Vitamin C

Vitamin C		Women	Men	Children		
	mg/d			2-5 y	6-9 y	10-13 y
Recommended intake	RI	75	75	30	40	50
Average requirement	AR	50	60			
Lower level of intake	LI	10	10			
Upper level of intake	UL	-	-			

Introduction

The term vitamin C refers to both ascorbic acid and dehydroascorbic acid, since both forms have an anti-scorbutic effect. Although the classical vitamin C deficiency, scurvy, is prevented by small daily intakes (about 10 mg/d) (1), current knowledge of the antioxidant functions of vitamin C has recently had a great influence on the research of daily vitamin C allowances.

Dietary sources and intake

The concentration of vitamin C is high in many vegetables, berries and fruits (e.g. citrus fruits). Moreover, intake from vitamin C-enriched products (e.g. juices) may be considerable. The average intake of vitamin C in the Nordic countries is 80-160 mg/10 MJ. As already pointed out earlier, plasma vitamin C is a biomarker of fruit and vegetable consumption (13). Therefore, the observed associations between plasma (and dietary) vitamin C and health may at least partly reflect other health-enhancing components in fruit and vegetables, or even other lifestyle variables.

Physiology and metabolism

Vitamin C is a cofactor for several enzymes involved in the biosynthesis of collagen, carnitine and neurotransmitters (2). In all these functions, the effects of ascorbic acid are based on its ability to be an electron donor. Consequently, ascorbic acid is oxidised to dehydroascorbic acid. The vitamin is also involved in the biosynthesis of corticosteroids and aldosterone and in the microsomal hydroxylation of cholesterol in the conversion of cholesterol to bile acids. Due to its reducing power, ascorbic acid also improves absorption of non-haem iron.

Ascorbic acid is a potent antioxidant. The vitamin readily scavenges reactive oxygen species and reactive nitrogen species, in addition to singlet oxygen and hypochlorite. It is evident that ascorbic acid provides meaningful antioxidant protection in, e.g., neutrophils, semen and

plasma (e.g. against LDL oxidation) (2,3). Ascorbic acid may also regenerate other antioxidants, such as vitamin E. As a reducing agent, ascorbic acid may also inactivate carcinogenic substances, such as nitrosamines.

Ascorbic acid is absorbed from the intestine by a sodium-dependent, active process that is saturable and dose-dependent. The bioavailability (efficiency of gastrointestinal tract absorption) is at least 80 % for doses of 100 mg or less, 60-70 % for 200-500 mg doses and less than 50 % for doses exceeding 1000 mg (3). Unabsorbed ascorbate is degraded in the intestine; this process may lead to diarrhoea and intestinal discomfort, sometimes reported by persons ingesting very large doses from supplements (4).

Vitamin C undergoes glomerular filtration and renal reabsorption. When the transport protein reaches saturation, remaining vitamin C is excreted in the urine. Up to 60 mg doses, no ascorbic acid is excreted (5) but at 100 mg dose, about 25 % is excreted. About 50 % of a 200 mg dose is excreted and about 80-90 % of a dose exceeding 500 mg. The estimated threshold for excretion is about 80 mg/day, meaning that essentially no vitamin C is excreted in urine if the daily intake is lower (6).

The body pool of ascorbic acid is increased up to a daily intake of approximately 100 mg (7). This point is reflected by saturation of neutrophils, monocytes and lymphocytes (5,8). At saturation level of white blood cells, plasma ascorbic acid concentration is approximately 50-60 μmol/l, but very large doses (2500 mg/day) are capable of increasing plasma levels up to 80 μmol/l (5,8). However, above about 100 mg/day of ascorbic acid, further increase in vitamin C intake leads to gradually smaller increases in plasma vitamin C levels (9). Plasma ascorbic acid concentration below 23 μmol/l reflects marginal vitamin C status (10). This level is reached by an estimated daily intake of 41 mg, depending obviously on body size (10). Marginal status may be reflected by e.g. decreased antioxidant capacity, fatigue and irritability (5). Symptoms of scurvy are observed when plasma levels are below 11 μmol/l (10) or the total body pool is below 300 mg (11). Scurvy is very uncommon, but cases have been reported even in Nordic countries (12).

Prospective, cohort studies

One way to study the associations between vitamin C and chronic diseases is to use longitudinal population samples, that is, cohort studies. Unfortunately, they are not ideal for many reasons. One is that it is almost impossible to make precise estimations of vitamin C intake by using the methods available in studying large population (mainly food-frequency questionnaires).

Another approach is to study the association of plasma ascorbic acid concentration and disease outcomes. The advantage of this approach is that the accuracy and reliability of plasma vitamin C measurements are better than that for dietary vitamin C intake. The drawback is that plasma vitamin C reflects many other dietary and lifestyle variables than directly vitamin C. For instance, consumption of fruit and vegetables correlate with plasma ascorbic acid concentration (13), but fruit and vegetables have also positive health effects which are not explained by their vitamin C content. In addition, even after multiple adjustments, a high intake of fruit and vegetables may still be associated with some unmeasured lifestyle variables which are positively related to health (14,15).

Eight large prospective studies were found with inverse association between plasma ascorbic acid (AA) concentration and cardiovascular and/or all-cause mortality (16–23). Moreover, five prospective cohorts studies, all using the EPIC data, have reported on associations between plasma ascorbic acid concentration and type 2 diabetes (24), coronary artery disease (25), stroke (26), blood pressure (27) and heart failure (28). All of these studies showed that the risk for mortality and morbidity was highest in subjects with the lowest plasma concentration. In contrast, Lawlor et al. (15) did not find an association between plasma vitamin C concentration and coronary heart disease, after adjustment for socioeconomic position.

The relationship between plasma vitamin C concentration and morbidity was curvilinear in most of the above studies, that is, the largest decrease in risk, compared to e.g. the adjacent lower quarter, was observed for those between the 20^{th} and 40^{th} percentile. Studies with cancer mortality as the outcome have also identified the lowest plasma AA category as being clearly associated with increased risk (23,29). However, in some studies (16,17,20,21,23), decreased risk for cardiovascular mortality (significantly different from the category with highest risk) was only seen in categories with higher plasma ascorbic acid concentration (e.g. above 40^{th} percentile). The same variation is seen in studies using disease incidence as outcome: in some cases, those above the 25^{th} percentile have similarly reduced risk ratios (25,28), while other reports show that the risk is still reduced at least up to median plasma ascorbic acid concentration (24,26,27) .

Supplementation studies

Supplementation studies are controlled interventions. The definite advantage – compared to observational cohort studies – is that the additional intake of vitamin C is known. However, the estimation of dietary intake (without supplements) is as difficult to assess as in observational studies. Another more principal problem is that the amount of supplemented vitamin C is often much above the assumed average and recommended intakes(30). Therefore, they don't tell much about variations of intakes that are more close to what can be achieved from ordinary diets.

Bjelakovic et al. (30) published a meta-analysis on mortality in randomized trials of antioxidant supplements for prevention of diseases. They identified only three trials with vitamin C as the single supplement, and only one of these trials (31) had an outcome with major relevance to NNR. Although Salonen et al. (31) in this study reported that vitamin C slowed down atherosclerotic progression in hypercholesterolemic persons, the overall conclusion in the meta-analysis was that vitamin C alone or in combination with other antioxidants had no significant effect on mortality (30).

More recently, two papers based on the Physicians' Health Study II (a randomized controlled trial), concluded that vitamin C did not reduce the risk of prostate or total cancer (32), or cardiovascular disease (33) in middle-aged and older men. In contrast, a meta-analysis on clinical trials concluded that vitamin C supplementation (median dose 500 mg/d) lowered blood pressure in both hypertensive and normotensive participants (34). However, most trials were short in duration (median 8 weeks) and the trial size was rather small (range from 10 to 120 participants). Therefore, larger studies with longer duration are needed to get more insight of the potential blood pressure lowering effects of vitamin C supplementation.

Dietary micronutrient recommendations are typically based on data on deficiency symptoms (lower intake level) and on associations with and effects on chronic diseases, such as cardiovascular disease, type 2 diabetes, cancer and osteoporosis. Vitamin C has – in addition to chronic diseases – a potential effect in the prevention and treatment of common cold. However, a meta-analysis has concluded that there is no scientific evidence supporting a protective role of vitamin C supplementation to reduce the incidence of colds in normal population (35). In contrast, randomized trials suggest that vitamin C supplementation may reduce common cold incidence in athletes and other individuals who are under extreme physical stress (36,37).

Requirement and recommended intake

Earlier Nordic recommendations (38), as well as the US RDIs from 1989 (11), were based on an estimated adequate body-pool (1500 mg) that would give an ample safety margin against scurvy (39). It was estimated that a daily intake of approximately 30-40 mg would provide a body pool of 900 mg and prevent scurvy for 30-40 days after cessation of this daily intake (11). This intake would also lead to plasma ascorbic acid concentration above 23 μmol/l (10). By assuming a large inter-individual variation (50 %) e.g. to ensure adequate iron absorption, the NNR 1996 was set at 60 mg for both males and females.

Due to the increased recognition of the antioxidant function of vitamin C, it has been proposed that the daily recommendations should be based on its antioxidant activity rather than on antiscorbutic activity or body pool (2). Moreover, it seems clear that the maximal antioxidant activity is reached after higher intakes than the levels needed to prevent scurvy (5). Based on these arguments, the recommendations for vitamin C intake NNR 2004 were grounded mostly on the role of ascorbic acid in preventing morbidity and mortality from chronic diseases, such as cancer and cardiovascular diseases (40). This reasoning may obviously be challenged, since it is mostly based on population studies with limitations noted earlier in this chapter.

By using the cut-off points in population studies for clearly lowered risk (in relation to the lowest 20%), the mean cut-off point was AA concentration 32 μmol/l (unweighed mean of the 8 studies with mortality as outcome) (16–23). This plasma level was chosen as the basis for the average requirement in the 2004 Nordic recommendation (40). The more recent studies on morbidity could indicate a slightly higher optimal level, roughly 40—50 μmol/l as a basis for the average requirements (24–28). However, the evidence may be biased due to the fact that all identified cohort studies relied on the same data. Therefore, these data were not regarded as sufficient for raising the average requirement [and subsequently the recommended intake (RI)].

Using the pharmacokinetic data of Levine et al. (5,8), a 32 μmol/l concentration in plasma corresponds to a daily vitamin C intake of approximately 60 mg/day in men and 50 mg/day in women. This is close to the intake when vitamin C starts to be excreted in urine (5) and corresponds to a body pool of approximately 1000-1200 mg (39). By giving a conservative 25 % allowance for the inter-individual variation, the daily recommendation is set to 75 mg. Hence, this recommendation can be seen as the meeting point of two approaches: one from population studies and another from pharmacokinetics (start of excretion of vitamin C into urine). An intake of 75 mg/d would moreover lead to plasma vitamin C concentration around

40 μmol/l (5,9), a level that has already been associated with inhibition of in vitro LDL oxidation (41).

The pharmacokinetics of vitamin C in women seem to be similar to those in men (8). However, at daily intakes below 100 mg, women have slightly higher concentrations of vitamin C in plasma with a given level of intake. These data suggest that the average requirements are slightly lower in women, which may be due to their smaller body size (11). However, to ensure adequate non-heme iron absorption, the coefficient of variation for women was assumed to be double that for men, and hence the same recommendation is applied for both sexes. Smokers may need about 30 mg more vitamin C daily to reach plasma vitamin C levels comparable to non-smokers (42).

The recommendation is increased by 10 mg/d during pregnancy, in order to cover the increased needs due to growth of foetus and catabolised vitamin C (11). Breast milk contains approximately 30 mg vitamin C per litre (11). If the average milk production is 750 ml/day, up to 25 mg/day of additional vitamin C would be needed during lactation. This then increases the daily vitamin C recommendations in pregnancy to 85 mg/day and during lactation to 100 mg/day.

The average requirements for children (< 14 years) were extrapolated from the adult values by assuming growth factors 1.3 (< 2 years) and 1.15 (2-13 years). The recommended intake was calculated as 1.25 times estimated average requirement.

Reasoning behind the recommendation

The 2004 Nordic recommendation was based on a mean AA cut-off point 32 μmol/l which was the unweighed mean of the 8 studies with mortality as outcome. The average dietary vitamin C intake leading to the above mentioned plasma AA concentration was estimated to be 60 mg. When adding an estimation for the intra-individual variance (2SD = 15 mg), the recommendation was set as 75 mg/day for adults. The more recent studies on morbidity could indicate a slightly higher optimal level, roughly 40 - 50 μmol/l as a basis for the average requirement. However, the evidence may be biased due to the fact that all identified cohort studies relied on the same data. Therefore, these data were not regarded as sufficient for raising the average requirement (and thereafter the recommendation).

Upper intake levels and toxicity

There is no evidence that high intakes (> 1000 mg/day) of vitamin C are carcinogenic or teratogenic (43). However, high intakes may cause diarrhoea and other gastrointestinal disturbances, and possibly also increased oxalate formation and kidney stone formation in susceptible individuals.

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