15. Vitamin C

Physiology and metabolism

Vitamin C (L-ascorbic acid) is involved in numerous metabolic reactions in ways not yet fully understood [1,2]. The most specifically defined biochemical function is as a cofactor in hydroxylations using molecular oxygen, notably of proline to hydroxyproline, as in the biosynthesis of collagen. Ascorbic acid participates in this and other reactions as a reducing agent. It reduces Fe(III) to Fe(II), which helps in improving the absorption of non-haem iron. It reduces superoxide radicals to hydrogen peroxide, and effectively quenches singlet oxygen, which is the basis of its ability to inhibit many destructive photo-dynamic effects, e.g. in the eye, and other beneficial effects of vitamin C in the human body have been ascribed to its antioxidative capacity.

Ascorbic acid is one of the main water soluble chain-breaking antioxidants in biological systems [3]. Much attention is now being paid to the role of vitamin C in the antioxidant defences of the body, but insufficient evidence is currently available to enable the antioxidant status of the body to be used as the basis of calculating vitamin C requirements.

At low doses, absorption of vitamin C may be almost complete, but over the range of usual intake in food (30-180 mg/d), 80 to 90 % is absorbed. When ingested in amounts higher than 100 mg/d, it is mainly excreted as such, while the percentage of gastrointestinal absorption decreases with the oral dose of vitamin C to values as low as 16 % [4].

Total body stores of ascorbic acid in adult man may reach levels up to 3 g at daily intakes exceeding 200 mg. The average body pool of vitamin C of healthy male subjects consuming a self-selected diet with a daily ingestion of 60-100 mg of ascorbate is around 1500 mg, i.e. about 20 mg/kg body weight [5].

Levels of deficiency and excess

Frank vitamin C deficiency appears in the adult as scurvy, in the child as Moeller-Barlow disease, which has somewhat different signs.

Scurvy affects primarily the mesenchymal tissues. Because collagen formation is impaired, wound healing is delayed. The deficient formation of intercellular substance and collagen leads to increased fragility of the capillaries and to bleeding in the skin, mucous membranes, internal organs and muscles.

In childhood scurvy, the bone tissue is most obviously involved, especially in the breast cage and the stressed epiphyseal cartilage of the extremities. The disease can occur in artificially nourished infants after the 6th month of life, when the transplacentally transferred reserves of the vitamin have been exhausted.

Clinical signs of scurvy appear in adult men on a daily intake of less than 10 mg/d, when the total body pool falls below 300 mg [6], and are associated with plasma (or serum) and whole blood vitamin C values of less than 2 mg/L (11 µmol/L plasma) and 3 mg/L (17 µmol/L blood); leukocyte levels of less than 2 $\mu g/10^8$ cells (85 µmol/L) are observed.

A lesser degree of hypovitaminosis C can manifest itself in "prescorbutic" symptoms such as weakness, lassitude, fatigue, increased susceptibility to infections, and perhaps to other disease conditions [2]. Behavioural abnormalities, delayed recovery from surgical procedures, weight loss and deficient immune system responses have been reported.

A common feature of vitamin C deficiency is anaemia, due to impaired iron and perhaps folic acid metabolism.

Reports that high intakes may be beneficial have led some individuals to take large doses of vitamin C. The only adverse effects consistently reported in apparently healthy subjects are transient gastrointestinal disturbances. These can occur after ingestion of as little as 1 g, but seem to be caused by the acidity rather than the ascorbic acid *per se* because the symptoms can be largely avoided by taking the vitamin as a buffered salt. Ill effects of higher doses have occasionally been reported, e.g. an increased urinary excretion of oxalate with a resulting higher risk of kidney stones in patients with defects of oxalate metabolism, but in general intakes up to 10 g/d seem not to be unsafe for healthy individuals [7].

Methods for establishing physiological requirements

Vitamin C status can be evaluated from signs of clinical deficiency (such as follicular hyperkeratosis, swollen or bleeding gums, petechial haemorrhages, and joint pain), or from its concentration in plasma, blood or leukocytes. It has also been estimated from isotopic studies of body stores [2].

The Sheffield experiment on the vitamin C requirements of human adults [8] and the later Iowa study [6] indicated that a daily amount of 6.5-10 mg ascorbic acid is sufficient to prevent or to cure signs of scurvy. The ultimate lowest physiological requirement of adults is presumably in that range.

It is generally assumed that the amount of vitamin C required for optimal functioning of metabolic processes within the body is higher than the amount to prevent classical signs of scurvy. However, the optimal tissue levels of vitamin C for these processes are not known. Blood levels of vitamin C are often considered, although these levels have their limitations. Plasma concentrations above 5 mg/L (28 µmol/L) are taken as indicating an acceptable supply. Such levels are reached at vitamin C intakes from about 30 mg per day. Vitamin C levels rise rapidly with increasing daily intake and reach a plateau of 12-15 mg/L (68-85 µmol/L) at intakes far above 80 mg per day [9]. The strong relation between plasma vitamin C and recent oral intake limits the value of the plasma level as a reliable indicator of vitamin C adequacy.

The ascorbic acid level in leukocytes approximately reflects that in the tissues. However, it may not be a reliable index of vitamin C status as the vitamin rapidly moves from plasma into cells, e.g. during infections [10].

A priori, the best means of determining vitamin C requirement would seem to be determination of the total body pool and its fractional rate of loss or catabolism. The appropriate intake would be that needed to replace losses and thus maintain the body pool, taking into account the bioavailability of vitamin C from the diet.

Translation of physiological requirements into dietary intake

Clinical signs of scurvy appear in adult males when the total body pool of vitamin C falls below 300 mg [6]. It is desirable to have vitamin C in amounts more generous than just to prevent the appearance of scurvy, and psychological abnormalities have been reported in men with body pools below 600 mg. There is no convincing evidence of extra benefits from a pool in excess of 600 mg, but a pool of 900 mg would provide reserves for periods of low intake or temporary higher needs, e.g. stress.

For a wide range of body pool sizes (12-1700 mg) and vitamin C intakes up to 60 mg/day, the mean first-order rate of urinary excretion of vitamin C and its metabolites in adult men has been calculated as 2.7 ± 0.5 % of the body pool per day [11].

During the depletion periods of the Iowa experiments [12], the body pool was catabolized at a rate of 2.9 ± 0.6 % per day. One can derive from this a daily intake of

vitamin C in adult men by assuming a body pool of 900 mg and an absorption efficiency of 85%. In this way the Average Requirement (AR) for an adult man is calculated as:

900 x 2.9/100 x 100/85 = 30.7 mg/d, which can be rounded off to 30 mg/d.

The Population Reference Intake (PRI) for adult men would be

900 x (2.9 + 1.2)/100 x 100/85 = 43.4 mg/d, which can be rounded off to 45 mg/d.

It is difficult to estimate a Lowest Threshold Intake (LTI) for vitamin C. It can be argued that it should be the amount that will certainly prevent scurvy – somewhat less than 10 mg/d in adult men – but many would consider that a too restricted view of the nutritional importance of the vitamin. Maintenance of an adequate body pool has been used as the basis for calculating the AR and PRI; a similar approach can be employed for estimating the LTI.

It would be unreasonable to calculate a LTI to maintain a body pool size of 900 mg, as failure to do so is unlikely to be harmful. However, it can be derived for a body pool of 600 mg as

600 x (2.9 - 1.2)/100 x 100/85 = 12 mg/d.

Women probably have a smaller body pool than men, and might therefore be expected to have a lower requirement. No comparable turnover studies have been carried out on women, however, and in a depletion experiment the plasma vitamin C concentration was reported to fall more rapidly in females than in males [13]. It therefore seems prudent to make the same recommendations for non-pregnant, non-lactating women as for men.

Requirements of other groups of the population

Children

Little information is available beyond that 7 mg/d is sufficient to prevent scorbutic signs in infants [14]. The amount of vitamin C in breast milk seems to reflect maternal dietary intake, not the infant's needs, and in Europe and USA intake may range down to 23 mg/d, while apparently satisfying all the needs of the infant [2,11,14,15].

The PRI for infants 6-12 months is therefore set, somewhat arbitrarily, at 20 mg/d, i.e. about three times higher than amounts known to prevent scurvy.

The PRIs of older children are increased gradually to those for adults.

Pregnancy

Plasma and leukocyte vitamin C drop during pregnancy [14]. It is not known whether this drop represents a normal physiological adjustment (haemodilution) or indicates an increased requirement. It is assumed that the requirement of vitamin C during pregnancy is somewhat higher than that of non-pregnant women but by not more than 10 mg/d. This increase would allow for the 50 % higher plasma levels and probably higher cell concentration of vitamin C in the fetus and the higher catabolic rate of the fetus.

Lactation

Lactating women should have a vitamin C intake which compensates for at least 20 mg vitamin C excreted in breast milk. On the assumption of a 85 % bioavailability, the dietary intake of lactating women should be 25 mg/d higher than non-lactating women for the entire lactating period.

The elderly

Conflicting results have been reported on the changes of blood levels of vitamin C as a result of ageing. It seems, however, that in the absence of pathological conditions that may influence vitamin C metabolism (e.g. digestion or absorption) or renal functioning, the vitamin C requirement of the elderly do not deviate from those of other adults [11].

Other factors affecting vitamin C requirement

There are indications that smoking and some other factors and conditions may influence the vitamin C requirement.

Smoking decreases the absorption and blood level of vitamin C and increases its catabolism. In heavy smokers (routinely more than 20 cigarettes per day) with a vitamin C intake of 60 mg/day, the mean absorption efficiency has been reported as 9 % lower and the mean half-life significantly reduced (by about 60 %) as compared with non-smokers [16]. A direct relationship has been demonstrated between the number of cigarettes smoked per day and levels of vitamin C. The daily turnover of vitamin C of heavy smokers would be about 40 % higher than that of non-smokers [16].

The function of ascorbic acid in the absorption of non-haem iron has been mentioned already. The section of this report dealing with iron discusses the difficulty some women have in obtaining an adequate supply of iron. The bioavailability of dietary non-haem iron can be substantially improved if the meal contains 25 mg or more ascorbic acid.

Some circumstances enhance the requirement for vitamin C, e.g. high physical activity, mental stress, alcoholism, drugs, and a number of pathological states, e.g. diabetes [14]. Unfortunately, the effects of all these factors have not been quantified and results of studies are not concordant. Therefore, the optimal intake of vitamin C in such stress conditions is not known.

Higher recommendations

There is a school of thought which believes that human requirements for vitamin C are considerably higher than the PRIs discussed above, e.g. more than 1 g/d. However, this is based on extrapolations to man from observations in animals that many consider unjustified. Intakes in excess of about 80-100 mg/d lead to a quantitative increase in urinary excretion of unmetabolised vitamin C, indicating that at this level tissue reserves are saturated. It is difficult to justify a requirement in excess of tissue storage capacity.

It is hoped that in the near future more information will become available on the quantitative role of vitamin C in the body's defences against free radicals and on epidemiological evidence that appears to link higher vitamin C intakes with a lower level of some diseases [1,2,9,17].

Summary

Adults	mg/d
Average Requirement	30
Population Reference Intake	45
Lowest Threshold Intake	12

Population Reference Intakes of other groups

Age Group	PRI (mg/d)
6-11 m	20
1-3 y	25
4-6 y	25
7-10 y	30
11-14 y	35
15-17 y	40
Pregnancy	55
Lactation	70

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