Nutri Notes

"Integrating the Nutrition-Health connection" Vol 12, #3

THE VERSATILITY OF VITAMIN E

Functions of Vitamin E:

Vitamin E is involved in maintaining the integrity, function, and flexibility of cell membranes. It stabilizes the cell membrane, which is a necessary feature for ensuring cell health. The d-alpha tocopherol portion of vitamin E serves an important antioxidant function in the body, which means that it prevents free radicals (harmful substances with unstable electron structure) from attacking and damaging the cell membrane. There are also synergistic, naturally occurring tocotrienols (alpha, beta, gamma, and delta) that are members of the natural vitamin E family, which all contribute to the health benefits of this essential vitamin. Structurally, natural vitamin E includes eight chemically distinct molecules: alpha-, beta-, gamma- and delta-tocopherol; and alpha-, beta-, gamma- and delta-tocotrienol. While d-alpha tocopherol (the natural form) gets most of the limelight for its antioxidant properties, the tocotrienols are being researched for their synergistic and stand-alone properties. **Lipid peroxidation** is a damaging chain reaction of destruction started by free radicals which have not been stopped by lipid antioxidants like vitamin E. Free radical damage is like saying "oxidation".

When the cell membrane is disrupted, the receptors for hormones, neurotransmitters, neuropeptides, and other physiologically active substances are also disrupted. DNA is particularly susceptible to damage by free radical attack. It is easy to see how free radicals can be associated with aging, and with such degenerative diseases as cancer, diabetes, and heart disease. "Free radical-mediated oxidative stress has been implicated in the pathogenesis of numerous chronic diseases" (Park OJ, et al. Effect of vitamin E supplementation on antioxidant defense systems and humoral immune responses in young, middle-aged and elderly Korean women. J Nutr Sci Vitaminol (Tokyo). 2003 Apr;49(2):94-9). Vitamin E, with all its healthful properties, is associated with having positive influences on many of these conditions.

Principle uses of vitamin E include:

- **Antioxidant**
- **Inhibits coagulation**
- **Strengthens capillary walls**
- **Stabilizes cell membranes**
- **Prevents proteins, lipids, hormones (such as pituitary, thyroid and adrenal hormones as well as the sex hormones), and other substances from being oxidized**
- **Supports skin conditions, menopause, restless leg syndrome, and heart health, to name a few, and all conditions either caused by free radical damage or resulting in free radical damage (including diabetes and eye disorders)**

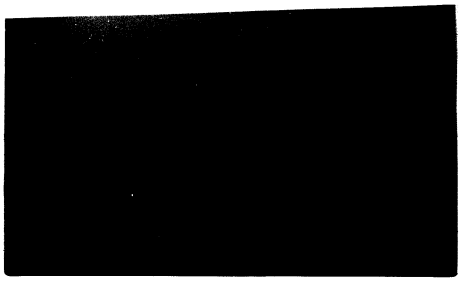
In this issue of the Nutri-Notes, we explore many of the versatile functions of vitamin E, and the conditions that relate to vitamin E supplementation.

Vitamin E Has Synergy with Other Antioxidants

Vitamin E is a powerful lipid antioxidant that **protects the double bonds in unsaturated oils, such as fish oil,** from oxidation, and also protects the unsaturated fatty acids that make up the cell membrane. Vitamin E has synergy with other antioxidants that work together to protect cells. **Vitamin C**, for instance, is able to recycle vitamin E back to a reduced state.

The body utilizes many nutrients to employ defenses against damage caused by reactive oxygen species, such as **vitamin E, vitamin C, grape seed extract, N-acetyl cysteine, glutathione, milk thistle, and silymarin, along with the minerals zinc, manganese, chromium and selenium** and the literature is full of references to document the power of combined antioxidant treatment with these nutrients (Bolkent S, et al. Int J Toxicol. 2008 Mar-Apr;27(2):217-22; Shao ZH, et al. J Cell Biochem. 2009 Apr 22; Gabrashanska M, et al. Parasitol Res. 2008 Dec;104(1):69-78), Koyuturk M, et al. Toxicol Ind Health. 2007 Aug;23(7):393-401; Stav D, Raz M. Chest. 2009 May 15; Gharagozloo M, et al. Fundam Clin Pharmacol. 2009 May 6; Esen Gursel F, Tekeli SK. Pol J Vet Sci. 2009;12(1):35-9 Chen WY, Life Sci. 2009 Apr 24;84(17-18):606-14.)

Some nutrients are part of the antioxidant enzymes in the body, such as **zinc**, that makes up Zn SOD (zinc superoxide dismutase), or **manganese,** that makes up MnSOD (manganese superoxide dismutase), and **selenium**, that makes up Se-GSH-Px (selenium glutathione peroxidase.)



Vitamin E and the Immune System:

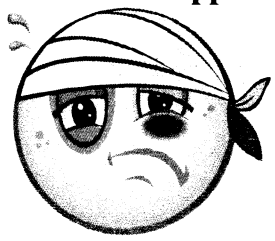
Vitamin E protects all cells, including the cells of the immune system. Vitamin E also has effects on the immune system by regulating substances produced by the various cells of the immune system.

One study demonstrated that **higher neopterin** production is associated with **lower** concentrations of **antioxidant** compounds in patients at risk for atherosclerosis. Neopterin is released from macrophages and is a sensitive indicator for cellular immune activation. "Results suggest that **lower concentrations** of antioxidant compounds (including **vitamin E** and **vitamin C**) may relate to a higher grade of **chronic immune activation** in patients (Murr C, et al. . Inverse association between serum concentrations of neopterin and antioxidants in patients with and without angiographic coronary artery disease. Atherosclerosis. 2009 Feb;202(2):543-9.)

Vitamin E "was capable of **restoring mucosal and systemic humoral immune responses** to mature adult levels" after vaccine-induced immune depression (Enioutina EY, et al. Enhancement of common mucosal immunity in aged mice following their supplementation with various antioxidants. Vaccine. 2000 May 8;18(22):2381-93.)

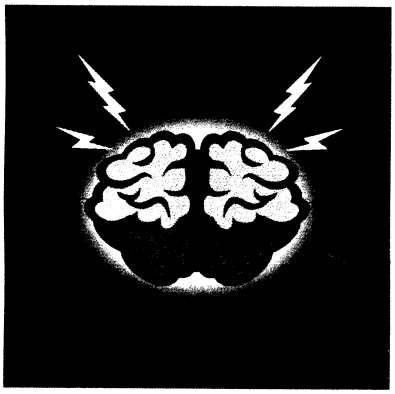
Vitamin E, the Immune System, Aging & Inflammation:

Aging is associated with **dysregulated immune and inflammatory responses**. Up-regulated inflammation with aging has attracted increasing attention as a result of its **implications in the pathogenesis of diseases.** One study looked at vitamin E and its effects on the dysregulated immune and inflammatory responses due to the aging process. The researchers described declining T cell function as the most significant and best-characterized feature of immunosenescence (gradual deterioration of the immune system brought on by age). Researchers also noted that among the factors that contribute to the **age-associated decline in T cell function**, increased production of T cell-suppressive factor PGE2 (prostaglandin E2), by macrophages is most recognized. **PGE2** is **pro-inflammatory** and correlated with **increased cytokine production** (cytokines are substances produced when the immune response is activated). **Vitamin E** is described as having a **positive influence on age-related immune and inflammatory changes**, and also as having an **ability to reduce this suppressive factor (PGE2), which is also a pro-inflammatory factor and an immune-activating factor**), and in fact, the researchers were quoted as saying, "**Vitamin E reverses an age-associated defect in T cells**, particularly naïve T cells. This effect of vitamin E is also reflected in a **reduced rate of upper respiratory tract infection** in the elderly and **enhanced clearance of influenza infection** in a rodent model" (Wu D. & Meydani SN. Age-associated changes in immune and inflammatory responses: impact of vitamin E intervention. J Leukoc Biol. 2008 Oct;84(4):900-14).



Vitamin E and the Eye: A study found that "micronutrients (including **vitamin E**) that **slow down the** onset and progression of **age-related macular degeneration** have the potential to **inhibit** the development of **diabetic retinopathy** **(Kowluru RA, et al. Arch Ophthalmol. 2008 Sep;126(9):1266-72.)** Additionally, "antioxidative agents (including **vitamin E**) may play a role in **delaying cataract formation**" (Nourmohammadi I, et al. Ann Nutr Metab. 2008;52(4):296-8.)

VITAMIN E STUDIES:



Vitamin E and Parkinson's: Vitamin E levels are decreased in Parkinson's patients. "Increased **oxidative stress** contributes to **neuronal dysfunction** in **Parkinson's disease (PD).** We investigated whether the pathological changes in PD brains may also be present in peripheral tissues... These results suggest increased oxidative damage and decreased anti-oxidant capacity in peripheral blood" (there was also a **significant correlation between oxidation and disease severity in PD**) (Chen CM, et al. Increased oxidative damage in peripheral blood correlates with severity of Parkinson's disease. Neurobiol Dis. 2009 Mar;33(3):429-35.)

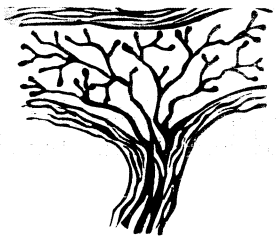
Vitamin E and Cancer: "Evidence indicates that **vitamin E has anticarcinogenic properties for gastrointestinal cancers**", and researchers report that "**higher alpha-tocopherol concentrations may play a protective role in pancreatic carcinogenesis in male smokers**" (Stolzenberg-Solomon RZ et al. Vitamin E intake, alpha-tocopherol status, and pancreatic cancer in a cohort of male smokers. Am J Clin Nutr. 2009 Feb;89(2):584-91.) In an epidemiological study of over 1,000 men with prostate cancer, higher dietary intake of **vitamin E was associated with lower incidence of prostate cancer** (Bidoli E, et al. Dietary vitamins E and C and prostate cancer risk. Acta Oncol. 2009 May 18:1-5.) In one study, **alpha tocopherol was one of the "nutrient signals" that "limit cell behaviors related to inflammation/angiogenesis**, which when deficient, may predispose individuals to risks associated with elevated angiogenesis (new blood vessels formed to feed a tumor) such as inflammation and cancer" (Wells SR, et al. alpha-, gamma- and delta-tocopherols reduce inflammatory angiogenesis in human microvascular endothelial cells. J Nutr Biochem. 2009 May 13.)

The tocotrienols downregulate the cholesterol synthesis enzyme, and it may be this pathway by which **delta tocotrienol "suppresses tumor growth" and reduced human pancreatic cancer cell proliferation** by 50% in vitro, causing researchers to announce that the tocotrienols "may have a **potential in pancreatic cancer chemotherapy**" (Hussein D, Mo H. Pancreas. 2009 May;38(4):e124-36.) The **vitamin E-binding plasma protein** afamin is being considered as a **potential novel tumor marker** (adjunct to CA-125) for ovarian cancer. One study demonstrated that afamin contributed "independent diagnostic information to CA125" (Dieplinger H, et al. Afamin and apolipoprotein A-IV: novel protein markers for ovarian cancer. Cancer Epidemiol Biomarkers Prev. 2009 Apr;18(4):1127-33).

Gamma tocotrienol analogs were tested on **human breast cancer cell lines**, and it was discovered that they "were **significantly stronger than the anticancer effect** of the other analyzed compounds" (Nikolic K, Agababa D. Design and QSAR study of analogs of gamma-tocotrienol with enhanced antiproliferative activity against human breast cancer cells. J Mol Graph Model. 2009 Apr;27(7):777-83). A recent study reported that "Telomeres play a critical role in maintaining the integrity and stability of the genome, and are susceptible to **oxidative damage** after telomere shortening to a critical length... These results provided the **strongest evidence to date** that **breast cancer risk** may be affected by telomere length among premenopausal women or women with low dietary intake of antioxidants or **antioxidant supplements** (statistical significance was only found within the lower **vitamin E subgroup**) (Shen J, et al. Telomere length, oxidative damage, antioxidants and breast cancer risk. Int J Cancer. 2009 Apr 1;124(7):1637-43.)

WHY TOCOTRIENOLS?

As mentioned previously, the tocotrienols (alpha, beta, gamma and delta) are important vitamin E molecules. It has been suggested that the vitamin E research done only with the alpha tocopherol portion of vitamin E does not do justice to the properties of the vitamin. Besides the fact that the tocotrienols balance the alpha tocopherol portion of the vitamin E molecule and work in synergy with it, tocotrienol research demonstrates that the tocotrienols have health benefits over and above that of alpha tocopherol alone. The tocotrienols have emerged as vitamin E moieties with functions in health and disease that are clearly distinct from that of alpha tocopherol, and properties that are synergistic with alpha tocopherol.



"**Tocotrienols possess powerful neuroprotective, anti-cancer and cholesterol lowering properties** that are often not exhibited by tocopherols. Current developments in vitamin E research clearly indicate that members of the vitamin E family are not redundant with respect to their biological functions" (Sen CK. Et al. Tocotrienols: Vitamin E beyond tocopherols. Life Sci. 2006 Mar 27;78(18):2088-98.

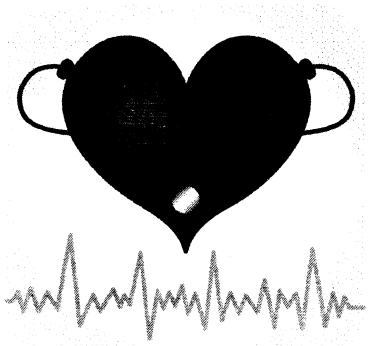
Another study reported that **tocotrienols** "possess potent **antioxidant, anticancer, and cholesterol lowering activities**", and they additionally reported that they possess potent **anti-inflammatory activity,** probably by inhibiting substances like nitric oxide, cox 2, and NF-kappaB expression (Wu SJ, et al. Tocotrienol-rich fraction of palm oil exhibits anti-inflammatory property by suppressing the expression of inflammatory mediators in human monocytic cells. Mol Nutr Food Res. 2008 Aug;52(8):921-9.)

Studies on Tocotrienols:

There are many who believe that studies done with just the alpha tocopherol portion of the vitamin would have been much more efficacious if the studies had taken advantage of the properties, both synergistic and stand-alone characteristics, that the tocotrienols possess.
"**Disappointments with outcomes-based clinical studies testing the efficacy of alpha tocopherol need to be handled with caution and prudence recognizing the untapped opportunities offered by the other forms of natural vitamin E"** (Sen CK, et al. Tocotrienols in health and disease: the other half of the natural vitamin E family. Mol Aspects Med. 2007 Oct-Dec;28(5-6):692-728.)

Tocotrienols and Diabetes: It has been reported that **tocotrienols** have "**prevented biochemical and molecular changes associated with diabetes**" and that they have a marked effect on the kidney, being able to attenuate diabetic nephropathy by modulating oxidative stress, ongoing chronic inflammation, and the release of profibrotic cytokines (Kuhad A, Chopra K. Life Sci. 2009 Feb 27;84(9-10):296-301.) Another study noted the therapeutic potential of the tocotrienols in **reducing diabetes-induced cognitive impairment** (Kuhad A,et al. Pharmacol Biochem Behav. 2009 Apr;92(2):251-9). In a randomized, double blind, placebo-controlled design involving 19 type 2 diabetic subjects with hyperlipidemia, **tocotrienols reduced the LDL** (bad) cholesterol from an average of 179 mg/dl to 104 mg/dl (Baliarsingh S, et al. Atherosclerosis. 2005 Oct;182(2):367-74). Another study demonstrated that tocotrienols effectively **prevented increase in AGE** (advanced glycosylation end products) and caused a **decrease in blood glucose and glycated hemoglobin**, a major cause for diabetic tissue damage (Wan Nazaimoon WM, Khalid BA. Malays J Pathol. 2002 Dec;24(2):77-82). **Alpha tocopherol and beta tocotrienol** were both suggested to be correlated to **reduced risk for getting diabetes type 2** (Montonen J, et al. Diabetes Care. 2004 Feb;27(2):362-6.)

Tocotrienols and the Heart:



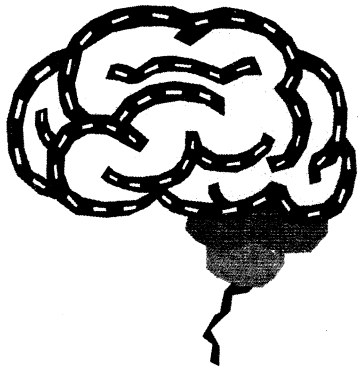
Several studies suggest that the **tocotrienols are very cardioprotective.** One study even rated the tocotrienols as to their cardioprotective power, and found that, "The **gamma-isoform of tocotrienol was the most cardioprotective** of all the isomers followed by the **alpha- and delta-**isoforms" (Das S, et al. Am J Physiol Heart Circ Physiol. 2008 Feb;294(2):H970-8.) "Tocotrienols **attenuate myocardial ischemia-reperfusion injury, atherosclerosis, and reduced ventricular arrythmias**", in addition to the fact that "tocotrienol-mediated cardioprotection is also achieved through the **preconditioning-like effect**, the best yet devised method of cardioprotection" (Das S, et al. Tocotrienols in cardioprotection. Vitam Horm. 2007;76:419-33.)

All of the tocotrienols in one study **"provided cardioprotection, as evidenced by their ability to improve postischemic ventricular function and reduce myocardial infarct size", with the gamma form being the most cardioprotective, followed by alpha and delta forms** (Das S, et al. Cardioprotection with palm oil tocotrienols: comparision of different isomers. Am J Physiol Heart Circ Physiol. 2008 Feb;294(2):H970-8.)

Tocotrienols and Cholesterol:

Tocotrienols "reportedly possess **hypocholesterolemic activity**", and researchers of one study conclude that their "study adds to existing evidence of the **favorable effect of tocotrienols on total cholesterol and LDL-C**" (Ajuluchukwu JN, et al. Comparative study of the effect of tocotrienols and -tocopherol on fasting serum lipid profiles in patients with mild hypercholesterolaemia: a preliminary report. Niger Postgrad Med J. 2007 Mar;14(1):30-3.) In the study, the **tocotrienols were more effective than alpha tocopherol in lowering cholesterol.**

Tocotrienols are **potent antioxidants**, in addition to having the ability to inhibit the HMG-CoA reductase enzyme (the same enzyme that makes cholesterol, and the same enzyme that is inhibited by statin drugs) (Rasool AH., et al. J Nutr Sci Vitaminol (Tokyo). 2006 Dec;52(6):473-8.)



Tocotrienols and Neuroprotection:

Tocotrienols have been found to function as **"potent neuroprotective agents against stroke"** (Das S, et al. Cardioprotection with palm oil tocotrienols: comparision of different isomers. Am J Physiol Heart Circ Physiol. 2008 Feb;294(2):H970-8.) Another study confirms the **neuroprotective qualities** of the tocotrienols, and reports that "oral **tocotrienol protects against stroke-associated brain damage",** and that "taken orally, tocotrienols are bioavailable to all vital organs" (Sen CK, et al. Tocotrienols in health and disease. Mol Aspects Med. 2007 Oct-Dec;28(5-6):692-728.)

Significant protection from mercury-induced neuronal cell death has been observed with both tocopherols and tocotrienols. Even though tocopherols were effective, researchers observed that tocotrienols are multi-fold more potent than tocopherols in protecting brain neuronal cells against mercury neurotoxicity, and that it only took a micromolar concentration of tocotrienols (but not tocopherols) to show complete protection by an antioxidant mechanism. "These results suggested that oxidative events may contribute to methyl mercury (MeHg) toxicity in isolated cerebellar granule neurons, and that **tocotrienols are potent supplements for pharmacological protection of the developing brain exposed to MeHg** (Shichiri M, et al. Protection of cerebellar granule cells by tocopherols and tocotrienols against methylmercury toxicity. Brain Res. 2007 Nov 28;1182:106-15.)