17. Vitamin E

Physiology

Vitamin E activity is manifested by two series of compounds. The more important are the tocopherols; the tocotrienols, differing in the degree of saturation of the phytyl side chain, are less potent biologically and provide only a little of the vitamin E activity of the diet. Within each series are four compounds (designated α, β, γ and δ) differing in the number and position of the methyl groups on the chromanol ring. Synthetic α-tocopherol is a mixture of isomers. The multiple forms differ in vitamin E potency, the most active being the natural isomer RRR-α-tocopherol, which accounts for about 90% of the vitamin E present in human tissues. The vitamin E activity of all is now conventionally summed in terms of the equivalent value of RRR-α-tocopherol [1] (1 mg α-tocopherol equivalent = 1.5 international units).

The biological action of vitamin E results principally and perhaps entirely from its antioxidant properties; it prevents propagation of the oxidation of unsaturated fatty acids by trapping free radicals. This is believed to be the basic function of vitamin E in animal tissues, where tocopherol is found in cellular membranes associated with polyunsaturated fatty acids (PUFA) in phospholipids. In vitamin E deficiency, the oxidation of PUFA leads to structural and functional damage to cellular membranes.

Levels of deficiency and excess

Most diets are an adequate source of vitamin E, and consequently for many years no clearly defined deficiency syndrome could be described in man, and no clinical signs of deficiency are ever seen in individuals without other metabolic defects. Children and adults unable to absorb or utilise vitamin E adequately can develop a characteristic and progressive neurological syndrome involving the central and peripheral nervous system, retina and skeletal muscles, after a period of years during which the plasma tocopherol concentration has been extremely low. Appropriate treatment with vitamin E can prevent this if given sufficiently early.

A specific syndrome comprising haemolytic anaemia, thrombocytosis and oedema has been reported in premature infants, but the introduction of milk formulas containing adequate vitamin E has resulted in its virtual disappearance.

Over the years there have been many claims that vitamin E in quantities much larger than those needed to prevent any detectable deficiency may have beneficial effects on various disease processes or in promoting better general health. Most have not gained wide acceptance. Currently however there is much interest in a postulated role of antioxidants in preventing pathological processes in which free radicals have been implicated; particular attention has been paid to vitamin E as it can act as a free-radical scavenger. It has been suggested that a generous intake of vitamin E might protect against, among other things, cancer, atherosclerosis, coronary heart disease, cataracts, arthritis, ageing and air pollutants [2]. For example, an inverse relationship has been reported between plasma vitamin E concentration and coronary heart disease [3,4].

Because of the numerous reports of the beneficial effects of high doses, it is not uncommon for individuals to consume large amounts of vitamin E. There have been a number of double blind trials to investigate high doses of vitamin E up to 3,200 mg/d. Few adverse effects were reported and none consistently but above 2,000 mg α-tocopherol equivalents per day some subjects showed intestinal disorders (diarrhoea and cramps) [5].

Methods of establishing physiological requirements

Since clinical vitamin E deficiency due to an inadequate supply in the diet does not exist, some other marker of E status is necessary, and a commonly used one is the plasma tocopherol concentration. This however changes with the concentration of serum lipids; as they rise tocopherol appears to partition out of cellular membranes into the circulation. The tocopherol concentration is therefore best expressed as the serum tocopherol: total lipid ratio, but the serum tocopherol:cholesterol ratio is almost as good, and is more convenient to measure [6].

The major function of vitamin E is believed to be the protection of cellular membrane lipids from oxidation and a widely employed test for this is to expose red cells *in vitro* to oxidizing agents such as dilute solutions of hydrogen peroxide. Below a plasma tocopherol concentration of 0.5 mg/dl (11.6 μmol/L; tocopherol:cholesterol ratio 2.25 μmol/mmol), the erythrocytes tend to haemolyse. A substantial decrease below this concentration is necessary to reduce red cell survival time *in vivo* [7]. Nevertheless a plasma tocopherol concentration of 0.5 mg/dl (11.6 μmol/L) or, better, a serum tocopherol: cholesterol ratio of 2.25 μmol/mmol, is taken as an indication of biochemical abnormality, and it is considered undesirable to have tocopherol concentrations fall below that.

In favourable circumstances the plasma tocopherol concentration can be maintained above that on not very large intakes of vitamin E – for some adult males, on not much above 3 mg α-tocopherol equivalents per day, provided they have a low intake of PUFA [8].

The requirement for vitamin E is determined to a large extent by the PUFA content of the tissues, which is influenced by the PUFA content of the diet. Numerous experiments have shown that increasing the PUFA content of a diet low in vitamin E has adverse effects on E status [8,9] and if there are very large amounts of PUFA, substantial quantities of extra vitamin E are needed to restore the plasma tocopherol concentration to an adequate level [9].

Translation of these physiological requirements into dietary intakes

A major problem in making recommendations arises from the fact that E requirements are influenced by the PUFA intake. There are wide variations in PUFA consumption; the intakes of individuals are not normally distributed but are skewed with some quite high values. In a recent study of adult men in UK [10] the 97.5 centile intake of n-6 PUFA was 29 g per day. The amount of vitamin E required for such an intake of PUFA would be high. To give such a value as the PRI would have the undesirable effect of indicating to people with a much lower, but adequate, intake of PUFA that they ought to take substantially more vitamin E when they had no need to do so.

However, widely differing intakes of PUFA are normally not a problem in practical vitamin E nutrition. Foods rich in PUFA tend to contain large amounts of vitamin E, so high intakes of PUFA are usually accompanied by comparably high intakes of vitamin E. This is not always the case with all individual foodstuffs, but taken over a mixed diet, the generalization seems to hold.

The difficulty in making recommendations about dietary intake of vitamin E is that there is no good evidence that dietary vitamin E deficiency exists, in part because vitamin E is widely distributed in common foodstuffs, and accompanies the PUFA that raise requirements. A recent demonstration of this was in a survey in UK [10]. Of 1,763 adult subjects only 11 (0.6%) had serum tocopherol:cholesterol ratios below 2.25 μmol/mmol.

There are various responses to this problem. One is to declare that, as virtually all diets are adequate with respect to vitamin E, recommendations are unnecessary except for infant formulas.

A second approach is to decide that since the diet as consumed is clearly adequate with respect to vitamin E, the recommendation should be based on current intakes. In prosperous societies, however, most people seem to ingest more vitamin E than they need to maintain apparent biochemical normality. In the recent survey of British adults [10], of which over 99% had acceptable serum tocopherol:cholesterol ratios, seven-day weighed dietary records (excluding vitamin supplements) showed that the 2.5 and 97.5 centile intakes of a group of 1,087 males were 3.5 and 19.5 mg α-tocopherol equivalents per day, and of a group of 1,110 females 2.5 and 15.2 mg per day.

Another apparently more logical approach is to make dietary recommendations for vitamin E in terms of the dietary PUFA intake. There is however no general agreement about what the ratio mg α-tocopherol equivalents:g PUFA should be, but about 0.4 seems adequate in a normal American diet [11,12]. Furthermore there is evidence that even on a very low intake of PUFA, a substantial amount of vitamin E is still needed [9].

Suggestions have been made that intakes of vitamin E in amounts much larger than normally considered essential would raise plasma α-tocopherol concentrations and have health benefits. The evidence for this is as yet insufficiently convincing, and there is even less certainty on what the effective daily amounts might be.

The claim should be kept under review as the results of more work, including, it is hoped, intervention trials, are published. Should it prove true, the problem could arise of distinguishing between true nutrient needs and the use of nutrients as prophylactic drugs [13].

Children and infants (6-11m)

A diet containing 0.4 mg α-tocopherol equivalents per g PUFA seems adequate for children. It is reasonable to assume that as in adults there is some basic requirement for vitamin E on a diet very low in PUFA, but there is no information about what the amount might be. In practice, there seems no cause for concern, as there is no evidence of E deficiency in metabolically normal children.

Infant formulae always contain adequate amounts of vitamin E.

Pregnancy and lactation

Since vitamin E deficiency has never been reported during pregnancy and lactation, even on quite low intakes [14], no recommendations for supplementation are made.

Summary of proposals

1. As the vitamin E requirement depends on the dietary PUFA intake, and dietary PUFA intakes vary greatly between individuals, it is inexpedient to set a single PRI value that would meet the known nutrient needs of practically all healthy persons as this would be misleadingly far too large for most of the group.

2. Similarly there seems little merit in giving an average requirement.

3. A requirement for vitamin E can be defined in terms of dietary PUFA intake. Vitamin E requirement (mg α-tocopherol equivalents) = 0.4 x (g dietary PUFA). There is no evidence that this level would be inadequate for anyone, provided the value did not fall below 4 mg/d for adult men and 3 mg/d for adult women (because of their smaller body size, women would have less PUFA in their tissues needing protection).

4. Large doses are usually harmless, but should not exceed 2,000 mg α-tocopherol equivalents per day.

5. Claims that very generous intakes of vitamin E have beneficial effects on health are not being taken into account in making the present recommendations.

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