Vitamin E

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Importance of vitamin E for health

Vitamin E is a fat-soluble antioxidant vitamin that exists in eight natural chemical forms with varying levels of biological activity. All forms are absorbed but α-tocopherol is the major biological form and is preferentially retained in the body through binding with α-tocopherol-transfer protein (α-TTP) and as such is the only recognised form to meet human requirements. However there are 7 other forms existing in nature: β-, γ-, δ-tocopherol, and α-, ß-, γ-, and δ-tocotrienol (1)

The liver takes up vitamin E ingested in the diet, and re-secretes preferentially only α-tocopherol; other forms of vitamin E are excreted (2). Serum concentrations of α-tocopherol therefore depend on the action of the liver, and the hepatic α-tocopherol transfer protein (α-TTP) is considered as the major regulator of vitamin E status in humans (3).

Vitamin E function

α-tocopherol neutralises free radicals and protects tissues and organs from oxidative damage. It is incorporated into cell membranes, prevents protein oxidation and lipid peroxidation, and therefore maintains the membrane integrity. α-tocopherol also modulates expression of various genes, has a role in neurological function, cell signalling, inhibits platelet aggregation, enhances vasodilation and can modulate the immune response by reducing the proliferation of immune cells (1, 4).

Vitamin E for health

There has been considerable research conducted about the benefits of vitamin E on certain medical conditions, due to its role as a potent antioxidant. Conditions include cardiovascular disease, cancer, age-related macular degeneration and Alzheimer's disease. To date, results are inconclusive and there are no recommendations in place. This is partially due to the lack of validated biomarkers of vitamin E linking intake to clinical outcomes (5), making this a research priority area.

Vitamin E supplementation to prevent morbidity and mortality of preterm infants

Premature infants are born before 37 weeks of gestation. Premature births are the leading cause of infant death in the first 4 weeks of life. Incidence of prematurity is increasing; prevalence is currently 1 in 10 births globally. Risks of mortality due to prematurity are highest in low-income settings (6).

Vitamin E is important for the health of premature infants, and may be able to prevent or limit morbidity associated with prematurity. Vitamin E is present at higher than usual levels in the breast milk of mothers who have given birth prematurely. However, though studies have shown some benefits of vitamin E supplementation to premature infants, supplementation with vitamin E may also increase the risk of life-threatening infections e.g. sepsis. Current evidence does not support the use of high-dose vitamin E supplementation, and WHO state that further research is needed before specific recommendations can be made.

Sources of vitamin E

Vitamin E is naturally abundant in the diet, with the principal sources being vegetable oils, particularly sunflower and safflower, nuts, seeds and green leafy vegetables such as spinach (3). Vitamin E in either natural or synthetic form, as α-tocopherol, is also commonly consumed as a dietary supplement (4), or in fortified ready-to-eat cereals (3).

Fortified cooking oils are used in many low- and middle-income settings, and the World Food Programme (WFP) currently recommends the addition of Vitamin A and Vitamin D as fortificants of vegetable oils, though vitamin E is currently not included in the recommendations (for more information, see http://foodqualityandsafety.wfp.org/fortification-of-oils). However, the stable form, α-tocopherol acetate form may be added to oils, and is converted to α-tocopherol in the intestine. Due to its stability it is a good food fortificant, however it offers the oil no antioxidant

protection (for more information, see https://www.dsm.com/content/dam/dsm/nip/en_US/documents/oils.pdf).

Deficiency A deficiency in vitamin E is rare, and most people with a healthy, balanced diet will obtain enough vitamin E from dietary sources (5). However, those with low-fat or severely fat-restricted diets may be at risk of insufficient intakes (5), because fat is required for vitamin E absorption. Persons at risk of frank vitamin E deficiency are those with genetic abnormalities in the α-TTP transfer protein in the liver, those with genetic abnormalities in lipoprotein synthesis, or those with fat malabsorption syndromes (3) Symptoms of vitamin E deficiency include peripheral neuropathy, ataxia, skeletal myopathy, retinopathy, and impairment of the immune response (5).

Excess: There are no documented effects of an excessive consumption of vitamin E from food sources (5). The excessive consumption of vitamin E from supplements appears to be of minimal risk however there may be a risk of haemorrhage. The precise effects are unclear and warrant further investigation (5).

Human biomarkers of population vitamin E status

Serum concentrations of α-tocopherol depend on the action of the liver, and the hepatic α-tocopherol transfer protein (α-TTP) is considered as the major regulator of vitamin E status in humans (3). α-tocopherol in serum is therefore the biomarker of choice of vitamin E status. The majority α-tocopherol in the circulation is associated with low-density lipid fractions and α-tocopherol concentrations may need to be considered in the context of circulating lipid concentrations and may be adjusted for cholesterol concentration (7, 8).

The vitamin E content of foods and dietary supplements is often listed on labels in international units (IUs), which is a measure of biological activity rather than quantity. Naturally sourced vitamin E is called *RRR*-alpha-tocopherol (commonly labelled as *d*-alpha-tocopherol); the synthetically produced forms RSR-, RRS- and RSS- are together known as *all rac*-alpha-tocopherol (commonly labelled as *dl*-alpha-tocopherol). Conversion rules are as follows:

To convert from mg to IU:

- 1 mg of alpha-tocopherol is equivalent to 1.49 IU of the natural form or 2.22 IU of the synthetic form

To convert from IU to mg:

- 1 IU of the natural form is equivalent to 0.67 mg of alpha-tocopherol
- 1 IU of the synthetic form is equivalent to 0.45 mg of alpha-tocopherol

(For more information, see https://ods.od.nih.gov/factsheets/VitaminE-HealthProfessional/#en2)

Laboratory methods of assessment

Samples are commonly analysed for Vitamin E and Vitamin A in the same preparation. This is performed by the addition of an internal standard (tocopherol acetate for Vitamin E), a protein crash to disrupt protein binding and solvent extraction followed by chromatographic separation using reversed phase HPLC on a C18 column and detection with UV/Vis or PDA detectors.

There is no primary reference method listed on the JCTLM database at the present time (November 2018). This information will be updated as applicable.

Collection and storage of samples:

Recommendations from the AACB vitamins working party in 2014 for the collection and storage of samples for vitamin E analysis (9):

- Patient preparation: No recommendation for or against the patient to be fasting.
- Sample collection: Recommend collection of blood into plain, gel separator, heparin or EDTA tubes for analysis of serum/plasma.
- Sample transport of whole blood for vitamin A, E and β-carotene:
    - No recommendation for or against specific transport conditions if delivered to laboratory within 24 hours of collection.
    - Recommend that samples are chilled to 4°C during transport to the laboratory if transport takes between 24 hours and four days.
    - Recommend against delaying sample transport and receipt by laboratory beyond four days.
    - Handling of serum/plasma samples for vitamin A, E and β-carotene: No recommendation for or against light protection of the sample during short term receipt and processing by the laboratory (up to 24 hours under laboratory lighting).
- Serum/plasma storage:
    - Recommend for short term storage up to one week that vitamin A and E samples are stored at ≤4°C.
    - Strongly recommend for vitamin E samples to be stored at ≤-20°C for up to six weeks and at ≤-70°C for longer term storage i.e. up to one year.

The stability of α-tocopherol seems to be intermediate compared to retinol and β-carotene with losses evident at higher temperatures and very long term storage. Vitamin E has demonstrated stability at -20°C for at least one year with deterioration evident past this time point.

Quality Control

QC material can be prepared from pooled serum or plasma samples, or can be obtained from the following commercial sources:

- Chromsystems (Gräfelfing, Germany)- Vitamin A/E serum controls
- Bio Rad (Watford, UK) – Vitamin A/E control set
- Recipe (Munich, German) – ClinChek Serum controls

NOTE: All manufacturers also provide a full HPLC kit for the analysis of Vitamins A/E

Accreditation schemes

For laboratory accreditation, validation and details on availability of proficiency testing, please see the OpeN-Global page https://open-global.kcl.ac.uk/accreditation/ For example, the NEQAS scheme in the UK include vitamin E. https://birminghamquality.org.uk/eqa-programmes/vit/

Technical assistance

For questions on methods of magnesium assessment or for technical assistance, please contact the OpeN-Global team at https://open-global.kcl.ac.uk/contact/ or write to Nutritional Biomarker Laboratory, University of Cambridge, UK Email: nbl@mrc-epid.cam.ac.uk

Useful links

National Institutes of Health, Office of Dietary Supplements:
https://ods.od.nih.gov/factsheets/VitaminE-HealthProfessional/

WHO eLENA library: Vitamin E supplementation for the prevention of morbidity and mortality in preterm infants: https://www.who.int/elena/titles/vitamine_preterm/en/

National Academies Press: DRIs for Vitamin C, Vitamin E, Selenium and Carotenoids:
https://www.nap.edu/catalog/9810/dietary-reference-intakes-for-vitamin-c-vitamin-e-selenium-and-carotenoids (free pdf download)

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