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Human vitamin C requirements

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Summary: The importance of vitamin C is reflected in its multifunctional roles which include participation in collagen and carnitine syntheses, promotion of iron absorption and the more recently discovered participation in noradrenaline synthesis, inactivation of free radical chain reactions, prevention of N-nitroso compound formation and more. Given the many extra-antiscorbutic functions of the vitamin, the Recommended Dietary Allowances (RDA) should not just prevent deficiency disease but should aim at providing sufficient amounts for all vitamin C-dependent functions to operate at full capacity. The concept of vitamin C tissue saturation is best able to meet this demand. The use of kinetic models has shown that the body pool is saturated with a daily intake of 100 mg vitamin C in non-smokers and 140 mg in smokers, amounts that may be regarded as optimal RDA values.

Certain disease states may be accompanied by still higher vitamin C requirements but the exact amounts are not yet known.

Zusammenfassung: Die Bedeutung von Vitamin C für den menschlichen Organismus wird aus den wichtigen Funktionen ersichtlich, an denen das Vitamin beteiligt ist, wie zum Beispiel Kollagen- und Karnitinsynthesen. In neuerer Zeit entdeckt wurde seine Rolle bei der Noradrenalinsynthese, der Inaktivierung von freien Radikalen sowie der Verhinderung der Nitrosaminbildung. Die Vielfalt dieser Vitamin-C-abhängigen Funktionen läßt erkennen, daß die Bedarfsfestsetzung für Vitamin C nicht nur die Verhütung der Mangelkrankheit Skorbut anvisieren, sondern auch berücksichtigen sollte, daß alle diese Funktionen jederzeit genügend Vitamin C zur Verfügung haben müßten, um optimal reagieren zu können. Das Konzept der Gewebesättigung kommt diesem Ziel am nächsten.

Studien mit einem kinetischen Modell haben ergeben, daß eine Sättigung mit täglicher Einnahme von 100 mg Vitamin C bei Nichtrauchern und von 140 mg bei Rauchern eintritt, Mengen, die als optimale Werte gelten können. Bei verschiedenen Krankheiten dürfte der Bedarf höher sein; die genauen Mengen müssen jedoch erst noch ermittelt werden.

Key words: vitamin C, functions, kinetics, pool, saturation, requirements, RDA

Introduction

It was not long after the era had come to a close in which micronutrients, notably vitamins and minerals, were discovered in food and found to be indispensable for survival and health, that governments started to issue recommendations on the amount of these essential nutrients considered adequate and toxicologically safe for daily consumption. In the United

States such recommendations were published as early as 1941. And they have since been periodically revised and updated, taking into account new scientific findings. Originally, the Recommended Dietary Allowances (RDA) were established to serve as a "guide for planning and procuring food supplies for national defense". Moreover, they were to "provide standards serving as a guide for good nutrition" on the basis of the best knowledge available at that time (1).

In the mean time scientists have considerably expanded knowledge about the value of vitamins and minerals in the prevention of disease and the active promotion of health. But at the same time they have been acutely aware of the many gaps that still exist in the understanding of the biochemical functions of these micronutrients and of their contribution to health.

The official definition of the Recommended Dietary Allowances in the USA today is that they are "the levels of intake of essential nutrients considered on the basis of available scientific evidence to be adequate to meet the known nutritional needs of practically all healthy persons" (2). Evidently this definition is still in need of an interpretation. Thus, vivid controversies are in progress in various countries, most notably the United States, on the criteria and goals that should guide the determination of RDA values (3). One group considers that amount adequate which prevents deficiency disease and includes an appropriate margin of reserve, a definition that is also valid in several countries, including Great Britain (4). Their opponents hold that one should aspire to find the optimum amount which, by definition, is the amount "that promotes the highest level of health" (5); thus they would rather err on the high side than risk to underrate the actual demands.

The definition of RDA levels does of course have far-reaching consequences politically, socially and economically, as RDA values have a great impact on the dimension of food assistance programs, on agricultural production patterns and economy as well as on legislation for food fortification and declaration.

The great differences existing between RDA values in different countries indicate that it is not scientific evidence alone that determines RDA levels but that political and socioeconomic considerations or pressures are involved as well. In the case of vitamin C the RDA lies in the range of 30 mg in Great Britain and 100 mg in the USSR with an intermediate value of 60 mg in the USA.

The limited understanding of the functions of vitamin C in the organism may account for the controversies that surround the determination of an RDA value. It is in any case advisable to base this value on a variety of approaches.

Another way of solving the controversies may be to work out different levels of requirements. The lowest could be that minimal value which prevents deficiency disease and includes a certain reserve. Then there could be an optimal level for healthy populations which would take into account the needs differing with age, sex, physical activity, physiological status, such as adolescence, pregnancy and lactation, environmental factors as smoking, pollution and alcohol intake and which would have a margin of reserve. Finally, a third level might be determined for patients

with certain acute or chronic diseases as those who have undergone surgery and who may have exceptionally high requirements for a certain time.

Extrapolation from animal data

Unlike other animal species, human beings, non-human primates (squirrel monkeys, macaques, baboons), guinea-pigs and certain birds have, in the course of evolution, lost the ability to synthesize vitamin C from glucose, glucuronic acid or galactonic acid in the liver, due probably to the absence of the enzyme L-gulonolactone oxidase. These species are therefore dependent on the provision of the vitamin through external sources.

Studies were carried out in several species with intact vitamin C synthesis estimating the rate of synthesis in hepatic microsomes (6).

These amounts are unexpectedly high when extrapolated to man on the basis of the rate per kg body weight.

It is quite obvious that human vitamin C requirements are not as high as these extrapolations might suggest. And the experiments estimating synthesis rates must be viewed with reservation as they reflect only in vitro synthetic capacity. Moreover, extrapolation from animal data to human requirements may be fallacious: turnover rates, metabolism and half-life of vitamin C in the human organism are not comparable to those in smaller animals. Nevertheless, the magnitude of the difference between the presumed rates of vitamin C synthesis and the 30–100 mg vitamin C recommended for human consumption suggests that human RDA values may not be optimal.

This impression is supported by findings in non-human primates and guinea-pigs, also unable to synthesize vitamin C (6). Macaques and squirrel monkeys were found to need 23–35 mg vitamin C per kg body weight (corresponding to 1610–2450 mg in a 70 kg man) to remain healthy in captivity. Baboons required 10 mg vitamin C per kg (700 mg in man) daily to maintain the vitamin C blood levels that were determined at the moment of capture. In guinea-pigs adequate growth and health could be

Table 1. Vitamin C synthesis rates in mammals: Extrapolations to man.

Mammal	Rate (mg/kg/day)	Extrapolated to 70 kg man (mg/day)
Goat	32.6–190	2300–13 300
Cow	15.7–18.3	1100–1300
Sheep	24.8	1700
Rat	39.1–198.6	2800–14 000
Mouse	33.6–275	2400–19 000
Squirrel	28.8	2000
Rabbit	22.1–226	1500–16 000
Cat	4.8–40	350–2800
Dog	5.0–40	350–2800
Pig	8.1	570

Adapted from Levine, 1986 (6)

achieved with the use of 10 to 16 mg per kg (700–1120 mg in man). Again, these animal data should not be transferred uncritically to man, but they too show that the differences between the low human RDA levels and the high animal intakes are remarkable.

All in all, these animals studies fail to provide incontestable data for the determination of an exact RDA level for humans but they do suggest that the intake of higher levels may be physiologically more appropriate even though the human organism can subsist on less.

Scurvy and its prevention

Compared with the scurvy epidemics that occurred quite commonly some centuries ago, the sporadic cases of frank vitamin C deficiency encountered today might be regarded as negligible. However, just because scurvy is not expected to be seen it is frequently overlooked when it does occur. In recent years experts have detected this potentially lethal disease in many alcoholics and in patients who avoid or neglect vitamin C containing food due either to ignorance, error or poverty (7–9).

The clinical picture of scurvy has been characterized as the disease of the four Hs (6):

1. Hemorrhagic signs (perifollicular hemorrhages, ecchymoses and bleeding gums)
2. Hyperkeratosis of hair follicles with coiled hair
3. Hypochondriasis
4. Hematological abnormalities (anemia due either to reduced iron absorption or aberrant folate metabolism).

Further signs include Sjögren's syndrome (dry mouth and eyes, dry itchy skin, hair loss, loosened teeth), edema, arthralgia and poor wound healing (10).

The signs of scurvy appear within 30 to 90 days of total vitamin C deprivation, but they may take longer to develop if there is a certain limited vitamin C consumption (11). On the other hand, if reduced vitamin C intake is paralleled by increased needs for the vitamin due for instance to a higher metabolic turnover (as in smokers) (12), to reduced uptake (as in those using aspirin) (13), or to an acute drop in blood levels (as in surgical patients and in those with myocardial infarction) (14, 15) scurvy is likely to appear more rapidly. It has been observed that clinical scurvy appears when the body pool of vitamin C is below 300 mg (10).

Treatment of scorbutic patients must begin immediately upon diagnosis as there is the danger of sudden death. The doses recommended are 100 mg vitamin C three times daily until all signs have disappeared (16).

The prevention of scurvy requires as little as 10 mg vitamin C a day. But this will not raise the body pool appreciably above 300 mg. In fact, a case was recently reported in which a young man developed florid scurvy after having subsisted on a mean vitamin C intake of 10.2 mg for many months in the mistaken belief that he had a food allergy against the typical vitamin C containing fruits and vegetables (17). Evidently, this minimal amount will in no way satisfy the needs of an active person who has to withstand the different types of stress of modern life. Indeed, vitamin C has many

roles in the organism other than the prevention of scurvy. Still, these 10 mg with an added safety margin have been used as a basis for the RDA value of 30 mg which is valid is several countries.

Biochemical functions of vitamin C

Even from the little that is known about the physiological role of vitamin C it is clear that the vitamin is a highly versatile nutrient.

While not being an actual coenzyme vitamin C participates in many enzymatic reactions due to its ability to act as an electron transmitter (18).

Collagen synthesis. Vitamin C is involved in the hydroxylation of proline to hydroxyproline and of lysine to hydroxylysine in the formation of collagen. Deficiency of vitamin C therefore leads to unstable connective tissue with poor wound healing. This is one of the few links between biochemical function and clinical signs of scurvy that are known.

Carnitine synthesis also involves hydroxylation reactions in which vitamin C plays a part. Carnitine itself is an important factor in the transport of fatty acids to mitochondria providing energy. It has been suggested that a reduction of heart and skeletal muscle carnitine due to inadequate availability of vitamin C will result in fatigue which is one of the earliest signs of deficiency, actually appearing already with subclinical deficiency (19).

Noradrenaline synthesis. Noradrenaline is synthesized in the adrenal medulla where the concentration of vitamin C is very high. It was recently found that one of the enzymes in the biosynthesis of noradrenaline, the copper-containing dopamine β-monooxygenase, requires stoichiometric amounts of vitamin C (20).

Microsomal hydroxylations. An important function of vitamin C is its participation in the microsomal cytochrome P_{450}-dependent hydroxylases which act as metabolizing enzymes in the liver dealing with carcinogens, pollutants, pesticides and certain drugs.

Many other enzymatic steps on the way from precursor substances to biologically active ones require vitamin C, either to accelerate hydroxylation reactions (e.g. in catecholamine biosynthesis) or to use its powerful reducing properties (e.g. to achieve full activity of peptide hormones) (6).

Iron absorption. It is probably also its reducing properties that turn vitamin C into one of the most important enhancers of iron absorption from non-meat sources. A further function of vitamin C is the formation of a complex with iron which is stable in the alkaline environment of the duodenum, thus facilitating absorption. With these properties vitamin C plays a key role in the prevention of iron deficiency anemia (21). An important aspect to remember is that the vitamin, in a dose of about 50 mg, must be consumed together with the meal in order to be effective.

Interaction with free radicals. The concept that there exist free radicals which induce tissue damage if not rendered inactive by free radical scavengers is quite new and rather fascinating. Biological free radicals are oxygen-derived chemicals with heightened reactivity because of an unpaired electron in their structure. When the production of such radicals exceeds the availability of free radical scavengers, tissue damage occurs in the form of peroxidation of lipid membranes and other structural damage.

There exist a great variety of scavengers, some in the form of enzymes as e.g. superoxide dismutases, others in the form of antioxidant vitamins as e.g. vitamin E, vitamin C and β-carotene (22, 23). Much is still a mystery regarding both the generation of free radicals and their inactivation.

Upon oxidation vitamin C forms an intermediary radical itself which due to its stability can function as a radical trap. The vitamin appears to have a dual function: (I) it directly quenches free radicals such as the hydroxyl radical and singlet oxygen and (II) it protects vitamin E maintaining it in its reduced form so that this powerful antioxidant can act as a free radical scavenger unimpeded (24).

The action of free radicals has been linked to a great variety of conditions such as aging, cardiovascular diseases, cancer, inflammatory diseases, cirrhosis or diabetic complications (25). But while such associations are plausible and may well be verified eventually they are still speculative given the limited knowledge we have today. There is some indication that vitamin C may play a role in the protection of the eye against free radicals produced by ionizing radiation in light. This would explain the high concentration of vitamin C in aqueous humour exceeding that in plasma by a factor of 10. Animal studies indeed suggest that vitamin C prevents cataract formation by its antioxidant effect (26–28).

For many observations of a vitamin C effect in the organism no clear physiological mechanism has been deduced yet:

Antimutagenic effect. A group of workers habitually exposed to halogenated ethers and thus having a high rate of chromosomal aberrations had a significantly decreased frequency after taking prophylactic doses of vitamin C of 5 times 1 g a week during the winter months (29).

Studies in coal-tar workers given three months' prophylactic supplementation with 5 times 1 g vitamin C a week again suffered considerably reduced mutagenic effects from the chemicals to which they were exposed. The authors offered as a hypothesis that vitamin C may have stimulated the cytochrome P_{450} systems thus enhancing detoxification or that it may have accelerated DNA repair. It must be noted that with 1.5 mg/L, the mean presupplementation blood levels of vitamin C in these workers were in the scorbutic range; but they reached satisfactory concentrations of 10.5 mg/L at the end of the supplementation period (3, 31).

In the Soviet Union persons working in a toxic occupational environment tend to receive prophylactic food supplements including 100–150 mg extra vitamin C (32).

But even under normal circumstances there is room for a reduction in mutagenetic effects. A study in healthy American students showed that the excretion of mutagens with the feces could be substantially lowered if the typical Western diets, which contained between 54 and 66 mg vitamin C and 3–8 mg vitamin E, were supplemented with 400 mg vitamin C and E (33). Here, the vitamin C status before supplementation was probably not as unsatisfactory as in the above studies since the intake corresponded to official recommendations. Still a reduction of mutagens could be achieved with supplements indicating that a higher intake may be desirable even in persons with a reasonably satisfactory vitamin C and E status due to adherence to recommended intakes and not exposed to exceptionally high amounts of mutagenic pollutants.

Inhibition of N-nitroso compound formation. N-nitroso compounds, mostly nitrosamines, are formed from the precursors nitrate or nitrite and a nitrosatable compound, as for instance an amine or amide, in foods, cosmetics, tobacco or industrial products as well as in the living organism of man and animals. Most of the nitrosamines known today have been found to induce cancer in animals and are believed to do so also in man (34, 35).

Thus it was an important discovery when researchers found that vitamin C prevented the formation of nitrosamines by competitive inhibition (36, 37). In animal studies vitamin C completely abolished the mutagenic effect of the administered nitrosamine precursors aminopyrine plus nitrite, indicating that nitrosamine formation was inhibited (38).

Studies in man equally demonstrated that nitrosamine formation was effectively suppressed by vitamin C (as well as by vitamin E). A surprising finding was that even using identical diets there were great interindividual variations in the response to vitamin C supplements (39). Another interesting study showed that the mutagenic action of gastric juice induced by nitrosamines could be considerably reduced by giving volunteers daily vitamin C supplements of 1 g, again indicating that nitrosamine formation was prevented (40).

A beneficial effect of vitamin C could also be demonstrated using moderate doses. Inhabitants of Lin-xian, a high-risk area for esophageal cancer in Northern China, excreted greatly reduced nitrosamine concentrations in the urine after the intake of only three times 100 mg vitamin C daily. And it was suggested that vitamin C could possibly reduce cancer risk in this area, a question that is being further investigated (41). There is epidemiological evidence from several countries that a low vitamin C status is associated with a higher risk of stomach cancer (42).

As in the promotion of iron absorption, the vitamin C status as such does not play a decisive role in the prevention of nitrosamine formation in the stomach. What is important is that vitamin C is consumed together with the precursors if it is to be effective. However, recent findings indicate that activated macrophages, as they occur for instance in inflammation, can synthesize nitrite. This means that vitamin C should act as an inhibitor of N-nitroso compound formation throughout the body (43).

Other biochemical effects. Among the little understood effects of vitamin C is its recently detected protection against alcohol toxicity in animals and man with reduced damage to liver cells and increased alcohol clearance. The dose used in man was five time 1 g a day. It will be interesting to see whether such an effect can be achieved also with lower doses of the vitamin (44–46).

Because the highest concentrations of vitamin C are found in endocrine tissues as the adrenal and pituitary glands (47) it has been suggested that the vitamin plays an important part in the optimal functioning of hormones (20).

Vitamin C has also been implicated in prostaglandin synthesis (48), in lipid metabolism (49), immune response (50, 51) and many other biochemical reactions. Much work is however still needed to understand the role of the vitamin in these and other processes.

Still, knowledge about the biochemical functions of vitamin C does not give an indication of the quantities required to fulfil its roles in the human body; it only underlines the significance of the vitamin with its multifunctional properties.

It has been proposed that an ideal approach to estimating optimal RDA values would be the biochemical measurement of the effect of vitamin C on enzyme systems in which vitamin C would promote maximum conversion of precursor substances to active chemicals (6). The use of such enzyme model systems would represent a sophisticated approach, which is however not yet practicable due to a lack of knowledge and methodology.

Kinetics of vitamin C

We do not know with certainty whether the concept of vitamin C tissue saturation represents the most adequate determinant of an optimal RDA value. But if we accept that requirements vary greatly depending on biochemical individuality as well as on innumerable environmental factors, it seems reasonable to accept – in the absence of a better concept – that an intake is optimal when it guarantees replenished body stores ready to meet any conceivable demand by vitamin C-dependent biochemical systems at any time.

Vitamin C is absorbed from the gastrointestinal tract by an active energy-requiring transport mechanism which, like other active mechanisms, is saturable. Even intakes in the physiological range of 30 to 180 mg vitamin C are absorbed only to the extent of 80 % to 90 % (52). With increasing intakes of the vitamin the percent absorption declines still further (53, 54): at intakes ranging from 1.5 g to 12 g relative absorption was found to decrease from 50 % to 16 % (55).

With the use of a sophisticated kinetic model and isotope-labelled vitamin C it could be demonstrated that the total turnover of vitamin C under steady-state conditions in non-smoking male volunteers was 60 mg daily. This value was calculated to reflect a total body pool size of about 1500 mg, and it corresponds to steady-state plasma levels of 8 to 9 mg/L. Above these levels elimination of vitamin C in the urine increases rapidly and metabolic turnover shows saturation.

As the vitamin is incompletely absorbed the amount required to achieve a total turnover of 60 mg daily lies in the range of 70 to 75 mg. And in order to obtain a value covering the needs of at least 95 % of a population the investigators added twice the standard deviation worked out in their study. The level of intake considered optimal was thus calculated to be in the order of 100 mg vitamin C daily corresponding to plasma levels of 8 to 9 mg/L (56).

This conclusion is supported by a study in adolescents showing that physical working capacity, expressed as oxygen consumption per kg body mass, could be increased by vitamin C supplementation up to the point when plasma levels had reached 8 to 9 mg/L (57). This may be an example of an optimal situation in which a vitamin C-dependent biological function has reached its full capacity. Another study in persons with a low vitamin C status showed that when supplementation had led to vitamin C plasma

levels of 9 mg/L there was a significant increase in proline and hydroxyproline content in gingival tissue. Non-supplemented control subjects showed no such improvement (58).

The recommended intake of 100 mg vitamin C daily is optimal only for the non-smoking part of the population. It has in fact long been known that smokers tend to have 20 to 40 % lower vitamin C plasma levels than non-smokers (59–61); this has been attributed to altered utilization or to reduced intake due to an appetite suppressant effect of smoking.

But a recent study in smokers and non-smokers using the same kinetic model as in the investigation assessing optimal intakes in non-smokers (56) could show that the 40 % reduction of vitamin C plasma concentration was due mainly to an increased metabolic turnover and a shorter elimination half-life of vitamin C. And it was calculated that saturated body stores with plasma levels of 8 to 9 mg/L could be achieved in smokers with a daily intake of 140 mg vitamin C (12).

These levels of intake of 100 mg vitamin C in non-smokers and of 140 mg in smokers may be considered optimal values which individuals with a sense of responsibility for their health should strive to achieve, irrespective of whether governments opt for lower RDA levels.

Situations with exceptional demands

Myocardial infarction. Acute infarction is accompanied by a dramatic fall in leucocyte vitamin C reflected in low vitamin C blood levels and by an increase in total white cell count. A study has shown that the acute fall in vitamin C cannot be prevented by presupplementation with the vitamin. However, recovery from vitamin C deficiency which, untreated, lasts at least 56 days, can be considerably shortened by giving vitamin C supplements. The doses used were in the order of several grams. But the amounts required are not yet known (62, 63, 15).

Surgical repair. Surgical operations are frequently followed by a marked decrease in vitamin C status regardless of the severity of the operation (14, 64). As vitamin C plays an important role in wound healing the use of supplements may be indicated. Again, no information is available on the amount that would be reasonable.

Chronic aspirin consumption. There is evidence that the intake of acetylsalicylic acid, e.g. aspirin, interferes with the vitamin C status though the mechanism of action is not yet known. Decreased absorption of the vitamin, reduced uptake by leucocytes as well as increased excretion have all been suggested (13, 65, 66). Patients taking aspirin continuously may benefit from paying special attention to their vitamin C status.

Other conditions. Many other situations have been described in which extraordinary demands are made on vitamin C status. Recently it was found that workers in a very hot climate had an inadequate vitamin C status despite abundant vitamin C containing food. The causes were found to be suppressed appetite by the heat as well as an extrarenal loss of vitamin C with sweat of about 20 mg daily (67).

Other groups with a frequently reduced vitamin C status include pregnant and lactating women (68–70), patients with inflammatory and other

acute diseases and cancer (71, 72). While vitamin C supplements may not act as therapeutic agents they at least serve to restore the vitamin C status.

Conclusion

It is accepted today that "nutrition is the single most important component" in the prevention of diseases affecting any organ system in the body (5). One important aspect of health promotion is the definition of desirable amounts of single nutrients that should be consumed. In the case of vitamin C, the desirable daily intake is that amount which leads to saturated body stores: 100 mg in non-smokers and 140 mg in smokers. These amounts may permit the many important vitamin C-dependent biochemical processes in the organism to function optimally.

Some groups may require higher amounts for shorter or longer periods due to exceptional situations. These groups include surgical patients, patients after myocardial infarction, patients with other acute diseases, aspirin consumers and further groups with depleted vitamin C body stores as, for instance, pregnant and lactating women. The amounts required to restore the vitamin C status in these groups still needs to be defined.

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