without balancing it with adequate gamma tocopherol (and possibly other tocopherols and tocotrienols) is not optimal. (Similarly, we have learned that the intake of mixed carotenoids is preferable to supplementing with beta-carotene alone.)

#### Sources of gamma tocopherol

Gamma tocopherol is abundant in nuts such as walnuts and pecans, and in peanuts (actually a legume, not a nut). Seed oils such as corn, soybean and sesame oil, are also rich sources of gamma tocopherol. The consumption of nuts is highly desirable, since in addition to gamma tocopherol nuts provide short-chain omega-3 fatty acids, magnesium and other nutrients, as well as fiber. The authors of the American Journal of Clinical Nutrition review point out that regular consumption of nuts, an excellent source of gamma

tocopherol, has been associated with a significantly lower risk of having a heart attack and lower cardiovascular mortality.

Those who wish to eat nuts every day often discover that health-food stores offer walnuts and pecans in bulk at surprisingly affordable prices.

When it comes to commercially available seed oils such as corn oil, however, the problem is toxic trans-fatty acids and excess omega-6 fatty acids. Both trans-fatty acids and excess omega-6 fatty acids have been found to promote various types of degenerative disorders. Consequently, these oils cannot be recommended.

Sesame oil represents a special case. It contains sesamin, a sesame lignan. Like polyphenols, lignans are generally beneficial compounds, especially in regard to cancer prevention. Sesame seeds have been shown to elevate the levels of both tocopherols and tocotrienols in rats. It turns out, however, that in rodents sesamin inhibits the formation of gamma-CEHC, with its natriuretic benefits (excretion of excess sodium). It will take further research to determine whether this finding is of clinical significance to humans, who do not degrade gamma tocopherol as rapidly as rodents.

If you are not a big nut eater, consider balancing your alpha tocopherol supplement with a quality gamma tocopherol supplement. Please remember that taking large amounts of alpha tocopherol lowers the plasma levels of gamma tocopherol; taking gamma tocopherol, on the other hand, increases the levels of both alpha tocopherol and gamma tocopherol. Taking only alpha tocopherol supplements results in gamma tocopherol depletion.

It will take controlled human studies using gamma tocopherol supplementation to explore its benefits more fully. There remains also the question of gamma tocopherol's probable synergy with other antioxidants. Much research is yet to be done. It is already clear, however, that gamma tocopherol, once the neglected "poor relative" of alpha tocopherol, is now beginning to get the attention it deserves. Its anti-inflammatory, cardioprotective, anticancer and overall antiaging properties make it an important part of the life extension nutritional arsenal.

Find out more about Gamma E Tocopherol/Tocotrienols

## References

1. Jiang Q et al. Gamma tocopherol, the major form of vitamin E in the US diet, deserves more attention. *Am J Clin Nutr* 2001; 74: 714-22.
2. Traber M. Comments made during panel discussion at 1999 AGE conference, Seattle.
3. Helzlsouer KJ et al. Association between alpha tocopherol, gamma tocopherol, selenium and subsequent prostate cancer. *J Natl Cancer Inst* 2000; 92: 2018-23.
4. London SJ et al. Carotenoids, retinol and vitamin E and risk of proliferation benign breast disease and breast cancer. *Cancer Causes Control* 1992; 3: 503-12.
5. Nomura AM et al. Serum micronutrients and upper aerodigestive tract cancers. *Cancer Epidemiol Biomarkers Prevention* 1997; 6:487-91.
6. Kushi LH et al. Dietary antioxidant vitamins and death from coronary heart disease in postmenopausal women. *New Engl J Medicine* 1996; 334:1156-62.
7. Saldeen T et al. Differential effects of alpha- and gamma tocopherol on low density lipoprotein oxidation, superoxide dismutase activity and nitric oxide synthase activity and protein expression in rats. *J Am Coll Cardiol* 1999; 34: 1208-15.

[Back to the Magazine Forum](#)

All Contents Copyright © 1995-2009 Life Extension Foundation All rights reserved.

**LifeExtension**<sup>®</sup>

These statements have not been evaluated by the FDA. These products are not intended to diagnose, treat, cure or prevent any disease. The information provided on this site is for informational purposes only and is not intended as a substitute for advice from your physician or other health care professional or any information contained on or in any product label or packaging. You should not use the information on this site for diagnosis or treatment of any health problem or for prescription of any medication or other treatment. You should consult with a healthcare professional before starting any diet, exercise or supplementation program, before taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.