A growing body of evidence is documenting the need for protection from oxidant free-radical damage throughout life. With this realization, a better understanding of the function of vitamin E is needed. Vitamin E has been shown to be one of the most potent biological antioxidants.

A number of compounds exhibit vitamin E activity. In fact, α-tocopherol has traditionally been the compound of interest, with the most market exposure as a supplement. The generic term "vitamin E" includes all tocopherol entities exhibiting the biological activity of α-tocopherol (RRR-; Figure 1). In nature, eight compounds have been found with such activity: d-α-, d-β-, d-δ-, d-γ-tocopherol and the tocotrienols (d-α-, d-β-, d-δ-, and d-γ-). These compounds differ chemically in the number and position of the methyl groups on the chroman ring.

Distribution of tocopherols varies widely. Crude corn and wheat oils contain as much as 200 mg tocopherols per 100 g, while coconut oil contains very little. Their relative amounts vary widely: α-tocopherol predominates in safflower oil, γ- and δ-tocopherols are more abundant than α- in soybean, and γ'-is the prevalent form in corn oil. β-Tocopherol is abundant in wheat germ oil, but is generally found only in traces in other vegetable oils. Tocopherols are extracted commercially from vegetable oil seeds, primarily soybean.

**Biological activity and bioavailability**

The biological activity of the major forms of vitamin E is based upon the "fetal resorption-gestation" method in rats. This assay determines the ability of various forms of vitamin E to maintain live fetuses in pregnant rats. Based on its biological activity, d-α-tocopherol (RRR-α-tocopherol) has the highest value of 100% while other tocopherol vary in their biological activity. The structure of tocopherols indicates three centers of asymmetry at C-2, C-4', and C-8'. The natural forms of vitamin E (all-rac-α-tocopherol; or dl-α) is a mixture of eight stereoisomers (RRR-,RRS-,RSS-,SRR-,SSS-).

Synthetic vitamin E is prepared commercially by coupling trimethyhydroquinone with isophytol (Figure 2). The resulting eight isomeric forms that comprise commercially available synthetic vitamin E have been evaluated using the "fetal resorption-gestation" method. The biological activity for the individual isomers range from 100% (RRR-; 21%) to 21% (SSS-). Both the natural and synthetic forms of vitamin E are available commercially, primarily as their acetate esters. All-rac-α-toctopheryl acetate is the form of vitamin E that has received the most market exposure in pharmaceutical preparations and vitamins. It has also been used in a number of clinical studies that address the long-term effects of vitamin E on cancer and heart disease.

It is well established that RRR-α-tocopheryl acetate is more potent biologically than all-rac-α-tocopheryl acetate, as exhibited in animal tests. Each of the synthetic stereoisomers has lower activity than the RRR-form in the resorption bioassay. Animal studies have provided evidence that the position of the phytol tail of vitamin E is the major determinant of the differences in bioavailability and biological activity. It is therefore of practical concern to know the relationships of the relative bioavailabilities of the stereoisomers.

Biological activity and bioavailability, although two different physiological processes, have often been used interchangeably when the biokinetics of vitamin E are addressed. The concept of bioavailability was first introduced by Oser et al. to describe the availability of vitamins in pharmaceutical preparations. Bioavailability is defined as the rate and extent of absorption of a substance from a dosage form to reach circulation. Biological activity, on the other hand, can be defined in terms of potency (the power of a medicinal agent to produce a desired effect); or in terms of efficacy (the ability to produce the purported therapeutic effect). To this end, it has been assumed that vitamin E forms of the same potency are equally bioavailable in humans.

The absorption and transport of α-tocopherol is well understood. It is absorbed in the form of micelles into the enterocytes of the small intestine and secreted in chylomicrons. Lipoprotein lipase acts upon the chylomicrons. Part of the α-tocopherol transferred to other lipoproteins (HDL and LDL) and to tissues. However, chylomicron remnants transport the majority to the liver, and α-tocopherol is then secreted in nascent VLDL. It has been shown that RRR-α-tocopherol is preferentially secreted into VLDL, presumably by the liver tocopherol-blinding protein. The conversion of VLDL to LDL results in the equilibration of RRR-α-tocopherol between LDL and HDL, and depends upon the plasma concentrations of these two lipoproteins. Little is known about the isomeric forms of synthetic vitamin E in regards to their metabolic fate in humans.

Recent evidence demonstrates that different forms of natural (RRR-) versus synthetic (all-rac-) vitamin E have different bioavailability. We have reported that the ratio of bioavailability. We have reported that the ratio of bioavailability of RRR-/all-rac-α-tocopherol acetate, following multiple doses of deuterated tocopheryl acetate, following multiple doses of deuterated tocopherols to male and female subjects, is 2:1 instead of the currently accepted ratio of 1:36.
Traber et al reported that humans discriminate between the naturally occurring RRR- and the SRR-α-tocopherol form. Presumably, this occurs by selective packaging of the RRR-form into VLDL by the liver tocopherol-binding protein. And recently, Burton et al demonstrated that the single RRR-stereoisomers are significantly higher in human tissue than the all-rac stereoisomers, following multiple doses of deuterium-labeled tocopherols.

Using High Performance Liquid Chromatography (HPLC) and a chiral column, Kiyose et al concluded that the 2R-isomers are preferentially incorporated into lipoproteins of subjects after multidose administration of all-rac-α-tocopheryl acetate, suggesting that the liver tocopherol-binding protein discriminates between 2R-and 2S-isomers, preferentially secreting the 2R-isomers into VLDL. This gate-keeping activity by the liver is presumed to be by a tocopherol-binding protein, which functions to selectively package RRR-α-tocopherol and distribute this form to tissues, while excreting SRR-α-tocopherol in the bile.

Recently, we reported the transfer of natural versus synthetic α-tocopherol across the human placenta to be more selective, with ratios approaching 4:1. This indicates that the placenta is even more discriminating than the liver in selecting the natural versus synthetic forms of vitamin E. This may result from the activity of the recently discovered placental tocopherol-binding protein.

**Functions of vitamin E forms**

Before conclusions can be drawn regarding the protective impact of antioxidants upon human health, it is important to ascertain their function in vivo. Just as with the issue of bioavailability - where animal studies indicated that the bioavailability of natural versus synthetic tocopherols was 1:36 and later proven to be 2:00 when evaluated in humans - the function of vitamin E must be addressed in the human animal. It is essential to ascertain its impact on disease prevention and treatment. To date, there have been no studies in humans addressing the difference in functionality of natural versus synthetic forms of vitamin E. Much of the debate surrounding the differences has rested on the issue of bioavailability following oral ingestion of the two compounds.

The earliest marker of vitamin E deficiency in humans is increased hemolysis of red blood cells (RBC) on exposure to peroxide radicals. The RBC is particularly prone to lipid peroxidative damage, and vitamin E has been shown to mediate a protective effect through its antioxidant properties. The RBC is susceptible unsaturation, the rich oxygen supply, and the presence of hemoglobin, which is a powerful catalyst capable of initiating lipid peroxidation.

Kitabchi and Wimalasena have demonstrated a specific binding site on the RBC membrane for RRR-α-tocopherol. They have further characterised the site in a subsequent report. We have examined RBC function following storage of blood to which natural or synthetic vitamin E has been added. We have found that natural vitamin E provides increased protection when the red cells are stressed, either through osmotic or peroxidative stress. However, the physiological importance of this finding is less well-defined because clinically overt dietary deficiency of this vitamin is rarely encountered in humans.

Additionally, it would be extremely difficult to remove natural and substitute synthetic vitamin E in the diet to test the impact of these two compounds on RBC function in humans.

The inclusion of indices of oxidative stress must be a part of studies comparing the differences between these two important biological antioxidants. It is well established that when prooxidant events change the balance of antioxidant defense, oxidative damage may occur to proteins, lipids, nucleic acids and carbohydrates. This process produces tissue damage and possibly leads to the development of chronic disease.

Recently, Morrow et al identified and described the discovery of a series of prostaglandin (PG) F₂-like compounds termed PG₁₂ isoprostanes. These are produced in humans by a noncyclooxygenase free-radical catalysed mechanism involving the peroxidation of arachidonic acid. Additionally, these authors have been able to assess oxidant stress in vivo by measuring the isoprostanes in biological tissue and fluids in normal humans. In this way, they can define normal ranges for comparison in individuals undergoing oxidative stress. It is possible that this is a biomarker that can be used to assess oxidative stress and therefore evaluate the impact of nutrients exhibiting antioxidant activity, including natural and synthetic vitamin E.

**Summary**

The bioavailability of natural versus synthetic vitamin E in humans is being elucidated, along with controlling mechanisms (e.g., the liver and placenta tocopherol-binding protein) of metabolism of these important antioxidants. It has been demonstrated that the natural (RRR-) form of α-tocopherol is more bioavailable than is the synthetic (all-rac; a mixture of eight isomers) compound in humans. The remaining issue to be resolved regarding these two compounds is the functionality of each in vivo, particularly given the fact that the natural form of vitamin E is a single chemical structure and the synthetic compound is a mixture of eight. The results of investigations into the differences in natural and synthetic vitamin E will determine their impact upon pro-oxidant events. They will also indicate which compound is most efficacious for the prevention and treatment of chronic diseases.

**References**


Acuff RV: Unpublished observations.

